CHROMOSOMAL ABERRATIONS IN FAMILIAL MULTIPLE MALFORMATIONS IN MAN

by

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To my Wife, Hélène

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I INTRODUCTION

A. HISTORICAL

One of the main unsolved problems of medicine today is the fact that the frequency of human congenital malformations has shown no reduction in spite of the recent spectacular advances in understanding and treatment of human disease. The twentieth century has seen the successful application of the Mendelian laws to problems of disease transmission in man, leading to the brilliant elucidation of gene action in biochemical terms exemplified by the inborn errors of metabolism (Garrod, 1923) and the abnormal hemoglobins (Ruchnagel and Neel, 1962) and the development of refined methods to study the morphology of human chromosomes, leading to the identification, within the last few years, of a new group of human diseases, the chromosomal aberrations. All these advances in Human Genetics were made possible by the work of devoted scientists who spent their lives trying to solve the mysteries of life in a variety of lower organisms, or attempting to establish the parallels existing in Nature between lower life and "homo sapiens".

The door is now open, but we have barely had a glance at the limitless field which spreads from the portal provided by establishment of the molecular structure of DNA, the basic structure of nearly all living material. One sector of the field is that concerned with the organization of DNA into the structure of the human chromosome, its replication and its relation to human health and disease. Such is the fertile but largely unexplored science of Human Cytogenetics.

The first application of cytogenetics to medicine was the demon-

stration of the chromosomal basis of mongolism, a condition which had for a long time been an etiological puzzle. Rosanoff (1934), published a review of the literature on studies done on mongolism in twins. In addition to the previous 59 reported cases, he added 5 of his own analysis to make a total of 64. His conclusions were that the etiologic factors operated in the germinal or early embryonic period. The statistical correlation between the incidence of mongolism and the age of the parents showed that the real etiologic factor was the mother's age and not the father's who was likely to be in the same age group as his wife. Rosanoff said that there was no part played by the size of the family, uterine exhaustion and the order of birth. Mongols were more frequent in males than in females, and that could be explained by the protection given by the presence in double dosage of the X chromosome. "All the known factors concerning mongolism seem to point to the same condition of the ovary as underlying its pathogenesis."

As far back as 1934, Bleyer suggested that mongolism could be due to an alteration in the number of chromosomes, the same mechanism that is responsible for the degressive mutations of plants. Taking for granted at that time, that the human chromosome complement was made of 48 chromosomes, Bleyer suggested in mongolism an abnormal aneuploid count of 47 or 49 chromosomes. He said that the germinal cells must be involved, and that a fixed irregularity in their constitution would produce a defect repeating itself with a strange regularity. Following De Vries ideas, mongolism would be a degressive mutation like the defective sterile Enothera Lata, a plant having 15 chromosomes instead of 14. Fanconi (1939) also suggested the gametic factor as being in-

volved in the etiology of mongolism.

Twenty-six years ago, Turpin and his collaborators (1937), presented a study of the pathogenesis of mongolism. Their conclusion was that in view of the facts that (1) where one of a pair of monozygotic twins was a mongol, the other one was also affected, (2) mongol mothers may have normal or mongol children, and (3) sometimes there was a tendency for the malformation to repeat in the same family, therefore the mechanism of this defect must be related to the chromosomal structure of the cell. But the general belief was that humans had a chromosomal count of 48, and no serious attempts were made at that time to elucidate the hypothesis just mentioned above, because of the limitations of the cytological techniques.

In 1956, Tjio and Levan, in a study of human embryonic cells in tissue culture, found that a normal human karyotype contains 46 chromosomes in mitotic metaphase, instead of 48. And it was only in 1959, that Lejeune and his collaborators associated a human disease with a chromosomal aberration. In a study of nine mongol children, they found that the somatic cells of those patients in tissue culture, had an extra small acrocentric chromosome. Almost simultaneously, Ford from Harwell (1959) and Jacobs from Edinburgh (1959), and their collaborators, published articles on the same problem. Ford presented a case of Klinefelter syndrome, associated with mongolism, having two Xs and a Y, instead of the normal sex constitution XY, plus an extra small acrocentric for a total count of 48. Jacobs described six cases of mongolism having one extra chromosome for a total count of 47.

B. TECHNIQUES OF HUMAN CYTOGENETICS

The rapid progress in this very new field, has resulted largely from the development of new techniques. In 1879, Arnold presented a drawing from tumor cells. But it was impossible to count the chromosomes. Fleming (1898) obtained low counts in the range of 20 to 22 chromosomes in normal human tissue. Painter (1924) was the first to recognize clearly the sex chromosomes in humans. He stated that the total complement had a count of 48 chromosomes including XX sex chromosomes in the female and XY in the male. All thœ e studies were made on tissue sections. The spreading and contraction of chromatids was very poor. Some cells were cut through and both the total c ount and the morphology were disrupted. Makino (1952), introduced a new technique making use of pretreatment of cells with water before fixation, to induce swelling of the cells and spreading of the nuclear components. In the same year, Hsu (1952), published a karyotype of the human chromosome complement from cultures of skin and spleen tissues taken from a 4-month old fetus. After one week of culture, the cells were washed by accident in Hypotonic Tyrode solution instead of isotonic saline. The results were obvious, as noted by the author: the chromosomes were spread and more easily observed under the microscope. It is understandable that the first tissues used for chromosomal analysis in humans came from tumours and different skin biopsies. But the tissue culture technique involves a great deal of work and a long culture time.

In 1956, Ford and Hamerton obtained good results from bone marrow preparations of rodents. The mammals were injected with colchicine and the bone marrow aspirated from the dead animals. The cells were

treated with an hypotonic solution of sodium citrate before fixation. Ford and Jacobs (1958), realized that the technique had to be modified for humans, and the colchicine injected in the bone marrow after the aspiration. For obvious reasons the authors decided to add the anti-mitotic agent a few hours after the cells were obtained from the patient. The chromosomal counts in ten studied individuals gave a modal complement of 46 chromosomes, which was in agreement with the previous reports on the human karyotype.

Moorhead (1960), introduced a technique for the culture of human leucocytes in vitro after a short incubation period of 72 hours. Many steps were needed before good results could be obtained in the culture of lymphocytes. One of the most important findings was the use of an extract of the bean Phaseolus vulgaris, as a mitogenic factor. It is known that the leucocytes, unless they are stimulated, die a few weeks after their transplantation, without going into division. The number of cells already in division at the time of the blood puncture is too low, since most of them are mature or degenerating. This of course does not apply to leukaemic patients, who have an abnormal growth activity. Nowell reported (1960) on the necessity of using a mitogenic agent. Li and Osgood (1949) previously demonstrated the value of the Phytohaemagglutinin in the leucocyte separation from the erythrocytes. Primarily used for this purpose the bean extract has finally been described as having no important agglutination action as compared to its mitogenic activity. Skoog (1956) and Chen (1958), reported that they could not obtain with the use of this agent more than 75% of the total leucocytes present in the blood sample. Today it is a well-known fact that most of the searchers have their own method of culturing leucocytes,

but yet no one has found a mitogenic agent which has proven to be as effective as Phytohaemagglutinin.

The media in use for the culturing process are commercially prepared and are the same as those in use for viral studies: they must contain enough nutritive ingredients to keep the leucocytes alive and be free of antigenic agents. The use of antibiotics in culture is optional. They should not be necessary if a sterile technique is followed and if the solutions used for the preparation of the cultures, anticoagulants, mitogenic agent and medium are kept sterile. Mellman (1962) suggested a concentration of at least 10% serum proteins in the culture tube with the leucocytes, and he added that a concentration of 20% would give better results. Usually the amount of plasma added to the medium to give a concentration of 1,500 W.B.C. per cmm of solution is sufficient to yield good mitoses. However Genest (1963) suggests the addition of 1 or 2 ccs of heterologous human serum.

When the time comes to terminate the culture, the procedures used do not differ essentially from the general principles described in the tissue and bone marrow cultures. The colchicine is added to the aliquots for a period of time varying from one to six hours before harvesting, in the case of the blood culture. The concentration and the time of exposure has been stressed by Sasaki (1961). Axelrad (1958) used colcicine for a period of 18 to 24 hours on the kidney tissues of a monkey, and Tjio and Puck (1958), experimented on the use of the mitostatic agent for a period of one hour only, but at a stronger concentration. On human blood samples, de Grouchy and Lamy (1961), used 4 mu gm of colcemid (desacetyl-methyl-colchicine) for a period of 2 hours

and Williamson (1962), used the same concentration for a period of one hour, both of them obtaining good results. Hungerford and his collaborators (1959) used colchicine for a much longer period of time, 17 to 19 hours, but at a very weak concentration of 0.04 mu gm.

Levine (1956), and Hastings (1961) suggested the elimination of the polynuclear cells; by adding iron particles to the blood, and removing the multinucleated cells with a magnet once they had completed the phagocytosis of the iron. This method introduces a new factor of contamination and very few workers adopted the idea. Edwards (1961) proposed a technique of chromosomal analysis from small blood volumes. The method is very useful especially in children, and whenever only small blood samples can be obtained from the patients.

Today the three different techniques are widely used. The tissue culture method is a great tool in cancer research, the bone marrow is examined almost routinely in haematology when the aspiration is needed for the diagnosis of leukaemia, and the blood culture technique serves as the basic examination in cases of congenital malformations suspected of being caused by a chromosomal aberration.

C. THE HUMAN KARYOTYPE AND NORMAL CHROMOSOMAL COMPLEMENT

The karyotype refers to the microscopic picture of the individual chromosomes arranged in pairs determined by their length and arm ratio relationship. The idiogram is a drawing made from the chromosomes as they are visualized under the microscope. It was not until Tjio and Levan (1956) , could demonstrate for sure that the number of human chromosomes was 46, that it was possible to establish a karyotype which could

serve as the basis for the normal human complement. Previous attempts made by Painter (1923) from a spermatogonium, by Shiwago (1932) also from germinal cells and by Hsu (1952) from tissue culture of embryonic spleen, failed to present the true chromosomal complement. As it was mentioned at the beginning of this work, the use of new techniques helped the workers in their preparation of the karyotype recognized today as being correct in number, but lacking many elements for the identification of the different chromosomal pairs.

In metaphase, the 46 chromosomes are spread, unordered, and the chromatids are usually clearly distinguishable, being contracted and densely stained by the proper colorants (see Figure 1). From the microscopic picture the chromosomes are cut and arranged by pairs in order of decreasing length.

A group of scientists, the Denver group (1960), interested in human cytology summarized the findings of various workers and came to an agreement which is to assign a number to each pair of chromosomes from 1 to 22, and to identify the sex chromosomes by the letters X and Y. The 22 pairs were broken down into 7 groups. Attempts to define the individual members of the karyotype were made in the past by Book (1959), Patau (1960) and Penrose (1960).

The different findings and propositions made in the last 4 years are summarized (see Table 1) and a karyogram (see Figure 2) illustrates the chromosomes and their place in the normal complement. The letters assigned to the different groups were proposed by Patau (1960).

TABLE I

HUMAN KARYOTYPE

PAIRS

GROUP A: CHROMOSOMES	1 to 3
	1: Metacentric
	2: Sub-metacentric
	3: Metacentric
GROUP B: CHROMOSOMES	4 and 5
	Both sub-metacentric
GROUP C: CHROMOSOMES	6 to 12
	All sub-metacentric. Arranged by size.
GROUP D: CHROMOSOMES	13 to 15
	Acrocentric chromosomes. Satellited.
GROUP E: CHROMOSOMES	16 to 18
	16: Metacentric chromosome. With variations.
	17: Sub-acrocentric
	18: Sub-acrocentric. Shorter than 17.
GROUP F: CHROMOSOMES	19 and 20
	Metacentric chromosomes
GROUP G: CHROMOSOMES	21 and 22
	Acrocentric chromosomes. Satellited.
SEX CHROMOSOMES	X Resembles those of the C group, but slightly longer. More metacentric than 6.
	Y Of the G group size. Not satellited. Long arms closer together than any of the G group.

FIGURE I - A CELL IN MITOTIC METAPHASE

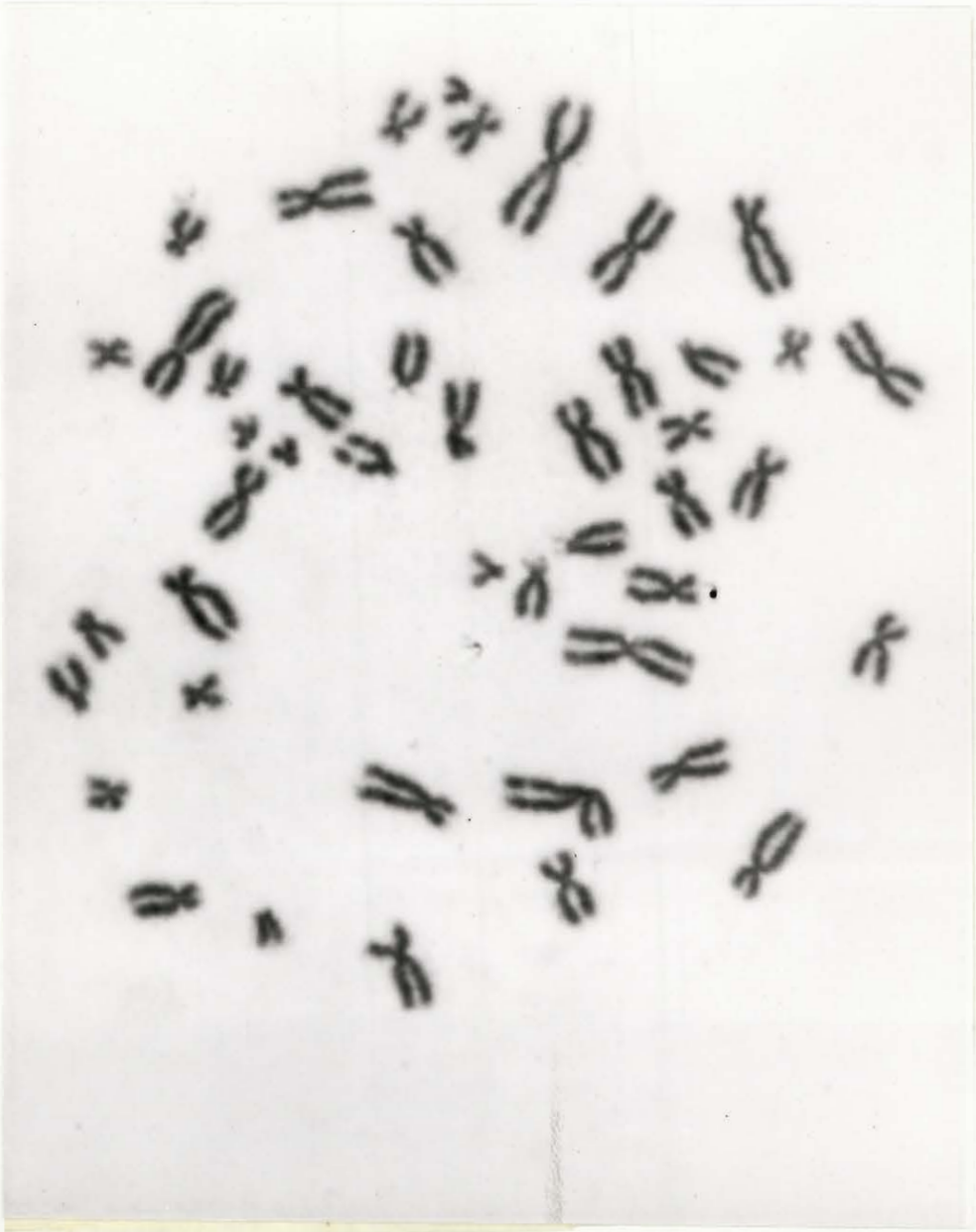
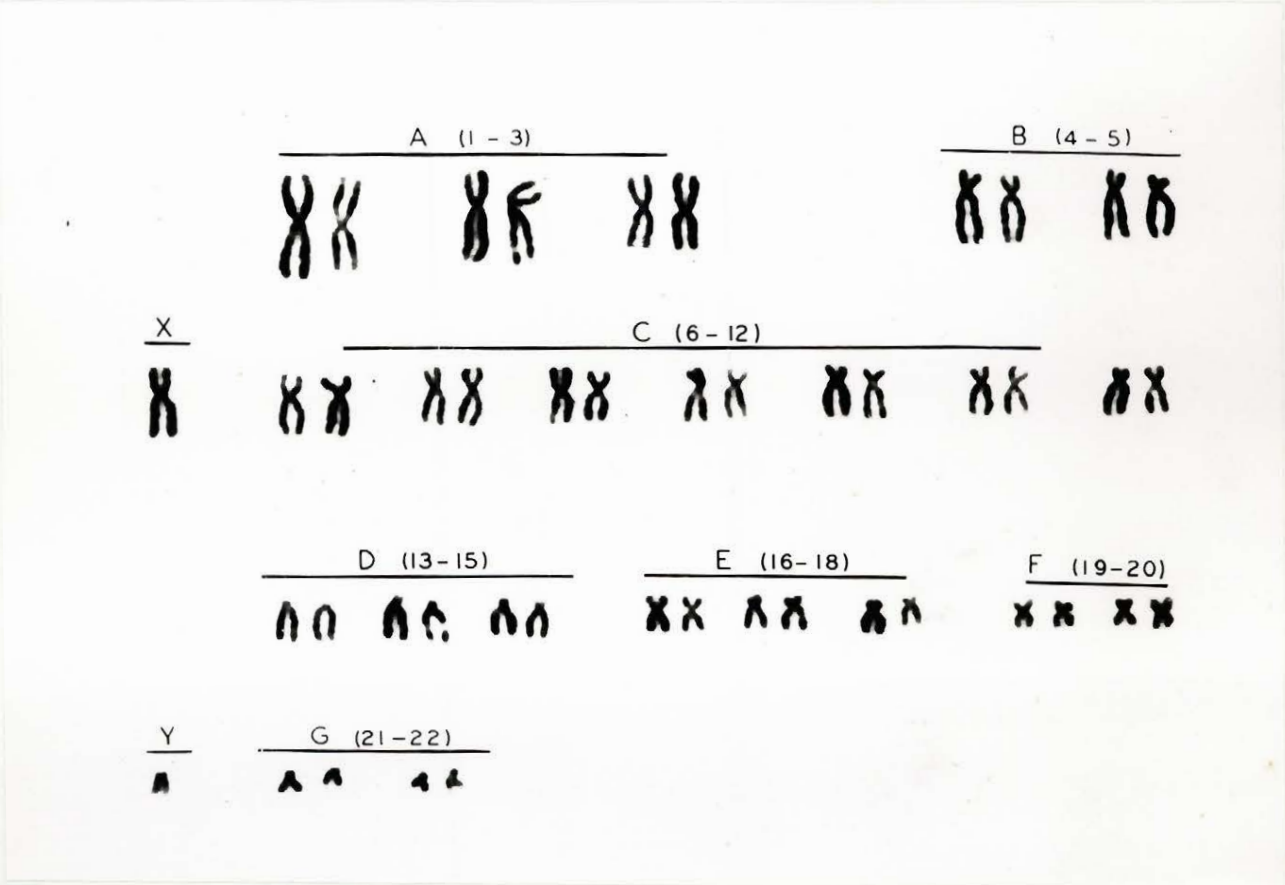


FIGURE 2 - A NORMAL MALE KARYOTYPE



D. HUMAN CHROMOSOMAL ABERRATIONS

In humans the chromosomal aberrations may be related to the autosomes or the gonosomes, as in any other organism. The most common types of aberrations found are:

a. the non-disjunction

b. the translocation

c. the deletion

d. the inversion

e. the duplication.

a. Non-disjunction

De Robertis (1960) described polysomy as follows: When one or more of the chromosomes reduplicate and are represented three or more times, the organism is said to be polysomic. Polysomy is a special kind of aneuploidy caused by a faulty separation of the chromosomes in the meiotic process. When one of the chromosomes along with its homologue passes to the same pole and, after the second meiotic division enters the same gamete, this is called meiotic non-disjunction: (n + 1). After fertilization by a normal gamete (n), the organism will be trisomic for one chromosome (2n + 1). An individual is monosomic by fertilization of the gamete lacking the particular chromosome that went went to the other pole (n - 1) + (n) = 2n - n. Both trisomic and monosomic individuals are found in humans. But the known monosomic individuals are always lacking a sex chromosome and are of type XO. The type YO is not viable apparently, since it has never been observed clinically or cytologically.

Mitotic non-disjunction takes place after fertilization: one or more of the chromosomes of the diploid cell forming the egg, or other somatic cell, fail to segregate normally. If the phenomenon involves the X chromosome, it may give rise to individuals with 2 types of cells XXX/XO, and they are called mosaics. The phenomenon itself is called mosaicism, or the presence in the organism of two different cell lines. In the case of the autosomes, the cells lacking one homologue chromosome or member, will degenerate. Bearn and German published in 1961 self explanatory diagrams demonstrating the way by which chromosomal abnormalities arise in human cells (see Figures 3, 4, 5).

b. Translocation

A translocation is a chromosomal rearrangement which is called reciprocal if parts of non-homologous chromosomes are exchanged and simple translocation if a part of one chromosome is transferred to another without exchange of segments. The process may take place during meiosis or mitosis, and is transmissible under certain conditions. An individual is a potential carrier, when the amount of genetic material has not changed or has changed very little (see Figure 5). In this case the chromosome which has been translocated to another may enter the same gamete as its non-translocated homologue (secondary non-disjunction) and the gamete is trisomic for the translocated segment. The presence of extra material usually has the same effect as the trisomy, though the complement count is 46. A carrier usually has only 45 elements. The simple translocation is believed to be more common in humans, since it tends to involve complete chromosomes in the transfer.

