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Chromosome Studies In Full-term Low Birth Weight Mental Retardates

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CHROMOSOME STUDIES IN FULL-TERM LOW BIRTH WEIGHT MENTAL RETARDATES

by

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Department of Anatomy

Submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy

Faculty of Graduate Studies
The University of Western Ontario
London, Canada
November, 1968

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ABSTRACT

A high proportion of infants affected with chromosome diseases are born with a low birth weight, even when they are delivered within the normal gestation period. Warkany et al. (1961) suggested that chromosome abnormalities might be associated with low birth weight, particularly in patients with mental retardation and multiple congenital malformations.

Chromosome analyses were done on 150 full-term low birth weight mental retardates, i.e., when the patient had a birth weight of 5 lb. 8 oz or less with a gestation period of 38 weeks or more. Peripheral blood leucocyte cultures showed that 29 patients had a chromosome abnormality. These included 18 with Down's syndrome, three with Klinefelter's syndrome, two with gonadal dysgenesis, one E trisomy syndrome, one D trisomy syndrome (familial D/D translocation), one with partial trisomy of the long arm of a B4 chromosome, one with metacentric G, one with the cri-du-chat syndrome and one with an inversion of a no. 2 chromosome. Three of the patients with Down's syndrome showed chromosome abnormalities other than regular trisomy 21. The abnormalities were 47, trisomy 21 (ring)/46, normal mosaicism, 48, XXX-trisomy 21 and 46, D/G translocation.

The control group consisted of 150 normal birth weight mental retardates who were matched for sex, age and etiological classification with the low birth weight retardates. Twenty-one patients possessed a chromosome abnormality. Eighteen were afflicted with Down's syndrome,
one had Klinefelter's syndrome, one had a triple-X sex chromosome constitution and one possessed a D/D translocation. All of those with Down's syndrome showed regular trisomy 21.

These data indicate that the frequency of chromosome abnormalities in the full-term low birth weight mental retardates of this study is approximately 19 per cent. In the normal birth weight mental retardate control group, the frequency is about 14 per cent. A patient with 48,XXX-trisomy 21, one with 47, trisomy 21 (ring)/46, normal mosaicism and one with a 46, D/G translocation were found among 18 full-term low birth weight Down's syndrome patients while only the regular form of trisomy 21 was found in the normal birth weight group. Although the finding of three atypical karyotypes in the low birth weight mongoloid group is not statistically different from the finding of only the regular trisomy 21 in the normal birth weight group, the relative rarity of 48,XXX-trisomy 21 and 47, trisomy 21 (ring)/46, normal mosaicism suggests that they might be associated with low birth weight. The more important finding, however, is that the frequency of chromosome abnormalities in the full-term low birth weight mental retardates, exclusive of those with Down's syndrome, was 8.3 per cent. This was higher than that in the normal birth weight controls (2.3 per cent) and while not significant at the five per cent level, reaches significance at the six to seven per cent level and suggests that chromosome abnormalities may be found in many low birth weight mental retardates.
I. INTRODUCTION

An association between mental retardation and full-term low birth weight has been observed during recent years (Warkany, Munroe and Sutherland, 1961; Bacola, Behrle, de Schweinitz, Miller and Mira, 1966). Chromosome abnormalities, on the other hand, have been known to be an important cause of mental retardation since Lejeune, Gauthier and Turpin (1959) first demonstrated that Down's syndrome was associated with the presence of an extra G group chromosome. The relationship between these phenomena became somewhat clearer with the observation that many children with chromosome disorders such as the D1 trisomy, E18 trisomy and cri-du-chat syndromes are born with a low birth weight (Polani, 1964; Taylor, 1967), even when they are delivered at term. Warkany et al. (1961) studied 27 full-term low birth weight infants in whom a variety of congenital malformations were found. They concluded that there were many possible etiological factors leading to full-term low birth weight; amongst these, chromosome abnormalities might be prominent, especially in those mentally retarded children who also exhibit multiple congenital malformations. This was also the conclusion of Brent and Jenseh (1967).

These reports encouraged us to carry out a chromosome survey on a group of full-term low birth weight individuals who were also mentally retarded. The aim of the study was to determine if there was an increased incidence of chromosome abnormalities in full-term
low birth weight mental retardates (LBWR) when compared with retardates of full-term normal birth weight (NBWR).

* LBWR and NBWR will be used throughout the thesis as an abbreviation for full-term low birth weight mental retardates and full-term normal birth weight mental retardates respectively.
II. LITERATURE REVIEW

1. Birth Weight and Its Influencing Variables

Fetal birth weight is affected by both the genetic constitution of the fetus and the maternal environment (Penrose, 1952). Rifle, Gerlaugh, Kunkle, Brandt and Synder (1943), in a study of crosses between Aberdeen-Angus and Herefordshire cattle, found that the birth weight of the calf depended mainly upon its own genetic constitution. In man, there is a positive correlation between the birth weight of sib pairs (Karn, Lang-Brown, MacKenzie and Penrose, 1951). This positive correlation could be due to the fact that sibs have the same mother, which implies either that their intrauterine environment is similar, or that they are genetically alike. Further evidence that birth weight may be in part genetically determined is provided by the description of a family in which there were seven infants, each born weighing over 13 lb. (Penrose, 1952).

Maternal environmental factors are important in the determination of fetal birth weight. Karn (1952) showed that the correlation coefficient of the birth weight of unlike-sexed twin pairs greatly exceeded that between brother and sister non-twin pairs. The difference could have been due to the more constant maternal environment of the twins. Furthermore, fetal birth weight is influenced by both the parity and the maternal age, i.e., birth weight increases with parity but decreases slightly with maternal age (Karn and Penrose, 1951). However, parity and maternal age have independent effects, with parity having the greater influence
and maternal age very little. On the other hand, maternal weight but not maternal height was found to be correlated with fetal birth weight (O'Sullivan, Gellis and Jenny, 1965). These authors attributed the increased fetal birth weight to the rise in blood glucose level that is seen with increases in maternal weight. However, Love and Kinch (1965) not only found that the weight, the body build and the weight gain of the mother were significantly and positively correlated with the fetal birth weight, but that the maternal height also played a role in fetal birth weight.

Earlier work (Bakwin, 1932; Dunham, Jenss and Christie, 1939) indicated that Negro infants in the United States were not only born with a lower birth weight than Caucasian infants but that they also grew more slowly during the first year of life. Although these authors suggested that racial differences should be considered to be the likely explanation for the results, the size of the groups studied was in fact small and the results could also be interpreted in terms of socioeconomic factors. Bakwin and Patrick (1944) gave evidence to the effect that there was no significant difference in the weight gain of Caucasian and Negro infants during the first year of life in comparable environmental situations. Scott, Jenkins and Crawford (1950) analysed a sample of 11,818 Negro infants and they found that the relatively high birth weight for some Negro infants was associated in large measure with more favorable economic conditions during the period of observation.

Gruenwald, Funakawa, Mitani, Nishimura and Takeuchi (1967), in studying hospital records of three large Japanese obstetric series,
found that the mean duration of pregnancy was not increased in infants
born after the Second World War, although the mean birth weight of the
post-war infants was higher when compared with those born in the pre-
war period. This attests again to the prominent influence of socio-
economic factors on fetal growth since the Japanese economy improved
greatly after the war. Results showing that socioeconomic factors
could play a more important role than genetic influences on fetal
birth weight were also obtained by Jayant (1964) who studied an Indian
population, and by Hollingsworth (1960) who studied an African
population.

The association between birth weight and socioeconomic factors
may be explained in terms of nutrition. Low birth weight was found to
be associated with undernourishment, particularly when present early in
the pregnancy (Clements, 1962). Conversely, there is evidence that an
overweight mother has a higher probability of giving birth to a large
baby (O'Sullivan et al., 1965).

Diabetes in the mother is often found to be associated with
high fetal birth weight. A number of studies show that the incidence
of diabetes among mothers of large fetuses is higher than that of
control groups (Bolton, 1959; Nathanson, 1950; Posner, Friedman and
Posner, 1955). However, Koskela (1965), after analysing the histories
of 15,147 newborns, found that the prevalence of diabetes in the
mother was not an etiological factor in the development of a large
fetus. Geographical differences, parity and maternal genetic consti-
tution were thought to account for the incidence of large fetuses in this
study.
2. Birth Weight and Infant Survival

Karn and Penrose (1951) found that infants with a birth weight of \(\frac{5}{2}\) lb. or less, particularly those with a birth weight below \(\frac{4}{2}\) lb., had a higher mortality than those with a normal birth weight. Newborns who weigh 1500 g (3.3 lb.) or less, represent only one per cent of all live births, but they account for approximately 40 per cent of the neonatal deaths (Wilson, Parmelec and Huggins, 1963). Similarly, Brimblecombe and Ashford (1968) found that in England and Wales, about seven per cent of all infants weighed less than 2501 g (5.5 lb.) at birth, although they accounted for about 65 per cent of the total perinatal mortality. It would thus appear that there is a high proportion of perinatal death among low birth weight infants. A study by Douglas and Mogford (1953) showed further that the high mortality of low birth weight infants extended beyond the first month of life. Those who died within the age period of one month to four years expired primarily from congenital defects and infections.

3. The Concept of Low Birth Weight

In 1950, a group of World Health Organization experts on prematurity endorsed the international definition that "an immature infant is a liveborn infant with a birth weight of \(\frac{5}{2}\) lb. (2500 g) or less". Immaturity and prematurity were taken as being synonymous. Since then, it has been recognized and generally accepted that this definition encompasses a dual population. Söderling (1953) first applied the term "pseudopremature" to distinguish infants born at term and who have failed to achieve a normal fetal growth from the true premature infants who were born after a short gestation period. In 1961, the Expert Committee on Maternal and Child Health of the World
Health Organization recommended that the concept of "immaturity" in the original definition in 1950 should give way to that of "low birth weight".

Recently, different methods for the identification and classification of newborn infants on the combined bases of birth weight and gestational age have been suggested. Battaglia and Lubchenco (1967) proposed a classification which divided newborn infants into nine groups, three of which were by gestational age. Within each of these groups there were subgroups by birth weight. Because the mortality of babies with similar birth weight but different gestational age varied considerably (Steiner and Pomerance, 1950; McKeown and Gibson, 1951; Yerushalmy, van der Berg, Erhardt and Jacobziner, 1965), Yerushalmy (1967) subdivided the newborn infants into five groups. The first group included infants with a birth weight of 1500 g or less, the second group of infants with a birth weight of 1501 g to 2500 g with a gestation period of less than 37 weeks, the third group included infants with a birth weight of 1501 g to 2500 g with a gestation period of 37 weeks or more, the fourth consisted of infants with a birth weight of 2501 g or more with a gestation period less than 37 weeks and the fifth group included infants with a birth weight of 2501 g or more with a gestation period of 37 weeks or more.

4. Factors Influencing Low Birth Weight

The detailed etiology of low birth weight in infants is virtually unknown. From the evidence in the literature, it is clear that it does not have a single cause but may result from many causes, both singly and in combination. On the basis of weight alone, Bacola
et al. (1966) divided the low birth weight infants into two groups: the first group consisted of infants with a birth weight of 1500 g and less and the second of 1500 g to 2500 g. In the first group, about 50 percent (out of a total of 40) were considered to be either mentally retarded or borderline in intelligence. Over half of the infants had serious respiratory difficulties in the neonatal period and there was a high frequency of maternal toxemia in the prenatal history. In the second group, neonatal respiratory distress and late-occurring apnea were not associated with an increased incidence of subnormal mental development. Maternal toxemia, on the other hand, was associated with an increased incidence of "small-for-date" infants in the second group. Socioeconomic factors also appeared to play a significant role in the mental development of the infants in this group.

Toxemia has been considered a major factor associated with fetal growth retardation (Rumolz, Edwards and McGoogan, 1961). Jarvinen, Pankamaa and Kinnunen (1958) studied 1301 cases of toxemia collected from the First and Second Women's Clinics of the University of Helsinki from 1951 to 1956. They found that the longer the duration of maternal toxemia, the poorer would be the growth development of the fetus. They also demonstrated that in preeclampsia, there was a considerable slowing-down of the uterine and utero-placental circulation, which caused impaired metabolism and that this may have led to retardation of fetal growth (Browne and Veall, 1953; Morris, Osborn and Wright, 1955).

A high incidence of toxemia and hypertension was found in the mothers of small-for-date infants (Gruenwald, 1963). Furthermore, the prenatal history of 762 infants weighing less than 2500 g (5.5 lb.) at
birth and born at 37 to 44 weeks gestation showed a higher incidence of maternal toxemia, hypertension and gestational bleeding that did weight-matched pre-term controls (North, 1966). Pre-term infants were defined as those born after 28 to 36 weeks gestation and who weigh 2000 to 2500 g.

Rumbolz and McGoogan (1953) discussed small "undernourished" full-term babies. They studied those infants who were born with a birth weight of 4½ lb. or less at or near term. In their series of 7058 pregnancies, there were 17 babies born after a gestation of 36 weeks or longer with a birth weight under 2000 g. This represents a frequency of 0.24 per cent. They added three infants from other sources, hence their study group consisted of 20 "undernourished" babies. Of these, seven pregnancies were complicated by toxemia or hypertensive disease. All placentae had infarcts and 10 of 19 placentae were small. It was suggested that maternal hypertension and toxemia would lead to poor development of the placenta and that this was the likely cause of the small size of the baby. Eight of the 20 infants were stillborn. There was one neonatal death and one patient with Down's syndrome among the survivors. According to the authors, the remaining 10 living infants had no difficulties in later life and their subsequent growth development was normal.

Söderling (1953) and Pick (1954) believed that if small-for-date infants were fed properly after birth they would gain weight rapidly and develop into normal children. In fact, Pick stated that they differed from "true-premature" children in that they regained their weight more rapidly since they doubled their weight in less than 10 weeks. However, the studies of both Baird (1959) and Hepner and
Bowen (1960) cast doubt on the foregoing optimistic prognosis for the small-for-date infants. Baird tested the intelligence of all the "premature" babies and found that those with a birth weight between 4 and 5½ lb. but born at or near term, had a much lower I.Q. than the others. They also found that full-term low birth weight infants did not grow well after the neonatal period.

A correlation between mental retardation and low birth weight has been noticed more recently. A number of studies are on record which indicate that a large proportion of very low birth weight premature infants have neurological defects (Knobloch, Rider and Harper, 1956; Harper, Fischer and Rider, 1959; Drillien, 1961; MacDonald, 1963; Dann, Levine and New, 1964; Robinson and Robinson, 1965; Bacola et al., 1966). Asher and Roberts (1949) showed that there was a high frequency of low birth weight individuals among a group of children with mild, moderate and severe mental retardation. Katz and Taylor (1967), in a study of a population of patients affected with severe mental retardation, found a high frequency of low birth weight individuals among those patients with mental retardation of unknown etiology. In summarizing their results, the authors stated that the high incidence of low birth weight among the mental retardates could not be due solely to socio-economic factors. Gruenwald (1963) believed that the cerebral defect in some of the low birth weight infants may have been the result of chronic fetal distress. This he arbitrarily defined as a consequence of nutritional deprivation lasting long enough to produce a deficit of birth weight.

Warkany et al. (1961) studied 27 cases of full-term very low
birth weight infants. They used the term "intrauterine growth retardation" to describe these infants, whose birth weights ranged from 4 lb. 9 oz to 2 lb. 8 oz. A variety of congenital malformations were found among them and mental development was subnormal in 15 of the 22 survivors.

A multiplicity of factors which may lead to intrauterine growth retardation has been reviewed (Warkany et al., 1961; Brent and Jersh, 1967). There is ample data which indicate that X-irradiation can retard fetal growth (Yamazaki, Wright and Wright, 1954; Warkany et al., 1961; Wood, Keen, Kawamoto and Johnson, 1965). Experimental drugs or chemicals can be responsible for abnormal fetal growth (Warkany, Beaudry and Hornstein, 1959; Warkany and Kalter, 1961). Furthermore, viruses may also be related to fetal growth retardation (Swan, Tovstevin, Moore, Mayo and Black, 1943; Giles, Cooper and Krugman, 1964).

In both the lower animals and humans, there have been reports of dwarfism occurring in successive generations (Pitch, 1961; Warkany et al., 1961), which may reflect a genetic control over fetal growth. Although in some species the birth weight can be modified by varying the size of either parent (Beatty, 1960; McLaren, 1965), the evaluation of the genetic aspects of intrauterine growth retardation in man is more difficult, except perhaps in the area of chromosome abnormalities.

5. Mortality and Congenital Malformations Associated with Human Chromosome Syndromes

There is a high mortality among low birth weight infants (Wilson et al., 1963; Brimblecombe and Ashford, 1968). On the other hand, a large proportion of children with chromosome disorders such as D1 trisomy, E18 trisomy and the cri-du-chat syndrome is born with a low birth weight at term (Polani, 1964; Taylor, 1967). Therefore, a brief
review of the principal chromosome abnormalities in terms of mortality, congenital malformations and birth weight appears to be appropriate.

(i) Down's Syndrome

Down's syndrome (Mongolism) was first described by Langdon Down in 1866. Lejeune et al. (1959) showed that Down's syndrome was associated with the presence of an extra G group chromosome. This was confirmed by Jacobs, Baikie, Court Brown, MacGregor, Maclean and Harnden (1959). Böök, Fracarco and Lindsten (1959) favored the interpretation that the extra G chromosome was no. 21. A year later, D/G and G/G translocation-type Down's syndrome patients were reported by Polani, Briggs, Ford, Clarke and Berg (1960) and Penrose, Ellis and Delhanty (1960), respectively. The clinical manifestations of the regular trisomy 21 and translocation-type Down's syndrome do not appear to show significant differences.

The incidence of Down's syndrome at birth in European populations is in the order of one in about 600 (Jenkins, 1933; Malpas, 1937; Penrose, 1954; Carter and MacCarthy, 1951; Oster, 1953; Collman and Stoller, 1962). The syndrome has also been reported in nearly all non-European populations, e.g. Africans, Indians, Japanese, Chinese, Eskimos and American Indians, but reliable incidence figures are not yet available (Penrose and Smith, 1966).

There is a high frequency of chromosome abnormalities among human spontaneous abortuses (Carr, 1963; 1965). Polani (1966) assembled 261 instances of chromosome analyses in spontaneous abortions, showing that 72 of the concepti had chromosome abnormalities and that nine of these were trisomy G. If the latter were trisomy 21, the incidence of potential Down's syndrome in spontaneous abortions would
be about one in 29.

The most common and constant feature of patients with Down's syndrome is mental retardation. The incidence of Down's syndrome among institutionalized mental retardates is about 98 per 1000 (Allen and Kallman, 1957; Forssman, 1960).