FIGURE 3 - DIAGRAM SHOWING THE NON-DISJUNCTION OF A CHROMOSOME

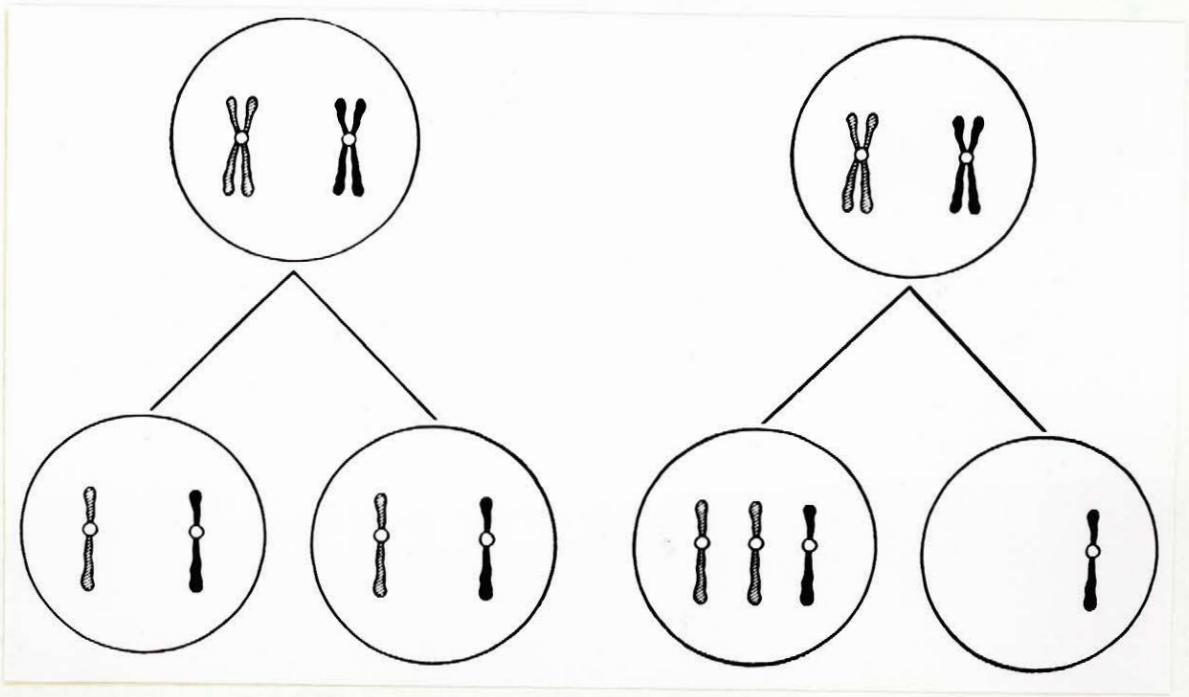


FIGURE 4 - DIAGRAM SHOWING THE NON-DISJUNCTION OF THE GONOSOMES

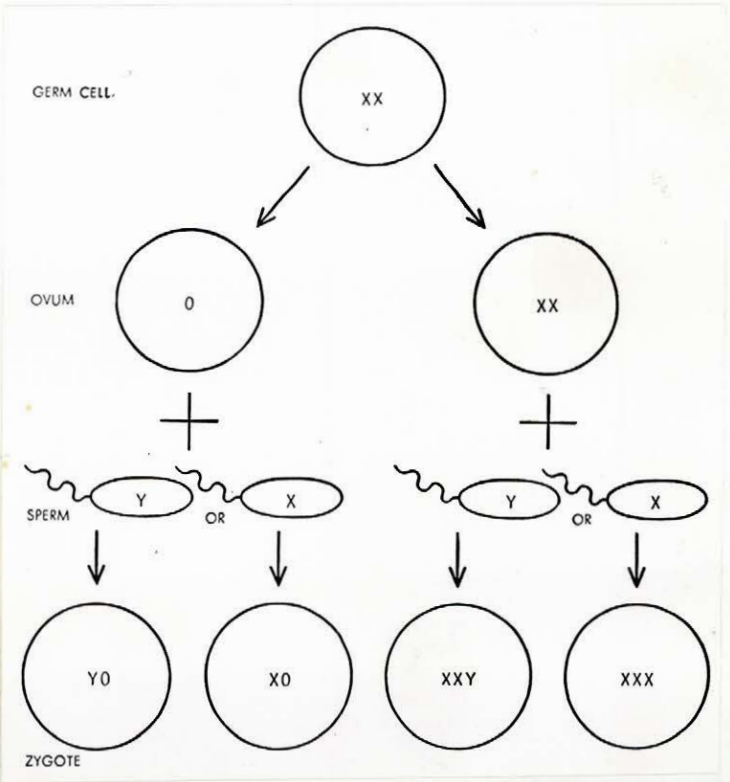
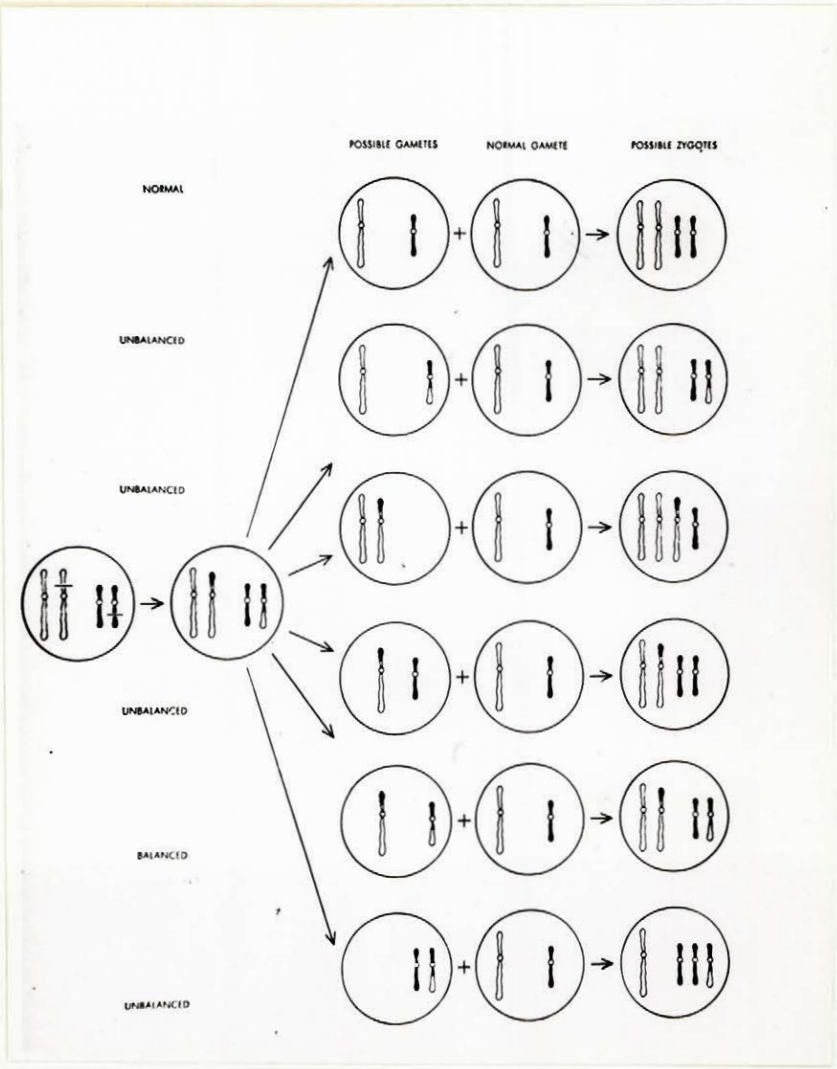


FIGURE 5 - DIAGRAM SHOWING THE TRANSLOCATION MECHANISM



c. Deletion

Deletion is a loss of a portion of a chromosome, and unless that piece is more than 1% of the total haploid chromosomal length, as suggested by Lejeune (1961), it will not be detected cytologically. The acentric portion, detached from the chromosome tends to get lost. Having no centromere, the fragment has no spindle orientation and may remain on the middle line when the telophase takes place.

d. Inversion

Sturdevant (1925) reported a phenomenon in the Drosophila chromosomes, that he called inversion. It consists of the transposition of a chromosome segment. It is pericentric when it includes the centromere and paracentric if the centromere is located outside the inverted segment. Inversions may be very difficult to recognize in the human karyotype. In the fly Drosophila, the inversion may produce a position effect and be identified by the new phenotype, or by its characteristic loop configuration in the salivary chromosomes. In humans we have not had the opportunity to observe such a phenomenon.

e. Duplication

Duplication takes place when a chromosome has a certain extra portion repeated two or more times. The duplication may be a chromosome free in the nucleus, or a part attached to a chromosome of the normal complement. All the chromosomes may reduplicate once or more times, to give the polyploid cells.

E. FACTORS INVOLVED IN THE ETIOLOGY OF CHROMOSOMAL ABERRATIONS

Several factors are involved in the production of chromosomal aberrations.

a. Intrinsic factors

i The role of the nucleolus organizing chromosome

ii Maternal and paternal age

iii Constitution of the egg

b. Extrinsic factors

i Radioactive substances

ii Antimetabolic agents

iii Infectious diseases

The first group (i) is related to the egg itself, and produces abnormal phenotypes detected by the analysis of the modal cells; the second group (ii) disarranges the normal chromosomal constitution determined by the fusion of the two normal gametes.

i. The role of the nucleolus organizing chromosome

The nucleoli are organized at specific regions of specific chromosomes: an association which can be seen best at early prophase. At this stage there is a region of the chromosome called the nucleolus organizing chromosomesection, that is stretched and breaks may occur along that part. During the metaphase the nucleic acid content diminishes and that region stains poorly according to Heitz (1933). The portion of a chromatid distal to the S.A.T. (sine acido thymonucleico) region is known as the satellite.

In Drosophila there are constrictions without nucleolus organizing function that are called gap constrictions. Dearing (1934), working on salamanders and Pathak (1934) on safran plants showed that there were an odd number of nucleolus organizing chromosomes in diploid somatic cells of the different species. Dearing found in Ambystoma Tigrinum the presence of two nucleoli, one being achromatic from prophase to the beginning of telophase, and the other in chromatic phase from telophase to prophase. In middle prophase the nucleolus seemed to diminish in size and become a fragment. The reduction of nucleoli in number seemed to be accounted for by the fusion of those organels. The author stressed the point that the nucleolus certainly plays a role in inheritance since it is constantly localized, and is in fact a portion of a specific chromosome which is perpetuated from cell generation to cell generation by mitosis.

Gates and Pathak working on Crocus Sativus a plant with 24 chromosomes and 3 of them satellited, observed the doubling of satellites in early telophase. Using the Feulgen technique they stained the chromosomes in red and the nucleoli in green. The latter could be visualized in telophase. The satellites seemed to be attached by a thread of chromatin to the nucleolus. There were two small bodies on that thread which seemed to fuse and form the nucleolus. It is Charles (1938) who demonstrated the role of the centromere and spindle attachment in synopsis. Those findings suggest that very likely in two different species there can be one inactive member of a single chromosomal pair.

Ohno and his group (1961) demonstrated in human foetal liver cells stained with Feulgen, without hypotonic treatment, the nucleolus organizing region of chromosomes. The constrictions and adjacent satellites

were seen on four to six chromosomes. There were never more than six seen at the same time. This idea is contradicted by Ferguson-Smith (1961) who showed the presence of satellites on all acrocentric chromosomes, i.e. pairs 13-14-15 and 21-22. Our findings are in complete agreement with Ferguson-Smith's demonstration. This may imply that, in cases where less than six are seen not all of them are functional, or that some of them are not true nucleolus organizing chromosomes. There is also the possibility that when two chromosomes are satellited, one of each pair of acrocentrics (21-22) has one satellited chromosome. The maximum number of nucleoli seen in foetal liver cells was six. But most of the cells have a lesser number.

The Philadelphia chromosome (deleted 21 or 22) or Ph chromosome found by Nowell and Hungerford (1960) is seldom engaged in satellite association. It is possible that it is due to a translocation of the short arm of the 21 onto the centromeric region of the 13-15. Since the breaks are more likely to occur during the nucleolus chromosome association, than any other phase of mitosis, this would explain the frequent 13/21 translocation in mongols or any other arrangement involving the acrocentric chromosomes. The satellites may be exchanged, or parts of the small chromosomes (21-22) may get attached to the short arms of the 13.

ii. Parental age

Non-disjunction in gametogenesis seems to be related to several factors of which one seems to have gained some importance many years ago, though at that time, the phenomenon of non-disjunction was not yet

proven to be a reality in man. Jenkins (1933) and Penrose (1933), demonstrated that the paternal age is not related to the etiology of mongolism but merely a coincidence of events. The maternal age effect seems to be consistent in mongolism, and Penrose (1961) found that the incidence of mongolism has a very low incidence up to 30 years of age. The increase seen in the early period of marital life, or in the early twenties is probably due to the translocations present indifferently in one of the two parents. The risk of producing a mongol child is much higher for a carrier than for normal people.

Jenkins (1933) showed that the risk of primary non-disjunction rises in an exponential manner after the age of 30. At that time the author did not mention non-disjunction however, and mongolism was known as a malformation due to intrinsic and environmental factors of unknown origin. In the cases of familial mongolism, the parental age seems to have no bearing on the etiology of mongolism. But Penrose (1961) suggested that there might be a maternal age effect in non-disjunction, which could be hereditary. In the case of the father this does not seem true, since the mean remains the same as in the general population, contrary to the mother where the incidence is increased.

What is true for mongolism, has also been found to a lesser extent in the Klinefelter syndrome (Lenz, 1959). But a well established fact is that the maternal age has an effect on the primary non-disjunction, giving rise to mongolism.

iii. Constitution of the egg

In a review of the literature on the effects of the over-ripeness of the egg as a cause of malformation in the embryo, Witschi (1952),

comes to the conclusion that genetic and environmental factors combined together play an important role in the induction of anatomical malformations. The discussion comes from work done on lower animals submitted to different environmental conditions and teratogenic agents. It is interesting to note that over-ripeness of the egg producing blastophthoria or blastemic degradation differs from the true hereditary degeneration brought about by genic mutations.

In humans as demonstrated by Hertig and Rock (1950) more than half of the ovulated eggs are not fertilizable or result in zygotes of so poor quality that they decompose during the first days of impregnation. The author suggests that the low quality of human eggs may sometimes be hereditary or even based on a chromosomal aberration. But as a rule the first stages of development may take place without disturbance even though the chromosomal arrangements are upset providing that the cytoplasmic constituents are normal. As suggested by Hertig and Rock (1950) in human eggs and by Witschi (1952) in lower animals, the cytoplasmic degradation in mammalian eggs plays an important part in the abnormal egg cleavage, gastrulation and neurulation, duplications, deficiency of organogenesis, cellular pathology and neoplasia.

There is a strong suggestion that many of the early miscarriages and abortions in humans are caused by a lethal chromosomal aberration, or any chromosomal aberration bringing too much disturbance in the cytoplasmic constituents in early development.

i. Radiation

Muller (1927) found that radioactivity could increase the rate of mutations in Drosophila. In the past years, in humans, more attention

has been paid to the problem, and radioactivity effects have been investigated on a fairly large scale, but progress was hampered by lack of experimental material in vivo. Chu, Giles and Passano (1961), made qualitative and quantitative analyses of X-ray induced chromosome aberrations in human cells in culture. Some of the conclusions are given here: first there are two types of aberrations, the chromatid aberrations seen shortly after irradiation and the complete chromosome aberrations appearing later, this being in general more than 48 hours after treatment.

Types of aberrations: a - chromatid break

b - isochromatid break.

The terminal deletions increase linearly with the dose. The chromatid aberrations and the chromosomal exchanges increase as the square of the dose. There is a period of maximum sensitivity: when the chromosomes double, they are five times more sensitive than during the interphase. In human somatic cells the proportion of chromosome aberrations produced by X-rays is not significantly different from that in certain plant cells.

Puck developed a method for long term tissue culture without induction of aneuploidy. Some inhibiting factors regarding the use of the medium were corrected. They proved that in human isolated cell clones in vitro the mean dose to produce one chromosome break per cell on the average in human euploid cells is less than 50 r. Bender (1957), also irradiated cell cultures with two different dosages of 25 and 50 r. He obtained 0.3 break per 100 cells per r. But there is no evidence that the effects of radiation on tissue in vivo are the same in vitro. Using dosages of 25 to 100 r. they obtained in 1,300 cells examined,

some irradiated and some as controls, results similar to radiation effects on Tradescantia microspores. After 18 hours they noticed the appearance of chromatid breaks, between 25 and 30 hours there was a mixture of both chromatid and chromosome aberrations and after 50 hours, they saw isochromatid breaks only.

Stewart in 1961 reported the case of a Klinefelter who had in addition to this XXY sex chromosomes a dicentric component, following a radiological bone survey. But as Conen pointed out (1961), this may well be the expression of a true genotype having no relation whatsoever to the X-rays received during the 4 days preceeding the chromosomal examination. Conen himself (1963), reports the case of a child who had received 29 different X-ray exposures, and showed a high non-modal count of dicentric and chromatid deletions in the days following the radiological diagnosis.

A total of 121 cells were analyzed, 28 of them showing a chromosomal aberration. Two cells had a dicentric chromosome. One fragment was found in 15 cells and achromatic lesions were seen in 11 cells. One cell had two fragments. An estimated dose of only 0.825 rads was received by the patient, and the author thinks that the radiation is responsible for the chromosomal aberrations though the child had multiple congenital anomalies. This explanation seems to be fairly good since the remaining cells in this case more than three-quarters of the total cell count are normal. Furthermore chromatid and chromosome breaks have not yet been reported as being a possible cause of congenital defects.

Boyd (1961) studied the effects of beta rays of radioiodine and found that the modal cell chromosome number was changed from 90% before to 60% after treatment, and that dicentric chromosomes appeared in the

circulating blood. A dose of 100 mC of radioiodine has been estimated to be equal to a dose of 250 rad to the spine. Even 10 mC would be sufficient to induce an abnormal karyotype.

Newer aspects of radiation effects

Somers and Hsu (1962) studied the effects of HA (hydroxylamine) in mammalian cells. It was known that some damage at specific regions of chromosomes may be induced by a known chemical agent, from a previous work of the same authors (Hsu, Somers, 1961). Freese and his collaborators (1961, a, b) proved that hydroxylamine had a mutagenic effect on cystosine in the phage T 4. Somers and Hsu following the same ideas worked on cells of the Chinese hamster in vitro and they demonstrated that the chromosome damage induced by the chemical substance is localized. They assume that this is related to the high content of guanine-cystosine in such localities. They have no evidence for the direct action of HA on chromosomes of mammalian cells, but they show that there is a specificity of action.

Bender and Gooch (1962), studied the chromosomes of eight men, who, by accident, had been exposed to radiation two years earlier and the same studies were done on five normal individuals. In the control subjects there was no variation from the expected low count cells due to cell breakage. The workers discuss the results obtained in the patients who received over 230 rad. They found altered chromosomes in cells with abnormal counts in a frequency of 2 to 20 per 100 cells.

Buckton and his group (1962) made a more extensive study of 58 patients with Ankylosing Spondylitis treated by radiotherapy. The study covers a period of twenty years. The authors reach the conclusion that

X-ray therapy produces extensive chromosome damage, and the resultant abnormal chromosomes can be classified in different categories (see Table 2), related to the morphology or the stability of the abnormalities. Some abnormal chromosomes may persist many years after the irradiation time. The unstable aberrations decrease gradually three weeks after the exposure.

TABLE 2

TYPES OF CELLS SEEN IN IRRADIATED TISSUES

A	1)	Normal diploid cells
	2)	Aneuploid cells
B	1)	Chromatid gap
	2)	Chromatid break
	3)	Isochromatid gap
C	1)	Isochromatid breaks
	2)	Abnormal chromosomes: dicentric, ring chromosomes
	3)	Abnormal distribution of apparently normal chromosomes

The abnormalities of type C1 are unstable. C2 and C3 are considered as stable, and may persist many years after treatment.

This classification may be used in any study of chromosomal defects.

ii. Antimetabolic agents

Blood culture studies were done by Conen and Lansky (1961) before and after treatment with nitrogen mustard, revealed that this substance has radiomimetic effects. Breaks in chromatids and dicentric chromosomes were seen four days after the treatment. The nitrogen mustard is widely distributed in the body and could cause damage to the germ cells. An average of 4.5 abnormal cells were seen.

iii. Infectious diseases

A preliminary report by Nichols and his collaborators (1962), suggests that measles virus may induce chromosome breakages which have a peak of incidence on the fifth day following the onset of the rash and that contrary to radiation effects, the aberrations tend to disappear, once the clinical picture has returned to normal, this being around the eighth day. The breaks were noted in 33-72% of the cells studied during the maximum period of activity, and very few rearrangements were present. The study is a preliminary approach to the problem of relationship between cancer and virus affinity for the nucleic acid components of the body, and also between the high incidence of acute cases of leukaemia following a measles epidemic. Hampar and Ellison (1961) previously reported the effects of the herpes simplex virus on tissues in vitro: there was an increase incidence of chromosome breakage. On the other hand Trentin et al (1962) demonstrated that a human respiratory virus injected into newborn hamsters can induce tumors. With very little doubt, at this point one can assume that radiation, chemical substances and viruses can induce chromosomal aberrations both in vivo and in vitro.

F. CHROMOSOMAL ABERRATIONS AS A CAUSE OF DISEASE IN MAN

During the months that followed the discovery of new techniques for chromosomal analysis a few aberrations were found, most of them corresponding to well documented syndromes, in which the physical signs vary very little from time to time. But the number of chromosomal defects responsible for congenital malformations is in fact very small, if we consider the astonishing amount of hereditary and congenital defects, apparently now showing a clear pattern of inheritance.