Malformations involving many systems occur in this disease. Among 184 such patients studied by Rowe and Uchida (1961), 40 per cent had cardiovascular anomalies and 17 per cent had congenital malformations of other systems. The mortality in this group was very high. Fifty-three of the 184 patients died during the 4½ years that followed the original ascertainment; of these, 32 had congenital heart disease. Hall (1964) found that 15 of 38 newborns with Down's syndrome died during the first twelve months, a mortality of 40 per cent; of these, 11 had congenital heart disease. A mortality of 50 per cent was reported by Wolff (1964) in a group of 134 patients during the two years of his survey. A more extensive study of mortality was carried out by Forssman and Akesson (1965) on a series of 1263 patients with Down's syndrome, of whom 681 were males and 582 were females. The group had a mortality of 10 per cent. There was no difference in mortality between the two sexes. The mortality was highest between ages one and five and after the age of 40, and only slightly above normal between ages five and 40.

(ii) Klinefelter's Syndrome

In 1956, Plunkett and Barr described the finding of sex chromatin-positive cells in patients with Klinefelter's syndrome. They suggested, among other possibilities, that the sex chromatin in these phenotypic male patients might indicate the presence of an extra X chromosome, hence the sex chromosome constitution would be XXY. Bradbury,
Bunge and Boccabella (1956) also reported sex chromatin in cells of patients with Klinefelter's syndrome. In 1959, Jacobs and Strong showed that there were 47 chromosomes in these chromatin-positive males. The extra chromosome was in the C group and was possibly an X chromosome. The fact that patients with Klinefelter's syndrome have an XXY sex chromosome constitution as the most common chromosome error has now been firmly established.

The frequency of Klinefelter's syndrome is one in about 500 males (Moore, 1959; Maclean, Harnden and Court Brown, 1961; Court Brown, 1962; Taylor and Moores, 1967). Ferguson-Smith (1959) estimated that about one quarter of patients with the syndrome were of subnormal intelligence, while Rabok and Šipová (1961) found that 12 out of 47 such patients were so affected. It appears therefore that there is an association between mental retardation and the Klinefelter's syndrome. Accordingly, the frequency of the disorder among mental retardates is about one per cent (Prader, Schneider, Züblin, Françes and Rüedi, 1958; Barr, Shaver, Carr and Plunkett, 1960; Mosier, Scott and Cotter, 1960; Maclean, Mitchell, Harnden, Williams, Jacobs, Buckton, Baikie, Court Brown, McBride, Strong, Close and Jones, 1962).

Isolated cases of Klinefelter's syndrome in which there were other congenital defects associated with the infertility have been reported. Court Brown, Harnden, Jacobs, Maclean and Mantle (1964) recorded aortic stenosis in one patient and probable congenital heart disease in another, among 99 cases of XXY Klinefelter's syndrome collected from various sources. In addition to these defects, Klinefelter's syndrome has been found to be associated with severe microcephaly (Barr et al., 1960), tetralogy of Fallot (Gautier and Nonaille,
1964), as well as failure to thrive (Khorsandi, Alexander, Bryans and Haust, 1964). Four sex chromatin-positive males who were stillborn or died soon after birth occurred among 212 male babies (Maclean, Harnden, Court Brown, Bond and Mantle, 1964) and there were 11 sex chromatin-positive males among 628 boys who died at an age of less than five years (Bochkov, 1966).

The sex chromosome complexes, XXXY, XXY, XXXY and XXXXY are also responsible for a smaller proportion of the Klinefelter disorder. Barr, Shaver, Carr and Plunkett (1959), Ferguson-Smith, Johnston and Handmaker (1960) and Carr, Barr, Plunkett, Grumbach, Morishima and Chu (1961) reported male patients with an XXXY sex chromosome complex. The clinical picture was not much different from that of the more frequent XXY variety, although there is no doubt a higher risk of mental retardation.

A male with an XXXY sex chromosome complex was first described by Muldal and Ockey in 1960. About 40 such men have now been reported in the literature (Garcia, Borgaonkar and Richardson, 1967), eight of whom are prepubertal. In addition to the characteristics found in the XXY Klinefelter's syndrome, aggressive behavior was noted in a significant proportion of XXXY men (Casey, Segall, Street and Blank, 1966).

Only one patient with an XXXXY sex chromosome complex is on record (Bray and Sr. Josephine, 1963). No defect other than those usually found in the Klinefelter's syndrome was noted.

Fraccaro, Kaijser and Lindsten (1960) described an XXXXY sex chromosome complex in a child with mental retardation, low birth weight, cleft scrotum, a bound-down penis, minor anomaly of one kidney and patent ductus arteriosus. Since then, a number of papers describing
this kind of chromosome complex have appeared, bringing the total number of such individuals described in the literature to about 30 (Zaleski, Houston, Pozsonyi and Ying, 1966). Mental retardation is a constant feature and other developmental defects involving the skeletal and other systems are frequently present.

An XYY karyotype was first recognized as such by Sandberg, Koepf, Ishihara and Kauschka (1961) in a normal man whose chromosomes were examined because of congenital defects in his pedigree. In a mentally retarded boy with the Sturge-Weber syndrome, originally reported as having trisomy 22 (Hayward and Bower, 1960) the chromosome anomaly has subsequently been interpreted to be XYY (Dent, Edwards and Delhanty, 1963). An XYY sex chromosome complex was also found in an obese boy who had an undescended testis (Sandberg, Ishihara, Crosswhite and Koepf, 1963), in a mental retardate with irregular teeth (Ricci and Malacarne, 1964) and in a patient who had benign congenital hypotonia, enamel dysplasia of the teeth and undescended testis (Uchida, Miller and Soltan, 1964). Jacobs, Brunton and Melville (1965) surveyed a group of mentally subnormal male patients with dangerous, violent or criminal propensities. Out of 197 patients they examined, seven had an XYY chromosome constitution and one an XYYY complex. The XYY chromosome constitution was thought to be associated with aggressive behavior and tallness of stature. The increased frequency of the anomaly among tall, aggressive and mentally sub-normal males has been subsequently reported (Price, Strong, Whatmore, and McClemont, 1966; Telfer, Baker, Clark and Richardson, 1968).

(iii) Turner's Syndrome

Turner's syndrome was first described in 1938. These phenotypic females are characterized by sexual infantilism, webbed neck and cubitus
valgus, associated with short stature. In 1956, using evidence from nuclear sexing and color blindness inheritance, Polani, Lessof and Bishop suggested that a 45(X0) chromosome complement might be responsible for the syndrome, and this hypothesis was later confirmed by chromosome analysis (Ford, Jones, Polani, de Almeida and Briggs, 1959).

Streak ovaries are an almost constant feature of Turner's syndrome. This led Jones, Ferguson-Smith and Heller (1963) to suggest that both X chromosomes are necessary for the development of the primitive germ cells. However, Singh and Carr (1966) showed that germ cells were present in the ovaries of human spontaneous abortuses with X0 sex chromosome constitutions. This confirms the suggestion by Kinch, Plunkett, Smout and Carr (1965) that germ cells are present in the gonads of X0 embryos early in intrauterine life and that the infertility in adults with Turner's syndrome is a result of the reduced number of germ cells that survive to birth or adulthood.

Lindsten (1963) studied a group of 57 girls and women with Turner's syndrome. A chromosome complement of 45(X0) was found in 35 persons. Nineteen of the remaining 22 were mosaics, who exhibited a normal cell line (XX) together with either an X0 cell line or a cell line with a structurally abnormal X chromosome. A wide spectrum of abnormalities involving the renal or skeletal systems in particular were found in these groups. There were renal anomalies in half of the 50 subjects in whom the urinary tract was studied. Webbing of the neck, one of the main signs described by Turner (1938), was present in only 17 of the 57 patients. Cardiovascular abnormalities were rare.

A similar study was carried out by de la Chapelle (1962). Ten of the 23 patients in this series were X0 and 11 of the remaining were
mosaics who had an XO cell line. Renal abnormalities were present in 10 of 21 patients and three of 23 patients had diverse skeletal anomalies.

Although there is good evidence for an X chromosome dosage compensation in the female (Lyon, 1961; 1962), the zygotic lethality of the XO error is high. Carr (1965) found that XO was the most frequent chromosome abnormality among his series of human spontaneous abortuses. On the other hand, the mortality that may occur perinatally as well as in infancy, in patients with Turner's syndrome, is difficult to assess in the absence of sufficient data. Maclean et al. (1964) encountered four sex chromatin-negative females among 10,000 newborn females. One of the infants died at 14 days of age, probably of renal and heart disease. Another died within 24 hours of birth and a preductal coarctation of the aorta with a widely patent ductus arteriosus was disclosed at autopsy.

(iv) Triple-X

Although most XO females have multiple congenital defects, triple-X females seldom have gross phenotypic defects. The first triple-X female reported (Jacobs, Baikie, Court Brown, MacGregor, Maclean and Harnden, 1959) had secondary amenorrhoea but no somatic anomalies. Since then, Day, Larson and Wright (1964) have reviewed 35 cases of triple-X females from the literature and added three of their own. From this and other work, it is apparent that the triple-X error does not give rise to a syndrome in the clinical sense, although there is clearly an increased risk of mental retardation. The frequency of the triple-X error among female mental retardates is about 4.5 per 1000 (Fraser, Campbell, MacGillivray, Boyd and Lennox, 1960; Maclean
et al., Johnston, Ferguson-Smith, Handmaker, Jones and Jones, 1961) compared with 1.33 per 1000 female births (Maclean et al., 1961).

(v) E18 Trisomy Syndrome

Edwards, Harnden, Cameron, Crosse and Wolff (1960) found an extra chromosome in skin and muscle cells from a female child with multiple congenital abnormalities who died at an early age. The extra chromosome was interpreted as a member of pair no. 17. Patau, Therman, Smith and De Mars (1961) believed that the extra chromosome was no. 18, whereas German, Rankin, Harrison, Donovan, Hogan and Bearn (1962) and Gottlieb, Hirschhorn, Cooper, Lusskin, Moloshok and Hodes (1962) thought that it was impossible to definitely identify the extra chromosome in these patients and that it could be either no. 17 or 18. Subsequent to this, large numbers of similarly affected infants have been described and they share the common characteristics of mental retardation, failure to thrive, low-set (and usually malformed) ears, small mandible, congenital heart disease, short sternum, prominent occiput, high palate and arches in the dermal ridge patterns of the fingers. The close similarity of the clinical features suggests a single underlying cause, i.e., trisomy of the same chromosome. Indeed, it has been shown that the no. 18 chromosome is the one involved in the E trisomy syndrome on the basis of its DNA-synthesis characteristics (Yunis, Hook and Mayer, 1964a).

Various investigators appear to be in essential agreement on the incidence of the trisomy-18 syndrome among live births. It ranges from one in 4000 to one in 4500 (Prader, 1962; Marden, Smith and MacDonald, 1964; Smith, 1964; Conen and Erkman, 1966b). Hecht, Bryant, Motulsky and Giblett (1963), however, estimated an incidence as high
as one in 500.

The lethality of 18-trisomy appears to be high. The incidence of 17-18 trisomy in spontaneous abortuses is about one in 87 (Polani, 1966). However, there was no supportive data which would determine whether the no. 17 or 18 chromosome was involved. Infants with trisomy-18 have a very short life-span. Weber, Mamunes, Day and Miller (1964), in a review of 101 cases, showed that half of them survived for two months, one third for three months and only one to two per cent survived beyond three months, the oldest being 10½ years of age. These authors pointed out that the foregoing mortality rate may be an underestimation because all the cases reviewed were diagnosed and studied by cytological methods. Consequently, the children reported survived at least long enough for the test to be done.

(vi) D1 Trisomy Syndrome

Another highly lethal autosomal trisomy syndrome, which is now known as D1 trisomy, was described clinically by Kundrat in 1882 (Smith, Patau, Theran, Inhorn and De Mars, 1963). In 1960, Patau, Smith, Theran, Inhorn and Wagner provided the chromosomal basis for the etiology of the syndrome. They found an extra chromosome, which was interpreted as being homologous to one of the D group chromosomes, in a female infant with multiple congenital anomalies. Another case was reported later in the same year by Ellis and Marwood. Since then, many infants with similar defects have been found in various parts of the world. The common features are, apparent mental retardation, microphthalmos and/or colobomata, abnormal and low-set ears, cleft palate, with or without cleft lip, polydactyly and cardiac and renal malformations.
The close resemblance of these children to one another indicates that there is a common etiology, e.g., trisomy of the same chromosome. It was shown by Yunis, Hook and Mayer (1964b) that the D1 trisomy syndrome is associated with trisomy of the late-replicating chromosome 13.

The reported frequency of D1 trisomy among live births varies from investigator to investigator. Terman, Patau, Smith and De Mars (1961) suggested a rough figure of one in 200,000 and rarer than one in 10,000. Marden et al. (1964) suggested a frequency of one in 2,222 while Smith (1964) reported a frequency of one in 5000. Prader (1962), without indicating the source of the figure, estimated that it was approximately one in 4000. Conen and Erkman (1966a) presented a thorough analysis of their material and arrived at a figure of one in 14,500.

An approximate estimate of the lethality of D1 trisomy can be made by considering its frequency in spontaneous abortuses. Of the 261 spontaneous abortions reviewed by Polani (1966), six had the D trisomy chromosome abnormality. If all of these were trisomic for the same chromosome, i.e., D1, then the frequency of D1 trisomy in spontaneous abortions could be in the order of one in 43.

The life-span of children with D1 trisomy is very short. Smith (1964) indicated that 69 per cent of them die by three months of age and the average life span has been estimated as only 131 days (Conen and Erkman, 1966a).

(vii) Cri-du-Chat Syndrome

In 1963, Lejeune, Lafourcade, Berger, Vialatte, Boeswillwald, Seringe and Turpin reported on three instances of deletion of a portion
of the short arm of a B chromosome. Numerous examples of the error have since been recorded in the literature. Individuals with the anomaly are characterized by mental retardation, low birth weight, abnormal cat-like cry in infancy, epicanthus, strabismus and simian lines in the palm of the hand. The syndrome is known as "le maladie du cri du chat" or the cat-cry syndrome because of the abnormal cat-like cry in early infancy.

Even though there are at least 50 cases of cri-du-chat syndrome reported (McGavin, Cant, Ferguson-Smith and Ellis, 1967), the mortality rate is difficult to assess. One female with the chromosome lesion died at the age of one year and 11 months (Lejeune, Gautier, Lafourcade, Berger and Turpin, 1964). Another female patient died at the age of 19 years. (Solitare, 1967).

(viii) Deletion-18 Syndrome

Another example of autosomal deletion, i.e., deletion of a portion of the long arm of chromosome no. 18, was first reported by de Grouchy, Royer, Salmon and Lamy in 1964. The patient had psychomotor retardation and her somatic malformations included microcephaly, hypoplasia of the maxilla, shortness in height, pointed vault of the palate, atresia of the middle ear, probable tapeto-retinal abiotrophy, horseshoe kidney and bilateral single palmar crease. To date, at least 15 similar patients have been reported, including two instances of normal/deletion 18 mosaicism (Law and Masterson, 1966; Lejeune, Berger, Réthoré and Lafourcade, 1966; Wertelecki, Schindler and Gerald, 1966; Insley, 1967; Destiné, Punnett, Thovichit, DiGeorge and Weiss, 1967; Lejeune, Berger, Réthoré, Lafourcade, Dutrilaux, Canlorbe and Labrune, 1967).

The mortality resulting from this autosomal deletion has not been presently assessed because all the patients reported were living
at the time of study. The oldest patient was a 10 year old girl (Destine et al., 1967).

6. Birth Weight Associated with Chromosome Abnormalities in Man

An attempt was made to obtain data from the literature concerning birth weights associated with different types of chromosome abnormalities. However, it must be noted that the data presented below may not necessarily reflect the true situation because there may be a tendency for investigators to report low birth weight and leave normal birth weight unrecorded. Nevertheless, the data may give some indication of the birth weight of patients with different chromosome abnormalities.

(i) Down's Syndrome

The mean birth weight of patients with Down's syndrome is given as about 1 lb. less than that of controls (Smith and McKeown, 1955; Hall, 1964). Schachter (1952) found that of 100 patients with Down's syndrome, 12.6 per cent weighed under 1500 g at birth, in contrast to three per cent in normal controls. It may be accepted, therefore, that the frequency of low birth weight individuals among patients with Down's syndrome is higher than that of the general population.

(ii) Klinefelter's Syndrome

The birth weight of patients with Klinefelter's syndrome has been recorded only sporadically in the literature. Court Brown et al. (1964) reviewed 99 cases of Klinefelter's syndrome; birth weight was recorded for 12 newborns and averaged out to be $7.4 \pm 1.4$ lb.*

Birth weight was not recorded in the few instances of XXXY reported (Ferguson-Smith et al., 1960; Carr et al., 1961; Maclean et al., 1962; Grumbach, Morishima and Taylor, 1963; Court Brown et al., 1964; Makino, Takagi and Hikita, 1964; Therkelsen, 1964). There have been

* All estimates of variability about the mean are presented as standard deviation unless indicated otherwise.
about 30 males with XXXXY reported (Zaleski et al., 1966), only 11 of whom had a record of birth weight (Fraccaro et al., 1960; Fraccaro, Klinger and Shutt, 1962; Scherz, Faap and Roeckel, 1963; Day, Levinson, Larson and Wright, 1963; Atkins, Böök and Gustavson, 1963; Schade, Schöller and Toberg, 1963; Joseph, Anders and Taylor, 1964; Blatch, 1964; Zaleski et al., 1966). The mean weight was 5.4 ± 0.9 lb. and the mean gestation period was 38.9 ± 2.1 weeks.

Since Muldal and Ockey (1960) first described an XXXY sex chromosome complex in a male, about 40 examples of the abnormality have now been reported (Garcia et al., 1967). In only three of them were birth weights recorded; these were 6.9 lb., 9.5 lb. and 6.4 lb. (Robinson, Miller, Dill and Kambursoff, 1964; Muldal, Ockey, Thompson and White, 1962).

(iii) YY Syndrome

Birth weights of XXY males were recorded in eight instances and were all normal. (Sandberg et al., 1963; Jacobs, Price, Court Brown, Brittain and Whatmore, 1968; Borgaonkar, Murdoch, McKusick, Borkowf and Money, 1968). Only one instance of an XXXY complex has been reported in the literature (Townes, Ziegler and Lenhard, 1965). The birth weight was 7 lb. 6 oz.

(iv) Gonadal Dysgenesis

A high frequency of prematurity was observed among female infants with Turner's syndrome (van der Worff ten Bosch, 1960). Grumbach, Van Wyk and Wilkins (1955) recorded birth weights between 2.8 lb. and 4.8 lb. in five of 22 patients with the syndrome. In a study by Lindsten (1963), the mean birth weight of 45 females with gonadal dysgenesis was 6.4 ± 1 lb.
(v) **Triple-X Syndrome**

The birth weight was seldom given for females with the XXX error. However, among 33 such newborns detected by Court Brown et al. (1964), the birth weights were noted for nine of them and the mean was 6.0 ± 1.1lb.