One of the first things to come out of these studies on human chromosomes was a clarification of the significance of the sex chromatin by Barr et al (1949), and the discovery that Turner Syndrome (Ford, 1959) represents a monosomy rather than a gametic male as previously supposed by Grumbach et al (1955). A large series of studies relating sex chromatin, sex chromosomes and phenotypes have contributed greatly to medical knowledge of the various anatomical sexual aberrations, (Jacobs et al, 1961). Barr had shown in mammals that the somatic non-dividing cells had a chromatin mass at the periphery of the nucleus. This dark stained body was present in females and not in males. The discovery was verified in humans and found to be of great value in the determination of the sexual phenotype, both in embryos and adult organisms presenting abnormal sexual development. It was also found that the number of masses seen in the nuclei correspond to the number of X chromosomes present in the cells of the individual, being always one less than the number of X s.

a. Monosomy and sexual anomalies

So far, only the Turner syndromehas been found (Ford et al, 1959) to be due to the presence of only one sex chromosome, being an X, in the female. The pathological conditions often associated with gonadal dysgenesis, include webbing of the neck, aorta coarctation, mental retardation, primary amenorrhea, motor retardation, undervelopment of the breasts, irregular distribution of the pubic and axillary hair, a straight hair line in the back of the head, and sometimes, especially in the newborn, the presence of oedema in the feet, legs and less often in the upper limbs. The skeletal structure of the patient resembles the male constitution. Usually they are sterile. The karyotype is made of 45 chromosomes and one of the 6 to 12 X group is missing. The sex chromatin is negative. Therefore we believe that one of the X chromosomes is missing.

The Turner syndrome has been, to date, the only case of monosomy ever described. The conditions involving the loss of the X chromosome in the males are probably lethal. In the autosomes, the absence of one member is always related to a translocation on to another chromosome. Jacobs and Strong (1959) described a case of Klinefelter syndrome, in which they found the presence of an extra chromosome of the medium-size group and since the phenotype of the patient showed sexual anomalies, the extra chromosome was then described as an X chromosome.

A trisomy involving an X chromosome was described by Jacobs and coworkers (1959). The triple X female or super-female, is a varient of the gonadal dysgenesis group, and is characterized by mental retardation and/or psychotic disorders, sterility due to maldevelopment of the gonads, aberrations of the secondary sexual characters, abnormal stature, quite

often associated with malformations of the cardio-vascular system, as well as of the genito-urinary or gastro-intestinal tracts. The chromatin studies done in the last two cases showed the presence of one nuclear mass in the XXY patient and two masses in the triple X female.

A survey of nuclear sex among mentally defective patients, revealed that two male patients had a double nuclear mass, as reported by Ferguson-Smith (1960). The two boys were both 22 years of age and were described as being severely retarded with an I.Q. below 50. They both had underdevelopment of the genitalia, abnormal hair distribution, and skeletal anomalies, including bilateral radio-ulnar synostosis in one case, who also had a webbed neck. They both had small testes and prostate. The other patient had gynecomastia and well formed nipples with large areolae. The cytological examinations revealed that both of them had an XXXY sex chromosome constitution.

Barr (1962) and others reported two cases involving the presence of three chromatin masses in male patients. Their chromosomal count was 49 and their sex chromosomes were of the type XXXXY. The authors suggest the presence of a triad constituting a definite syndrome for this particular anomaly. First there are skeletal anomalies including the radio-ulnar synostosis, also found in one the XXXY described by Ferguson-Smith (1960), hypogenitalism and a greater risk of severe mental deficiency. Up to date, five other cases of anomalies have been described in the literature by Fraccaro et al (1960), Miller et al (1961), Fraccaro et al (1962), and Anders et al (1960). Among the other malformations noted in the seven patients, there were: cleft palate in two, hypertelorism in three, an osseous abnormality of the forearm in six of them, and strabismus in at least four of them.

Among the other sex chromosome anomalies that have been reported, we should mention the XXYY syndrome described by Carr, Barr and Plunkett (1961) and the XYY man found by Hauschka et al (1962). The XXYY type is more likely due to a double non-disjunction, and the XYY type probably originated from the fertilization of a normal ovum by a sperm containing 2 Y chromosomes. These two syndromes were found to be compatible with a fairly normal male development. Finally, all types of mosaicism may exist in intersex organisms. The combination of two or three different cell lines in the patient usually results in unbalanced sexual development, in which, if the Y chromosome is present in the greater proportion of the cells, it will influence the organism towards the male constitution.

b. Autosomal trisomies

Following the discovery of the first chromosmal aberration involving mongolism, as we discussed earlier in this paper, a few more trisomies were found. Edwards and co-workers (1960) described a syndrome characterized by micrognathia, skull and heart malformations, low set ears and flexion of the fingers, as having one extra chromosome in the E group (17/18). Patau (1960) presented another case of aneuploidy due to an extra autosome, this time a large acrocentric of the D group (13/15). The patient, a young infant, had a cerebral defect, a cleft palate and hare lip, simian creases, apparent anophtalmia, trigger thumbs, polydactyly, haemangiomata and a heart defect. Since 1960, many more cases of trisomies D and E were published, and all of them confirmed that the presence of an extra autosome of either group was associated with a definite syndrome, within which there were only a few variants from time to time. Among others, Smith (1961), Patau (1961) and Wijck (1961) publish-

ed articles on the E syndrome, and Smith (1960), Smith (1961), Thermann (1961) and Miller (1963) on the D syndrome.

Dunn (1961) found a case of benign congenital hypotonia in which there was an extra chromosome of the G group. Since the patient was not a mongol, the authors discussed the different possibilities for the presence of an extra autosome or gonosome. The supernumerary chromosome could by a Y chromosome, a number 21 or 22 if we exclude the theory that mongolism is caused by a 21, or finally an extra chromosome with no corresponding pair in the karyotype. Fitgerald (1962) found apprently the same extra chromosome in a case of dystrophia myotonica. The author studied seven cases and in five of them found an extra small acrocentric in a very low percentage of cells. The number of abnormal cells seemed to be in relation with the severity of the disease.

Fraccaro (1960) examined the normal father of a mongol child, and found that his cells had an extra member in the F group, for a total count of 47. However, the son had 46 chromosomes with an extra member in the F group, and one chromosome missing in the G group. Though the child is believed to have a G/G translocation, the presence of the extra material in the father has not been explained yet. The importance of the extra chromosome of the F group has been brought up again for discussion by Book and collaborators (1961). They found in a familial congenital heart disease (atrium septal defect), the presence of 47 chromosomes in the mother and 46 chromosomes in the child including a monosomy for one pair of the G group.

Gagnon (1961) reported a case of double trisomy 17/18 and 21 in a young baby boy who died shortly after birth. The infant had a skull malformation, low set and malformed ears, hypertelorism, micrognathia,

a chest malformation, a heart malformation, short fingers, simian creases and an imperforate anus. We previously mentioned a case of double trisomy involving a sex chromosome and an autosome that was found by Ford et al (1959). Lehman et al (1960) and Lanman et al (1960), also described similar cases. However, it seems that the double autosomal trisomy is lethal and the chances of finding them are very small, since all of them will result in spontaneous abortions or stillborns due to the presence of so severe malformations.

c. Autosomal translocations

The first report of an autosomal translocation in humans, not related to abnormal growth of tissues induced by radiation or in neoplastic cells, came from Turpin and his group (1959). They studied a patient affected with Polydyspondylitis, and found that two of his autosomes, one member of the G group and one of the D group, were fused together and gave a total count of 45. The loss of some chromatin material in the translocation process may be responsible for the phenotype described. If this is true we have reasons to believe that any member of the D group (13-14-15) and any one of the G group (21-22) may be involved in the translocation and consequently give rise to a number of different combinations being pathogenic if the fusion involves a break in one or both of the chromosomes and also some loss of material. The patient had multiple malformations of the spine and a low intelligence.

Penrose (1960) and Carter (1960) and their collaborators found the first known cases of mongolism transmission through a translocation in two different families. The translocation involved one member of the G group and one of the D.group. G/G translocations were described in the same

year by Polani (1960) and Fraccaro (1960).

Zellweger and co-workers (1963), found an unusual translocation between two members of the G group, in which the supernumerary chromosomes got attached to the long arms of the G member, thus giving a long acrocentric chromosome instead of a metacentric member. Gray (1962), previously described a pericentric inversion giving a similar chromosome in a normal woman. In the first case the child was a typical mongol, and the authors state that the loss of material involved in the attachment was minimal.

Zellweger (1961) found in a girl having epicanthal folds and severe muscular hypotonia, a D/E translocation, in which the E member missing in the karyotype, got attached to the top of the acrocentric chromosome. There were 45 chromosomes and no extra material. Again in this case the loss of material seems to be responsible for the phenotype of the patient.

Delhanty and Shapiro (1962) studied the chromosomes of a two-year-old girl who was mentally retarded,had microphtalmia, micrognathia, a high arched palate, a heart malformation and a kidney malformation. The cytological examination revealed the presence of an unusually long acrocentric chromosome, and only 5 members of the D group, for a total count of 46 chromosomes. The authors believed that the long acrocentric was a member of the D group with a duplication for the long arms, or a translocated piece from an unknown donor.

d. Partial trisomy

Patau et al (1961) studied a mother and her child, who both presented an OFD syndrome, that is characterized by malformation of the orofacial region, as well as defects of the upper extremities. The physical

examinations also revealed some hypertelorism in the child, as well as mental retardation. The atypical finger anomalies are not a constant feature of the syndrome, but seems to be fairly frequent. The cytological studies revealed the presence in both affected patients of an insertion in the centromeric region of a chromosome number I, that made this chromosome look much longer than the corresponding member of its pair. The centromeric region of the abnormal autosome was very thin. The authors state that the condition is seen in females only, being lethal for males, and that the inserted piece corresponding to a specific chromosome segment, may not be seen on cytological examination of all cases.

We previously mentioned the presence of an extra chromosome in a case of Sturge-Weber syndrome. Patau (1960) studied three patients affected with the same disease, and found one of them to have a partial translocation onto a member of the D group. The author believes that in the cases where the anomaly is not seen, the small translocated piece is undetectable by usual means of chromosomal examination. In the published case the chromosome bearing the extra material was a number 13/15, and the abnormal chromosome had the appearance of a mamber of the C group (6 to 12), with a partial deletion of the short arms.

Both Bottura (1961) and German (1961) described an unusually long chromosome in the Waldestrom's macroglobulinemia, which was found in the A group (1 to 3). Patau (1961) suggested in relation with those two cases, that the anomaly is real and could come from rearrangements following a break in the centromeric region, and a misdivision of the chromatids. Another possibility was that the biochemical disturbances found in the disease was responsible for the unusual state of the chromosome.

Biesele (1962) found in two mentally retarded schizoid twin girls,

47 chromosomes, the supernumerary member being a chromosome of the size of the G group but with different characteristics like the Y chromosome, having the two long arms closer together and the short arms being more prominent.

Gagnon (1963) reported the case of a child showing anomalies similar to the E syndrome, in addition to which the index finger was missing in both hands. The child's karyotype contained 46 chromosomes and one member of the B group (4 to 5) was consistently longer than any other of the group. The authors suggested a partial B/E translocation as being responsible for the abnormal phenotype. Both parents had normal chromosomes.

Ellis et al (1962) reported the case of a 13-year-old girl, who was mentally retarded but exhibited no mongoloid features. The cytological analysis of her chromosomes revealed the presence of an extra small acrocentric chromosome having satellites both on the long and short arms, with the long arms being kept together. The authors discussed in the article the origin of the aberrant chromosome, pointing out that a number 22 was probably involved in the rearrangment.

e. Blood chimera and Mosaicism

A blood chimera may be defined as "an individual who has in his blood stream, cells which are the linear descendants of cells transplanted from another individual." In vivo blood chimerae have been described by Woodruff et al (1962), who demonstrated in human dizygotic twins of either sex, the presence in the male of 8.7% of female cells and in the female of 1.7% of male cells. This means that in certain conditions there is no true incompatibility for transferred cells to survive in vivo in the host organism.

Chromosomal mosaicism has been described before as a process by which, for an unknown reason a non-disjunction occurs some time after the first cell cleavage. This gives rise to two types of cells, or more, depending on the time of occurrence of the error of division. The same mosaicism may exist in all tissues, or may be specific to one according to the time of differentiation. That type of mosaicism differs from the one produced by transplantation or tranfusion of heterogenous cells.

Leon and his group (1961) showed the existence of discrepancies between the bone marrow and the peripheral blood constitution in two cases of Klinefelter syndrome, who had a sexual karyotype of XXY in the bone marrow, and two types of cells in the blood XY and XXY. The second case was a patient with gonadal dysgenesis where again the bone marrow had a unique chromosomal type XO, when the blood had two types XX and XO. He advanced the explanation that in the blood cells the hormone level would be higher than in the marrow and could facilitate the growth of normal cells. Fraccaro et al (1960), in a study of plasma level of growth hormone, found in four patients described as cases of gonadal dysgenesis, mosaicism involving the bone marrow and the skin tissues. The cells were mostly XO in the skin and XX/XO in the bone marrow. Harnden (1960) pointed out that the differences between bone marrow and blood cultures may come from differences between the marrow and the lymph nodes and other tissues of the reticulo-endothelial system. The chromosomes obtained from the blood culture would then reflect a more complete picture of the patient than the bone marrow. Furthermore, to have a complete analysis of a case who has a normal blood constitution, skin cultures should be done, especially in sexual abnormalities.

Nowakowski et al (1960), reported 13 cases of Klinefelter syndrome in which the chromosome number varied between 45 and 49. This is another

situation in which the patients may be mosaics and in which cell lines XO/XY/XXY/XXXY type may exist due to a double non-disjunction at the first egg cleavages. We must be very careful in reporting chromosomal counts. Some cells may be broken especially when one uses the squashing technique, which, let us say here, has been proven not to be useful where the air drying technique is applied. We then obtain results which do not involve abnormal counts due to cell breakages.

Finally another type of mosaicism has been described in 1958 by Kodani. From chromosomal analysis of spermatogonials and first meiotic metaphases obtained in testes biopsies of 15 Japanese and 8 white people, the author concluded at the time of the study that the chromosomal counts were 46/47/48 in Japanese population and mainly 46 and 48 in the white population. The explanation was that one or more supernumerary chromosomes could be the normal constituents of different races. Today we have good reason to believe that the Human Race has the same complement. However, within the same individual some tissues may have a different count: for example, the liver cells seem to have a high percentage of tetraploid cells, and of course the sexual gametes are haploid or n = 23.

f. Chromosomal abnormalities of unknown origin

Jennings and Turner (1961) studied the chromosomes of a 13-year-old girl affected with a cleft palate, bilateral talipes equinovarus, genital infantilism, mental defect, deafness, webbing of the neck, epicanthic folds, narrow shoulders and general hypotonia. The cytological examination revealed the presence of an unusually long member of the group E (16). The relative lengths of 14 cells showed that the abnormal member was of the same size as any other member of the C group and consistently longer

than a number 13. We will discuss the possible mechanism of this abnormality later on in this paper.

Carr (1963) made the same observation regarding an abnormally long number 16 in a family in which the normal father and two sons had the unusual chromosomes as part of their karyotype, whereas one of the daughters showed physical abnormalities usually found in cases of gonadal dysgenesis. She had a short webbed neck, hypogenitalism, mental retardation. Her general development was retarded.

Bray and Mukherjee (1963) recently published an article on a presumably reciprocal translocation involving two chromosomes of the E group. The chromosomes involved seemed to be two members of the 16 and 17 pairs. The child showed some motor retardation, dysphagia, became hypertonic gradually and developed clonic movements of the extremities. It is interesting to note that there were no gross clinical abnormalities. The karyotype published by the authors exhibited a long number 16 and also an abnormally long number 17.

A rather interesting finding of the last months was made by Carr (1963) in a stillborn presenting with multiple anomalies and having a translocated segment onto one member of the G group. The same abnormality was present in the normal father. The Y chromosomes seemed intact. The mother had normal chromosomes. She gave birth to only one normal child. She had one miscarriage and delivered one stillborn.

g. Ring chromosomes

Morgan (1933) in Drosophilia, and McClintock (1958) in maize showed that the formation of a ring chromosome may be persistent in the same organism and also be transmitted from one cell generation to another. A

study of two different patients made by Wang et al and Carr et al (1962) was reported in the same paper. One of the patients had a phenotype resembling the E syndrome with a member of the 13/15 group missing, a ring chromosome and a number 3 carrying a translocation. The second case had an atresia of both ear canals, hypertelorism, epicanthic folds and bilateral syndactyly of the second and third toes.

In Australia Jennings and his group (1962) found a ring chromosome probably originating from a member of the 6 to 12 group in a young boy who was severely mentally retarded, had a heart defect, hypospandias and malformed ears. The total cell count including the ring chromosome was 46. Linsten (1962) found an X ring chromosome in a case of gonadal dysgenesis.

The existence of the ring chromosomes had previously been reported in humans by Levan (1956) and Ising (1957) in carcinogenesis studies, and by Baikie (1959) in acute leukaemia. Finally Tough (1960) reporting on radiation effects described the occurrence of the ring chromosome as being induced by an ionizing agent.

h. Triploidy

Book and Santesson (1960) found triploid cells in a mentally retarded boy presenting syndactyly. The patient also had normal cells. Penrose and Delhanty (1961) and Ellis and Rowley (1961) found triploid cultures in aborted foetuses. Finally Ellis et al (1963) reported the case of a 6-year-old girl who was mentally retarded and had a left-sided hemiatrophy and zygodactyly. Her cells contained both normal diploid and triploid chromosome members.

Triploidy seems to be compatible with life as long as the patient also has normal diploid cells.

G. ABNORMAL PHENOTYPES WITH APPARENTLY NORMAL KARYOTYPES

The discovery of the previously described chromosomal aberrations, has been made possible throughout the study of hundreds of patients. The incidence of chromosomal defects is low, and still, many suspected cytolotical aberrations turned out to have a normal chromosome pattern. Some of the normal findings are listed in Table 3, against the description of the various anatomical defects.

The list is far from being complete, by lack of publications of the normal complements in malformed individuals. The purpose of the table is to establish some criteria for further analysis of the incidence of chromosomal malformations.

The first section of the table (A) deals with the recognized syndroms, while the second part (B) is an enumeration of congenital malformations involving the major anatomical systems.

TABLE 3 A

LIST OF ABNORMAL CONDITIONS WITH APPARENTLY NORMAL KARYOTYPES

This table includes only the conditions which were fairly well described by the authors. It omits cases of mongolism with apparantly normal chromosomes, undescribed multiple malformations and cases of sexual anomalies cited merely as Hypogonadism. Most of the cases were mentioned in "THE HUMAN CHROMOSOME NEWSLETTERS".

ACRO FACIAL SYNDROME

AMAUROTIC IDIOCY FAMILIAL

ARTHROGRYPOSIS

BILE DUCTS ATRESIA CONGENITAL

CATARACT CONGENITAL

CHONDRODYSTROPHIA

CRYPTORCHIDISM

DWARFISM PRIMORDIAL

EHLERS DANLOS SYNDROME

EUNUCHODISM

EXOSTOSES MULTIPLE

FANCONI SYNDROME

HALLERMANN-STREIFF SYNDROME

HEMOCHROMATOSIS FAMILIAL

HIRSCHPRUNG'S DISEASE WITH MENTAL RETARDATION

HYPOGONADISM FAMILIAL

HYPOGONADISM ISOLATED

HUNTINGTON'S CHOREA

PIGMENTI INCONTINENTIA

LAURENCE-MOON-BIEDL SYNDROME

LEUKAEMIA MONOCYTIC

MARFAN'S SYNDROME

MENTAL RETARDATION FAMILIAL

MICROCAULIA

MOEBIUS SYNDROME

MYELOMAS OF KAHLER MULTIPLE

NEPHROSIS INFANTILE

PANHYPOPITUITARISM

PHARYNGEAL PARALYSIS CONGENITAL

PHENYLKETONURIA

PIERRE ROBIN SYNDROME

POLYCYTHEMIA

PRIMARY AMENORRHEA

PROGERIA

STEATORRHEA

STEINERT'S SYNDROME

STURGE-WEBER SYNDROME

TAY SACH'S DISEASE

TABLE 3 B

(The following conditions are described as various congenital malformations not known as a definite syndrome.)

Anal atresia	Low set ears, preauricular tags, reduplication of left thumb and accessory ossification of right thumb.
Arachnodactyly	Atrial septal defect, undescended testes, paralysis of the soft palate.
Brain defect	Paralysis of right facial nerve, patent ductus arteriosus agenesis of left kidney, ureter, renal artery and vein, patent foramen ovale, absence of cartilaginous rings of external ear. Bilateral posterior staphylomata.
Cerebral hypoplasia	Low set ears and high arched palate, broad thumbs with triangular terminal phalanges and congenital glaucoma.
Craniostenosis	And syndactyly.
Cretinism	And multiple haemangiomata.
Epicanthic folds	Slanty eyes, mental retardation, hypertelorism, accessory nipples, bilateral proximal radio-ulnar synostosis, failure to thrive.

Epidermolysis bullosa hereditaria lethalis Herlitz.

Familial	Ulnar polydactyly and mental retardation, sometimes associated with a heart defect or convulsions.
Haemangioma	With thrombocytopenia.
Heart defect	Webbed neck and short stature.