(vi) **E18 Trisomy Syndrome**

A birth weight below normal is characteristic of the trisomy-18 error. Taylor (1967) brought together data on 92 infants with this disease and found that the mean birth weight was 4.9 ± 0.1 (SEM) lb. The mean gestation age for 77 of these infants was 40.3 ± 0.4 (SEM) weeks.

(vii) **D1 Trisomy Syndrome**

The birth weight of infants with this error is also low. In the study by Taylor mentioned above, the mean birth weight of 35 D1 trisomy infants was 5.6 ± 0.3 (SEM) lb. and the mean gestation period of 31 of these was 38.8 ± 0.4 (SEM) weeks.

(viii) **Translocation**

Birth weight was rarely recorded for the more than 50 instances of translocation Down's syndrome in the literature (Polani, Hamerton, Giannelli and Carter, 1965, for review). A female patient with a D/G translocation reported by Polani et al. (1960) had a birth weight of 6 lb. 14 oz at term. A male patient with the same translocation error had a birth weight of 6 lb. 2 oz and a gestation period of 40 weeks (Sergovich, Soltan and Carr, 1962).

Patients with the D/D translocation form of D1 trisomy are not clinically different from those with regular D1 trisomy (Conen and Erkman, 1966a). Two of four instances of this error reported by Erkman, Basrur and Conen (1965) and Conen, Erkman and Metaxoton (1966) were associated
with low birth weight.

A familial D/D translocation was first described by Walker and Harris (1962). Since then, several familial D/D translocations have been reported (de Grouchy, Mlynski, Maroteaux, Lamy, Deshaies, Nenichou and Salmon, 1963; Hamerton, Giannelli and Carter, 1963; Jagiello, 1963; Pitt, Ferguson and Baikie, 1964; Yunis, Alter, Hook and Mayer, 1964; Zergollern, Hoefnagel, Benirschke and Coxcoran, 1964; Engel, McGee, Hartman and Engel de Montmollin, 1965; Erkman et al., 1965; Richards and Stewart, 1965; Zellweger and Abbo, 1965; Dekaban, 1966; Hustinx, 1966; Marsden, Mackay, Murray and Ward, 1966). Recently, from studies of the general population, Court Brown (1967) found that the D/D translocation was the most common structural heterozygosity in man.

The vast majority of "balanced" D/D translocation carriers are phenotypically normal although a few are affected with mental retardation (Dekaban, 1966). Of the many such carriers reported, birth weight was recorded in only one instance and this was 7 lb. (Zergollern et al., 1964). This individual had an atypical chromosome complement because there was trisomy 21 in addition to the balanced D/D translocation. Thus the birth weight may not be related to the D/D translocation.

Birth weights are recorded in a few patients with different translocations. A birth weight of 4 lb. 9 oz was found in a full-term female with a D/F translocation in whom trisomy 21 was also present (Gripenberg and Airaksinen, 1964). Townes and Ziegler (1965) reported a birth weight of 6 lb. 10 oz in an infant with a D/E translocation. An apparent translocation between chromosome no. 2 and a D group chromosome occurred in a boy weighing 4 lb. at birth, with a gestation
period of seven months (Mercer and Darakjian, 1962). A full-term male
with apparent De Lange's syndrome and a 2/C translocation weighed 3 lb.
6 oz at birth (Craig and Luzzatti, 1965).

(ix) Duplication

Duplication of a portion of a chromosome (commonly referred
to as partial trisomy) has also been recorded in man. Usually, this
occurs in the offspring of parents who carry a balanced translocation.
For example, there are three published examples of partial trisomy B
(Gustavson, Finley, Finley and Jalling, 1964; Lejeune, Lafourcade,
Berger and Turpin, 1964; Shaw, Cohen and Hildebrandt, 1965) and four
of partial trisomy C (Edwards, Fraccaro, Davies and Young, 1962; Rhode
and Catz, 1964; de Grouchy and Canet, 1965). Five cases of partial
trisomy D (Vislie, Wehn, Brogger and Mohr, 1962; Bray and Sr. Josephine,
1964; Jacobsen, Mikkelsen, Frøland and Dupont, 1966; Craig and Luzzatti,
1967) and one of partial trisomy E (Gagnon, Archambault, Laberge and
Katyk-Longtin, 1963) are also on record. The origin of the chromosome
duplications reported by Gendel and Wasserman (1966), Trujillo, Zeller,
Plessala and List-Young (1966), Atkins and Feingold (1967) and Tischler,
Corey and Co-Te (1968) is unknown because the parents' chromosome
complement were normal.

Birth weight was reported in some of the above mentioned reports.
A female patient with partial trisomy B had a birth weight of 3 lb. 14
oz and a gestation period of 43 weeks (Shaw et al., 1965). The birth
weight of both the sibs who had the partial trisomy C reported by
Edwards et al. (1962) was 7 lb., but the gestation period in one sib
was normal while it was 36 weeks in the other. A full-term female
patient with a partial trisomy C reported by Rhode and Catz (1964) weighed 5 lb. 11 oz at birth. A birth weight of 5.4 lb. with a gestation period of 37 weeks was recorded in another partial trisomy C patient (de Grouchy and Canet, 1965). All the five patients with partial trisomy D had normal birth weights. Tischler et al. (1968) recorded a birth weight of 5 lb. 4 oz and a normal gestation in a child with a long B group chromosome.

(x) Deletion

A large proportion of patients with the cri-du-chat syndrome was found to have a low birth weight. Taylor (1967) reviewed 17 such patients and found that the mean birth weight of 15 of them was 5.7 ± 1.2 lb. and that the mean gestation period of 13 cases was 39.6 ± 4.3 weeks. Almost identical results were obtained by McGavin et al. (1967), who reviewed 50 case reports of the cri-du-chat syndrome. They found that the mean birth weight of 38 individuals was 5.6 lb. and the mean gestation period 39.7 weeks.

About 15 patients possessing a deletion of a portion of the long arm of chromosome no. 18 have been reported in the literature (de Grouchy et al., 1964; Law et al., 1966; Lejeune et al., 1966; Wertelecki et al., 1966; Insley, 1967; Destine et al., 1967; Lejeune et al., 1967). The mean birth weight of six of them was 5.7 ± 0.4 lb. and the mean gestation period 37.6 ± 2.9 weeks. Two normal/deletion 18 mosaic patients were female and had birth weights of 6.7 lb. (full term and 5.4 lb. (37 weeks gestation) (Lejeune et al., 1967).

Deletion of essentially the whole of the short arm of chromosome no. 18 has been reported in a few individuals (de Grouchy, Lamy, Thieffry, Arthuis and Salmon, 1964; Buhler, Buhler and Stalder, 1963; Summitt, 1964;
Van Dyke, Valdmanis and Mann, 1964; Uchida, McRae, Wong and Ray, 1965; McDermott, Insley, Barton, Rowe, Edwards and Cameron, 1968; Gorlin, Yunis and Anderson, 1968). However a specific group of clinical features diagnostic of a well delineated syndrome does not occur. The birth weights of the patients reported by Summitt (1964), Van Dyke et al. (1964) and Uchida et al. (1965) were between 6.3 and 7.8 lb. with a normal gestation period. Low birth weight was recorded in two patients (McDermott et al., 1968; Gorlin et al., 1968).

A partial deletion of a chromosome is presumably a necessary concomitant of ring chromosome formation. About 26 instances of this type of chromosome abnormality have been described in man (Palmer, Fareed and Merrit, 1967). Birth weight was recorded in 13 patients with different ring chromosomes. Full-term low birth weight was reported in ring-1 (Gordon and Cooke, 1964; Wolf, Peterson, LoGrippo and Weiss, 1967) and ring-D individuals (Bain and Gauld, 1963; Sparkes, Carrel and Wright, 1967). Patients with ring 17-18 (de Grouchy, Lévéque, Debauchez, Salmon, Lamy and Marie, 1964) and ring-5 (Rhode and Tompkins, 1965) were born prematurely and birth weights were less than 5 lb. in both cases. Although the gestation period was not recorded in a ring-X patient, her birth weight was only 5 lb. (Cohen, Sandberg, Takagi and MacGillivray, 1967). Normal birth weight was found in ring-3 (Makarjee and Burdette, 1966), ring-C (Butler, France and Jacoby, 1967), ring-X (Paolini, Berger, Réthoré, Lafourcade and Lejeune, 1966), ring-18 patients (Gropp, Jussen and Offertinger, 1964; Palmer et al., 1967) and in an unidentified ring chromosome (Atkins, Sceery and Keenan, 1966). (xi) Inversion

Inversion in man has been rarely reported. Perhaps part of
the reason for this is that a paracentric inversion cannot be detected in human mitotic cells, although pericentric inversions which involve a shift in the position of the centromere of the chromosome can often be recognized.

Birth weight was recorded in only two instances of pericentric inversion. The male patient described by de Grouchy, Emerit, Corone, Vermant, Lamy and Soulie (1963) with an inversion in a no. 2 chromosome had a birth weight of 8.4 lb. A patient possessing a possible inversion of a G group chromosome weighed only 5 lb. at birth, but he was also afflicted with Down's syndrome (Gray, Mutton and Ashby, 1962).

In summary, evidence from the literature indicates that a large proportion of infants with autosomal errors such as E and D trisomy is born with a low birth weight whereas patients with Down's syndrome tend to weight only 1 lb. lighter than controls at birth. Deletion appears to play an important role in the etiology of low birth weight since the mean birth weight of patients with cri-du-chat and deletion-18 syndromes is low. Qualitative effects of different chromosomes on fetal growth are also observed in chromosomal aberrations such as duplication and translocation.

Birth weight in XXXY males is almost 2 lb. lower than that of XXY men. No intrauterine growth retardation was observed, however, in XYYY and XXY errors. On the other hand, XO and XXX females are born lighter than controls. These show, evidently, that sex chromosomes also play a role in embryonic growth.
III. MATERIALS AND METHODS

1. Selection of the Study Group

The present study has been carried out primarily at the Children's Psychiatric Research Institute, London, Ontario. A total of 2750 consecutive case histories of the Institute patients were examined for birth weight, gestation period, sex and etiological classification. The clinical assessments of the patients had previously been done by various physicians, using the classification system of the American Association of Mental Deficiency (Heber, 1961) as part of the routine assessment given to all patients seen at the Institute. Of the 2750 patients, 2435 had complete records of birth weight, gestation period, sex and etiological classification and 252 were found to have normal intelligence. Hence the total number of mental retardates which form the population pool for the present study was 2183.

Full-term low birth weight patients were selected according to the criteria that they were individuals with a birth weight of 5 lb. 8 oz or less and with a gestation period of 38 weeks or more. (Second Report of Perinatal Mortality Study, 1967). Estimates of birth weight as well as gestational time were obtained by an examination of the original hospital records which were usually available in the Children's Psychiatric Research Institute case book. In those instances as well as in those where the original records were not available, the parents were
again questioned as to these parameters on follow-up interviews. Among 2183 mental retardates, 174 satisfied the foregoing criteria. However, 13 of them died before this study began and an additional 25 in the group were either uncooperative or could not be located. In order to increase the sample size, 14 patients from the Ontario Hospital School, Cedar Springs, Ontario, whose clinical files contained the necessary information were added to the series. Chromosome analysis was thus carried out on a total of 150 LBWR, of whom 10 were members of twin pairs.

2. Selection of the Control Group

The aim of the study was to determine whether there was any significant increase of chromosome abnormalities among LBWR. Two alternate populations were considered in our deliberations on the choice of an appropriate control group. The first was the selection of a sample of NBWR matched for age, sex and clinical classification with the study group, since these three factors have a bearing on the type of chromosome anomaly found, the survival of the patients and the general severity of the anomaly. For example, patients with Klinefelter's syndrome and the YY syndrome are phenotypically male and those with Turner's syndrome are phenotypically female. It is known that the mortality rate of patients with chromosome disorders such as Down's syndrome (Rowe and Uchida, 1961; Hall, 1964; de Wolff, 1964), $E_{18}$ trisomy (Weber et al., 1964) and $D_{1}$ trisomy (Smith, 1964; Conen and Erkman, 1966a) is high during early life. Furthermore, the etiological classification is important because Down's syndrome, itself a chromosome anomaly, is clinically classified as 64.* Likewise, an accumulation of chromosome errors might be found in those diagnosed as 61 (congenital

* The numbers refer to the classification system of the American Association of Mental Deficiency (Heber, 1961).
cerebral defect), as opposed perhaps to 89 (unknown functional reaction). Therefore, in order to eliminate biases that these three factors may introduce into the study if not accounted for, the control group should consist of the same number of males and females, have the same pattern of etiological classification and the patients should be of similar age to those in the full-term low birth weight group.

The second alternative under consideration was the selection of a random sample of mental retardates. In view of the difficulties of selecting a "true" random sample of control patients, the second alternative would not appear to be a favorable choice. Thus, the first alternative was chosen as the method of selecting the control group.

3. Cytogenetic Procedures

(a) Peripheral Blood Leucocyte Culturing Technique

The technique was carried out according to a modification of the method of Moorhead, Nowell, Mellman, Batts and Hungerford (1960).

The procedure can be briefly described as follows:

(i) Separation of Leucocytes

About 5 c.c. of venous blood were mixed with 0.1 c.c. of Burroughs Wellcome brand phystiohaemagglutinin in a sterile bottle in order to agglutinate the red blood cells. The mixture was stored in the refrigerator at 5° C for 15 minutes and then transferred to a centrifuge tube which was spun at 300-400 r.p.m. for five minutes. Two distinct layers were found - a colorless supernatant layer containing plasma and leucocytes and a colored bottom layer containing red blood cells.

(ii) Culturing of Leucocytes

The supernatant was transferred to a fresh culture in which
10 c.c. of tissue culture medium (BBL CulturStat 1066) and 0.1 c.c. of phytohaemagglutinin were added. The bottle was finally sealed with a silicone rubber stopper and incubated at 37° C for 60-72 hours.

(iii) Accumulation of Mitotic Cells

On the morning of the third day, Colcemid (desacetyl-methyl-colchicine, CIBA) was added to the culture to make a final concentration of 2-4 μg/c.c. The culture was reincubated for an additional two hours.

(iv) Dispersion of Chromosomes

The broth was swirled gently to loosen cells that may have adhered to the bottom of the culture bottle and the suspension of cells was centrifuged at 800 r.p.m. for about 10 minutes. The supernatant was removed with a Pasteur pipette or by decantation and discarded. The button of cells was resuspended in the remaining fluid by gentle tapping. About 2 c.c. of a 0.9% sodium citrate solution at 37° C was added to swell the cells. After 10 minutes, the tube was centrifuged for an additional 10 minutes at 800 r.p.m. The supernatant was discarded and the button of cells was resuspended by gentle tapping.

(v) Fixation

The cells were diluted with 1 c.c. of cold 45% acetic acid. After 20-30 minutes, the suspension was centrifuged at 1000 r.p.m. for 10 minutes. The supernatant was discarded and the cells resuspended in the remaining drop.

(b) Preparation of Slides

Slides were prepared by the squash technique and stained by the method of Genest and Auger (1963), in which an ammoniacal Giemsa stain is used.
(c) Microscopy and Photography

The slides were scanned, using a 10X objective. When a well spread metaphase figure was observed, the chromosomes were counted at a magnification of 1,000X. At least 30 metaphase plates for each patient were examined and the chromosomes counted. In some instances, particularly when a chromosome abnormality was suspected, many more cells were analyzed. Photomicrographs were taken using high contrast copy film (Kodak) and the film developed in D-11 (Kodak). Enlargements were made and the chromosomes were cut out and paired according to the morphological numbering system recommended by the International Study Group, Denver Conference (1960) and London Conference (1964) on the normal human karyotype. Finally, the paired chromosome array was mounted on Bristol board using Kodak photographic dry mounting medium.

(d) Autoradiographic Technique

In the event that a chromosome abnormality was found and could not be precisely identified on morphological grounds alone, autoradiographic studies were done to give a more accurate assessment of the anomaly. The technique was carried out according to the following method (Shaw, 1968).

The chromosomes were labeled by adding 2.5 uc of $^3$H thymidine to each cubic centimetre of culture medium six hours prior to termination of the culture which was treated with colcemid for the last two hours. The carbol fuchsin solution of Carr and Walker (1961) was used as a stain, instead of the ammoniacal Giemsa solution, because the latter becomes decolorized during the developing procedure.

Metaphase figures with well spread and morphologically good
chromosomes were photographed and their coordinates on the microscopic stage were recorded. The cover slip and the mounting medium were then removed. Stripping film (Kodak Ar-10) was cut by razor blade in a tray of 95% alcohol under a ratten series 1A (red) safe light. It was then spread on distilled water in another tray. The slide was immediately dipped under the floating stripping film and coated. After exposure for nine or ten days, the slide was developed in D-11 or occasionally in D-19 (Kodak). The previously recorded metaphase figures were located by means of stage coordinates and the pattern of silver grains over individual chromosomes was studied.

4. Statistical Methods

(a) Comparison of Birth Weights Between Different Populations

All mean birth weights used in this thesis have the notation of standard deviation as the estimate of variability. Likewise, unless otherwise indicated, all which are said to be significant are based on the 5 per cent level. Mean birth weights are statistically compared to each other using the following formulation:

\[
t = \frac{(\bar{X}_1 - \bar{X}_2) \sqrt{\frac{N_1 N_2}{N_1 + N_2}}}{\sqrt{\frac{(N_1 - 1)S_1^2 + (N_2 - 1)S_2^2}{N_1 + N_2 - 2}}}
\]

\[\bar{X} = \text{Mean}\]
\[S = \text{Standard Deviation}\]
\[N = \text{Sample Size}\]

(b) Comparison of Frequencies

Comparisons are made using the Chi square test as described on page 187 of the above mentioned text book.
IV. RESULTS

1. The Population Pool

As previously stated, the number of mental retardates from which the full-term low birth weight individuals were selected for chromosome analysis was 2183. The case book of each of these patients contained complete records of birth weight, gestation period and etiological classification. Of this number, 1297 were male and 886 female, showing that considerably more male than female patients are referred to the Children's Psychiatric Research Institute for evaluation.

The mean birth weight of the 1297 males was $7.0 \pm 1.5$ lb. and that of the 886 females was $6.5 \pm 1.4$ lb.; the difference is statistically significant ($P < 0.001$).

Of the 2183 retardates, 271 were patients with Down's syndrome (159 males and 112 females). The mean weight of the 159 males at birth was $6.6 \pm 1.2$ lb., which is not significantly different from that of the total male group ($P > 0.2$). The mean birth weight of 112 female patients with Down's syndrome was $6.4 \pm 1.1$ lb. which is also not significantly different from that of the total female group ($P > 0.2$).

The correlation coefficient of the mean birth weight and the length of gestation period of the 2183 retardates was 0.98 for both males and females, indicating a positive correlation between birth weight and gestation period.