Heart disease	With simian crease on one hand.
Hypertelorism	Mental retardation, short broad hands with one sibling and one paternal step-sibling showing similar defect.
Hypogonadism	Obesity, dwarfism and mental retardation.
Hypotonia	Hypertelorism, epicanthic folds, squint small head with premature closing of fontanels, mental deficiency and unusual hands.
Imperforate anus	Polydactyly, aganglionic mega colon, failure to thrive.
Lutheran factor	Absence of.
Malformed ears	Imperforate anus, double thumb, hypo-spadias, bifid uvula, and pilonidal sinus.
Mental retardation	Brachycephaly, non-pitting oedema of hands and feet.
Mental retardation	Cleft palate, trilobed tongue, hypertelorism.
Mental retardation	Incomplete cleft palate, hare lip, and co-eliac disease.
Mental retardation	Hypsarrhytmia and ectodermal dysplasia.
Mental retardation	Microcephaly and hypogenitalism.
Mental retardation	Microphtalmia, concussion of the eye.
Mental retardation	Short flat nose, mild hydrocephalus, hypo-plastic kidneys, short small intestine.
Mental retardation	Thyrotoxicosis, prognathism.
Mental retardation	Malformed ears and face.
Microcephaly	And cleft palate.
Microcephaly	Hare lip, cleft palate, congenital luxation of the left hip joint.
Microcephaly	Hare lip with incomplete nasal septum, low set ears and large, short neck, convulsions.
Micrognathia	Short neck, premature fusion of metopic suture. Polydactyly of hands and feet.
Muscular atrophy	High palate, short neck, widely spaced nipples, kyphoscoliosis.

Neurodermitis	Micrognathia, bird-like face, low set ears, infertility.
Normal parents	Of two children that died early in life with micrognathia.
Polydactyly	Hypertelorism, diming of the skin, high arched palate, short neck and low set ears.
Progeroid appearance	
Sacrum, agenesis of	Anomalies of the ribs.
Underdeveloped child	Webbed neck, mental retardation, cleft palate, undescended testes, "bat ears", congenital ichthyosis and negative sex chromatin in a male.
Webbed neck	Low set ears, slight cubitus valgus, hypoplastic nipples, high arched palate, epicanthic folds and anterior displacement of anus, short incurved fifth finger. Bilateral complete coloboma.

H. RATIONALE FOR THE PRESENT STUDY

In the records of the Department of Medical Genetics of the Montreal Children's Hospital, there are a number of families in which more than one child of the same sibship was found to be affected with several malformations involving the major anatomic systems. In those families, the incidence of miscarriages seems to be high in some instances, and as we will see later, this may correspond to a lethal condition induced by a deficient chromosomal complement. Taking into consideration this possibility, it was decided to include in the study not only the families in which there was more than one affected child, but also cases showing several malformations in at least one offspring born to a mother who also had a mis-

carriage.

The purpose of this work was to perform cytological studies on the patients selected by the above criteria and the parents of the propositi in order to determine how effective cytogenetic analysis can be as a method of determining the cause of multiple malformations. The supplementary examinations included:

a. a thorough family history

b. a physical examination

c. blood grouping studies

d. dermatoglyphic analysis

e. an electrocardiogram.

Some of the family histories were taken several years ago, before anything was known of human chromosomal malformations. Many patients were already dead, and therefore sometimes we had to rely on the examination of the parents only, to determine if the condition was transmitted through a chromosome aberration. This will not exclude a cytological anomaly that has arisen in the patient himself, but since we are looking for a cause of familial malformation, one would not need to include aberrations not present in the parents.

With the recent advances in human cytogenetics, it became evident that all efforts possible should be made to determine the location of the different alleles on the chromosomes, or at least search for evidence that specific genes were present in triplicate by looking for dosage effects. A search for autosomal linkage was made by Shaw and Gershowithz (1962). A total of 793 mongols were studied in comparison with 1508 controls. The following systems were used: ABO, MNs, RH, Kell, Duffy, Kidd and ABH secretor. The findings were not significant, and the distribution of the blood groups did not deviate very much from the expected incidence, but

did vary in the direction expected if the ABO locus were on the chromosome trisomy in mongolism. It will appear evident later in this work, that the genotyping of both parents and patients should be done when there is a translocation, or familial malformation accompanied by extra chromosomal material.

The physical examination of the phenotypically normal parents may help to eliminate the formes frustres of the syndrome not associated with a recognizable cytogenetic defect, and which could be due to the presence of a gene in triplicate. Any malformation present in the parents as well as in the sibs should be noted, or in other ways, any congenital defect is of great importance if noted in any member of the family. Walker (1958) has stressed the importance of the palmar print study in mongolism, and it has proven to be of great value in the diagnosis of the disease.

Penrose (1954), studying the incidence of high triradii in the parents of mongoloid children, obtained some results that led him later to suspect a relation between parents being carriers for a translocation and their mongol offsprings.

More recently, some workers (Uchida et al, 1961) found some abnormal dermatoglyphic patterns corresponding to new autosomal trisomy syndromes. In the case of the E syndrome, there are a high number of arches found on the tip of the fingers. The number may vary, but usually it is between six and ten. In the D syndrome or trisomy 13/15, simian creases are found, as well as high triradii and an S shape pattern in the hallucal area of the foot.

It is often a problem to decide which method of culture to use for cytogenetic studies. The chromosomal studies on our patients were done by means of peripheral blood andbone marrow cultures. Facilities for

long term tissue culture were not available at the time of the study. Discrepancies have been noted between blood and tissue cultures by some workers (Lindsten, 1963; de Grouchy et al, 1963), but mostly in the case of sex anomalies. If we take into consideration the fact that we should try to make human cytogenetics available to the ordinary clinical laboratories, as a method for evaluating the clinical condition of malformed subjects, all efforts should be focused on blood chromosome studies as the most useful test in diagnosis. Since we are looking here for transmitted chromosomal aberrations, there is no reason why all tissues should not be of the same type. Of course, even then there is still a possibility that a secondary non-disjunction happened after fertilization, thus producing mosaicism.

II MATERIALS AND METHODS

A. MATERIALS

Phytohaemagglutinin M and P. Difco.

Medium Glaxo. (TC 199). Difco.

Colcemid Ciba (0.1%) diluted to 0.02% with distilled water.

Acetic Orcein Gurr's. Synthetic.

Plastic tubes for culture: Falcon, clear tubes. Capacity 10-15 ccs.

Heparin. Liquaemin Sodium. B.D.H. 1/1000 units/cc.

B. METHODS

a. Peripheral blood culture technique

The method was described by Moorhead (1960), and some modifications came from Doctor D.G. Harnden in a personal communication. A few points of the technique have been modified as a result of experiments carried out in this laboratory. An outline of the technique is presented below. The technique must be carried out under perfectly sterile conditions.

i. Blood is drawn from the patient in a heparinized syringe, and 2-10 ccs are injected into a plastic culture tube. 0.2 cc of Phytohaemagglutinin (type M), is added to the universal container along with 4 drops of Phytohaemagglutinin (type P), before the blood is injected into the tube.

ii. The blood is left in icy water for 45 minutes.

iii. The blood is centrifuged at room temperature for 7-9 minutes, at a speed of 700-900 r.p.m.

iv. By this time the red cells have spun down and the majority of the nucleated cells are in suspension in the plasma.

v. The plasma is removed by inserting a 10 cc syringe and needle, gauge 18, through the cap. The culture tubes are already prepared and filled with medium 199. Two ccs of plasma are added to the tubes containing 8 ccs of medium. The quantities may be adjusted, especially in leukaemic bloods where a white count is indispensable before a final concentration is made. The cell count is of the order of 1000 to 2000 WBC per mm 3 of plasma, to give an adequate concentration. Smaller aliquots may be prepared by adding 1/4-1 cc of plasma to 2-4 ccs of medium.

vi. The different aliquots are left at 37°C, in an incubator for a time varying between 76-92 hours. Recently we obtained ranges of optimum activity in the order of 90 + or - 9 hours.

vii. The tubes are shaken once or twice a day, to prevent clumping of the cells at the bottom of the tube.

viii. The pH should be adjusted in the first 36 hours, when necessary. But as a rule we avoid adjusting the pH of the solutions. In normal conditions, the change of the pH should not affect the normal growth of the lymphotic cells. If the medium is acid, the culture turns yellow and we then add one drop of sodium bicarbonate at a concentration of 10%. If the medium is basic, the culture turns pink and one adds HCl 0.1 N.

Note: The plasma mixed with medium is highly favourable to growth of bacteria and fungi. Infection may come from the contact of needles with foreign objects, or from frequently used bottles of Heparin and Phytohaemagglutinin.

b. Preparation of the cultures

i. One hour before harvesting, 0.1 cc of Colcemid per cc of culture medium, at a concentration of 0.02% is added to the aliquots. For non-leukaemic bloods, the optimum time for maximum mitotic activity is 3-4 days after the culture has been set up.

ii. The culture is poured into a 15 cc centrifuge tube, spun down for 9 minutes, at 800 r.p.m., at room temperature.

iii. The supernatant fluid is removed, except for one drop in which the cells are resuspended.

iv. Approximately 2 ccs of a Sodium Citrate solution, 0.95%, previously heated to 37°C is added to the clot. The cells are resuspended and left in the water bath for 30 minutes.

v. After centrifugation at 900 r.p.m. for 7-9 minutes, the sodium citrate is removed, and the cells are resuspended in one drop of solution. Then the fixative is added very slowly (3 parts absolute alcohol to 1 part of glacial acetic acid). While adding the fixative the tube is shaken to prevent clumping of the cells. The destruction of the red cells will give a brown solution. Enough fixative is added, 1/2-1 1/2 ccs, to obtain a clear solution. The quantity of the fixative may be relative to the amount of red cells left in the culture.

vi. Then the fixed material is left in the refrigerator for at least one hour. It may be left for more than 24 hours if necessary, but it is not advisable to leave it for more than 36 hours before making the slides.

vii. The solution is centrifuged again for 9 minutes at 900 r.p.m. The fixative is removed, and replaced with fresh (1/2 - 3/4 cc of fixative is added to the resuspended cells).

c. Preparation of the slides

The slides may be kept in a jar filled with absolute alcohol, and one drop of HCl 5 N, or kept dry.

i. A clean slide is immersed in icy water for 30 seconds, or left in a freezer for a few minutes. Keeping the slide at an angle of 45 degrees, 2 or 3 drops of the cell suspension is allowed to cover the slide, and it is dried by flaming the surplus of alcohol. The air drying method has been used and found to be very effective.

ii. The slide is then left in a staining bottle for 20 minutes. The stain is made of the following ingredients:

Orcein stain: 1 gm synthetic Orcein
60 ccs glacial acetic acid
40 ccs distilled water.

iii. After at least 20 minutes of staining, the excess stained is removed by tilting the slide over a filter paper. The slide is passed through a solution of acetic acid at a concentration of 45%. Then the dehydration phase should include three quick changes through 2-ethoxy-ethoxy-ethanol. The slide is washed in a mixture of xylol and acetic acid 45% (equal parts), for 7 minutes, and finally passed through a xylol solution before being mounted with Depex. The slides may be examined under oil immersion within 20 minutes.

Notes: A small quantity of red cells seems to help culturing. For leukaemic blood, the culturing time varies between 36-48 hours. AB + serum may be used to dilute leukaemic blood, when the concentration of white blood cells is excessive (over 30,000). The phytohaemagglutinin M has a mitotic activity. The type P on the contrary, is rather a strong agglutinant of the red cells, and should be used in very small and diluted quantities.

(The powder is diluted 10 times, and 4 drops of the solution are used for 10 ccs of blood.)

A new method for chromosomal analysis, from small volumes of blood has just been published by Edwards (1962). This new technique is particularly useful in children.

d. Bone marrow culture technique

To analyse the chromosomes from a bone marrow specimen, as suggested by Tjio and Whang (1962), a colcemid solution is prepared that contains 0.000125 mgm of colcemid per cc of TC medium 199. An amount of 3/4-1 cc of bone marrow is injected into a vial or a conical tube containing 20 ccs of the prepared solution. This preparation is washed with the same type of solution to get rid of the red blood clots that may have formed at the time of aspriation. The bone marrow specimen is kept at room temperature for two hours. Then two or more tubes containing the solution are centrifuged, depending on the amount of bone marrow aspirated in order to dilute the final concentration of white cells. In the case of leukaemic patients a white cell count is necessary to adjust the concentration of the white cells to 10 - 15,000 W.B.C. per mm 3 per tube. The remainder of the technique is carried out in the same way as the blood culture technique.

All the photographic reproductions of mitotic chromosomes are made at a magnification of 1500 times.

III RESULTS

A. OBSERVATIONS MADE ON CELLS IN CULTURE

What happens to the cells in culture? Once they are in the incubator, the cells start a division cycle that has definite phases. For the first 24 hours there is very little or no change in the Ph. Then on the second day, the cellular activity begins and the Ph drops from normal 7.2 to about 7.1. These figures are approximate, and do not constitute the result of an accurate study.

After 24 to 36 hours the cells, if examined under the microscope, using the regular method for counting white cells, show very little change in the morphology compared to their original appearance. They are small, and at this stage it is difficult to say what type of cells are going to divide. On the third day, or after 60 to 72 hours, an increase in the size of some of the mononucleated cells occurs. At least 50% of the cells show this feature. Some cells can be seen that are in division: the nuclear membrane has disappeared and the cytoplasm is filled with organelles.

The culture may be terminated then, or one can wait to the fourth day for maximum activity. If the tubes are injected with colcemid in the first 48 hours, no division is observed in non-leukaemic bloods. In our laboratory, the maximum number of divisions is obtained after 90 hours of incubation. Many factors are involved in the change of time of the optimum activity: the amount of stimulating factor used (Marshall, 1961), the amount of red cells incorporated in the culture tube, liberating some oxygen and adjusting the Ph in the maximum periods of activity, and finally the condition of the patient himself. A newborn has polycythemia and an excess of immature white blood cells (Nelson, 1959). Finally certain path-

ological conditions provoke an increase of the polynucleated cells and a decrease of lymphocytes.

It is interesting to compare those findings with the work of MacKinney (1961), who demonstrated by using H^3 thymidine that the cell division follows a definite cycle described in terms of hours: between 0 and 24 hours of culture the granulocytes degenerate. The DNA synthesis increases slowly for the first 48 hours, and the curve reaches a peak at 72 hours of incubation. After 3 days, 40% of the cells have some DNA radioactivity, and 40% of them are large mononucleated cells.

In conclusion there is no rigid rule determining the exact time of division nor the amount that will undergo cell division. Each patient has his own physiological characteristics that still apply once his blood cells are cultured in vitro. For example, it is noted that the patients who undergo treatments with salicylates or other antirheumatoid drugs seem to have a slower rate of division. But those observations have not been verified in vivo, that is no patient has been given drugs on purpose before the chromosomal examination was done.

A patient who has a bacterial infection shows an increase of polynucleated cells, and a reduction in the lymphocytes or mononucleated cells. In this case one should not expect to have a high number of cells in division unless one of the methods described above is used to remove the polynucleated leucocytes. A viral infection may on the other hand decrease the number of white cells considerably as for instance the measles virus does. In those cases it is desirable to wait until the infection has cleared before any attempt to culture the chromosomes is made.

B. CASE REPORTS

It would be practically impossible at this stage to classify the different types of congenital malformations in groups that would identify clearly in each of them. But one can divide the patients by criteria related to their referral. Such a classification raises many problems connected with the essential origin of the physical malformations, but one should understand that the purpose of the following table is to separate as much as possible the various families so that they can be more easily identified. In addition to the familial multiple malformations are included typical cases which, by the nature of their phenotype, may help one to understand the role of the chromosomal aberrations itself.

TABLE 4

CRITERIA OF ASCERTAINMENT

a. Blood dyscrasia

b. Cardio-vascular defects

c. Cervico-cephalic abnormalities

d. Central nervous system malformations

e. Gastro-intestinal malformations

f. Genito-urinary malformations

g. Mongoloid features

h. Skeleton abnormalities

a. Blood dyscrasia — Anemia of unknown origin.

i Family (I)

Frank A. (M.C.H. 246638) was referred to The Montreal Children's Hospital for diagnosis and treatment of chronic anemia. The boy was born on October 6, 1952. At the time of admission the child presented with weakness lethargy and anorexia. He had been under treatment for the past three years, receiving blood transfusion, packed cells and steroids. He was referred to the Genetics Department for diagnosis.

Family History

The proband was the first child of a family of three. The second pregnancy was a stillbirth and the third child died at birth following a severe haemorrhage suffered by the mother who also died shortly after. The medical history related that she had a blood disease of unknown etiology. The father is now 35 and healthy. There is no history of anemia, consanguinity or congenital malformations in the other members of the family.

Physical examination

On admission, the patient was pale with a Cushingoid appearance and hirsutism probably secondary to steroid intake. Liver and spleen were enlarged significantly. A Grade ii/iv systolic murmur could be heard on the left sternal border, radiating towards the carotid. There was no sign of cardiac insufficiency.

Laboratory examinations

The blood examination showed a low reticulocyte count. The platelet count was normal. There was some variation in size and shape of the red cells. There was a marked leukopenia and neutropenia. The bone marrow

puncture revealed a fair number of megakaryocytes. The erythroid precursors were predominantly pre-normoblasts and early normoblasts. The red cell survival curve showed a normal 50% red cell survival after 20 days. The radiological examinations revealed minor variations of development of the vertebral arches at the level of L5 and S1. The kidneys were grossly normal though each of them presented foetal lobulation.

Cytological examination

Two different examinations were done on the patient, by means of bone marrow and peripheral blood cultures. In the two instances the chromosomes were found to be normal in count and appearance.

Final diagnosis

A final diagnosis of anemia of unknown origin was made when the child left the hospital. There was no reason to suspect that a malignant process was involved.

b. Cardio-vascular Partial E syndrome

i Family (2)

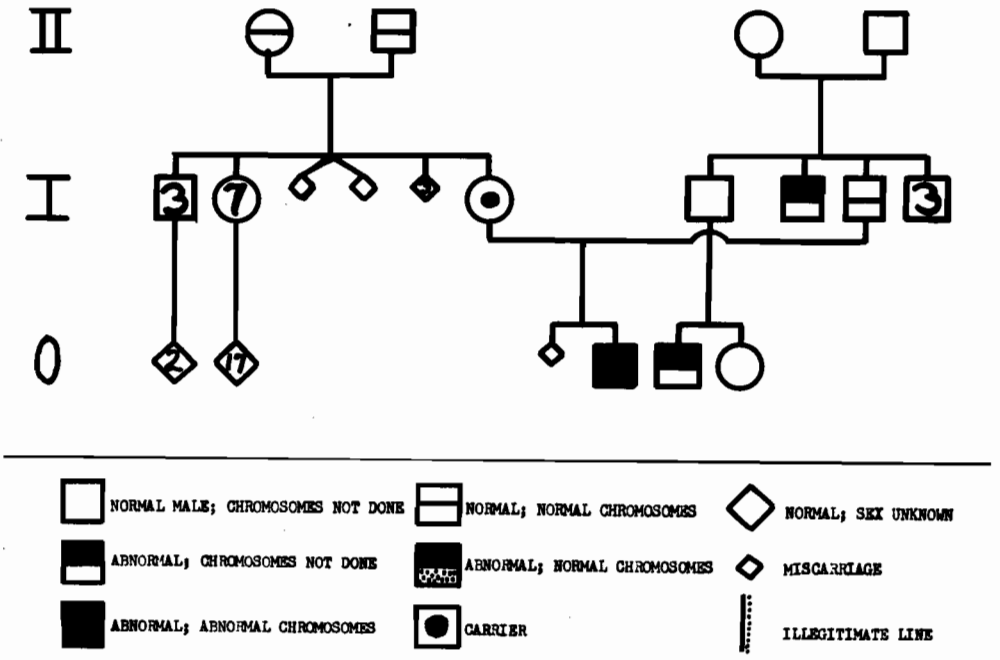
Baby boy C. (M.C.H. 220860) was born on October 17, 1961 at the Catherine Booth Hospital after a 40-week gestation. The birth weight was only 1,650 gm and the child was transferred to The Montreal Children's Hospital for investigation of a cardiac defect and other congenital anomalies.

Family History (Fig. 6)

Both parents were French Canadians. The mother was 20 and the father 23 years old when the infant was born. They were both in good health and not related. The first pregnancy of the mother in 1960 resulted in a spontaneous abortion after three months of gestation. A maternal aunt of the mother was said to be a mongoloid imbecile. One brother of the father (I-8) died at the age of one week of a heart malformation, and one of his nephews (O-5) died of Von Gierke's disease at the age of two months. We note in the pedigree that two miscarriages followed the birth of the patient's mother. Three miscarriages happened when the grandmother was over 40 years of age. They were all spontaneous and after 5 or 7 weeks of gestation.

A careful investigation was made of the parents' pre and perinatal history to uncover any severe disease which could have affected either one of them. But apart from the usual contagious diseases of childhood, there was no history of severe episodes of illness in the grandparents or the parents themselves. No physical anomaly was found during the physical examination of the parents.

FIGURE 6 PEDIGREE OF FAMILY (2)



Physical examination (Fig. 7)

Several unusual features were noted shortly after the birth of this infant. He had a peculiar birdlike facies with a prominent nose, hypertelorism, micrognathia, high-arched palate, low set ears and webbing of the neck. The first toes were both relatively short and small, with a bullous terminal phalanx, and were somewhat dorsiflexed. The pulse rate was 160 per minute, and the respiratory rate 60 per minute. A Grade II harsh, systolic murmur was heard along the left sternal border. The patient was maintained in an isolette with an oxygen flow rate of 6.1 lit. per minute. A reduction in this flow, or the removal of the infant from the isolette resulted in severe cyanosis within 15-30 seconds.