Among the 2183 retardates, 174 (8.0 per cent) were of full-term
low birth weight, 227 (10.4 per cent) were "premature" i.e., with a
gestation period of less than 38 weeks regardless of birth weight, and
1782 (81.6 per cent) had full-term normal birth weights. Twenty-one
(7.7 per cent) of the 271 patients with Down's syndrome were of full-
term low birth weight, 33 (12.3 per cent) "premature" and 217 (80 per
cent) full-term normal birth weight. The results are summarized in
Table 1.

As stated previously, the clinical evaluation of all patients
at the Children's Psychiatric Research Institute was based on the classi-
fication system of the American Association of Mental Deficiency (Heber,
1961). A comparison of the number of LEWR in each etiological clinical
classification with that of the NBWR is presented in Table 2.

The table shows that the number of LEWR is significantly higher
than that of NBWR in the following etiological classifications: 11 (pre-
natal infection), 61-69 (unknown prenatal influence) and 78 (prematurity),
but lower in 12 (postnatal cerebral infection) and 89 (unknown functional
reaction). It appears possible that LEWR may have somewhat different
etiologies for their condition, according to the formal classification,
from NBWR. Because the frequency of prenatal infection is significantly
higher in LEWR than in the normal birth weight group, it is possible
that prenatal infection may play a significant role in the etiology of
low birth weight. There is, on the other hand, a much higher incidence
of "unknown prenatal influence" in the full-term low birth weight group
(32.8 per cent), compared to that in normal birth weight retardates
(20.4 per cent).
Table 1

Birth Weight and Gestation Period in Mental Retardates

<table>
<thead>
<tr>
<th></th>
<th>B.W. &gt; 5.5 lb.</th>
<th>B.W. &lt; 5.5 lb.</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G. = or &gt; 38 weeks</td>
<td>G. &lt; 38 weeks</td>
<td></td>
</tr>
<tr>
<td>Down's Syndrome</td>
<td>217</td>
<td>33</td>
<td>271</td>
</tr>
<tr>
<td>Others</td>
<td>1565</td>
<td>194</td>
<td>1912</td>
</tr>
<tr>
<td>Total</td>
<td>1782</td>
<td>227</td>
<td>2183</td>
</tr>
</tbody>
</table>

B.W. = Birth Weight  
G. = Gestation Period
Key to Tables 2 and 3

S. = Significantly Different
N.S. = Not significantly Different

<table>
<thead>
<tr>
<th>Code</th>
<th>Title of Category (Heber, 1961)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Prenatal Infection</td>
</tr>
<tr>
<td>12</td>
<td>Postnatal Cerebral Infection</td>
</tr>
<tr>
<td>21-24</td>
<td>Intoxication</td>
</tr>
<tr>
<td>31-34</td>
<td>Birth Injury</td>
</tr>
<tr>
<td>41-49</td>
<td>Disorder of Metabolism</td>
</tr>
<tr>
<td>51-59</td>
<td>New Growths</td>
</tr>
<tr>
<td>61-69</td>
<td>Unknown Prenatal Influences</td>
</tr>
<tr>
<td>64</td>
<td>Down's Syndrome</td>
</tr>
<tr>
<td>78</td>
<td>Prematurity</td>
</tr>
<tr>
<td>79</td>
<td>Unknown Structural Reaction</td>
</tr>
<tr>
<td>81-84</td>
<td>Cultural-Familial and Emotional</td>
</tr>
<tr>
<td>89</td>
<td>Unknown Functional Reaction</td>
</tr>
</tbody>
</table>
Table 2
Frequency of Full-Term Low Birth Weight and Normal Birth Weight Mental Retardates
According to Etiological Classification

<table>
<thead>
<tr>
<th>Etiological Classification</th>
<th>11</th>
<th>12</th>
<th>21-24</th>
<th>31-34</th>
<th>41-49</th>
<th>51-59</th>
<th>61-69</th>
<th>64</th>
<th>78</th>
<th>79</th>
<th>81-84</th>
<th>89</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Birth Weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>10</td>
<td>1</td>
<td>0</td>
<td>30</td>
<td>9</td>
<td>3</td>
<td>8</td>
<td>8</td>
<td>7</td>
<td>81</td>
</tr>
<tr>
<td>O</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>13</td>
<td>3</td>
<td>0</td>
<td>27</td>
<td>12</td>
<td>7</td>
<td>8</td>
<td>6</td>
<td>12</td>
<td>93</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>23</td>
<td>4</td>
<td>0</td>
<td>57</td>
<td>21</td>
<td>10</td>
<td>16</td>
<td>14</td>
<td>19</td>
<td>174</td>
</tr>
<tr>
<td>%</td>
<td>2.3</td>
<td>1.2</td>
<td>2.3</td>
<td>13.2</td>
<td>2.3</td>
<td>0</td>
<td>32.8</td>
<td>12.0</td>
<td>5.7</td>
<td>9.2</td>
<td>8.1</td>
<td>10.9</td>
<td>100</td>
</tr>
<tr>
<td>Normal Birth Weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>6</td>
<td>51</td>
<td>21</td>
<td>113</td>
<td>19</td>
<td>10</td>
<td>217</td>
<td>125</td>
<td>16</td>
<td>155</td>
<td>144</td>
<td>210</td>
<td>1087</td>
</tr>
<tr>
<td>O</td>
<td>1</td>
<td>35</td>
<td>18</td>
<td>71</td>
<td>15</td>
<td>3</td>
<td>147</td>
<td>92</td>
<td>7</td>
<td>104</td>
<td>81</td>
<td>121</td>
<td>695</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>86</td>
<td>39</td>
<td>184</td>
<td>34</td>
<td>13</td>
<td>364</td>
<td>217</td>
<td>23</td>
<td>259</td>
<td>225</td>
<td>331</td>
<td>1782</td>
</tr>
<tr>
<td>%</td>
<td>0.4</td>
<td>4.8</td>
<td>2.2</td>
<td>10.3</td>
<td>1.9</td>
<td>0.8</td>
<td>20.4</td>
<td>12.1</td>
<td>1.3</td>
<td>14.6</td>
<td>12.6</td>
<td>18.6</td>
<td>100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>( \chi^2 )</th>
<th>10.3</th>
<th>5.0</th>
<th>0.009</th>
<th>1.4</th>
<th>0.1</th>
<th>0.007</th>
<th>14.3</th>
<th>0.002</th>
<th>18.9</th>
<th>3.7</th>
<th>3.1</th>
<th>10.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>(&lt; 0.05)</td>
<td>(&gt; 0.9)</td>
<td>(&gt; 0.25)</td>
<td>(&gt; 0.75)</td>
<td>(&gt; 0.9)</td>
<td>(&lt; 0.005)</td>
<td>(&lt; 0.005)</td>
<td>(&lt; 0.05)</td>
<td>(&lt; 0.05)</td>
<td>(&lt; 0.05)</td>
<td>(&lt; 0.005)</td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>S</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>S</td>
<td>N.S.</td>
<td>S</td>
<td>N.S.</td>
<td>S</td>
<td>N.S.</td>
<td>S</td>
</tr>
</tbody>
</table>
2. Full-Term Low Birth Weight Mental Retardates for Chromosome Analysis

Chromosome analysis was carried out on a total of 150 LBWR. The etiological classification of these 150 patients is presented in Table 3. The distribution of the number of patients in each classification is not significantly different from that in the complete full-term low birth weight mentally retarded population (0.25 > P > 0.1) as determined from case records; hence the experimental population is not heavily weighted to any particular etiological group.

The ages of the 150 patients in 1967 are presented in Table 4. Twenty of them were between ages 1-5, 39 between ages 6-10, 40 between ages 11-15, 42 between ages 16-20, seven between ages 21-25, one was 26 years old and one was 36 years of age.

3. Chromosomal Abnormalities in Full-Term Low Birth Weight Mental Retardates

Of the 150 patients comprising this group, 18 were afflicted with Down's syndrome. Fifteen showed the usual complement of 47 chromosomes with an extra G group chromosome (trisomy 21). The chromosome constitution of the remaining three were: one 47, trisomy 21 (ring)/46, normal mosaicism, one 48, XXX-trisomy 21 and one 46, D/G translocation.

Among the remaining 132 patients in this group, 11 chromosome abnormalities were found; these are catalogued in Table 5. Each type of chromosome abnormality will now be described separately.
Table 3

The Etiological Classification of 150 Full-Term Low Birth Weight

Retardates Undergoing Chromosome Analysis

<table>
<thead>
<tr>
<th>Clinical Classification</th>
<th>11</th>
<th>12</th>
<th>24</th>
<th>34</th>
<th>49</th>
<th>59</th>
<th>69</th>
<th>64</th>
<th>78</th>
<th>79</th>
<th>84</th>
<th>89</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>♂</strong></td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>2</td>
<td>0</td>
<td>31</td>
<td>8</td>
<td>2</td>
<td>5</td>
<td>7</td>
<td>5</td>
<td>72</td>
</tr>
<tr>
<td><strong>♀</strong></td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>32</td>
<td>10</td>
<td>2</td>
<td>6</td>
<td>4</td>
<td>7</td>
<td>78</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>19</td>
<td>2</td>
<td>0</td>
<td>63</td>
<td>18</td>
<td>4</td>
<td>11</td>
<td>11</td>
<td>12</td>
<td>150</td>
</tr>
<tr>
<td>%</td>
<td>3.4</td>
<td>2.0</td>
<td>1.3</td>
<td>12.7</td>
<td>1.3</td>
<td>0</td>
<td>42.0</td>
<td>12.0</td>
<td>2.7</td>
<td>7.3</td>
<td>7.3</td>
<td>8.0</td>
<td>100</td>
</tr>
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</table>
Table 4

Age Distribution of the 150 Full-Term
Low Birth Weight Mental Retardates

<table>
<thead>
<tr>
<th></th>
<th>Age in Years</th>
<th>1-5</th>
<th>6-10</th>
<th>11-15</th>
<th>16-20</th>
<th>21-25</th>
<th>26</th>
<th>36</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Σ</td>
<td>Down's Syndrome</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>9</td>
<td>17</td>
<td>18</td>
<td>17</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>64</td>
</tr>
<tr>
<td>Γ</td>
<td>Down's Syndrome</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>8</td>
<td>18</td>
<td>16</td>
<td>21</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>68</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>20</td>
<td>39</td>
<td>40</td>
<td>42</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>150</td>
</tr>
</tbody>
</table>
Table 5
Chromosome Abnormalities in 132 Full-Term Low Birth Weight Mental Retardates (Exclusive of Down's Syndrome)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Birth Weight</th>
<th>Gestation Period (Weeks)</th>
<th>Karyotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>L.P.</td>
<td>4 lb. 8 oz</td>
<td>40</td>
<td>47,XXY</td>
</tr>
<tr>
<td>A.U.</td>
<td>4 lb. 3 oz</td>
<td>40</td>
<td>47,XXY</td>
</tr>
<tr>
<td>R.B.</td>
<td>5 lb. 2 oz</td>
<td>40</td>
<td>47,XXY</td>
</tr>
<tr>
<td>J.L.</td>
<td>5 lb. 3½ oz</td>
<td>40</td>
<td>45,XO</td>
</tr>
<tr>
<td>S.H.</td>
<td>5 lb.</td>
<td>40</td>
<td>45,X0/46,XX</td>
</tr>
<tr>
<td>P.W.</td>
<td>4 lb. 5 oz</td>
<td>40</td>
<td>47,Trisomy E</td>
</tr>
</tbody>
</table>

| K.N.    | 5 lb. 2 oz   | 40                       | 46,Trisomy D|
| P.J.    | 5 lb         | 40                       | 46,Partial Trisomy B|
| G.A.    | 4 lb. 10 oz  | 38                       | 46,Meta centric G|
| J.W.    | 5 lb. 8 oz   | 40                       | 46,Partially Deleted B|
| W.M.    | 5 lb. 8 oz   | 39                       | 46,Inversion A₂ |
A. Chromosome Abnormalities in Full-Term Low Birth Weight Retardates Exclusive of Down's Syndrome

(a) Numerical Abnormalities

(i) 47,XXY

The phenotypically male patients A.U., L.P. and R.B., showed a single sex chromatin body in interphase nuclei of buccal mucosal cells. Peripheral blood leucocyte cultures of each showed the presence of 47 chromosomes. The extra chromosome was in the C (6-12+X) group, hence the karyotype was consistent with that found in Klinefelter's syndrome.

(ii) 45,X0

Analysis of 100 cells from the buccal mucosa of patient J.L. indicated that she was sex chromatin-negative. Only 45 chromosomes were demonstrated in cell culture from the peripheral blood leucocytes. After counting a total of 30 cells and karyotyping 10, the chromosome constitution of the patient was interpreted to be 45,X0 since the missing chromosome was one of the C (6-12+X) group.

(iii) 45,X0/46,XX

The cytogenetic analysis of patient S.H. had been done by Dr. D.H. Carr when he was in the Department of Anatomy, University of Western Ontario. The frequency of sex chromatin and the relative sizes of the two cell populations are not presently available, nor could the leucocyte culture be repeated since the patient died subsequent to the original report.

(iv) 47,E Trisomy

The presence of a 47 chromosome complement was revealed
by an analysis of the peripheral blood leucocytes of patient P.W., the
extra chromosome being either E₁₇ or E₁₈ (Fig. 1). Her clinical features
(Fig. 2) were suggestive of the E₁₈ chromosome disorder, hence the
abnormal chromosome is likely to be no. 1₈ rather than 1₇.

(b) Structural Abnormalities

(i) 4₆,D Trisomy (Familial Translocation)

The chromosomes of patient K.N. were not studied because
the cytogenetic laboratory at the Children's Psychiatric Research
Institute was not operational while the patient was still alive. However,
the chromosome complement of her first cousin was found to contain a non-
homologous D/D translocation within a complement of 4₅ chromosomes
(Fig. 3) and further studies in the family showed that the translocation
chromosome was familial. Because the mother also carried the trans-
location chromosome (in a complement of 4₅), the karyotype of the patient
was assumed to be that of the translocation type D trisomy. In addition,
many of the phenotypic features she presented with were those of the D₁
trisomy syndrome.

The patient's first cousin (Fig. 4, III, 8) was ascertained
through a chromosome study of a large series of mentally retarded
patients with congenital cerebral defects (Sergovich, 1968). The modal
number of his chromosomes was 4₅. Thirty cells were counted in each of
three separate cultures and 15 cells were karyotyped. There are four
large acrocentric D group chromosomes and an extra large metacentric
chromosome similar to no. 3 in size and morphology.

The pedigree data (Fig. 4) suggest that the translocation
involves two non-homologous chromosomes in the D group. An autoradio-
graphic study of chromosomal DNA replication patterns was carried out
Figure 1. Karyotype of patient P.W. showing trisomy in the E group.
Figure 2. Front and profile views of patient P.W. (47, trisomy E).
Figure 3. Autoradiograph showing a D/D translocation in a 45/XY chromosome complement. Two D group chromosomes were not labeled, one was labeled at the proximal end of the long arm and one was heavily labeled at the distal end. The extra metacentric chromosome was labeled proximally at one arm and distally at the other. The translocation was probably between a chromosome no. 13 and a no. 14.
Figure 4. Family pedigree of patient K.N.

(46, D trisomy).
to determine which two chromosomes were involved. The following labeling pattern was observed: two of the D group chromosomes were either not labeled or had very few grains; one D chromosome was intermediated labeled at the proximal end of the long arm. The extra metacentric chromosome appeared to have a pattern that showed one arm labeling proximally and the other arm labeling distally. The results therefore indicate that the translocation was between a chromosome from pair no. 13 and a chromosome from pair no. 14 (Fig. 3), since it is known that chromosome pair no. 13 is the last, pair no. 14 the second-to-last and pair no. 15 the first in the D group to complete DNA synthesis (Giannelli and Howlett, 1966).

The Pedigree

I-5 (Fig. 4) is the oldest known living translocation carrier in the family. He migrated from Poland some 40 years ago and has lost contact with his sibs (1-1, 2, 3). Of the four children from I-5's first marriage only the youngest daughter (II-4) was cooperative; she proved to be a non-carrier. All 10 children from the second marriage cooperated in the study. Five of them proved to be translocation carriers and four of these five, in turn, transmitted the translocation chromosome to their children. The second wife of I-5 reported a total of 19 pregnancies. Nine pregnancies resulted in the 10 living children and 10 early spontaneous abortions. No descriptions of these abortions are available because they occurred in a farm home between 1926 and 1946. I-6 cannot accurately recall the order of their occurrence with reference to the living children. There was no Rh problem in this family because I-5 was Rh-ve.

From the pedigree one can see that five translocation
carriers in the family had a total of 24 children. Chromosome analysis was done on 20 of them. Ten had a normal chromosome complement, nine were translocation carriers and one had a presumptive D1 trisomy syndrome. Therefore, it appears that the empiric risk of producing a D1 trisomy syndrome in this family is of the order of 5%, whereas chromosomally normal and translocation carrier offspring occur with almost identical frequency.

(ii) 46,Partial Trisomy B

Forty-six chromosomes were consistently found in the peripheral blood culture of patient P.J. However, in each of metaphase plates studied, one arm of a no. 1 chromosome was much longer than that of the normal member of the pair. The morphology of the remaining chromosomes was within normal limits of variability (Fig. 5).

The chromosomes of the parents and sibs were analysed in the same way. The mother had a normal chromosome complement. The father, on the other hand, had 46 chromosomes but possessed the "abnormally long" no. 1 chromosome. In addition, the long arm of one of the B group chromosomes was partially deleted (Fig. 6). The "abnormally long" no. 1 chromosome and the partially deleted B chromosome were also present in the peripheral blood leucocytes of both sibs of the propositus. Because the father and sibs were phenotypically normal, their karyotypes were thought to contain a balanced I/B reciprocal translocation.

The results of the chromosome analysis of the rest of the members of the family are summarized in the pedigree (Fig. 7). One of the uncles was an I/B translocation heterozygote. Two of the three aunts were mentally retarded; one died prior to our investigation; the other was found to have a normal chromosome complement. The karyo-
Figure 5. Karyotype of patient P.J. illustrating the enlarged no. 1 chromosome.
Figure 6. Karyotype of the father of patient P.J.
Figure 7. Family pedigree of the propositus P.J.

(46, partial trisomy B).
Pedigree of the family of a "Partial Trisomy B" patient.

- **Propositus "Partial Trisomy B"**
- **1/\text{B} Translocation Heterozygote**
- **Mentally Retarded**
- **Stillbirth or Abortion**
- **Decedent**
- **Normal Karyotype**
- **Karyotype Unknown**
type of the third aunt was normal and the chromosomes of the grandparents have not yet been studied.

(iii) 46, Metacentric G Chromosome Abnormality

The blood leucocyte culture of patient G.A. revealed a chromosome complement of 46/XY. However, only four small acrocentric chromosomes (including the Y chromosome) were present and there was an extra chromosome which was morphologically similar to those in the F group (Fig. 8). Because the patient showed no signs of Down's syndrome (Fig. 9), the "abnormal chromosome" could not be a G/G translocation. In three separate cultures, established at different times, no satellites were seen on the end of the abnormal chromosome. This chromosome may represent a translocation from an unknown donor chromosome or it may be an isochromosome for the long arm of chromosome 22. The chromosomes of the parents could not be studied because they have moved to another province and are unavailable.

(iv) 46, Partially Deleted B

The karyotype of patient J.W. showed a chromosome complement of 46/XY but a portion of the short arm of one of the B group chromosomes was deleted. Due to the poor chromosome morphology in the first culture, a second culture was attempted. Again the partially deleted chromosome was present (Fig. 10) in all of 30 cells counted. Buccal smear tests showed that the patient was sex chromatin-negative which was in agreement with his phenotypic sex. Cytological evidence combined with certain clinical characteristics (Fig. 11) indicated that the patient is representative of the cri-du-chat syndrome. The karyotype of the mother was normal. The whereabouts of the patient's father was unknown.
Figure 8. Karyotype of patient G.A. showing the metacentric G chromosome.
Figure 9. Front and profile views of patient G.A.
at nine years old (46, metacentric G chromosome).
Figure 10. Karyotype of patient J.W. pointing out the partially deleted B chromosome.
Figure 11. Front and profile views of patient J.W. at nine years of age (46, partially deleted B).
(v) 46, Inversion A2

Two separate cultures showed that the chromosome complement of patient W.M. was 46/XX. However, in each of the 30 cells counted, the position of the centromere on a member of chromosome pair no. 2 was different from its homologue. No deletion or duplication of chromosome material was detected in the remainder of the chromosome complement (Fig. 12). The parents' chromosomes were morphologically normal.

Measurements were carried out in 10 leucocyte culture cells. The long arm over short arm ratio in both the no. 2 chromosomes was calculated and it was found that one of the no. 2 chromosomes had a ratio of 1.51 ± 0.12 while that of the other 1.19 ± 0.08. These values are significantly different from each other (P < 0.001). In normal cells, the L/S ratio of pair no. 2 chromosomes is 1.5, according to Reitalu (1968). Thus, the no. 2 chromosome with a L/S ratio of 1.19 ± 0.08 (Fig. 12) likely represents a pericentric inversion.

B. Atypical Karyotypes in Full-Term Low Birth Weight

Patients with Down's Syndrome

(i) 47, Trisomy 21 (ring)/46, Normal Mosaicism

Peripheral blood from patient P.S. was cultured on two separate occasions and skin fibroblasts were cultured on one occasion. In each culture, the karyotype showed the presence of two cell lines. One of the cell lines, which constituted about 80 per cent of the cells counted, showed a chromosome complement of 47, the extra element probably consisting of a portion of a no. 21 chromosome in the form of a small ring and illustrated in Fig. 13. The ring chromosome was usually dumb-bell shaped, although in about five per cent of cells it was circular in outline and double the usual size. The other cell line, which consisted of about 20 per cent of the cells, showed a normal chromosome complement.
Figure 12. Karyotype of patient W.M.
(ii) 48,XXX-Trisomy 21

A buccal smear test on patient C.E. showed that 35 per cent of nuclei contained one, and 25 per cent of nuclei two, masses of sex chromatin (200 cells were studied). A vaginal smear also showed two sex chromatin masses in a proportion of interphase nuclei.

A chromosome number of 48 was found in the peripheral blood leucocyte culture (Fig. 14). There were five G group chromosomes instead of four and 15 C (6-12+X) group chromosomes instead of 14. Since buccal and vaginal smears showed the presence of double sex chromatin bodies in interphase nuclei, the extra C group member was interpreted to be an X chromosome. Therefore, the patient had a chromosome constitution of 48,XXX-trisomy 21.

(iii) 46,D/G Translocation

The chromosome complement of the 30 cells analysed in a leucocyte culture for patient T.R. contained four G group chromosomes and a Y chromosome, five D group chromosomes and an extra element in the C (6-12+X) group. Since the phenotype of the patient was indicative of Down's syndrome, the karyotype was interpreted to be that of a D/G translocation. Although the count was 46, the patient was genetically trisomic for no. 21. The parents' chromosomes were normal.

4. Chromosome Abnormalities in Full-Term Normal Birth Weight Retardates

Of the 150 patients in this control group, 18 has been diagnosed clinically as Down's syndrome. On cytogenetic analysis, each of the 18 was found to have the complement of 47 chromosomes with trisomy 21 that is usually present in the disorder.

There were three chromosome abnormalities among the other 132
Figure 13. Partial karyotype (F and G group chromosomes) of patient P.S., showing the extra no. 21 chromosome in probable ring form.
Figure 14. Karyotype of patient C.E. showing an extra X and an extra no. 21 chromosome.
patients; one was an XXY male, one a triple-X female and the other possessed a non-homologous D/D translocation that was not of the centromeric fusion type. The cytogenetic data for these three patients will now be summarized.

(i) 47,XXY

A single sex chromatin mass was present in the buccal smear of the male patient, K.R. A total of 30 cells were counted in his peripheral blood leucocyte culture and all showed a chromosome complement of 47, the extra chromosome being in the C(6-12+X) group. Therefore his karyotype was interpreted as 47,XXY. In addition, there was a large satellite on the short arm of one of the G group chromosomes in all metaphase figures studied (Fig. 15). This is probably a normal variant since it is present in about one per cent of phenotypically normal persons (Court Brown, Jacobs and Brunton, 1965). However, chromosome studies were not done on the patients' parents as a test of the significance of the large satellite.

(ii) 47,XXX

The cytogenetic analysis of patient M.O. had been done by Dr. D.H. Carr prior to the initiation of this study. She was reported to have a chromosome complement of 47, the extra chromosome being in the C (6-12+X) group. Buccal smears showed the presence of two sex chromatin masses, hence the karyotype was interpreted as 47,XXX.

(iii) 46,Non-Homologous D/D Translocation

Chromosome analysis of the blood leucocyte culture of patient R.W. showed a chromosome complement of 46/XY (Fig. 16), within which there were four normal D group chromosomes and one with a greatly elongated long arm. However, five small acrocentric chromosomes were
Figure 15. Karyotype of patient K.R. An XXY sex chromosome complex is present as well as a G chromosome with "enlarged satellite".
present in addition to the Y chromosome. Morphological differentiation between the five acrocentrics was difficult but one of them was interpreted as consisting of the proximal portion of a "missing" D group chromosome. The distal portion of this chromosome presumably was translocation to another D chromosome resulting in the "abnormally long" acrocentric chromosome. A similar chromosome constitution was found in the blood leucocyte cultures of the father and the younger brother. The chromosomes in the other members of the family who were studied cytogenetically were morphologically normal. The female member of the pedigree Il-4 (Fig. 17) could not be tested; she was reported to be in good health.

The observation that the father, the propositus and his younger brother carried the two abnormal D chromosomes indicated that the translocation was not a homologous D/D translocation.

5. Comparison of the Incidence of Chromosome Abnormalities in Full-Term Retardates of Normal and Low Birth Weights

Since the selection of the full-term normal birth weight controls was done by matching them for age, sex and clinical classification with the full-term low birth weight group, the number with Down's syndrome in the control group is the same as that in the study group. A total of 20 patients with chromosome abnormalities were found in the 150 LBWR including the 18 with Down's syndrome. On the other hand, a total of
Figure 16. Karyotype of P.W. showing the non-homologous D/D translocation.
Figure 17. Family pedigree of patient R.W.
Pedigree of the family of a "D/D translocation" patient

PROPOSITUS  N  NORMAL KARYOTYPE  Q  STILLBIRTH OR ABORTION

D/D TRANSLOCATION AND MENTALLY RETARDED  O  KARYOTYPE UNKNOWN
21 chromosome abnormalities were found among the 150 NBWR, which also included 18 with Down's syndrome. There was no significant difference between the two groups in the incidence of chromosome anomalies ($0.25 > P > 0.1$). However the data can be more properly analysed by a comparison of the chromosome constitution between low birth weight and normal birth weight patients with Down's syndrome and the frequency of chromosome abnormalities in the study and control groups exclusive of Down's syndrome.

Among 18 full-term low birth weight Down's syndrome patients, there was one 47, trisomy 21 (ring)/46, normal mosaic, one 48, XXX-trisomy 21, one 46, D/G translocation and 15 patients with regular trisomy 21. In the control group, each of the 18 was of regular trisomy 21 type. Statistical analysis shows that the occurrence of three chromosome abnormalities other than trisomy 21 among the 18 full-term low birth weight patients with Down's syndrome is not significantly different from the finding of regular trisomy 21 in all the 18 normal birth weight group ($0.1 > P > 0.05$). However, the finding of three rare and unusual karyotypes in the full-term low birth weight group and not in the control group is interesting and may hint at some relationship that may not be revealed by simple mathematical analysis. A total of 11 chromosome abnormalities were found in the remaining 132 full-term low birth weight patients compared with three in the same number of patients in the control group, indicating that chromosome abnormalities occur at a significantly higher rate in the non-Down's syndrome portion of the low birth weight group compared with the controls ($P < 0.025$). Thus there appears to be a definite association between chromosome abnormalities and low birth weight in mental retardates.
6. Maternal Age

Information regarding the maternal age of full-term low birth weight patients exclusive of Down's syndrome was obtained in 129 cases. The mean maternal age was 26.7 ± 7.1 years. This is significantly lower than the mean maternal age of 132 full-term normal birth weight patients which was calculated to be 28.7 ± 6.5 years (P < 0.05).

It has been shown by Karn and Penrose (1951) that birth weight increases with parity. In other words, the first-born babies are lighter at birth than their subsequent sibs. In this study, the number of first-born among the full-term low birth weight patients was significantly higher than that in the control group. This might be an explanation for the lower maternal age in the study group. The paternal age for the non-Down's syndrome low birth weight group was available in 120 cases, while that of the control group was available in 128 cases. The mean paternal ages were 30 ± 8.8 years and 32 ± 7.3 years respectively, which are not significantly different from each other (0.1 > P > 0.05). This result suggests that paternal age does not have an effect on fetal birth weight, but caution must be taken with respect to this suggestion because the number of patients for which data are available was small. However, this is an interesting observation that perhaps deserves further investigation.

The mean maternal age for the 18 full-term low birth weight patients with Down's syndrome was 33.3 ± 8.7 years, which is not significantly lower than that of the full-term normal birth weight patients with Down's syndrome (36.7 ± 6.8 years) (0.3 > P > 0.2). Likewise, the paternal ages of these two groups were not significantly different from each other. However, inferences cannot be drawn from the foregoing
observations because of the small number of Down's syndrome patients (18) in each group.

It is well known that the incidence of Down's syndrome is associated with increasing maternal age (Penrose, 1963) and that a similar but less marked effect has been found in the E18 and D1 trisomy syndromes (Taylor and Polani, 1964). The mean maternal ages of our patients with chromosome anomalies were therefore analysed. The mean maternal age of the 29 LBWR with various chromosome abnormalities was $31.5 \pm 8.1$ years, which is significantly higher than the $26.5 \pm 6.8$ years of 118 LBWR without chromosome abnormalities ($P < 0.001$). When the 18 patients with Down's syndrome were excluded, the mean maternal age for the remaining 11 patients was $29.4 \pm 5.7$ years. This is not significantly different from the mean maternal age of those with no chromosome abnormalities ($0.2 > P > 0.1$). Thus, the elevation of the mean maternal age with respect to those with chromosome abnormalities in the low birth weight group over those with normal karyotypes in the same group is likely due to an elevated maternal age for those with Down's syndrome.
V. DISCUSSION

1. Birth Weight and Gestation Period in Mental Retardates

It has been demonstrated and generally accepted that male infants are born heavier than female infants. A positive correlation similarly exists between birth weight and gestational age in both male and female infants who result from normal pregnancies (Karn and Penrose, 1951; Love and Kinch, 1965). These relationships may also hold true for the 2183 mental retardates who formed the population pool for this study. Of these, there were 1297 males who had a birth weight of 7.0 ± 1.5 lb. A birth weight of 6.5 ± 1.4 lb. was found for the 886 females, a value significantly less than the male birth weight. A relationship between gestational age and birth weight was also found since the correlation coefficient between the average birth weight and the length of gestation period was calculated to be 0.98 for the male and female retardates in the population pool. It appears likely then that the relationship of birth weight to sex and gestation period that is found in a normal population also applies to our retarded population. These relationships may be generally true in mammals since birth weight and gestational age are positively correlated in domestic cattle and buffalos; in addition, males of these species are born heavier than females (Anderson and Plum, 1965; Touchberry and Bereskin, 1966).

2. Etiologies of Low Birth Weight

Full-term low birth weight has been regarded as synonymous with
prematurity (World Health Organization, 1950, 1961). However, it was soon recognized that many premature infants have a normal birth weight with respect to their gestation period and some of them are small-for-date. Occasionally, children are born at full-term but weigh less than $5\frac{1}{2}$ lb. This suggests that growth of fetuses can be impeded in utero. Warkany et al. (1961) used the term intrauterine growth retardation (IUGR) to describe this phenomenon. Brent and Jensh (1967) expanded this term to include premature infants who are small-for-date.

It is believed that birth weight is determined by both environmental influences and genetic factors (Penrose, 1952). Fetal growth retardation, then, can be either the result of an environmental effect, genetically controlled, or a combination of both.

Increasing literature in the field shows that a wide variety of factors play an important part in the etiology of intrauterine growth retardation. For example, full-term low birth weight has been shown to be associated with low socioeconomic class (Bacola et al., 1966) and placental insufficiency (Rumbulz and McGoogan, 1953); toxemia, hypertension and heart diseases were more frequent in pregnancies of low birth weight infants (Fitzgerald and Clift, 1958; Gruenwald, 1963; Jarvinen et al., 1958). Maternal toxemia and heart disease can cause abnormalities of the vasculature and circulation of the uterus and placenta, leading to "placental insufficiency". Consequently, inadequate nutrition of the fetus may occur which could lead to fetal growth retardation or weight loss. A relationship between hypoxia and intrauterine growth retardation has been observed (Brent and Jensh, 1967). Likewise, parental smoking habits were found to have an association with low birth weight (Abernathy, Greenberg, Wells and Frazier, 1966; MacMahon, Alpert
and Salber, 1965). Furthermore, the finding that intrauterine growth retardation was associated with hypoglycemia (Cox and Dunn, 1966) and galactosemia (Hsia and Walker, 1961) points out that biochemical imbalance might also lead to low birth weight. Certain clinical syndromes such as the De Lange syndrome (Abraham and Russell, 1968), Bloom's syndrome (Bloom, 1966) and Fanconi's anemia (Warkany et al., 1961) are intimately associated with low birth weight. On the other hand, X-irradiation (Yamazaki et al., 1954; Warkany et al., 1961; Wood et al., 1965) chemicals (Warkany et al., 1959; Warkany and Kalter, 1961) and viruses (Swan et al., 1943; Giles et al., 1964) can also retard fetal growth.

An important difference has been found in birth weight between babies born to mothers with apparently normal placentae and those babies born to mothers whose placentae were heavily infected with parasites of Plasmodium falciparum (Cannon, 1958). The data indicate that malarial infection may be a contributing factor in low birth weight and subsequent high neonatal and perinatal death in tropical countries. Hockey and Hawks (1967) have shown that there was a higher percentage of very small and moderately small-for-date mentally retarded patients (61 per cent) that could be attributed to congenital rubella infection compared with a control group (16 per cent). In the present study, the frequency of prenatal infection was significantly higher in the low birth weight group than in the normal birth weight mentally retarded population (Table 2).

A genetic control of fetal growth is suggested by the reports of hereditary dwarfism in both animals and man (Fitch, 1961; Warkany et al., 1961). Although the evaluation of the genetic aspects of low birth weight in man presents more difficulties than in other species, chromosome
aberrations may provide an area where these aspects can be studied.

It is well known that chromosome abnormalities are associated with mental retardation which, in turn, has been shown to be occasionally associated with full-term low birth weight (Warkany et al., 1961; Bacola et al., 1966). Of 2183 mental retards evaluated at the Children's Psychiatric Research Institute, 174 were full-term low birth weight individuals, representing a frequency of eight per cent. This is significantly higher than that, (three per cent) in a random newborn series (Sergovich, 1968). The mean birth weight of the 1297 male mental retards was 7.0 ± 1.5 lb., which is significantly lower than the 7.2 ± 1.3 lb. average of male newborns, and the mean weight of the 886 female mental retards at birth was 6.5 ± 1.4 lb., a value which is significantly lower than the 6.9 ± 1.2 lb. of the female newborns.

As recorded in previous sections, chromosome analysis was carried out on a group of 150 LBWR. The normal birth weight control group was chosen by matching them for sex, age and clinical classification with the LBWR. Table 2 shows that the frequency of Down's syndrome among LBWR is 12 per cent, a value which is not significantly increased over that of the NBWR population (12.1 per cent). Using this matching method no bias for or against the incidence of Down's syndrome in the control group will be introduced.

In both the study and control groups, there were 18 patients with Down's syndrome. Chromosome analysis revealed 29 chromosome abnormalities in the low birth weight group (19 per cent), compared with 21 with chromosome anomalies (14 per cent) in the normal birth weight group. The difference was not significant statistically. However, the data can be analysed in another way. Two questions are asked here, namely: Is
there any difference in the chromosome constitution between full-term low birth weight and normal birth weight patients with Down's syndrome? Is there a significant increase in the frequency of chromosome abnormalities among LBWR when compared with the normal birth weight controls, exclusive of those with Down's syndrome? These questions will be dealt with in sections 3 and 4 of this discussion.

3. Patients with Down's Syndrome

In 18 full-term low birth weight patients with Down's syndrome, of whom ten were females and eight were males, there was one 47, trisomy 21 (ring)/46, normal mosaic, one 48, XXX-trisomy 21, and one 46, D/G translocation and 15 with regular trisomy 21. Statistical analysis shows that the occurrence of three chromosome anomalies other than regular trisomy 21 among these 18 patients is not significantly different from the finding of regular trisomy 21 in all of the 18 patients with Down's syndrome whose birth weights were normal.

However, it has been estimated that the frequency of 48, XXX-trisomy 21 may be as low as one per 500,000 births (Day, Wright, Koons and Quigley, 1963). Only two instances of 48, XXX-trisomy 21 have been reported in the literature (Day et al., 1963; Yunis, Kook and Alter, 1964). No estimation has been made regarding the frequency of 48, XXX-trisomy 21 among female patients with Down's syndrome but in this laboratory, it was found to be one in about 250 (Sergovich, 1968). Thus, the finding of one 48, XXX-trisomy 21 among 10 full-term low birth weight females with Down's syndrome suggests that 48, XXX-trisomy 21 might also be associated with low birth weight. The 48, XXX-trisomy 21 patient reported by Day et al. (1963) had a birth weight of 5.8 lb. with a
gestation period of eight months and the similar patient reported by Yunis et al. (1964) had a birth weight of 5.3 lb. with a gestation period of 42 weeks.