The haemoglobin value, white blood cell count and differential cell count were within normal limits throughout the period of hospitalization. The urinary findings were normal until November 27, 1961 when a mass became palpable in the region of the left kidney, and at the same time red and white blood cells were seen in a voided urine specimen. Culture of this urine revealed a moderate growth of Aerobacter aerogenes, sensitive in vitro to chloramphenicol. Treatment with this drug was followed by a return to normal in the microscopic appearance of the urine. The electrocardiogram suggested combined ventricular hypertrophy, and a low P-R segment was noted. Radiographs of the chest revealed findings consistent with severe congenital heart disease, a probably left-to-right shunt, and pulmonary congestion. Radiographs of the skull demonstrated that the mandible was smaller than normal, the forehead appeared flattened and the right parietal area appeared larger than the left. Ophtalmological examination was normal. The infant was extremely ill throughout its hospital stay, and although there was a slight gain in weight (2,250 gm at the time of death), the clinical condition deteriorated steadily and the infant died on December 4, 1961.

Post mortem

At the autopsy the heart revealed a large basilar ventricular septal defect, without overriding of the aorta, a biscuspid slightly stenotic aortic valve, and an abnormally patent ductus arteriosus. A complete double ureter from the right kidney was noted, with stenosis of both ducts distal to the ureteropelvic junction and a ureterocele of the bladder associated with the upper ureter on the right side. The left kidney showed a single ureter, with stenosis distal to the ureteropelvic junction. Both kidneys showed minimal hydronephrosis. No chromatin masses were seen from

biopsy specimens.

Cytological findings (Figs. 8, 9)

The blood was drawn from the patient for chromosomal analysis 24 days after birth. Fifty-nine cells were analyzed under the microscope, and ten karyotypes were prepared from photographs. Forty-seven cells had 46 chromosomes. One member of the 13-15 group was missing and there was an unusually long acrocentric chromosome on which satellites could sometimes be seen on the short arm. The latter chromosome was interpreted as being a member of the 13-15 group with an addition to the long arm. The relative lengths of all other chromosomes appeared normal. Six cells had 47 chromosomes, the extra chromosome being apparently acentric, and similar in size to the 21-22 group (see karyotype of patient). The chromosomes of the parents were examined three months later . The father had a normal karyotype, 44 XY. The mother had the unusually long chromosome, like that of the patient, in all 50 cells examined. In 43 of her cells there were only 45 chromosomes, with one member of the 17-18 group missing (karyotype of the mother). In almost all of these, a fragment (not counted here as a chromosome), much smaller than a group 21-22 chromosome, was also present.

The unusually long chromosome was interpreted to be the result of a reciprocal translocation between a chromosome of the 13-15 group, or D group and one of the 17-18 group or E group. The chromosome fragment in the mother is presumably the short arm of an E chromosome left behind after the transfer of most or all of its long arm to the long arm of a chromosome of the 13-15 D group. The presence of the fragment in most, but not all, of the mother's cells suggests that the translocation occurred early in her developmental history.

The origin of the fragment seen in the child remains uncertain. But we should mention here that the patient received some radiation prior to the chromosomal analysis. As we have seen before, the X-rays used for diagnosis are sufficient to induce a chromosome breakage in more than one cell. Before the blood was drawn, the child had a skull, chest and abdominal radiophotography. The infant also received chloramphenicol. There is still no evidence that antibiotics can cause chromosome breaks in humans but this possibility cannot be excluded.

The cytological examination of the maternal grandparents was also done, and both were found to have normal chromosomes.

Number of chromosomes	44	45	46	47	48	poly-ploid	Total
Proband	1	3	48	6	1	0	59
Mother	4	43	1	0	0	2	50
Father	6	2	24	2	0	0	34
M.G.M.	4	0	30	0	0	0	34
M.G.F.	3	3	24	0	0	0	30

Since the cytological examination of the maternal grandparents did not reveal any modal abnormality or mosaicism, we assume that the translocation is present in the mother only. Furthermore the presence of the acentric fragment in the mother is in favour of a recent accident, if we accept that an acentric fragment will tend to be lost in two successive generations.

DeRobertis (1960) states that a terminal segment does not survive if it lacks a centromere. The terminal segment arises usually by the pro-

duction of a reciprocal translocation involving two non-homologous chromosomes. The broken ends will fuse; in this case one chromosome of the D group and the long arm of one of the E group became attached, and most likely the short arm of this 17-18 chromosome remained free in the cytoplasm. Simple deletions of chromosomes, not involving any translocation, are rare in Drosophila, but quite common in Maize. In man the incidence is low.

As to the etiology of the aberration, it is rather difficult to assume that either the use of antibiotics or X-rays were responsible for its occurrence. There is no history that the mother has been overexposed to X-rays, and she is too old to have been treated by antibiotics in her early childhood. Since her modal cells are all of the abnormal type, this suggests strongly that the event occurred before or during the first stages of her development during intra-uterine life. But her mother has never been treated in a hospital, and she is known to have had good health up to now. Was the translocation purely accidental and due to the pairing of two non-homologous chromosomes, one 13-15 and one 17-18, in the germinal cells of the grandmother? Unless we can prove the contrary, this last explanation stands as the most likely one.

Relative lengths of chromosome in mother and child

The relative length of the chromosomes, including the unusual number 13-15, was calculated for the patient and his mother. The results are given in Table 5. As defined by the Denver group (1960), "The relative length is: the length of **each** chromosome relative to the total length of a normal, X containing, haploid set - i.e., the sum of the lengths of the 22 autosomes and of the X chromosome, expressed per thousand." We can see that in each cell examined, the total length of a number 13

plus a number 17 gives a relative length longer by about 10 units, on the average, than the relative length of the unusual number 13 of the D group. This is true in each individual cell, and the numbers cannot be interchanged since the absolute value of chromosomes vary greatly in the same individual between two cells, in any stage of metaphase. The morphology of the chromosomes depends on the time of division and also on the reaction of the chromosomes to the colcemid and the fixative.

FIGURE 7 - PICTURE OF PROBAND FAMILY 2

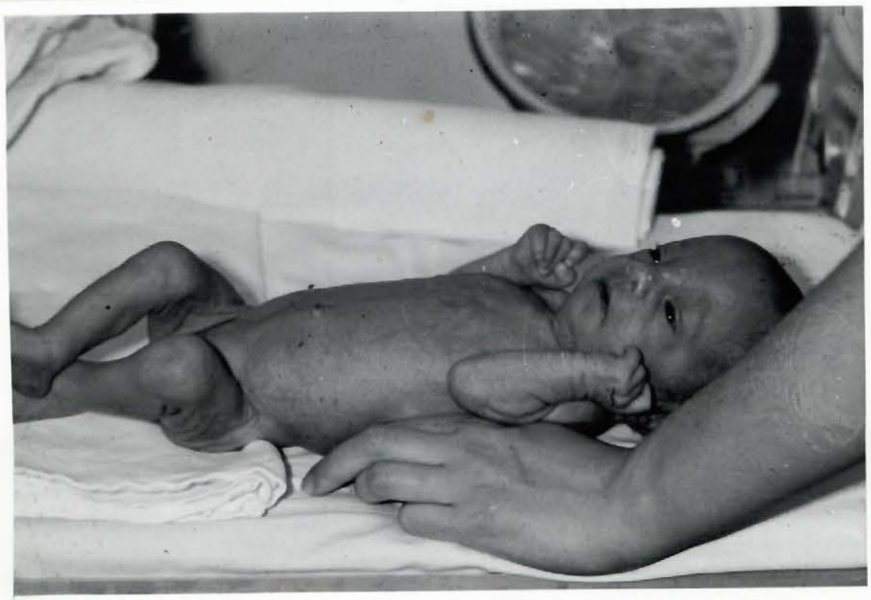


TABLE 5

RELATIVE LENGTH OF CHROMOSOMES IN FAMILY 2

Chromosome Number (Denver)	Cell Number														Range
	Child							Mother							
	1	2	3	4	5	6	7	1	2	3	4	5	6	7	
1	97	80	88	78	97	80	83	86	89	96	89	91	89	88	79-97
2	87	82	76	87	83	79	76	90	85	89	89	91	79	88	76-91
3	75	62	65	72	68	70	66	73	61	71	85	63	75	73	61-85
4	64	59	66	61	61	56	63	64	75	68	67	63	70	63	57-75
5	59	55	59	55	58	56	56	60	70	61	58	59	75	59	55-75
x	55	57	59	52	54	51	56	60	52	61	58	52	61	54	52-61
6	58	52	54	52	61	51	53	52	52	58	54	59	51	54	51-62
7	52	50	50	49	48	51	53	47	47	54	54	52	47	49	47-54
8	44	50	47	43	48	51	50	51	47	50	45	49	47	49	44-522
9	44	45	43	46	44	45	43	47	47	46	40	46	42	44	40-47
10	43	47	43	46	44	48	43	39	47	43	40	42	47	44	39-49
11	41	45	39	46	41	45	40	39	42	39	45	42	37	39	37-47
12	38	45	39	40	41	37	39	34	42	36	40	42	37	39	34-46
13	29	40	32	35	31	37	36	39	38	32	40	39	33	34	30-41
14	26	35	33	32	27	34	33	34	38	29	36	28	33	34	26-38
15	29	30	36	32	27	34	33	30	33	29	31	28-	28	29	27-36
16	26	27	29	32	31	31	30	30	24	25	27	28	28	29	24-32
17	26	30	29	26	24	25	26	26	28	25	27	28	28	29	24-30
18	26	25	29	23	24	25	26	26	24	29	22	25	28	24	22-29
19	20	22	22	23	20	25	23	22	24	21	18	25	23	24	18-25
20	20	22	18	23	20	25	20	22	14	18	18	21	19	20	14-25
21	12	15	18	17	17	17	20	17	9	14	9	14	14	20	9-20
22	12	12	14	14	14	14	16	13	9	7	9	11	9	15	7-16
TR 13	47	55	55	58	48	57	53	52	56	54	54	52	56	54	47-58

FIGURE 8 - KARYOTYPE OF PROBAND FAMILY 2

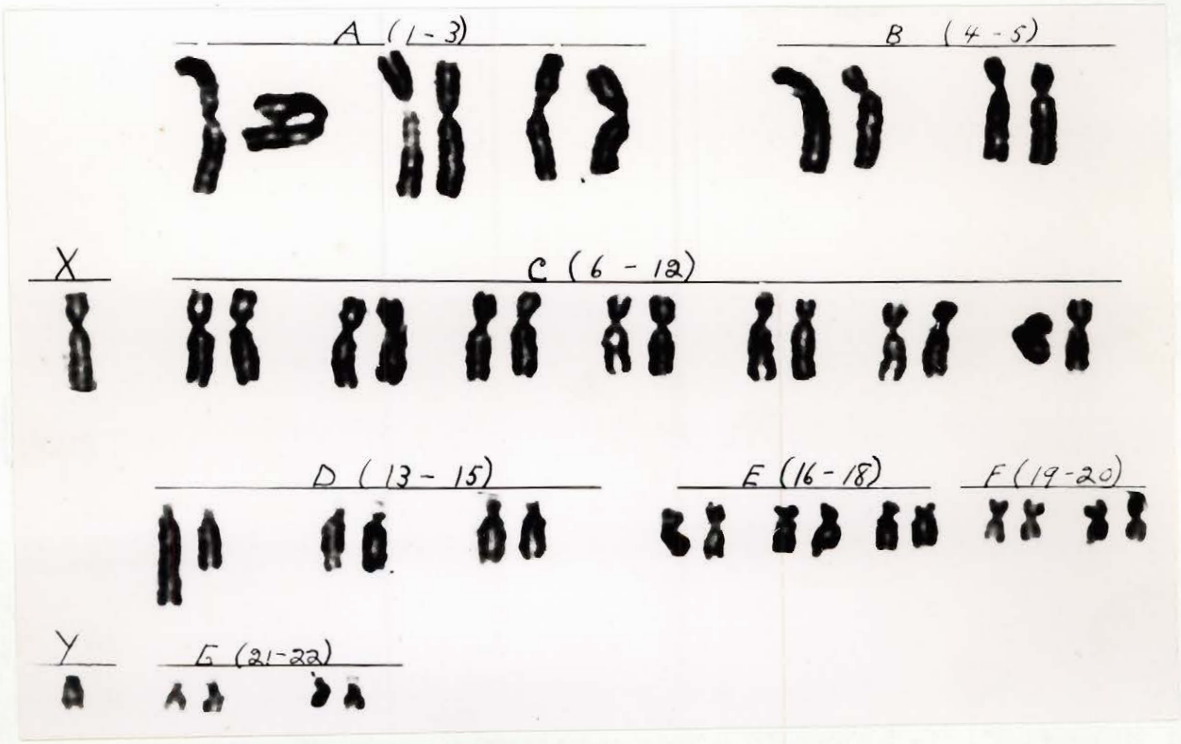
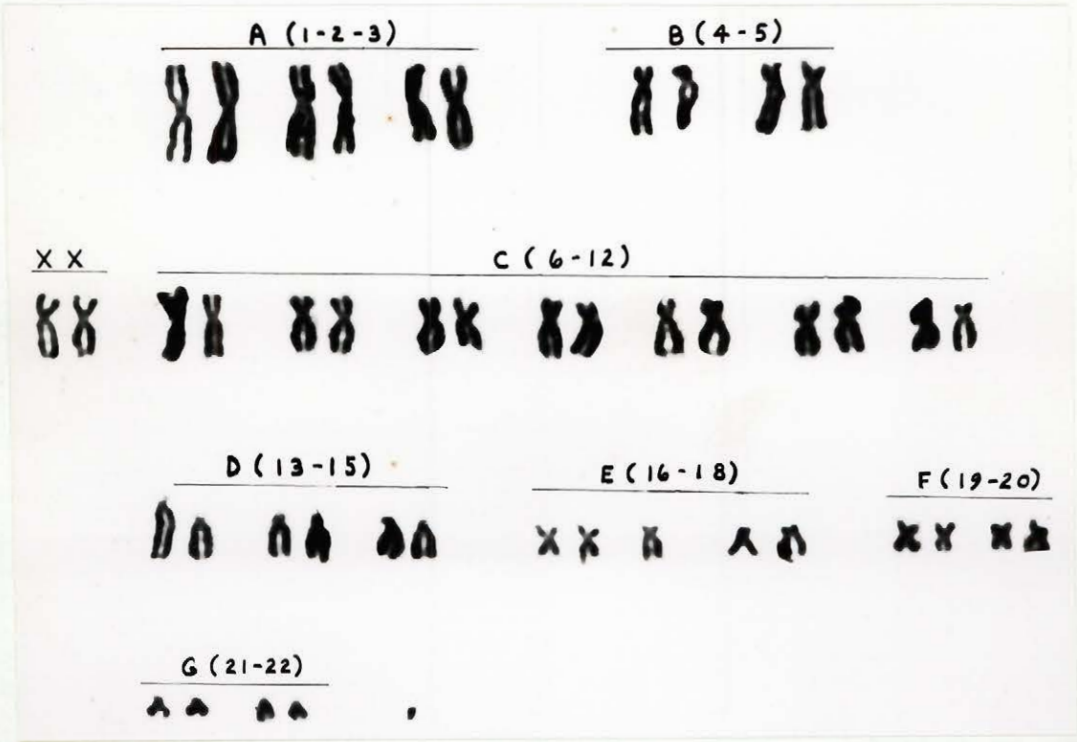


FIGURE 9 - KARYOTYPE OF PROBAND'S MOTHER FAMILY 2



Final diagnosis

This case represents a partial E syndrome. The mother was the carrier of D/E translocation and the patient had in addition to the complete genotype, the long arms of an extra number 17/18.

ii Case (1) E syndrome

Doreen B. (M.C.H. 237960) **was the product of a full-term gestation and was delivered after an uneventful prenatal history. She was admitted to the hospital for investigation of failure to thrive and cyanosis.**

Family History

Both parents were 26 years of age when the infant was born, and in normal health. They had another 16-month old child. There was no consanguinity and no history of congenital abnormalities in the family.

Physical examination (Figs. 10, 11)

The examination done at the age of two months revealed an 8-week old baby in no acute distress. The head circumference was 36.2 cms and the length 52.5 cms. Both measurements were below the third percentile for that age. The ears were low set and the external canals were narrow. The palate was high and arched. The inferior mandible was very small. The heart rate was 160 per minute and the sounds were regular. A Grade II/IV systolic murmur could be heard in the mesocardiac region. The liver was one cm below the costal margin. The kidneys were not palpable. The second finger was flexed over the third bilaterally. The child was hypertonic and both legs were crossed. The big toe was smaller than normal and in dorsi-flexion. There was a marked umbilical hernia. Both feet were rotated internally, and the abduction of both legs was reduced.

The electro-encephalogram revealed a non-specific T wave abnormality. At the radiological examination the heart was enlarged; there was a bilateral dilatation of the ureters and a pelvis smaller than normal. The child died at the age of 109 days of aspiration pneumonia.

Post mortem

The autopsy revealed a prominence of the occipital bone, a small

umbilical hernia, inter-atrial and inter-ventricular communications - that is, a complete form of persistent common atrio-ventricular canal of Wakai and Edwards. The left kidney was slightly hydronephrotic. There was also minimal hydronephrosis on the right. Both ureterovesical junctions were stenotic. There was a side-to-side ileo-coecal junction. The surface of the liver was herniated through the diaphragm. There was also some fatty necrosis of the liver.

FIGURES 10, 11 - PICTURES OF CASE 1

FIGURE 10

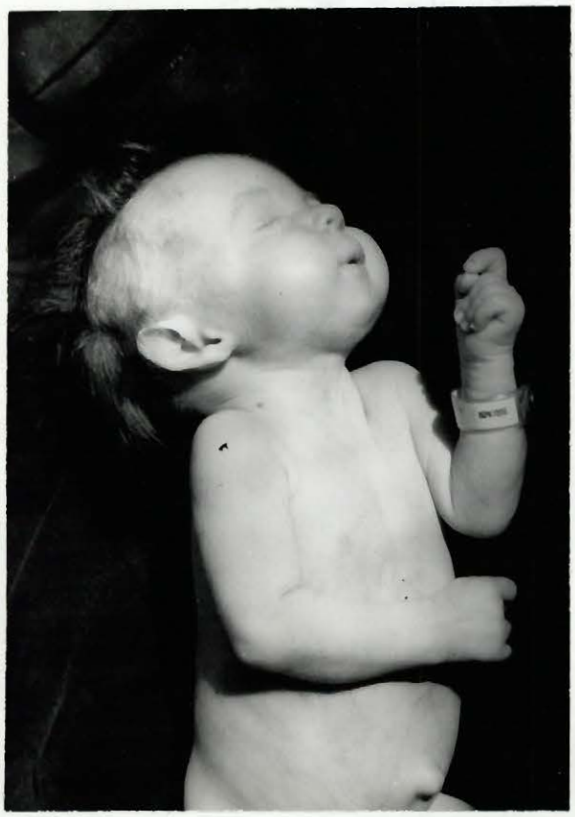
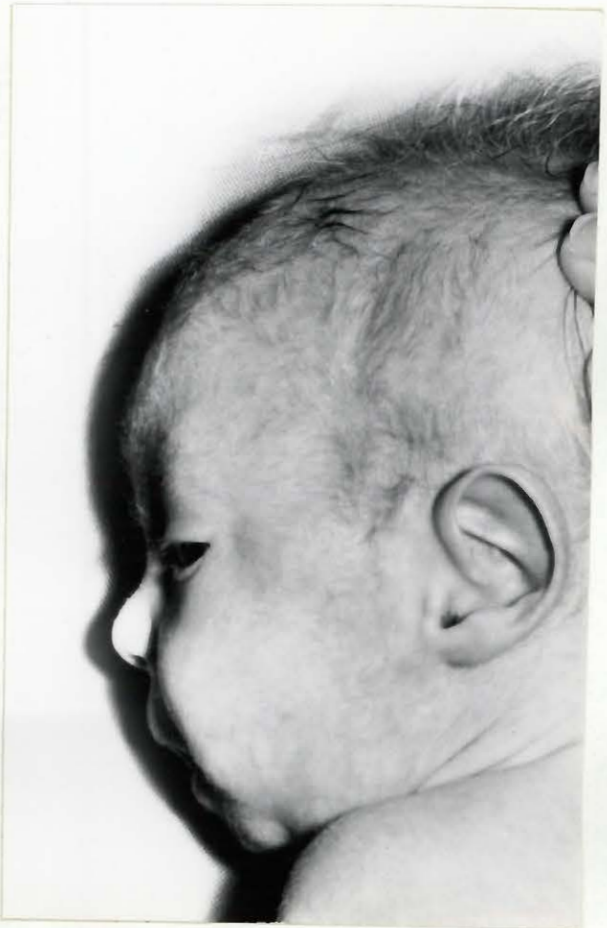


FIGURE 11



FIGURES 12, 13 - PICTURES OF FINGERS AND TOES OF CASE 1

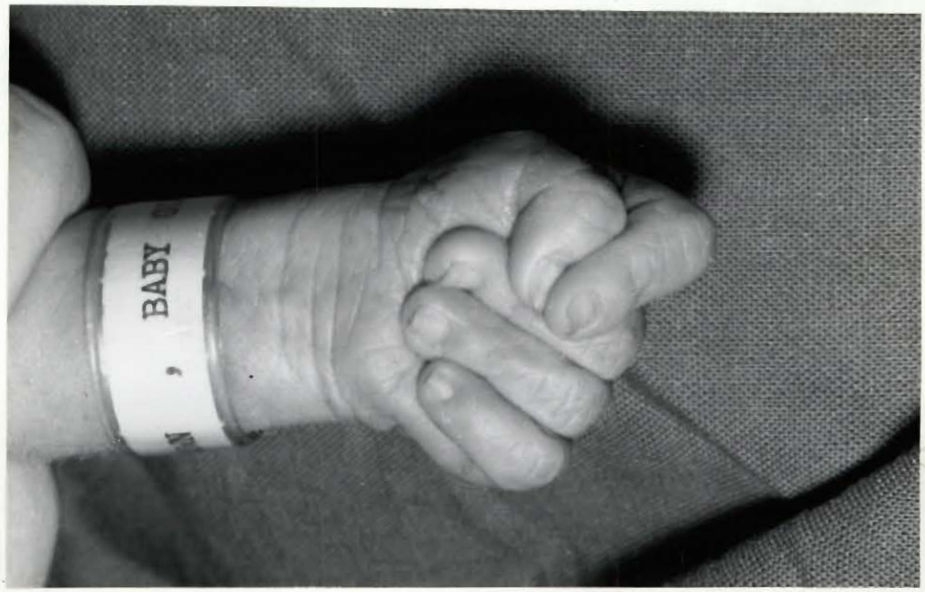


FIGURE 12

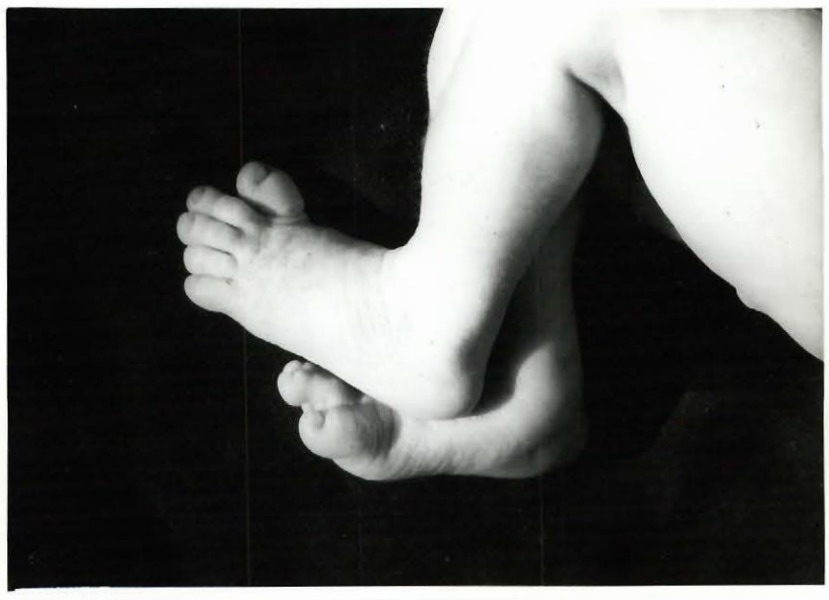


FIGURE 13

Dermatoglyphics

There were arches on all fingers and toes. The triradius was high on the right hand. There were no simian creases. There was an open field in the hallucal area.