The occurrence of a 47, trisomy 21 (ring)/46, normal mosaic among the 18 low birth weight Down's syndrome patients also suggests that certain ring chromosomes, implying chromosome deficiency, may sometimes be associated with fetal growth retardation. Four of the 13 patients with different ring chromosomes reported in the literature had a low birth weight at term (Bain and Gauld, 1963; Gordon and Cooke, 1964; Sparkes et al., 1967; Wolf et al., 1967).

Polani et al. (1965) estimated that the incidence of D/G translocation heterozygotes in Down's syndrome was about three per 100. When this value is compared with the present finding of one D/G translocation among 18 such patients of low birth weight at term, no significant difference is obtained. Birth weight was rarely recorded in patients with the D/G translocation type of Down's syndrome. The two D/G patients reported by Polani et al. (1960) and Sergovich et al. (1962) had normal birth weights.

The mean birth weight of patients with Down's syndrome is significantly different from that of the other mental retardates, it is lower than that of normal control groups (Smith and McKeown, 1955; Hall, 1964). The mean birth weight of 159 males with Down's syndrome who were seen at the Children's Psychiatric Research Institute was $6.6 \pm 1.2$ lb., which is significantly lower than that of male newborns ($7.2 \pm 1.3$ lb.). The mean birth weight of 112 females with Down's syndrome was $6.4 \pm 1.1$ lb., which is also significantly lower than that of female newborns ($6.9 \pm 1.2$ lb.).
It is possible that the high mortality of patients with Down's syndrome during early life (Rowe and Uchida, 1961; Hall, 1964; de Wolff, 1964) may have some influence on the frequency of full-term low birth weight patients with the disorder observed in the present study. In Hall's study (1964), the birth weights of the 15 newborns with Down's syndrome who died in the first 12 months were not recorded. However, five of the 38 newborns with the syndrome were of full-term low birth weight. This represents a frequency of 13 per cent. In our study, the frequency of full-term low birth weight among patients with Down's syndrome was 7.7 per cent. Thus, this crude comparison suggests that full-term low birth weight patients with Down's syndrome might have a slightly higher mortality in early life, although a statistical analysis shows that the difference is not significant.

4. Chromosome Abnormalities in Full-Term Low Birth Weight Patients

Exclusive of Down's Syndrome

A total of 11 patients with chromosome abnormalities were found among the 132 LBWR exclusive of Down's syndrome, while only three were found among the normal birth weight controls. The difference is statistically significant. Therefore, exclusive of those with Down's syndrome, chromosome abnormalities appear to be associated with full-term low birth weight in mental retardates.

A preliminary result of a cytogenetic study of newborns (Sergovich, 1968) shows that no chromosome abnormalities were detected in about 70 full-term low birth weight newborns according to the definition used in this thesis. Although the number is still too small to make an accurate assessment and the mental status of these 70 newborns is still unknown, this important piece of evidence indicates that the
frequency of chromosome abnormalities in the full-term low birth weight newborns is very much lower than that in the LBWR. The comparison also indicates that chromosome abnormalities do not affect birth weight independently. Furthermore, the finding that there is an incidence of 14 per cent of chromosome abnormalities in NEWR suggests that chromosome abnormalities play a more vital role in the etiology of mental retardation than of birth weight.

Turpin and Lejeune (1965) estimated that the frequency of chromosome abnormalities in infants was one per cent. Court Brown (1967) concluded that it was about 0.98 per cent in male and 0.88 per cent in female newborns. Recently, a neonate chromosome survey has been carried out at Victoria Hospital, London, and the frequency of chromosome abnormalities actually observed among 2159 newborn babies is 0.48 per cent (Sergovich, Valentine, Chen, Kinch and Smout, 1968). In institutionalized mental retardates, Sergovich (1967) estimated that the frequency of demonstrable chromosome abnormalities was about 15-20 per cent. If the present results, i.e., 14 per cent of the NBWR and 19 per cent of the LBWR who had chromosome abnormalities are taken as approximate figures, then the frequency of chromosome abnormalities in mental retardates will be about 15 per cent. This estimation is based on the finding in the present study that full-term low birth weight patients constitute about eight per cent of the mental retardates evaluated at the Children's Psychiatric Research Institute. There remains, naturally, a question whether the patients seen here are representative of all institutionalized mentally retarded populations.

Thus, the incidence of 19 per cent of chromosome abnormalities in the low birth weight group is obviously higher than that in newborns
and slightly higher, although not significantly so, than that estimated in mental retardates generally (15 per cent). It must be noted however, that the low birth weight patients who were studied here are those who were born at term and who survived to the time of chromosome analysis. Indeed, the patient with the $D_1$ trisomy syndrome did not survive even to that time and her karyotype was inferred on the basis of the phenotypic features and the chromosome heterozygosity of the mother. Table 4 shows the range of the patients' ages. There are many mental retardates who were born prematurely (10.4 per cent of the patients seen at the Children's Psychiatric Research Institute, Table 1) and about four per cent of these are small-for-date. Also, there is a high mortality during the early life of patients with Down's syndrome (Rowe and Uchida, 1961; Hall, 1964; de Wolff, 1964), $E_{18}$ trisomy syndrome (Weber et al., 1964), and $D_1$ trisomy syndrome (Smith, 1964; Conen and Erkman, 1966a). It is unfortunate that there is no information with respect to the birth weight of these patients but in view of the fact that low birth weight infants constitute a large proportion of neonatal deaths (Wilson et al., 1963; Brimblecombe and Ashford, 1968), a certain number of the patients with chromosome abnormalities who died during early life may have had low birth weight. Furthermore, about 20 per cent of human abortuses have chromosome abnormalities (Carr, 1963; 1965; Clendenin and Benirschke, 1963; Hall and Källen, 1964; Thiede and Salm, 1964; Inhorn, Therman and Patau, 1964; Szulman, 1965; Kerr and Rashad, 1966). It can be assumed that a portion of these abortuses would have been mentally retarded and small-for-date if born, therefore the frequency of chromosome abnormalities in small-for-date mental retardates may be somewhat higher than 19 per cent.
The chromosome abnormalities that were found in the low birth weight group took a variety of forms, ranging from sex chromosome anomalies to autosomal inversion. They can be divided into numerical and structural abnormalities (Table 5). Each type of chromosome anomaly will be discussed separately.

(1) Klinefelter's Syndrome

The frequency of chromatin-positive children among male births is approximately one in 500 (Moore, 1959; Bergemann, 1961; Maclean et al., 1961; Court Brown, 1962; Taylor and Moores, 1967). Among male institutionalized mental retardates, the incidence of Klinefelter's syndrome is about one in 100 (Prader et al., 1958; Barr et al., 1960; Mosier et al., 1960; and Maclean et al., 1962), indicating that Klinefelter's syndrome is often associated with mental retardation.

In the present study, there were three patients with Klinefelter's syndrome among the 72 males in the low birth weight group. This represents a frequency of 4.2 per cent, which is significantly higher than the frequency of Klinefelter's syndrome among male mental retardates as reported in the literature. Thus, in this study at least there seems to be an association between low birth weight and Klinefelter's syndrome in male retardates.

It has been estimated that about 25 per cent of Klinefelter males are mentally retarded (Ferguson-Smith, 1959). A total of 40 patients with the syndrome have been seen at the Children's Psychiatric Research Institute and the Department of Anatomy, University of Western Ontario. Thirteen mentally retarded patients were ascertained from institutions such as the Ontario Hospital School, Orillia, and the Ontario Hospital School, Cedar Springs, and later referred to the
Institute. The remainder of the 40 patients were referred to the
Department of Anatomy from St. Joseph's and Victoria Hospitals and
by private physicians. Only 20 of these patients had records of birth
weight, duration of gestation period and I.Q. score. Seven of them had
normal intelligence while the remaining 13 were mentally retarded. Their
mean birth weight was $7.3 \pm 1.5$ lb. which is not significantly different
from that of male newborns ($7.2 \pm 1.3$ lb.). However, three of the 13
mentally retarded patients had low birth weights while all those who
were not mentally retarded were of normal birth weight. Court Brown
et al. (1964) reviewed 99 cases of Klinefelter's syndrome but birth
weight was recorded in only 12 newborns, whose I.Q. was unknown. However,
the mean birth weight of these 12 infants was $7.4 \pm 1.1$ lb.

The finding that three mentally retarded patients with Kline-
felter's syndrome were of low birth weight while those who were not
mentally retarded had a normal birth weight suggests that there may be
an association between low birth weight and mental retardation in this
disease. There is good evidence that the risk of mental retardation
increases in proportion to the number of X chromosomes in males
(Ferguson-Smith et al., 1960; Carr et al., 1961; Zaleski et al., 1966).
Although birth weights of the three XXXY mental retardates reported by
Barr et al. (1959) and Carr et al. (1961) were not recorded, a review
of their hospital records showed that two of them were of full-term low
birth weight. It is unfortunate that birth weight was not recorded in
the few instances of XXXY reported in the literature (Ferguson-Smith et
al., 1960; Maclean et al., 1962; Grumbach et al., 1963; Court Brown et
al., 1964; Makino et al., 1964; Therkelsen, 1964).

As for the XXXXY anomaly, there have been at least 30 such
patients described (Zaleski et al., 1966). Birth weights were recorded in only 11 of them (Fraccaro et al., 1960; 1962; Scherz et al., 1963; Day et al., 1963; Atkins et al., 1963; Schade et al., 1963; Joseph et al., 1964; Blatch, 1964; Zaleski et al., 1966). Two individuals were "premature", six were of full-term low birth weight and three had a normal birth weight at term. The mean birth weight of these 11 subjects was $5.4 \pm 0.9$ lb, which is significantly lower than that of the male newborns ($7.2 \pm 1.3$ lb).

Thus, in Klinefelter's syndrome there appears to be an association between the presence of extra X chromosomes and low birth weight, probably in proportion to the number of extra X chromosomes. The addition of a Y chromosome, however, does not appear to be correlated with low birth weight. There are about 40 XXY patients reported in the literature (Garcia et al., 1967). Only three of them had records of birth weight and none of the three had a low birth weight (Muldal et al., 1962; Robinson et al., 1964). The birth weights of the two XXY men reported by Carr, Barr and Plunkett (1961b) and Barr, Carr, Soltan, Weins and Plunkett (1964) were not recorded, but a review of the patients' case histories indicated that they both weighed about 7 lb. at birth. Furthermore, none of the eight instances of the XXY chromosome error with records of birth weight in the literature (Sandberg et al., 1961; Borgaonkar et al., 1968, Jacobs et al., 1968) and eight found in this laboratory (Sergovich, 1968) were of low birth weight. One case of XYYY has been reported (Townes et al., 1965) and the birth weight of this patient was 7 lb. 6 oz.

(ii) Gonadal Dysgenesis (X0 and X0/XX)

Patients with XO sex chromosome constitution have gonadal
dysgenesis, but not all female patients with gonadal dysgenesis have the XO chromosome complement. Barr (1959) estimated that 80 per cent of females with gonadal dysgenesis were sex chromatin-negative while the remainder were sex chromatin-positive. Some chromatin-positive females with gonadal dysgenesis have an XX cell line in addition to the XO line or one of their two X chromosomes is partially deleted or an X-isochromosome; others have no demonstrable chromosome abnormality (Lindsten, 1963; Ferguson-Smith, 1965).

A rough estimate of the frequency of chromatin-negative females with gonadal dysgenesis can be made by combining the data from six surveys (Taylor and Moores, 1967). There are a total of eight chromatin-negative children in 22,068 female births giving a frequency of 0.36 per 1000. This, however, must represent a minimal value for chromosomally determined gonadal dysgenesis because XO/XX mosaics, X/deleted X and X/isochromosome X errors, which also cause gonadal dysgenesis, are difficult to detect in a buccal smear survey.

In the present study, two patients with gonadal dysgenesis (one XO and one XO/XX mosaic) were found in 78 low birth weight female retardates. This frequency of 2.5 per cent is much higher than that of the pooled female births that have been previously mentioned.

An analysis of a group of 21 XO patients seen at the Department of Anatomy and the Children's Psychiatric Research Institute shows that the mean birth weight was 6.4 ± 1.1 lb. Lindsten (1963) reported that the mean birth weight of his 45 XO subjects was 6.5 ± 1 lb. Thus, the mean birth weight of XO patients is lower, although not significantly, than that of the female neonates (6.9 ± 1.2 lb.).

Four of the 21 XO patients who were studied locally were
mentally retarded and one of the four was of full-term low birth weight. However, there were also three with full-term low birth weight among the remaining 17 who had normal intelligence. Statistical analysis of this result shows that there is no apparent association between low birth weight and mental retardation in Turner's syndrome.

(iii) E18 Trisomy Syndrome

A 3:1 sex ratio of affected females to males in the E18 trisomy syndrome was noted by Smith (1964). He suggested that an XY embryo may be less likely to survive prenatal life with this severe genetic imbalance than does an XX embryo. Conen and Erkman (1966b), however, did not find any significant difference in the sex ratio among their patients with E18 trisomy syndrome, although they observed that the female patients had a longer survival time. The mean survival time of the seven male patients in their series was 58.5 days compared with 282 days for the ten females. The difference is statistically significant. Similar results were obtained when they pooled the published data on 15 males and 47 females. The shorter life expectancy for males appears to be the most likely explanation for the preponderance of females in the cases reported in the literature.

Carr (1965) found that the number of abortuses with E17-18 trisomy is small (one in 200) compared to those with D trisomy (six in 200), although Kerr and Rashad (1966) found two E17-18 trisomies among 35 abortuses. The frequency estimated for the 18-trisomy syndrome among live births by various workers appears to be similar: one in 4000 to one in 4500 (Prader, 1962; Marden et al., 1964; Smith, 1964; Conen and Erkman, 1966b). One report by Hecht et al. (1963), on the other hand, suggested a frequency as high as one in 500.
The average life-span of patients with the E18 trisomy syndrome is very short. These babies seldom live past the age of six months. Weber et al. (1964) surveyed over 101 cases and found that 50 per cent of the infants with this disease died by two months of age, 75 per cent by three months and that only 13 per cent lived past the age of one year. The oldest patient on record was 10½ years old when she was studied. The mean birth weight of 18-trisomy patients was $4.9 \pm 0.11$ (SEM) lb. with a mean gestation period of $40.3 \pm 0.4$ (SEM) weeks (Taylor, 1967).

Mental retardation is almost a constant feature of the E18 trisomy syndrome. In view of the fact that these patients have a high mortality during early life and a majority of them are born with a low birth weight at term, it can be assumed that a large number of those who die could have had low birth weights. Therefore the true frequency of 18-trisomy syndrome among LBWR may be higher than the present finding of one in 150.

(iv) D1 Trisomy Syndrome

The frequency of D1 trisomy syndrome among live births cannot be accurately estimated because of the wide disparity in estimates by various authors. Thermer et al. (1961) suggested an incidence as low as one in 200,000 and Marsden et al. (1964) reported a frequency as high as 2,222. Conen and Erkman (1966a), in a more extensive analysis of available data, arrived at the figure of about one in 14,500.

Patients with D1 trisomy are generally short lived (Conen and Erkman, 1966a) and they have a low mean birth weight of $5.6 \pm 0.3$ (SEM) lb. (Taylor, 1967). It is possible that a large proportion of those who die during early life are born with a low birth weight. Thus, the finding of one D1 trisomy syndrome among 150 LBWR in the present retrospective
study may be lower than the true incidence.

The patient ascertained in this study died before chromosome analysis was done. She was assumed to be suffering from the D₁ trisomy syndrome (translocation type) because of the clinical findings and because her mother was found to be a 45 D/D translocation carrier.

As can be seen from the pedigree (Fig. 4), five D/D translocation carriers had a total of 24 children and chromosome analysis was carried out on 20 of them, yet only one of these (the propositus) showed clinical features of the D₁ trisomy syndrome. It appears therefore that the empiric risk of producing a D₁ trisomy syndrome in this family is of the order of five per cent. This is significantly lower than the theoretical risk (33 per cent) based on segregation ratios of gametes from a translocation heterozygote. Apparently there is either a selection against gametes with an extra D chromosome or the relatively high frequency of early spontaneous abortion in this family indicates the production of D trisomy fetuses. Carr (1965), in a study of 200 spontaneous abortions, found six abortuses with D group trisomy among 44 chromosome abnormalities, which would indicate that a large proportion of these fetuses do not generally survive the effects of the extra D chromosome in utero.

(v) 46, Partial Trisomy B Chromosome Abnormality

Among the patients reported with B chromosome abnormalities (Edwards et al., 1962; Lejeune et al., 1963; Gagnon et al., 1963; Gustavson et al., 1964; Bray and Sr. Josephine, 1964; Shaw et al., 1965; Gendel and Wasserman, 1965; Trujillo et al., 1966; Atkins and Feingold, 1967; Tischler et al., 1968), only one had a partial trisomy for the long arm of a B chromosome (Shaw et al., 1965). The chromosome complement
of the patient described in their report was 46, but the short arm of a B chromosome was elongated. The mother of the patient was found to be a B4/B5 balanced translocation carrier. The partial trisomy B propositus exhibited numerous malformations, including low birth weight (3 lb. 14 oz), a single umbilical artery, abnormally shaped head, a premature synostosis of the sagittal suture, unusual progeric face, low-set and malformed ears, small mandible, receding jaw, protruding right eye, sunken left eye, short neck, long tapering fingers, webbing of the second and third digits of both hands and both feet and undescended testes. The infant died six hours after birth.

In marked contrast to the foregoing infant, the patient who possessed a partial trisomy of a B group chromosome in our study (Fig. 21) showed relatively minor congenital malformations, namely: mental retardation, low birth weight (5 lb.), short thumbs, slight webbing of the neck and bilateral single palmar creases. The differences in clinical pictures might be attributed to the fact that the long arm of the B group chromosome involved in the translocation was different in the two instances. It was that of B5 in Shaw et al.'s case and B4 in the present case. Furthermore, the chromosomes to which the additional B chromosome material was attached were different. In Shaw et al.'s patient, it was attached to the short arm of a B4 chromosome while in the present case, the recipient was one of the arms of a no. 1 chromosome.

Other abnormalities involving the B group chromosomes have been described. Gustavson et al. (1964) reported an infant with multiple congenital malformations who was trisomic for the short arm of a B group chromosome. A portion of this chromosome was attached to a member of the G group. Clinical features of this child included some of those
Figure 18. Front and profile views of patient P.J. at twelve years of age (46, partial trisomy B).
commonly found in other trisomy syndromes, such as hypotonia, low-set ears, colobomata in the irides, micrognathia, macroglossia, high arched palate, renal anomaly and a large gap between the first and second toes. In addition, a single umbilical artery, unusually long fingers and toes and premature synostosis of the sagittal suture were present. The latter three malformations were also found in the patient studied by Shaw et al. (1965), although the two families were different cytologically.

Edwards et al. (1962) described a patient and her older brother who had chromosome complements of 46 including a long unpaired chromosome which was thought to be a B group chromosome. This long B chromosome was interpreted to be the result of a partial trisomy C because the phenotypically normal father was a balanced B/C carrier. There were phenotypic similarities between the two sibs with the same abnormal chromosome. These included mental retardation, normal birth weight, hypertelorism, narrow auditory canals, a large anterior fontanelle, adduction and flexion deformities of the thumbs, shortened middle phalanx of the fifth fingers, bilateral palmar transverse creases, broad halluces and webbing of the second and third toes. Gendel and Wasserman (1965) reported that they found a patient whose karyotype resembled that reported by Edwards et al., but they had no clue as to the origin of the unpaired long B chromosome.

Two other isolated cases of B chromosome translocations have been reported by Gagnon et al. (1963) and Bray and Sr. Josephine (1964). Gagnon et al. suggested that the translocation in their patient involved a portion of a no. 18 chromosome attached to the long arm of a B chromosome. They based their interpretation on measurements of the chromosomes and the phenotypic resemblance of their patient to that of
the trisomy 18 syndrome. Bray and Sr. Josephine, on the basis of cytological evidence, interpreted their finding as representing partial trisomy D by virtue of translocation to a B chromosome. Although the patient exhibited several anomalies such as failure to thrive, mental retardation and congenital cardiac and renal defects, he lacked the distinct features of the D_1 trisomy syndrome. The birth weight was 6 lb. 5 oz.

(vi) 46, Metacentric G Chromosome

Böök, Santesson and Zetterquist (1961) found a chromosome abnormality in the cultured bone marrow and skin cells of a boy with an atrial septal defect. The birth weight was not recorded. In a complement of 46, there were only three G group chromosomes, together with a chromosome that was similar in shape and size to a member of the F group. The mother of the patient, who herself had a large atrial septal defect associated with mitral insufficiency, had the same metacentric chromosome as an extra element in one cell line which was mosaic with a clone of cells with 46 chromosomes. Böök et al. offered two alternative explanations of the son's karyotype. There could be trisomy for an F group chromosome and monosomy of a chromosome no. 22, or alternately, a chromosome no. 22 could have been translocated on to an F chromosome, which implies that the karyotype carried a partial deletion of a no. 22 chromosome and a partial duplication of an F chromosome.

A karyotype similar to that described by Böök et al. was found in the present case (Fig. 8). The chromosome complement was consistently 46 and there was an extra small metacentric chromosome and three small acrocentric chromosomes present. Although the patient's heart was slightly enlarged, no other defect was found. The origin of the extra
small metacentric chromosome in this patient is unknown. It is very unlikely that this represents an F trisomy and G monosomy because both of these types of aneuploidy are extremely rare. A "true" trisomy F has not been described and only a few instances of monosomy G have been reported (Thorburn and Johnson, 1966; Al-Aish, Cruz, Goldsmith, Volpe, Mella and Robinson, 1967; Hall, Gredga and Svenningsen, 1967; Gagnon, 1968). Therefore, the chance of two such rare events occurring simultaneously is almost negligible. Because the patient did not show any feature of Down's syndrome (Fig. 9), it is very unlikely that the extra small metacentric chromosome represents a 21/21 translocation. The extra metacentric chromosome cannot be accounted for in terms of a pericentric inversion of a G chromosome because no satellite was found on either end of the abnormal chromosome. The most likely explanation appears to be that it either represents an isochromosome for the long arm of chromosome no. 22 or that it has resulted from a translocation from some unknown chromosome to a member of the G group. These hypotheses could not be tested because the karyotypes of the parents could not be studied.

(vii) Cri-du-Chat Syndrome

It has been generally believed that deletion of a large proportion of an autosome is lethal in man, although a small deficiency may be compatible with life. This became evident in 1963 when a B group chromosome with a portion of its short arm absent and giving rise to the symptomatology known as the cri-du-chat syndrome, was discovered by Lejeune et al.. Another chromosome deletion syndrome which involves the loss of a portion of the long arm of chromosome no. 18 was first reported by de Grouchy et al. (1964). A few instances of a deletion of the short arm of chromosome no. 18 have been reported (de Grouchy et al.,
1963; Bichler et al., 1964; Summit, 1964; Van Dyke et al., 1964; Uchida et al., 1965; McDermott et al., 1968; Gorlin et al., 1968). However, in patients with no. 18 short arm deletion, there does not appear to be a specific group of clinical features diagnostic of a well delineated syndrome.

The partially deleted chromosome in the cri-du-chat syndrome appears to be chromosome B₂ because autoradiographic studies show that it displays early DNA synthesis in the long arm (German, Lejeune, MacIntyre and de Grouchy, 1964; Miller, Breg, Warburton, Miller Firschein and Hirschhorn, 1966). This characteristic has been attributed to the no. 5 chromosome. The present case of cri-du-chat syndrome is also caused by a partially deleted B₂ chromosome since it was shown that the abnormal chromosome was always the shorter chromosome among the B group and an early replicator (Fig. 13). However, reports are on record of patients who had most of the clinical features of the syndrome except the cat-cry but in whom autoradiographic studies showed that the partially deleted chromosome was B₄ instead of B₂ (Wolf, Reinwin, Porsch, Schröter and Bätsch, 1965; Leão, Neu and Gardner, 1966; Miller et al., 1966). This can be accounted for by assuming that there is a certain degree of homology between the short arms of chromosomes B₄ and B₂ (Miller et al., 1966) or that there may be a B₄ short arm deletion syndrome that has not yet been well delineated (McGavin et al., 1967).

Lejeune et al. (1964), de Grouchy and Gabilan (1965) and Rohde and Tompkins (1965) provided evidence that the cri-du-chat syndrome is the result of a partial deletion of chromosome B₂ rather than an interchange in which the missing part is attached to another chromosome and hidden within the normal morphological variability of the karyotype.
Lejeune et al. (1964) described a pedigree in which the mother of the family possessed a balanced translocation between the short arm of chromosome B₅ and the long arm of a D group chromosome. Segregation of these two abnormal chromosomes in the family accounted for malformed and defective offspring who were trisomic as well as monosomic (cri-du-chat syndrome) for the short arm of chromosome B₅. In de Grouchy and Gabilan's case (1965), the translocation carrier was also the mother but the chromosomes involved were in the G and B groups. Rohde and Tompkins (1965) reported a female infant with the characteristics of the cri-du-chat syndrome in whom a B group chromosome was replaced by a large ring chromosome. The latter was interpreted to be the result of a fusion between two broken ends of the missing B group chromosome with subsequent loss of most of the short arm.

No estimates of the frequency of the cri-du-chat syndrome in the general population are on record. In a neonate chromosome survey, one instance of cri-du-chat syndrome was found in 2159 newborns (Sergovich et al., 1968), while one was found in 150 LBWR in the present study.

Taylor (1967) found that the mean birth weight of 13 cases of cri-du-chat syndrome was 5.7 ± 0.3 (SEM) lb. with a mean gestation time of 39.6 ± 1.2 (SEM) weeks. Almost identical results were obtained by McGavin et al. (1967) who reviewed 50 cases. Thirty-six of these 50 patients had records of birth weight and gestation period and two had records of either birth weight or gestation period. The mean birth weight was 5.6 lb. and the mean gestation period was 39.7 weeks. Of the 36 instances in which the birth weight and the gestation period were recorded, 14 (39 per cent) were of full-term low birth weight, five (14 per cent) were "premature" and 17 (47 per cent) had full-term normal birth weights.
These data clearly indicate a high correlation between the cri-du-chat syndrome and low birth weight.

(vii) 46, Inversion A2

While inversion is well known in Drosophila, there are only a few isolated reports of pericentric inversion in man (Carr, 1962; Ellis, Marshall and Penrose, 1962; Gray et al., 1962; de Grouchy et al., 1962; Chandra and Hungerford, 1963; Lele, Dent and DeLhanty, 1965; Sergovich, 1967; Schmid, 1967). Pericentric inversion can be easily detected in mitotic chromosomes (especially when the chromosomes involved are large) because of the shift of the position of the centromere. On the other hand, paracentric inversions (which do not involve a shift in the centromere) have not been described, probably because they cannot be detected in mitotic chromosomes.

The patient found in our survey had an inversion of a no. 2 chromosome. Her clinical features included mental retardation, low birth weight (5 lb. 8 oz), poor coordination, small weight and height (below the 3rd percentile), small jaw and small chest (Fig. 22). The chromosome complements of both her parents were normal. de Grouchy et al. (1962) have reported an inversion of a no. 2 chromosome in a child of normal birth weight, whose malformations included congenital heart disease, oxycephaly, hypertelorism, bilateral cubitus valgus, bilateral genu valgum, hyperlaxity of the ligaments, malformations of the fingers and slight mental retardation. These abnormalities obviously do not bear any important resemblance to those of the patient in the present study. It is possible that the portions of the chromosome that are involved in the interchange are different.

Pericentric inversions involving chromosomes other than no. 2
Figure 19. Front and profile views of patient W.M. who has a pericentric inversion of a no. 2 chromosome.
have been reported. Ellis et al. (1962) favored pericentric inversion as the most plausible explanation for the presence of satellites on both ends of an extra small acrocentric chromosome in a mentally retarded girl. Her birth weight was not recorded. Pericentric inversion has also been found in one of the D group chromosomes (Chandra and Hungerford, 1963). Sergovich (1967) reported a probable inversion in the X chromosome of a boy who presented a wide variety of congenital anomalies, including severe mental defect. The birth weight of the patient was not recorded in the published report, but a review of the patient's file showed that it was 7 lb. 12½ oz.

To summarize, a wide variety of chromosome abnormalities was found in the non-Down's syndrome LBWR group. These include 47,XXY, 45,X0, 45,X0/46,XX, 47,E trisomy, 46,D trisomy, 46,partial trisomy B, 46,metaacentric G, 46,partially deleted B and 46,inversion A2. The results indicate that many genes or group of genes can be responsible for low birth weight at term.

5. Chromosome Abnormalities in Full-Term Normal Birth Weight Mental Retardates Exclusive of Down's Syndrome

Three chromosome abnormalities were found among the 132 NBWR exclusive of Down's syndrome. These included one 47,XXY, one 47,XXX and one 46,D/D translocation. The XXY error has been discussed in previous sections.

(i) Triple-X

Maclean et al. (1961) reported the frequency of XXX females as 1.33 per 1000 female live births. Although most XXX females do not show any gross deviation from the normal female phenotype, the XXX frequency is elevated among institutionalized mental retardates. Pooling
three sets of data (Fraser et al., 1960; Maclean et al., 1962; Johnston et al., 1961) gives the frequency of XXX females as 4.5 per 1000 female retardates.

The fact that one XXX error was found among the 150 NEWR while none was found among the 150 LBWR, does not necessarily imply that XXX females are generally born with a normal birth weight. The finding may be due to chance. In fact, the mean birth weight of nine XXX females identified by Court Brown et al. (1964) was 6.0 ± 1.1 lb., a figure which is significantly lower than that of female neonates (6.9 ± 1.2 lb.).

(ii) 46,D/D Translocation

Several instances of familial D/D translocation of the centromere-fusion type have been described (Walker and Harris, 1962; de Grouchy et al., 1963; Hamerton et al., 1963; Jagiello, 1963; Pitt et al., 1964; Yunis et al., 1964; Zergollern et al., 1964; Engel et al., 1965; Erkman et al., 1965; Richards and Stewart, 1965; Zellweger and Abbo, 1965; Dekaban, 1966; Hustinx, 1966; Marsden et al., 1966). Three familial D/D translocations have also been found in this laboratory (Sergovich, Chen, Soltan, McKim and Cushman, 1968). Translocations involving the D and C group chromosomes have been reported (Pitt, Webb, Wong, Robson and Ferguson, 1967; Stalder Buhler, Godola, Widmer and Freuler, 1964; Weller, Apley and Raper, 1966). Jacobsen et al. (1966) described a boy whose birth weight was 6 lb. and who possessed 47 chromosomes, the extra one approximating a G group chromosome in size, although the boy was not afflicted with Down's syndrome. Subsequent cytogenetic studies revealed that the mother, the grandfather and several members of the family had a balanced translocation between two non-homologous D group chromosomes. A portion of the long arm of a chromosome in this group had become
attached to the long arm of another, resulting in a particularly large acrocentric chromosome and a small acrocentric which is morphologically similar to a member of the G group. The propositus with 47 chromosomes was thus thought to have a partial trisomy D.

The 46 chromosome complement of the patient found in this study (Fig. 16) included an extra chromosome similar in size and shape to that of a G group chromosome, a particularly large acrocentric chromosome and only four D chromosomes with normal morphology. This was interpreted to be the result of a translocation between the long arms of two non-homologous D chromosomes.

Whether the translocation was a balanced or an unbalanced one cannot be determined at the present time. Testicular material of the propositus's father who had the same abnormal chromosome constitution was not obtained for the study of synaptic configurations. In view of the fact that the three family members who carried the translocation showed abnormal phenotypic features which included mental retardation, large ears, prominent sclera visible below the iris and notched teeth (Figs. 20 and 21), it may be that the translocation was an unbalanced one. Since the karyotypes of both paternal grandparents were normal, the translocation likely arose as a de novo event during gametogenesis in one of the grandparents. It is possible that one of the chromosomes in the interchange may not have been attached reciprocally to the broken end of the other and had become lost. It is assumed that gametes with the unbalanced chromosome complement were viable and that there was no selection against them.

The translocation may also be a balanced one. If this is the case, the observed relationship between the chromosome anomaly and the
abnormal clinical features is likely due to a position effect, in which an altered chromosome environment produces an abnormal phenotype although there is no loss or gain of chromosome material.

There is a very small possibility that the atypical acrocentric chromosomes may have resulted from an insertion. This explanation is not favored because the chance of an insertion, which needs at least three simultaneous breaks, is presumably much less than for a translocation, for which only two breaks are required.

The association of similar clinical features in the father, the propositus and his younger brother, all with the D/D translocation, suggests that this may represent a new chromosome disease. However, this is the only known instance of such familial translocation and the claim will not be justified until similar examples are reported in the future.

6. Genetic Control of Birth Weight

Since different forms of chromosome abnormalities are associated with low birth weight, it seems likely that many genes on different chromosomes are involved in the diverse and complex aspects of fetal development that have a bearing on birth weight. Different chromosomes appear to have different effects on fetal growth because some anomalies are more closely associated with intrauterine growth retardation than others. For example, patients with trisomy 21 tend to weigh only one-half lb. to 1 lb. lighter than normal babies at birth (Smith and McKeown, 1955; Hall, 1964), whereas a high percentage of trisomy E18 and trisomy D1 infants are born with a distinctly low birth weight (Polani, 1964; Taylor, 1967). On the other hand, there
Figure 20. Front and profile views of patient R.W. at 12 years of age.
Figure 21. Front view of the father (a) and younger brother (b) of patient R.W.
are few instances of partial trisomy D on record which tend to refute this suggestion. In one patient, a partially deleted D chromosome existed as a free extra chromosome (Jacobsen et al., 1966), while in other patients it was either translocated to a B group chromosome (Bray and Sr. Josephine, 1964) or to an E group chromosome (Vislie et al., 1962; Craig and Luzzatti, 1967). A partial trisomy E involving a translocation to a B group chromosome has also been described (Gagnon et al., 1963). None of these patients had a low birth weight. Furthermore, normal birth weights were noted in two children with a D/E translocation (Breibart, Mellman and Eberlein, 1964; Townes and Ziegler, 1965). It is possible that a complete dose of an extra D or E chromosome is necessary for slowing of embryonic growth or that the retarding effect of a partially deleted D or E chromosome on fetal growth is diminished by translocation to other chromosomes. An alternate hypothesis would be that intrauterine growth is retarded as a response to the total amount of chromosomal excess rather than to the type of genes carried on the particular chromosome involved.

Autosomal deletion appears to play an important role in fetal growth retardation because a large number of patients with cri-du-chat syndrome (Taylor, 1967; McGavin et al., 1967) and deleted 18 syndrome are born with a low birth weight. Full-term low birth weight has also been recorded in patients with deletion of the long arm of a D group chromosome (Laurent et al., 1967), with a ring-1 chromosome (Gordon and Cooke, 1964; Wolf et al., 1967) and a ring-D chromosome (Bain and Gauld, 1964; Sparkes et al., 1967). However, normal birth weights were recorded in patients with a ring-3 chromosome (Mukerjee and Burdette, 1966), a ring-C (Butler et al., 1967), a ring-X (Paolini et al., 1966) and a ring-E
chromosome (Gropp et al., 1964; Palmer et al., 1967). This attests again to the different qualitative effects of different chromosomes upon embryonic development and in particular underlines the necessity of providing information concerning birth weight and gestation period in reports of cytogenetic abnormalities. In this way, a clearer picture of which chromosomes are more vital to fetal growth can perhaps be obtained.

Whether chromosome inversions are associated with intrauterine growth retardation or not cannot be determined at this time since there are only a few cases of this kind of chromosome error on record. The chief biological effect of inversion is to hold genes together by preventing crossing over within the inverted segment. There does not appear to be any deleterious effect on the phenotype of the carrier and this innocuous effect is probably reflected in the normal tempo of development of the fetus.

It is well known that the X chromosome is concerned with many developmental processes other than sex determination (McKusick, 1964), which suggests that errors involving the X chromosome may lead to intrauterine growth retardation. In Klinefelter's syndrome, evidence has been offered that lower birth weight is correlated with an increased number of X chromosomes, since XXXXY patients' birth weights are often about 2 lb. lower than that of XXY patients. Triple-X females weigh about 1 lb. lighter than normal females at birth. Whether this observation suggests that XXX also leads to intrauterine growth retardation cannot be assessed since the birth weights of the three XXX patients reported by Carr, Barr and Plunkett (1961a) and de Grouchy, Brissaud, Richardt, Repesse, Sanger, Race, Salmon and Salmon (1968) were normal. Further-
more, one XXXXX patient had a normal birth weight (Brody, Fitzgerald and Spiers, 1967) while another was premature (Kosaree and Woolley, 1963). The observation that lower birth weight is correlated with the increase in number of X chromosome seems definite enough in Klinefelter's syndrome and yet this does not appear to be true in XXXX and XXXXX patients. A possible explanation is that there are too few instances of the XXXX and XXXXX chromosome errors known for an accurate assessment of their association with birth weight or, alternately, that the interaction of the Y and poly-X chromosomes may play a role in the etiology of low birth weight.

XXY males tend to have normal birth weights while deletion of a Y chromosome has been found in a small-for-date patient (Nakagome, Sasaki, Matsui, Kawazura and Fukuyama, 1965). While it is dangerous to speculate from one case, it is at least possible that a partial loss of a Y chromosome is more important that the presence of an extra Y chromosome with respect to low birth weight.