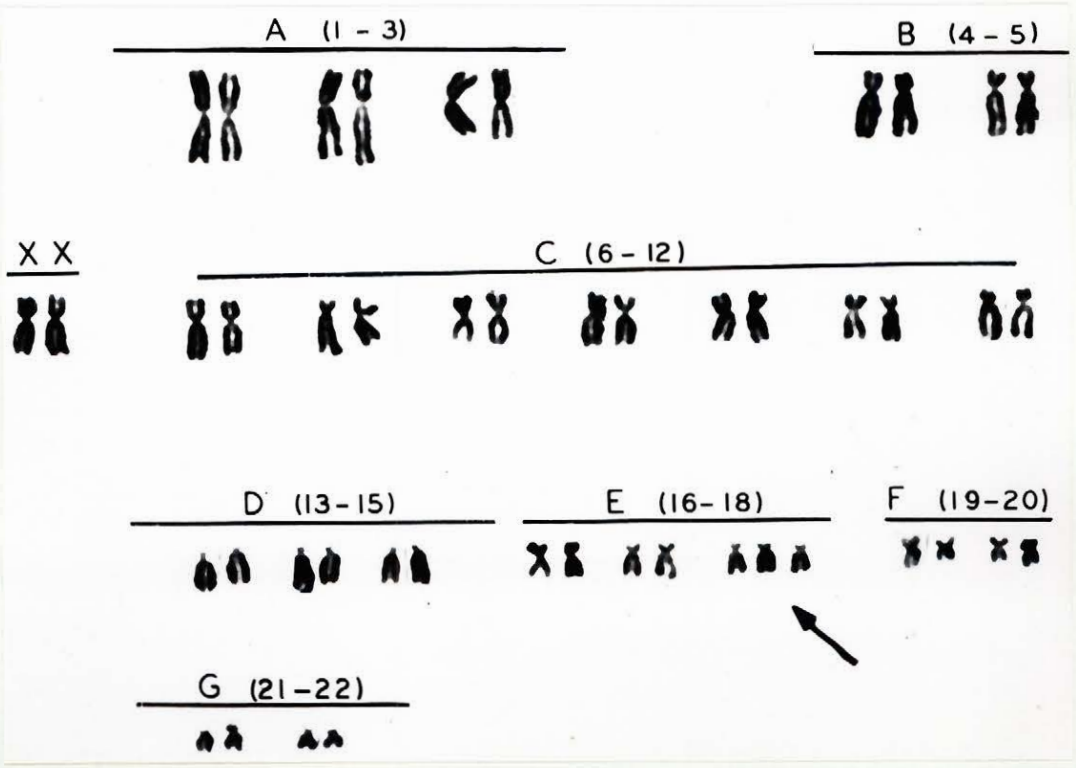
Cytolological examination

The chromosomal studies were done by means of peripheral blood cultures. All the cells examined showed an extra chromosome identified as a member of the group 17-18.

Chromosome number	44	45	46	47	48	Poly-ploid	Total
Patient	0	0	0	52	0	0	52

The sex chromatin was positive.

FIGURE 14 - KARYOTYPE OF CASE 1



Final diagnosis

A final diagnosis of E syndrome was made. Since the parents were very young and the infant did not have a translocation the chances of recurrence of the syndrome in future siblings were assumed to be quite low.

iii Case (2) E syndrome

Patricia M. (M.C.H. 242560) was born on September 21, 1962. At birth nothing unusual had been noticed during the physical examination. She was admitted to the hospital at the age of two and a half months for investigation of cyanotic spells and convulsions.

Family History

The patient had two brothers and one sister in good health. Both parents were in their late thirties when the child was born, and unrelated. The pregnancy had been uneventful. At the time of admission it was noted that one of the mother's sisters was under treatment for seizures of unknown etiology, probably of epileptic nature.

Physical examination (Figs. 15, 16)

The birth weight was 5 lbs. The head circumference was 33.5 cms and the length was 49 cms. The skull was malformed: the occiput was prominent and there was a slight depression of the left parietal bone. Though it was not mentioned in the medical reports done prior to admission, the infant presented a marked failure to thrive. She was hypertonic. Her ears were low set and the cartilage of the pavilion was thinner than normal. The neck was short and a loud systolic murmur could be heard all over the cardiac region. There was an umbilical hernia, the big toes were smaller than normal, the second finger was flexed and rotated over itself in both hands instead of being flexed over the third. The micrognathia was present but not prominent. The child developed septicemia and died 82 days after birth.

Dermatoglyphics

There were arches on all fingers and toes. There were no simian creases

or high triradius. There was no pattern in the hallucal area.

Laboratory data

Radiologically the heart was enlarged and both kidneys and ureters were dilated. The electro-encephalogram showed a diffuse disturbance of cerebral function. The electrocardiogram suggested a probable left ventricular hypertrophy and a possible right ventricular hypertrophy.

FIGURES 15, 16 - PICTURES OF CASE (2)

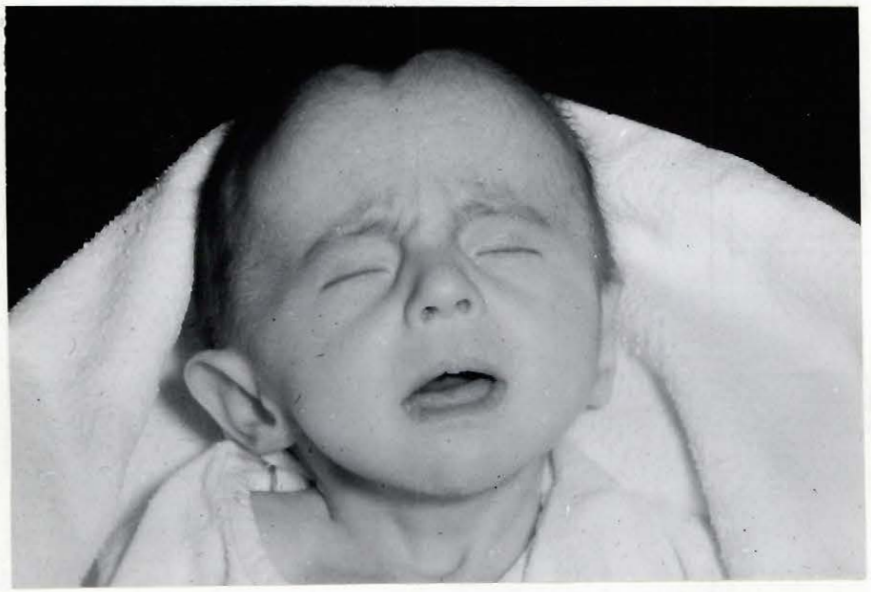


FIGURE 15

FIGURE 16

Post mortem

The autopsy revealed an occipital bone protuberance, a ventral abdominal hernia, an abnormal rotation of the cartilage of the distal phalange of the second fingers and an hyperextension of the big toes. The infant had a pes cavus, a single left umbilical artery and a possible Eisenmenger complex. Both the small and large bowels had a common mesentery. There was a deficiency of the anterior ends of the first and second costo-cartilages on the left and of the second on the right.

There was a marked right hydronephrosis with a stenosis at the uretero-pelvic junction bilaterally. The kidneys were fused and had a horseshoe configuration. There was hypoplasia of the ventricular horns on both sides. The uterus was unicornuate and the left Fallopian tube was blind.

Cytological examination (Fig. 17)

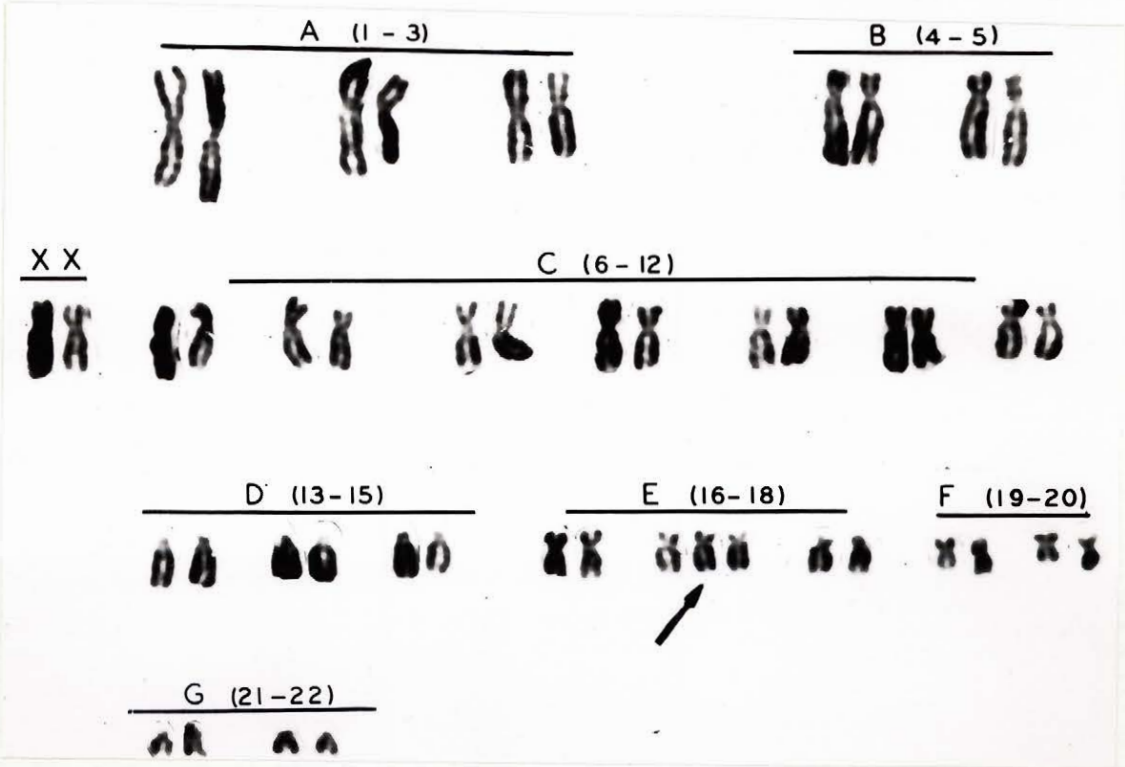
The cells found in the blood culture studies had an extra chromosome identified as a chromosome 17-18.

Chromosome number	44	45	46	47	48	Poly-ploid	Total
Proband	0	1	2	30	0	0	33

The sex chromatin was positive.

The chromosomal studies were not done on the parents because the child did not carry a translocation.

FIGURE 17 - KARYOTYPE OF CASE (2)



Final diagnosis

A final diagnosis of trisomy 17-18 was made. The syndrome is typical of the malformations caused by the presence of an extra member of the E group. However one can note that the flexion of the fingers is atypical in the sense that the second finger is rotated on itself instead of being flexed on the third.

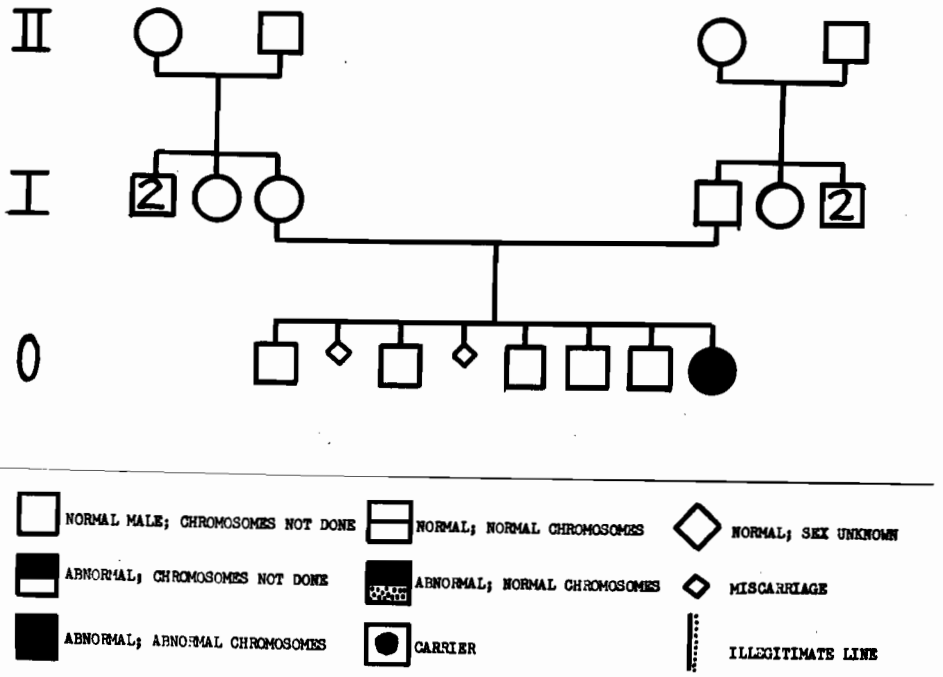
iv Family (3) E syndrome

Baby girl St. G. (M.C.H. 252475) was born on May 26, 1963 at the Catherine Booth Hospital after 40 weeks of gestation. She was immediately transferred to The Montreal Children's Hospital and referred to the Genetics Department because she presented multiple anomalies.

Family History (Fig. 18)

The father was 43 years old and of French origin and the mother 41 years old and of English origin, when the child was born. The mother had 8 pregnancies. Five boys are normal and alive. She also had one stillbirth (0-2) and one miscarriage (0-4). The gestation was normal except for the premature rupture of the membranes five days before the delivery.

FIGURE 18 - PEDIGREE OF FAMILY (3)



Physical examination

The head circumference was 12-1/2 inches. The infant birth weight was 1,850 gms. She was cyanotic and had a very poor tone at the time of delivery. Her ears were low set, and there was a lack of cartilage in the helix. The palate was high and arched. She had marked micrognathia. The second fingers on both hands were rotated on themselves and not flexed on the third. The fifth fingers were incurved. There was hypertonicity of all limbs and rocker bottom feet. The patient also presented a marked failure to thrive.

The intravenous pyelogram showed a right hydronephrosis, and a partial obstruction at the level of the urethra and the bladder neck. The electrocardiogram demonstrated some non-specific T wave changes, with a right ventricular hypertorphy and an extreme right axis deviation. The radiological examination also suggested a diaphragm defect on the left hand side. The skull radiography showed a narrow sagittal suture with no premature synostosis.

The dermatoglyphic studies showed a high triradius on the right hand, a total of five arches on the fingers and no simian creases.

The patient was discharged from the hospital and placed in an institution.

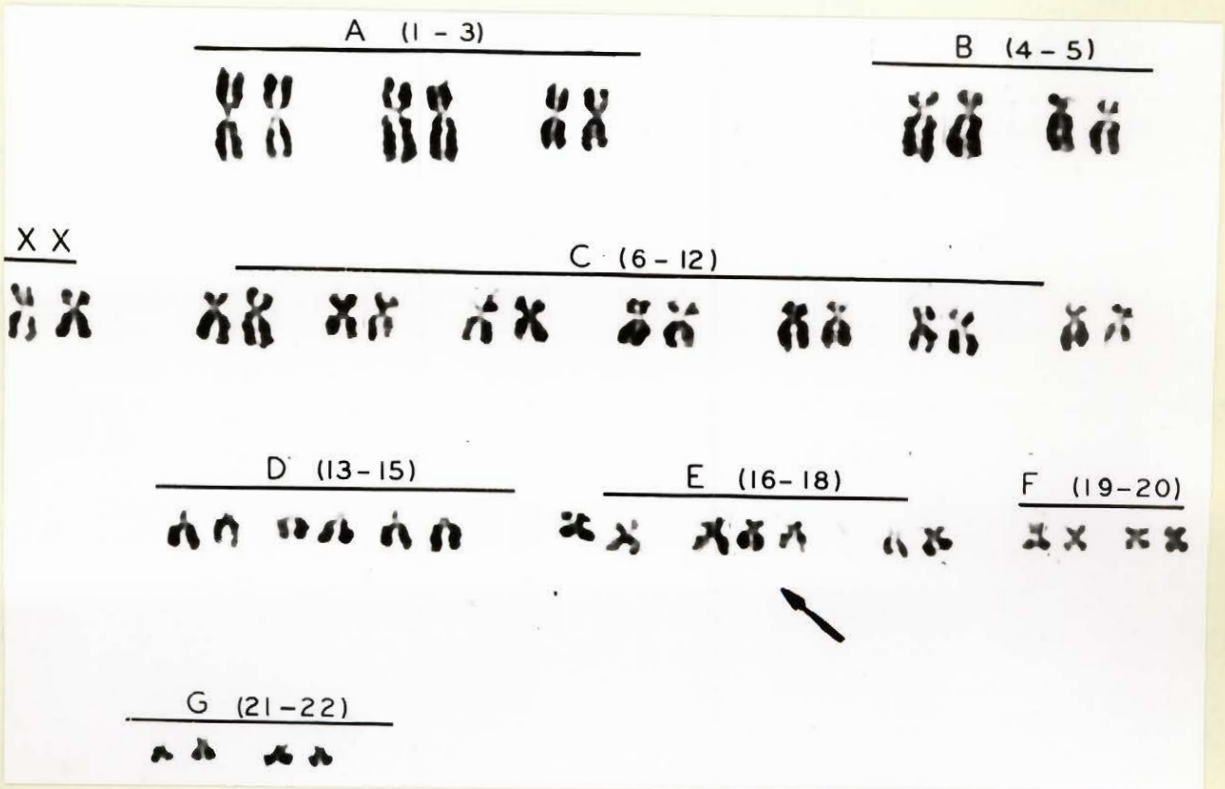
Cytogenetic studies (Fig. 19)

The chromosomal analysis was done from a culture of peripheral blood leucocytes. The total count was 47 and the extra member was identified as a member of the E group or a chromosome 17-18. The child was then trisomic for an autosome.

Chromosome number	44	45	46	47	48	Poly-ploid	Total
Patient	0	0	0	49	2	0	51

The chromosomes of the parents were not studied since they were assumed to be normal.

FIGURE 19 - KARYOTYPE OF PROBAND FAMILY (3)



Final diagnosis

The syndrome described in this patient is typical of an E syndrome. However the index finger defect differs from the reported cases in the literature. The digit is not flexed on the third finger but rather rotated on itself. The number of arches on the fingers is high, being five but seven and more arches are usually seen.

v Family (4) Chondrodystrophia calcificans

Baby girl Pat (M.C.H. 245017) was born on January 18, 1963 and was referred to our hospital shortly after birth for diagnosis and treatment of multiple congenital anomalies, of which the most severe at the time seemed to be the heart defect. The baby was born after 28 weeks of gestation. The birth weight was 1,600 gms. The delivery was spontaneous.

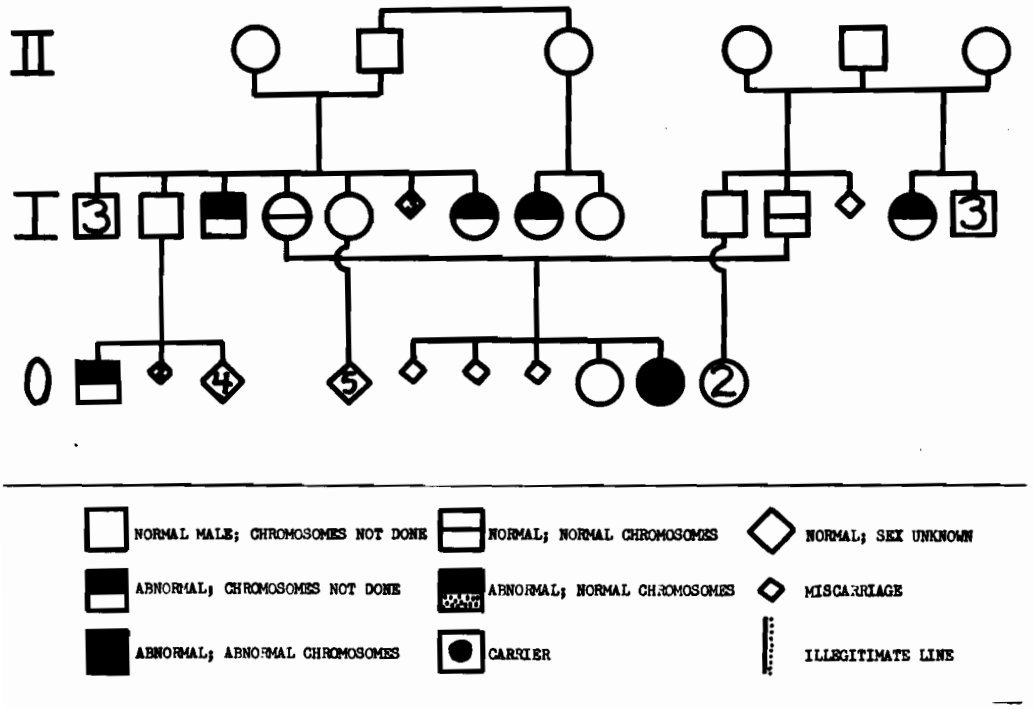
Family History (Fig. 20)

Both parents were thirty-two years of age at the time of conception, and unrelated. The mother had an ovarian dermoid cyst removed when she was 25 years old. One of her brothers (I-3) died at birth of anencephaly. One of her sisters (I-7) died at 16 days of age and had a cyanotic heart condition and club feet. One paternal cousin (I-13) died at 16 years of age. She had multiple bone anomalies and a heart defect, while her sister has been under treatment for many years for a severe scoliosis. Both mother's cousins were of average intelligence. The mother had a total of 5 pregnancies, 3 of which resulted in miscarriages and one in a normal child. The proband (O-9) described below was the product of the fifth conception.

Physical examination (Fig. 21, 22)

The patient, a premature baby girl was examined by the Genetics Department two days after birth. The child had micrognathia, a short neck, flexion of the second toe over the third bilaterally, and a palpable mass in the right upper quadrant of the abdomen. A systolic murmur could be heard over the mesocardiac region. The dermatoglyphics revealed a total of six arches on the fingers. Apart from the fact that the child was premature, the neurological examination did not reveal anything abnormal.

FIGURE 20 - PEDIGREE OF FAMILY (4)



FIGURES 21, 22 - PICTURES OF PROBAND FAMILY (4)

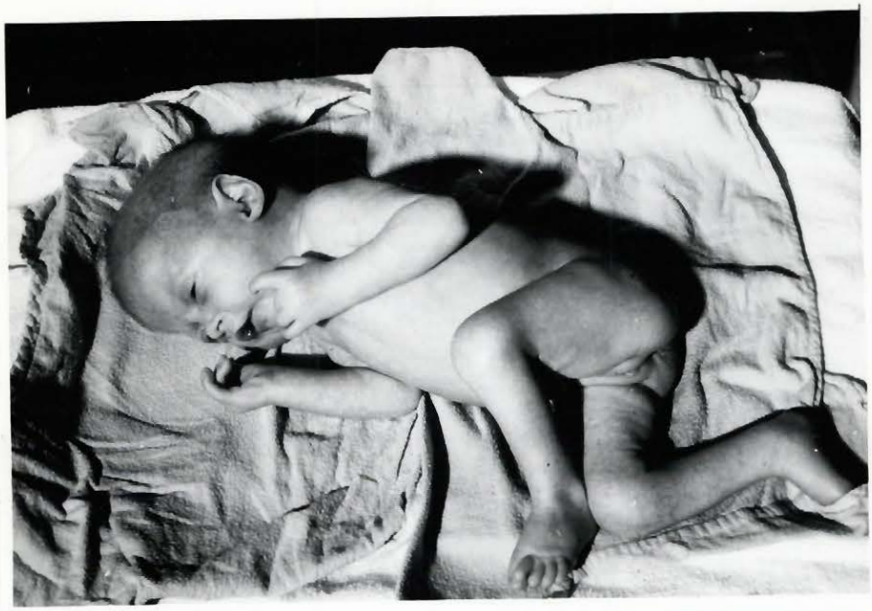


FIGURE 21

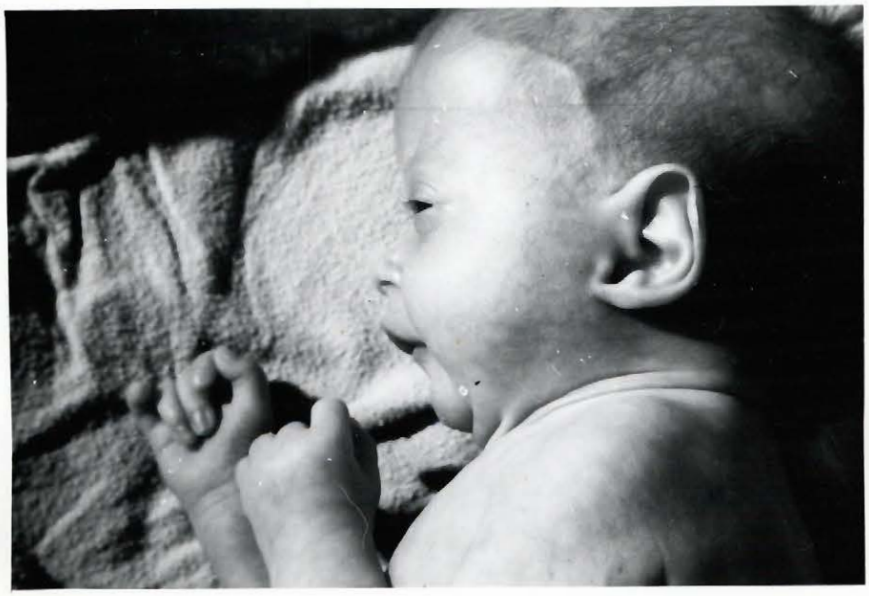


FIGURE 22

Laboratory examinations

All biochemical studies done were normal. The radiological examination of the kidneys revealed that the calices of the right kidney were dilated and that the left kidney was hypoplastic.

Cytogenetic studies

The chromosomal studies were done on the proband and both parents, by means of peripheral blood cultures. No gross abnormality was found. More than forty cells were counted in each case, and twelve cells were analyzed in the proband.

Final diagnosis

The presence of a total of six arches on the fingers, along with the micrognathia, the kidney malformation and the heart malformation were enough to suggest an E trisomy. However, the typical flexion of the fingers was not present, no hernia was noted, and the ears were normally set. There was no deformity of the skull. The subsequent laboratory examinations were in favour of a diagnosis of chondrodystrophia calcificans.

vi Case (3) Polycystic disease

Baby girl T. (M.C.H. 227941) was born on March 23, 1962 and died six days later of multiple congenital anomalies. The parents were seen in consultation because they were afraid of having another abnormal child.

Family History

The proband was the second born in the family. The first child was normal. Both parents were of French Canadian origin and unrelated. The mother was 27 and the father 29 years old when the child was born. The family history did not reveal any incidence of congenital malformations in the family. The pregnancies were uneventful.

Physical examination

The proband was delivered by breech after 8 months of gestation. The birth weight was 2 lbs. 14 oz. The baby was cyanotic at birth. Her head circumference was 12 inches. The skull was abnormally shaped. The occiput was high and prominent. The ears were low set, the neck was short and there was marked hypertelorism. The abdomen was prominent and a mass could be felt in each flank. The arms were webbed at elbows and axillae. The fifth fingers were longer than the others. The X-ray showed a heart enlargement. There was a congenital dislocation of both hips.

The post mortem revealed:

1. polycystic kidneys
2. polycystic liver
3. polycystic pancreas
4. webbing of the neck
5. normal female genitalia

6. heart grossly normal

The dermatoglyphic studies were normal.

Cytogenetic studies

The chromosomal studies were done on the proband and both parents and found normal. A buccal smear of the patient was positive and hence normal. All chromosomes of the patient were normal, and there was no sign of translocation in the parents.

Chromosome number	44	45	46	47	48	Poly-ploid	Total
Mother	0	0	22	1	0	1	24
Father	0	0	15	0	0	0	15
Proband	2	0	35	0	0	0	37

Final diagnosis

The syndrome described here and affecting many major anatomical systems seems to be a "polycystic disease" affecting the kidneys and other glandular systems of the body. The chromosomes in this case are normal and the transmission of the syndrome is probably due to a recessive gene in the congenital type. The parents seemed normal, and there was no suggestion that one of them was carrying the disease. The relatives were all normal by history. There is probably a one in four chance for each subsequent child to be similarly affected (Dalgaard, 1957).

vii Case (4) Multiple malformations of unknown origin

Denis L. (M.C.H. 240560), was born on September 3, 1962. He was admitted to the hospital for treatment of a heart defect and other congenital anomalies. This child was the first born in the family, and the parents were referred to the Genetics Department for diagnosis.

Family History

The mother was 39 and the father 30 years old when the child was born. Their racial origin was French Canadian and they were not related. The family history was not contributory. The gestation lasted 10 months.

Physical examination

The proband weighed 9 lbs at birth. His head circumference was 16 inches. He had a congenital right microphthalmus. The heart examination suggested a tricuspid atresia. The intravenous pyelogram showed that the right kidney was smaller than the left. The dermatoglyphic studies were normal except for the presence of a loop in the third interdigital space on both hands.

Cytogenetic studies

The chromosomes of the child were normal. The sex chromatin was negative.

Final diagnosis

The syndrome seen in this patient is apparently not due to a chromosomal abnormality. The risk of recurrence of the malformations in the next child is unknown. The parents were not related, and there was no indication that it was due to a recessive gene. The possibility of congenital toxoplasmosis was considered and subsequently ruled out by negative laboratory results.

viii Case (5) D syndrome

Baby girl S. (M.C.H. 244307) was born on January 1, 1963 and died on May 25 of the same year at The Montreal Children's Hospital. The infant presented many congenital anomalies at birth, and was referred to the Genetics Department for diagnosis.

Family History

The father was 43 and the mother 40 when the child was born. They were both Polish and immigrated from behind the Iron Curtain in the early 1940's. They have never been in contact with their families.

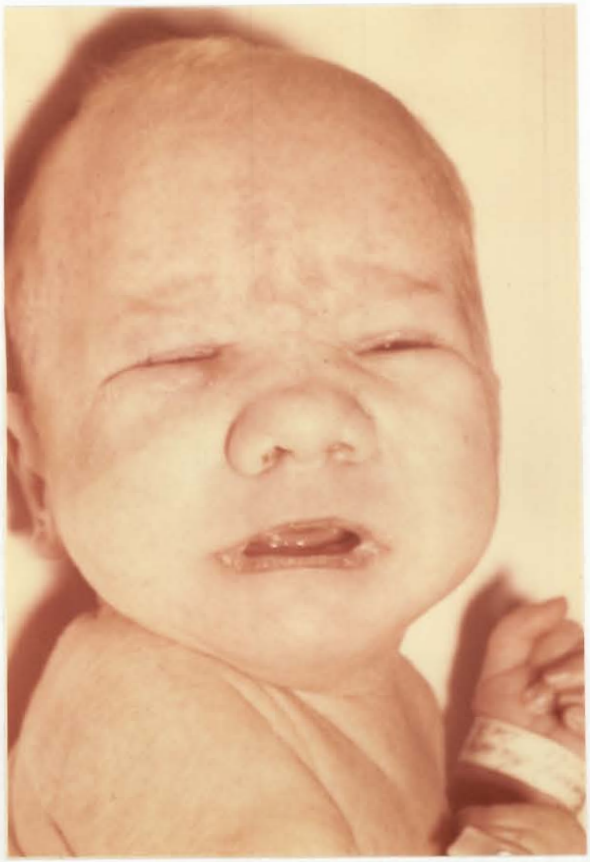
Physical examination (Figs. 23, 24, 25)

The girl was born after an uneventful pregnancy that lasted 40 weeks. The birth weight was 2,430 gms and the newborn was noted to have a poor tone, apnea and an irregular respiration. Because of her cyanosis and her apneic spells the girl was transferred to the M.C.H. for investigation of her heart condition. The physical examination revealed a grossly abnormal infant with an abnormal skull presenting large and asymmetric sutures. There was some telangiectasia of the forehead, nose and neck. The ears were low set. The root of the nose was recessed giving the appearance of an incomplete formation of the septum limiting the two nostrils. The neck was short. The head circumference was 12-1/2" and the length 18".

The child presented a dacryocystitis since birth and the ophtalmological examination was delayed due to the formation of a big abcess in the inside corner of the right eye. However, some degree of microophtalmia was noted. The palate was high and arched. There were six fingers and six toes bilaterally. The extra digit being the fifth one on each side.

The radiological examinations suggested an abnormal heart condition from the enlargement of the ventricles. At birth no murmur was noted, however after 10 days a systolic murmur could be heard at the apex. The X-ray pictures obtained from an intravenous pyelogram showed that both kidneys were enlarged and seemed to be fused on the medial line.

FIGURE 23 - PICTURE OF CASE (5)



FIGURES 24, 25 - PICTURES OF CASE (5)

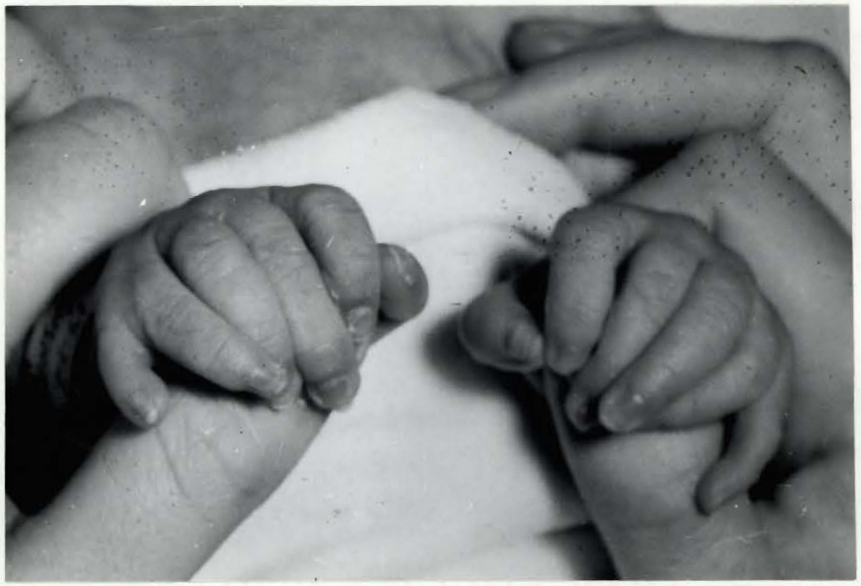


FIGURE 24

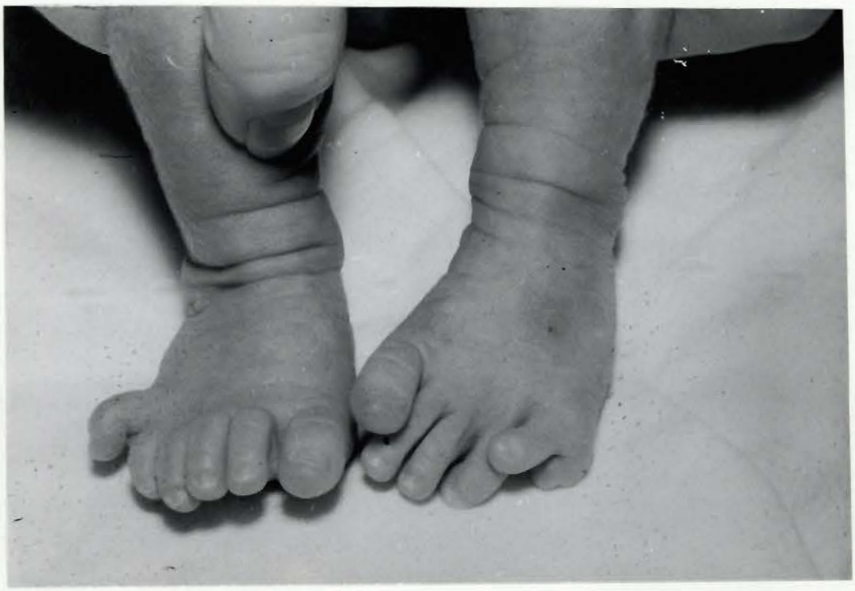


FIGURE 25

The dermatoglyphic studies were not typical of mongolism but there was a high triradius on both hands, as well as simian creases, and on the feet, in the hallucal area, there was a fibular arch pattern.

The electroencephalogram showed some epileptiform disturbance from the left centro-parietal region and an independant area in the right parietal and postero-temporal region. There was evidence of lack of maturation in the brain.

The child's condition deteriorated rapidly. She had had an eye infection since birth, and soon after birth she developed a renal infection which also necessitated some antibiotic therapy. She had frequent episodes of convulsions and her blood sugar level was extremely low especially in her first month of life. The girl died five months later after repeated episodes of cardiac arrest. Throughout her hospitalization she had presented a severe failure to thrive.

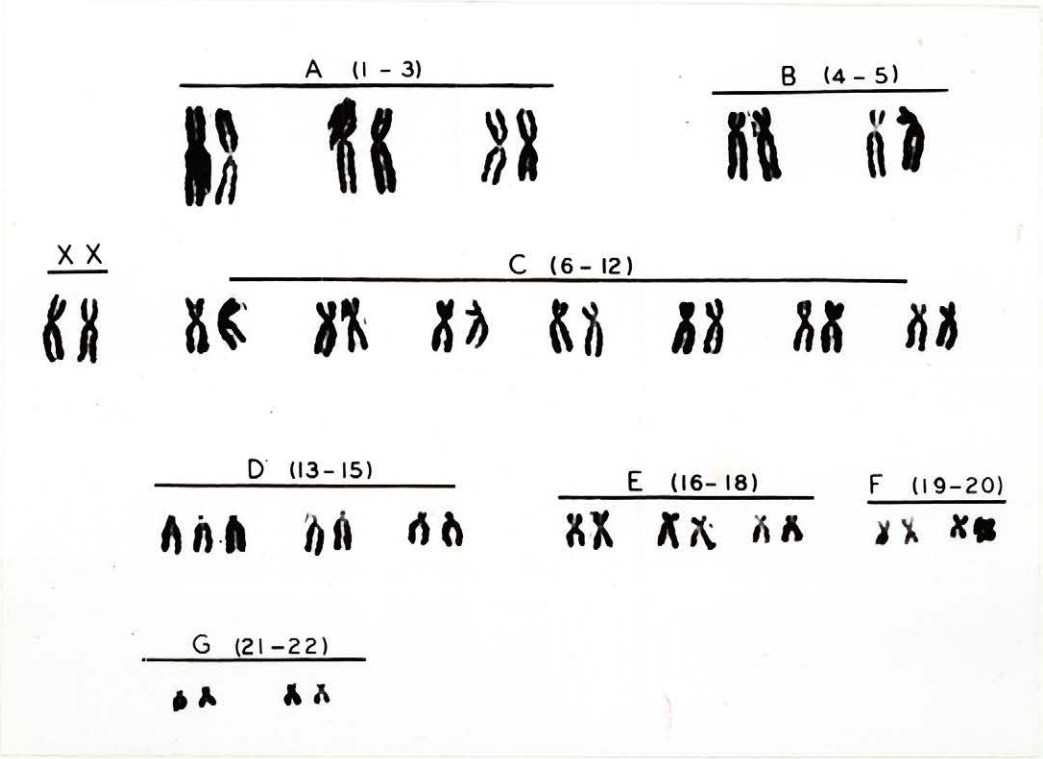
Cytogenetic studies (Fig. 26)

The buccal smear was done and found to be positive and normal for her sex. The chromosomal count was 47: the extra member was a chromosome of the D group. The infant was then trisomic for a 13-15.

Chromosome number	44	45	46	47	48	Poly-ploid	Total
Patient	0	0	1	42	0	0	43

All the cells examined showed the presence of the same extra chromosome. Also in most of the cells there were always three satellited chromosomes which suggested that the extra member was one of the 13 pair, if one accepts that the satellited chromosomes always come first in the classification.

FIGURE 26 - KARYOTYPE OF CASE (5)



Final diagnosis

Patau et al (1960) was the first to describe the trisomy 13-15. Most of the cases reported so far have been found to present a severe malformation of the palate and superior lip. In the present case there was no cleft palate or hare lip but the formation of the nose and medial septum seemed to have been disturbed. The ophthalmological examination was inconclusive regarding the eye condition. It was also impossible to determine if the child was deaf. In summary: the telangiectasia, the heart malformation, the kidney defect, the polydactyly and the cerebral anomaly are typical of the trisomy 13-15.

ix Case (6) Turner syndrome

Anne O. (M.C.H. 254212) was born on June 5, 1955. She was hospitalized for the first time at the age of 8 for investigation of adiposity and heart defect, and referred to the Genetics Department for diagnosis.

Family History

The father was 37 and the mother 31 when the child was born. She was the second child of a family of four. Both parents were in good health and unrelated. They were concerned about the child's health because she had a limited exercise tolerance and was too short for her age. The parents stated that the girl was very bright and that her intelligence has developed normally since birth. The patient occasionally complained of headaches, especially early in the morning.

Physical examination

At the time of admission her weight was 34.2 kg. Her height was 47-1/2 inches. The blood pressure was 120/80. She looked rather obese and her neck was webbed. There was a slight ptosis of the right eyelid. The heart ausculatation revealed a loud systolic murmur radiating towards the left sternal border with a maximum intensity at the second intercostal space. There was some swelling of the hands probably due to lymphoedema.