7. Etiology of Chromosome Abnormalities

The association of different chromosome abnormalities with low birth weight necessitates a brief discussion of the probable etiological factors with respect to chromosome anomalies. Many factors are known to be implicated or suspected of being involved. Chromosome diseases such as Down's syndrome (Penrose, 1963), E18 trisomy and D1 trisomy syndromes (Taylor and Polani, 1964) are associated with advancing maternal age, although no satisfactory explanation has yet been proposed to account for this association. Fialkow (1966) showed that the mothers who had positive thyroid autoantibody tests had a higher risk of producing children with Down's syndrome. He suggested that the autoimmunity may
predispose to chromosome anomalies or, alternately, that the two are related to a common etiologic factor. One such factor could be the effect of a viral infection on the various cells of the body.

Hoefnagel and Benirschke (1962) noted an association between twinning and Klinefelter's syndrome. Twinning is considered to be one of the causes of low birth weight in infants (North, 1966) because of the intrauterine "crowding". The data presented in this thesis show that two out of 29 chromosome abnormalities found in 150 LBWR were members of twin pairs. These included one with Klinefelter's syndrome and one with the metacentric G chromosome anomaly. The mechanism of such an association is unknown although advancing maternal age has been shown to play a role in the etiology of twinning (Gedda, 1961).

Genetic factors may also predispose an individual to chromosome errors. Data in this area of research are scanty. Hecht, Bryant, Gruber and Townes (1964) presented evidence to suggest a non-random and familial aggregation of aneuploid individuals and Penrose (1961) observed an increased consanguinity in the maternal grandparents of subjects with Down's syndrome.

A chromosome anomaly in itself may predispose to other chromosomal errors. Dekaban, Bender and Economas (1963) found evidence that two out of twelve mothers and two out of five fathers of children with Down's syndrome had varied "minor" chromosome abnormalities. Furthermore, 13 instances of numerical or structural chromosome variations were found in 240 families of patients with Down's syndrome (Uchida, Ray and Ursel, 1967).

Mutagen such as radiation, whether ionizing (X-rays) or non-ionizing (UV), and chemicals such as streptonigrin (Cohen, Shaw and Craig, 1963; Cohen, 1963) and mitomycin C (Cohen and Shaw, 1964) have
been shown to be potent in producing chromosome breakages in mammalian cells. Viruses were likewise shown to induce mammalian chromosome breakages both \textit{in vitro} (Stich, Hsu and Rapp, 1964) and \textit{in vivo} (Nichols, 1963). It is possible that many chromosome abnormalities are produced by contact of an individual with these or similar mutagenic agents.

8. Concluding Remarks

Radiation, chemicals and viruses have been mentioned as important in the etiology of chromosome abnormalities in mammalian cells. Likewise, we have offered evidence that different chromosome abnormalities can be associated with low birth weight. The question arises whether these two phenomena are linked or to put it another way, whether low birth weight with chromosome abnormalities can be artificially induced by these mutagens.

There is some evidence that intrauterine growth retardation can be produced by mutagenic agents. Growth retardation has been produced experimentally in the offspring of female rats exposed to X-irradiation during pregnancy (Warkany and Schraffenberger, 1947; Wilson, 1954). Vitamin A and pterolyglutamic acid deficiency in female animals during pregnancy also lead to growth retardation in the young (Warkany and Roth, 1948; Nelson, Ashling and Evans, 1952). A low birth weight child was born to a leukemic mother who was treated with myleran during pregnancy, a drug which has alkylating and radiomimetic properties (Diamond, Anderson and McCreadie, 1960). Viruses can also be responsible for embryonic growth retardation in patients with infectious diseases (Swan \textit{et al.}, 1943; Giles \textit{et al.}, 1964).

Thus, it has been shown that low birth weight can be produced experimentally by mutagenic agents and it would be of great interest to
know what proportion of the experimentally produced "small-for-date" young animals have chromosome abnormalities, how many of them are born at term and how many of them are premature or aborted. Animal experiments in this direction may lead to a better understanding of the relationship between chromosome abnormalities and low birth weight.
VI. SUMMARY

(1) Of 2183 mental retardates who were evaluated at the Children's Psychiatric Research Institute, 1297 were male and 886 were female. The mean birth weight of the males was $7.0 \pm 1.5$ lb., which was significantly lower than that of males generally. The mean birth weight of females was $6.5 \pm 1.4$ lb., which was also significantly lower than that of females generally.

(2) The mean birth weight of the male retardates was significantly higher than that of the female retardates.

(3) The mean birth weights of males and females with Down's syndrome were not significantly different from those of corresponding sex among mental retardates as a group. However, the mean birth weights of males and females with Down's syndrome were significantly lower than those of corresponding sex in a general population.

(4) There were 174 full-term low birth weight patients among 2183 retardates for whom data were obtainable, representing a frequency of eight per cent. This is significantly higher than that in newborns generally.

(5) Chromosome analysis was carried out for 150 full-term low birth weight retardates and 150 full-term normal birth weight retardates who served as controls.

(6) Twenty-nine patients with chromosome abnormalities were found among the 150 low birth weight retardates. These included 18 patients with Down's syndrome, three with Klinefelter's syndrome, one
with an XO sex chromosome complex, one XO/XX mosaic, one E trisomy syndrome, one D trisomy syndrome (familial D/D translocation), one with partial trisomy of the long arm of a B chromosome, one with a meta-centric G chromosome, one with the cri-du-chat syndrome and one with an inversion of a no. 2 chromosome.

(7) Twenty-one patients with chromosome abnormalities were found among the 150 normal birth weight group. These were: 18 with Down's syndrome, one with Klinefelter's syndrome, one triple-X and one with a 46,D/D translocation.

(8) Three patients with Down's syndrome in the low birth weight group showed chromosome abnormalities other than the usual form of trisomy 21. These included a patient with 47, trisomy 21 (ring)/46, normal mosaic, one with 48, XXX-trisomy 21 and one with a 46, D/G translocation. The remainder of this group showed regular trisomy 21. Every patient with Down's syndrome in the control group showed regular trisomy 21. Statistical analysis indicated that the occurrence of three chromosome abnormalities other than the standard form of trisomy 21 among the 18 low birth weight patients was not significantly different from the finding of regular trisomy 21 in all the 18 normal birth weight patients with Down's syndrome.

(9) Exclusive of those with Down's syndrome, there were 11 chromosome abnormalities in 132 low birth weight retardates, while only three were found in the control group. The difference is statistically significant and it is concluded that there is an association between chromosome abnormalities and low birth weight in mental retardates.
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APPENDIX

Clinical Summary of Patients* with Chromosome Abnormalities

A. Low Birth Weight Retardates

1. P.S. (47,Trisomy 21(ring)/46,Normal Mosaic)

   This female patient, third in a sibline of five, was born weighing 5 lb. 3 oz after a full-term normal delivery. The ages of the mother and of the father were 17 and 30 at that time. The mother was described as having limited intelligence and the paternal grandfather was blind and mentally retarded.

   The patient was examined at the age of one year and ten months. The head circumference was 46 cm and there were several features of Down's syndrome: upward slanting eyes, epicanthal folds, hypotonia of the musculature, enlarged tongue and strabismus. The hands were short and stubby although there was no simian lines. The I.Q. was estimated to be 64 (Gesell Developmental Norms Test). The patient subsequently succumbed from acute leukemia.

2. C.E. (48,XXX-Trisomy 21)

   The birth weight of this female child was 5 lb. 8 oz after a full-term pregnancy. The mother was 39 and the father 40 at the time of the patient's delivery. The patient was the 5th of five children and there was no family history of any significant illness.

   The child was examined at the age of three years. She then weighed 24 lb. and was 34 inches in height. The head was small and round.

* All patients were examined at the Children's Psychiatric Research Institute, London.
and the circumference was 44 cm. She had a typical mongoloid facies with epicanthal folds. The ears, tongue and palate appeared to be normal. The hands were short and stubby, with bilateral incurved 5th fingers. There was a simian line on the palm of the right hand and an increased distance between the first and second toes. There was hyper-flexibility of all the joints and generalised hypotonia. The estimated I.Q. was 25 (Kuhlmann Test).

3. T.R. (46, D/G Translocation)

The patient, a male, was born with a birth weight of 5 lb. 4 oz after a full-term normal pregnancy and delivery. The mother was 28 years old and the father was 31 years old when the child was born. There were three older siblings, all in good health.

The patient was examined at the age of 16 years. He was 61 inches tall and weighed 124 lb.; the head circumference was 51 cm. He had an appearance highly suggestive of Down's syndrome. Features such as slanting eyes, epicanthal folds, short and stubby hands and fingers, bilateral simian lines and fissured tongue were all present. The ears were small and low-set. The estimated I.Q. was 34 (Stanford-Binet L-M Test).

4. A.U. (47, XXY)

The patient was born to a 30-year-old mother and 37-year-old father after a full-term normal pregnancy and delivery, weighing 4 lb. 3 oz. He was the 4th of the seven living children. Three sibs died of congenital heart diseases. A nephew of the patient was mentally retarded.

The child did not walk until two and a half years of age or talk until three and a half years. He spent four years in grade IV.
He was examined at the age of 31. He was tall (74 inches) and weighed 223 lb. The pubic hair was feminine in distribution and the testes and genitals were smaller than normal. The I.Q. was 58 by the W.A.I.S. Test.

5. L.P. (47,XXY)

The patient was born after a full-term normal pregnancy. He was one of a pair of twins and weighed 41/2 lb. at birth. The twin weighed 51/2 lb. The maternal age was 33 and paternal age 38. The mother was mentally retarded and psychotic.

The patient was examined when 13 years old. He was 61 inches tall and 207 lb. in weight. The head was asymmetrical with a circumference of 54 cm. There was a slight strabismus of the right eye, the eyes were long and narrow and the testes were small and the penis infantile. The sexual hair development was pre-pubertal. The I.Q. was 59 on the W.A.I.S. Test.

6. R.B. (47,XXY)

The patient was born after 40 weeks of gestation, weighing 5 lb. 2 oz. The pregnancy was normal but delivery was by caesarian section because of cephalo-pelvic disproportion.

The mother was 28 and the father 30 at the time of the patient's birth. There was no significant illness in the history of the family. The patient had an older healthy brother.

The patient was examined at the age of 15 years. He was 651/2 inches tall and weighed 133 lb. There was no gynecomastia; the testes were firm and small. The pubic hair was gynecoid in distribution. The I.Q. was estimated to be 60 by the W.A.I.S. Test.

7. J.L. (45,XO)

The patient was born to a 35-year-old mother and 37-year-old
father, after a full-term and normal pregnancy. She weighed 5 lb. 3½ oz. There was an older sibling and previous to this pregnancy the mother had a five-month miscarriage. There was no family history of any pertinent illness. The child was examined at the age of two years and 10 months, having been referred because of slowness in development.

The child was below the 3rd percentile in height and weight. The head circumference was only 43.5 cm and the head was flattened in the occipital area. The ears were low-set and the neck was short and webbed. There was an internal strabismus, of the right eye, together with a peculiar roving nystagmus of both eyes suggestive of cortical blindness. The patient also had spastic quadriplegia. The clinical features were strongly suggestive of Turner's syndrome and the diagnosis was confirmed cytologically.

8. S.H. (45,X0/46,XX Mosaic)

This 13-year-old girl was the oldest of the four children. There was no significant family history other than syndactyly and cleft palate in a maternal cousin. Labor was induced at term and the patient weighed 5 lb. at birth. Her development was very slow; she did not walk alone until seven years old.

On examination the patient weighed 41 lb. and was 41 inches tall; the head circumference was 47 cm. The neck was short but webbing was not marked. The ear lobes were deformed, the bridge of the nose was broad and a kyphoscoliosis was present. There was a grade two systolic murmur at the 3rd and 4th left sternal border. There was bilateral hyperactivity of the knee jerks and the joint movements of the left side were limited by flexion contracture. The feet were flat and in an extreme talipes calcaneo-valgus position. A thyroid stimulation test
indicated that there was thyroid aplasia. The I.Q. was estimated to be
less than 20 (Kuhlmann Test).


The patient, a female, was born with a birth weight of 4 lb.
5 oz after a nine month gestation period. She was the 4th child of a
40-year-old mother and a 40-year-old father. The first pregnancy ended
with a stillbirth.

On examination at two years and eight months of age, the
height and weight were below the third percentile. There was a general-
ized hypotonia. The ears were low-set and simple, the jaw was very small
and the body was covered with lanugo hair. There were bushy eyebrows and
a prominent occiput. There was flexion of the fingers, but no over-
lapping of the second and third fingers, and the left foot was flexed
in an equinovarus position. There was a grade two systolic murmur over
the precordium. Hydronephrosis was diagnosed by intravenous pyelogram.
The estimated I.Q. was less than 20 (Gesell Developmental Norms Test).
This patient died when five years old.

10. K.N. (46, D Trisomy, Familial Translocation)

This girl was born to a mother of 19 and a father of 24 and
was the second of three children. She was a breech birth at full-term
weighing 5 lb. 2 oz. The Apgar rating was 1.

On physical examination at the age of three months, the
weight was only 7 lb.; the head was relatively large (37 cm circumference)
when compared to a chest of 32 cm circumference. The occiput was
prominent and the jaw small. The pupils were fixed and unresponsive
to light. The right eye-ball was especially small. The simplified
ears were low-set and the hands were clenched in an ulnar position.
There was a systolic murmur over the whole precordium and the heart was enlarged.

The estimated I.Q. was about 40 by the Kuhlmann Test. The child died when six months of age and permission for a postmortem examination was not obtained.

11. P.J. (46, Partial Trisomy of B Chromosome)

This female patient was referred at the age of five years because of a speech problem and mental retardation. She was born of a normal full-term pregnancy and the birth weight was 5 lb. She was slow in development, starting to walk at 16 months. Her speech was poor and she said simple words and phrases very indistinctly.

The mother, of Austrian descent, was 32 years old at the time of the patient's delivery. She was short (56 inches) and stout, and the arms and legs were very short in proportion to the rest of the body. The father, of Irish descent, was 34 years old when the child was born. He was a tall, healthy and intelligent man, the third of six sibs. An older mentally retarded sister died when nine years old. An older brother, two younger sisters and a younger brother were still living. One of the sisters was mentally retarded and "never went to school".

The patient had an older sister and younger brother, both healthy and doing well in school.

The patient was seen again when 10 years old. Physical examination revealed a weight of 66 lb. (25th percentile), a height of 49 inches (3rd percentile) and a head circumference of 51 cm (3rd percentile). The face was broad and flat, the bridge of the nose was depressed and the nostrils were somewhat flattened. The eyebrows were bushy. The 5th fingers were incurved and simian lines were present on
both hands. There was webbing between the second and third toes and the legs were very short. The tendon reflexes were increased in all four limbs. The I.Q. was estimated to be about 57.

12. G.A. (46, Metacentric G Chromosome)

This patient, a boy, was born to a 29-year-old mother and a 31-year-old father. The delivery followed a 38 week gestation period. He was one of twins and weighed 4 lb. 10 oz at birth. In addition to the twin, there were four older and two younger sibs. There was no history of significant family illness.

On examination at the age of seven and a half years, he was 48 inches tall (25th percentile) and weighed 46.5 lb. (3rd percentile). He was normocephalic with a head circumference of 50.5 cm. The ears were large and sail-like and an alternating strabismus was present. The estimated I.Q. was 74 by the Stanford-Binet L-M Test.


This male child was born after a full-term normal pregnancy, weighing 5 lb. 8 oz. The mother was 24 years old and the father was not identified.

The mother stated that the child had a high pitched cry at birth and that he was slow to develop. He was not able to walk or talk when first examined at the age of six and a half years. The patient was very small for age. He was 48 inches in height (3rd percentile) and was microcephalic, with a head circumference of only 44.5 cm. There was hypertelorism, the ears were low-set and the testes were small. Bilateral simian lines on the palm of the hands were present. There was also spasticity and increased reflexes in all the four limbs with a bilateral Babinski sign. There was also a marked kyphoscoliosis. The patient was
profoundly retarded mentally as the I.Q. was less than 20 by the Kuhlmann Test.

14. W.M. (46, Inversion in a no. 2 Chromosome)

This child, a girl, was born after a full-term normal pregnancy. She weighed 5 lb. 8 oz at birth. The mother was then 29 and the father 33 years old. The patient had been slow in her development and on examination at the age of nine years she was 44 inches tall (3rd percentile) and weighed 44 lb. (3rd percentile).

This girl was normocephalic; there was a high arched palate, the ears were low-set and physical coordination was very poor. The whole appearance was "bird-like". The I.Q. was 40 by the Stanford-Binet (Form L-M) Test.

B. Normal Birth Weight Retardates

1. K.R. (47, XXX)

The patient was born after a full-term pregnancy weighing 6 lb. 11 oz. The mother and the father were then 38 and 36 years old. There was no history of significant family illness.

On examination at the age of 16 1/2 years, he was 64 inches tall and weighed 108 lb. There was no evidence of puberty and the testes and penis were small. There was some gynecomastia. Bilateral incurved fifth fingers were observed. The I.Q. was 83 by the W.A.I.S. Test.

2. M.O. (47, XXX)

The patient, a girl, weighed 6 lb. at birth. The mother was 30 and the father 45. There were no sibs, abortions or stillbirths.

The patient was referred for study when 13 years old, because of obesity and slow development. She was then 59 1/2 inches tall and very obese (170 lb.). The head circumference was 53 cm. There were no signs
of breast development. The estimated I.Q. was 41.

Laboratory findings showed that serum levels of cholesterol esters were slightly elevated while the phospho-lipids levels were low. There was also a below normal urinary excretion of 17-ketosteroids.


The boy was seen at the age of six years because of his slowness to learn and inability to enter regular school. The I.Q. was 33 (Stanford-Binet).

He was born of a full-term normal pregnancy and the birth weight was 8 lb. 4 oz. There were no previous abortions or stillbirths. On the second day of life, a cleft palate was noticed and it was repaired at the age of 20 months.

He was slow to develop, standing at 17 months and walking at two years. He did not hold his head up until five-six months of age.

At the age of 12, the patient weighed 110 lb. (90th percentile) and was 54 inches tall (3rd percentile). The head circumference was 53 cm (50th percentile). The ears were large and flabby with little cartilaginous support. The eyebrows came close together and almost met in the mid-line. There was a high arched palate and evidence of the old cleft palate repair. The eyes were large with much of the sclera visible below the iris. The teeth were notched. Bone age was retarded by one and a half years. The genitalia were normal.

The patient's mother, of German descent, was 21 at the time of delivery. Two children of her cousins had a cleft palate. The patient's father, who carried the same abnormal chromosome constitution as the propositus, was of Dutch descent and was 29 at the time of the patient's birth. The father was slow at school although he worked
steadily for 14 years. He presented facial features similar to those of the index patient.

The propositus was the second of four children in the family. There was one older brother and one younger sister and brother. The younger brother had many clinical features in common with the patient and the father. He was also mentally retarded. He had the large ears, prominent sclera visible below his iris and high arched palate. He was small in weight and height (3rd percentile). His karyotype appeared similar to that of the propositus and the father. The other two children were normal.