Laboratory data

The electrolytes and the protein electrophoresis were normal. The 17 ketos teroids and the 17 hydroxycorticosteroids were also in the normal limits. The radiological examination of the chest was normal, but the picture of the hands revealed a short fourth metacarpal bone, which is a common feature of gonadal dysgenesis.

Cytogenetic studies

A buccal smear taken from both sides of the mouth showed no chromatin in the nuclei. The chromosomal studies were done from a peripheral blood culture and all cells had an aneuploid count of 45. One chromosome of the group C was missing and was believed to be an X member.

Final diagnosis

The patient was diagnosed as being a Turner syndrome with coarctation of the aorta.

c. Central nervous system — Spina bifida and other anomalies

i Family (5)

Baby boy L. (M.C.H. 234419) was born on July 19, 1962, and died in hospital 9 days later. Three of his brothers died of spina bifida and since the proband presented the same anomaly, the parents were referred to the Genetics Department for counselling.

Family History

Both parents were French Canadian and unrelated. The mother was 23 and the father 30 years old when the child was born. They had six children: two normal females and four abnormal boys including the proband. Of the three other abnormal boys who all died of spina bifida, one was born in 1958, and the other two were born in 1961 and were twins.

Physical examination

The boy was grossly abnormal at birth; his head circumference was 16 inches, and the fontanelles were largely open. There was from D1 to the sacrum a dorso-lumbar spina bifida, plus a meningocoele. The post-mortem examination also revealed a patent ductus arteriosus, an occlusion of the posterior end of the aqueduct of Sylvius, a hypolasia of the right hemisphere, an agenesis of the right dentate nucleus and finally an aplasia of the vermis. There was absence of the adrenal, the kidney, the ureter and the testis on the left side.

Cytogenetic studies

The cytogenetic studies were done on the proband and on the parents. They all had normal chromosomes, with no evidence of translocation.

Chromosome number	44	45	46	47	48	Poly-ploid	Total
Proband	0	0	40	1	0	0	41
Mother	0	0	20	0	0	0	20
Father	0	0	20	0	0	0	20

Final diagnosis

No other malformation was described in the first three boys who were affected with a spina bifida and hydrocephalus. The proband on the other hand had a severe heart malformation and an aplasia of the left genito-urinary system.

Four out of six were affected in the family, all of them males. The two living girls were females.

ii Case (7) Multiple malformations of unknown origin

Antonio R. (R.V.H. 204568) was born in July, 1961, and he was eight months old when the Genetics Department was asked to see him. He was then hospitalized for treatment of recurrent pneumonias and evaluation of his cardiac anomaly.

Family History

The father was 28 and the mother 24 years old when the child was born. They were not related. On either side of the family no one was known to have died of congenital malformations. The pregnancy was normal and the mother had not been under drug therapy at any period of the gestation.

Physical examination (Fig. 27)

The birth weight of the patient was 4 lbs. He was underdeveloped physically and mentally. The head circumference was 15 inches and the length 37.5 cms. The eyes were bulging. All over the body the skin was loose and there were prominent umbilical and inguinal hernias, though the last two had been repaired shortly after birth at the same time as correction of an imperforate choana. The venous system was very superficial and the vessels were bulging loosely at the surface of the skin. A faint systolic murmur could be heard when the child was excited, and the heart beats were noted to be irregular. There was a marked hypotonia, with no demonstrable pathology of the sensorial or motor nervous systems. The patient was extremely irritable. The palate was high and arched. The boy was edentulous.

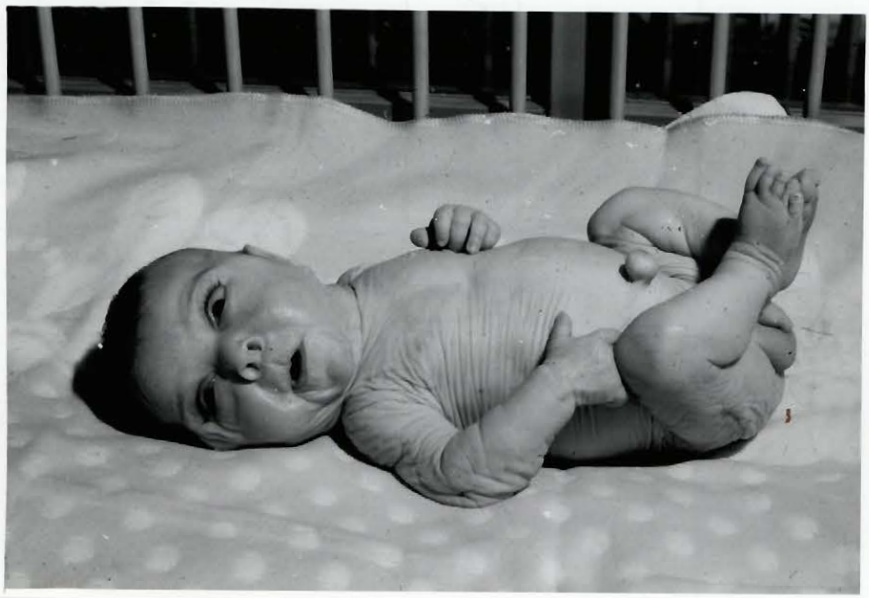
The biochemical and serological tests failed to demonstrate any abnormality which could have been responsible for the clinical condition

of the child. A skin biopsy showed that the skin was hyperkeratotic.

Dermatoglyphic studies

The finger prints were studied and the child was found to have a high triradius on the left hand. There were no simian creases. There was an arch tibial on the left foot in the hallucal area, and a small loop distal on the right.

FIGURE 27 - PICTURE OF CASE (7)



Cytogenetic studies

The chromosomes were analyzed by means of peripheral blood culture. All the cells examined had 46 chromosomes and a normal male sexual complement. There was no sign of translocation.

Final diagnosis

The patient died at the age of nine months. The final diagnosis was: multiple congenital anomalies of unknown origin.

d. Cervico cephalic — Multiple malformations of unknown origin

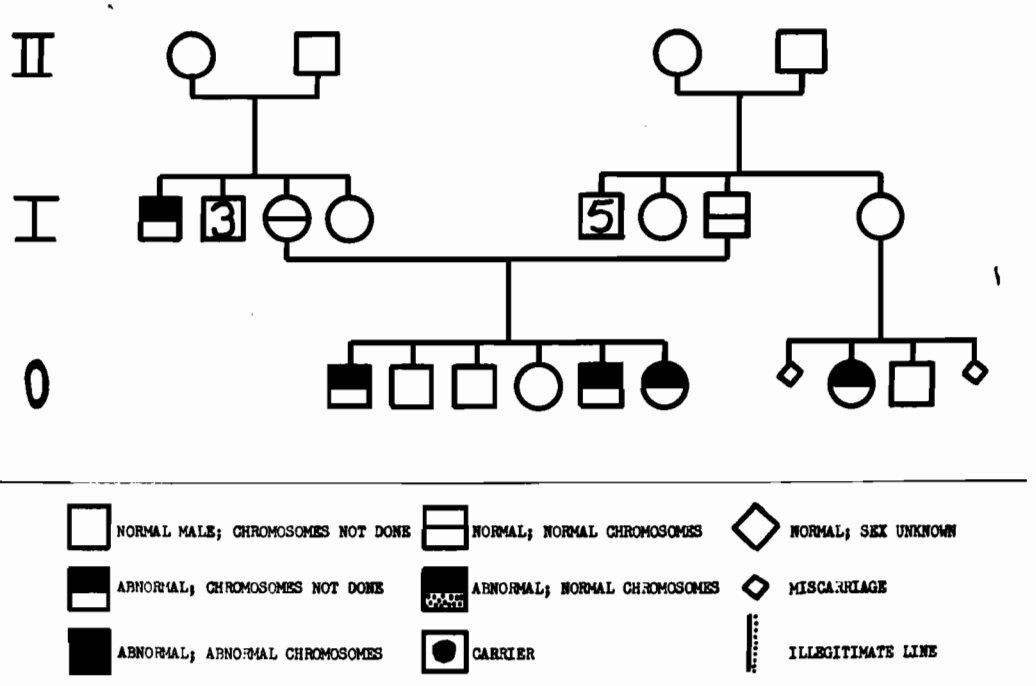
i Family (6)

Mary S. (M.C.H. 172682) a premature female infant was born on March 10, 1959 and immediately referred to the Genetics Department for diagnosis of multiple congenital anomalies.

Family History (Fig. 28)

The father was 26 and the mother 29 when the child was born. They were both Irish in origin. One proband's paternal first cousin (0-8) was known to have died of a severe malformation, probably anencephaly. The first pregnancy (0-1) resulted in a malformed child Joseph. The next three children were normal. In 1957 the mother delivered another malformed boy (James, 0-5) and the sixth child (0-6) born two years later was the affected proband. The parents were not related and there was no other affected child in the family.

FIGURE 28 - PEDIGREE OF FAMILY (6)



Physical examination (Figs. 29,30,31)

The physical examination of the proband is summarized in Table 6 with the malformations of the other two children.

TABLE 6

	Joseph (0-1) (R.V.H. 48-6461)	James (0-5) (M.C.H. 137028)	Mary (0-6) (M.C.H. 172682)
Skull anomaly	+	-	+
Low set ears	+	+	+
Cleft palate	+	+	+
Micrognathia	+	+	+
Tongue retro displaced	+	+	+
Heart normal	+	+	+
Urinary system normal	+	+	+
Ext. genitalia normal	+	+	+
Mental retardation	+	+	+
Joint dislocations	+	+	+
Club feet	+	+	+
Abnormal vertebrae	+	+	-
Hydrocephalus	+	+	+
Spina bifida	+	-	+
Thyroid	+	+	+
Short limbs	+	+	-

The postmortem examination of the proband revealed on dissection an absence of the anterior cruciate ligament, flattening of the tibial joint surface and poor development of menisci in both knee joints. Both knees were dislocated posteriorly. There were club feet and sub-luxation of toes on the left foot. The hands had a sub-luxation and deviation of phalanges

radially at the metacarpophalangeal joints and ulnarly at the proximal interphalangeal joints. The surface of the acetabulum was more horizontal than normal. The cortex of the clavicle was too thick and the fourth ribs were incomplete.

FIGURE 29 - RADIOLOGICAL PICTURE OF THE PROBAND FAMILY (6)

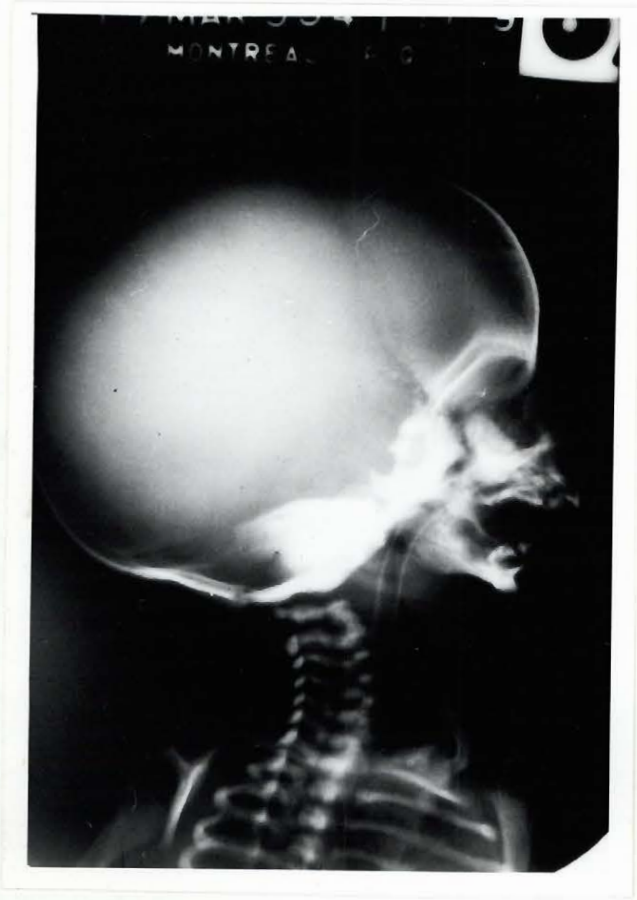


FIGURE 30 - RADIOLOGICAL PICTURE OF THE PROBAND FAMILY (6)

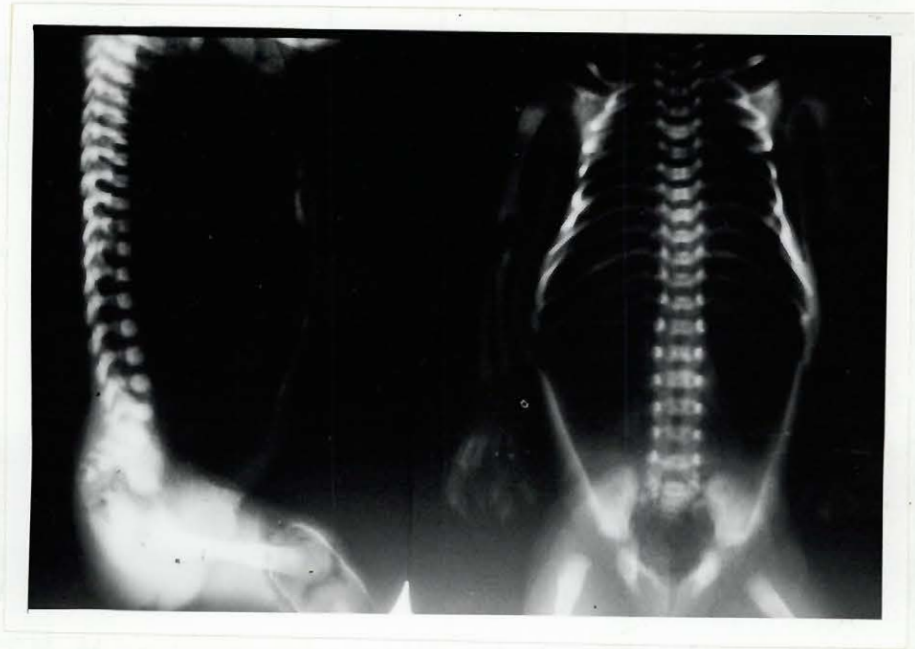


FIGURE 30

FIGURE 31 - PICTURE OF JOSEPH (O-1) FAMILY (6)

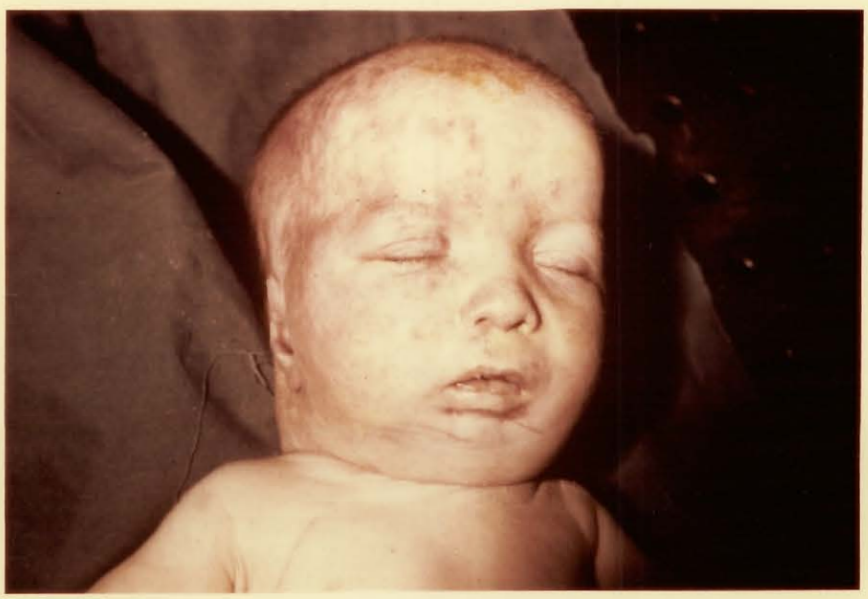


FIGURE 31

Cytogenetic studies (Fig. 32,33)

The chromosomal studies were done on both parents. The karyotypes were found normal in each case. The children had died before the study was begun.

Chromosome number	44	45	46	47	48	Poly-ploid	Total
Mother	0	3	56	0	0	1	60
Father	0	0	32	0	1	0	33

FIGURE 32 - KARYOTYPE OF THE MOTHER FAMILY (6)

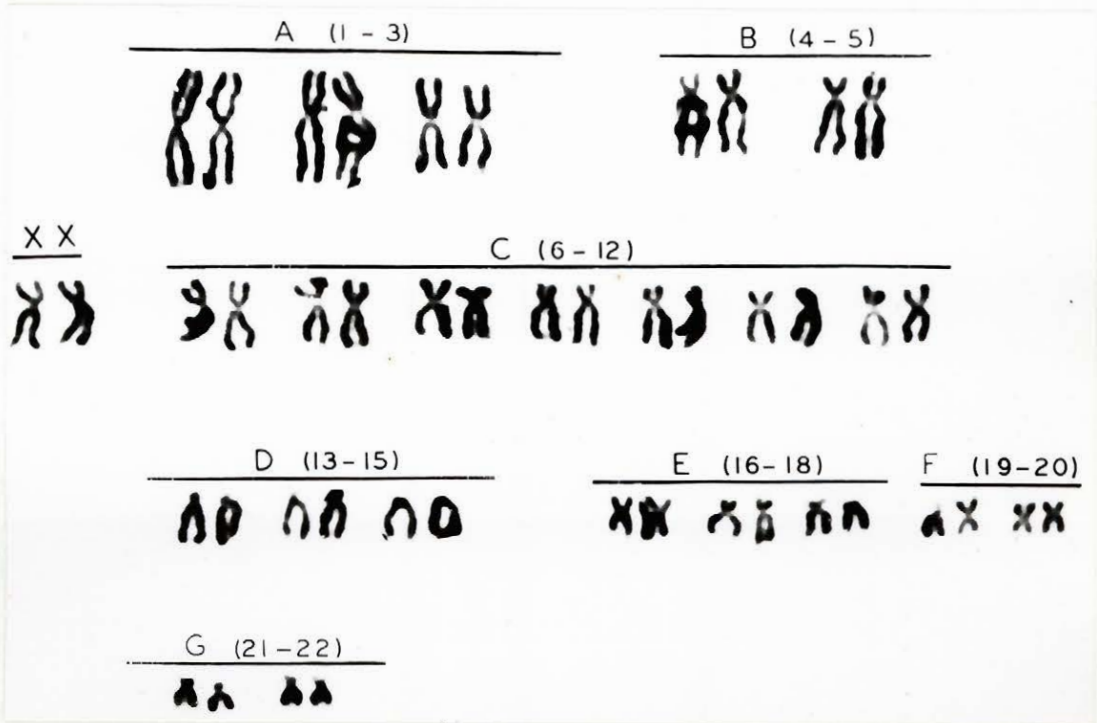
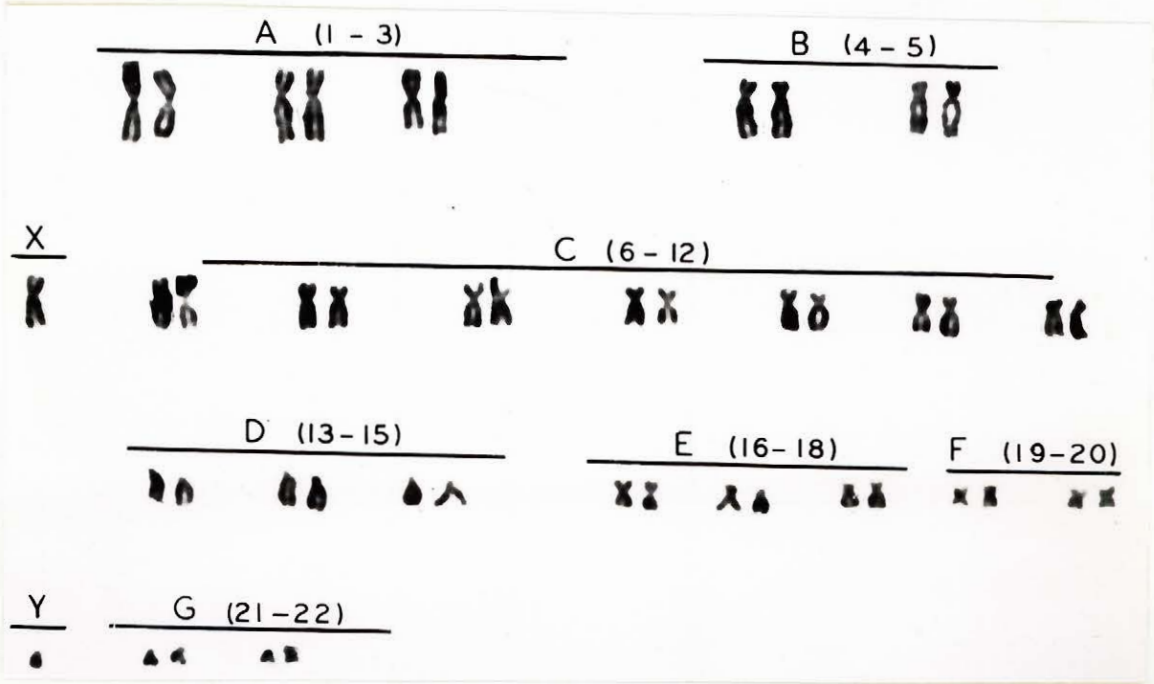


FIGURE 33 - KARYOTYPE OF THE FATHER FAMILY (6)



Final diagnosis

The syndrome present in the three affected children has a striking characteristic: the skeleton is involved as well as the ligaments. But one should note that the other systems seem to be intact. The cleft palate suggested previously since it was accompanied with club feet and malformed ears that a member of the D group might be involved. However the cardio-vascular and genito-urinary systems are normal and the eyes as well as the internal ears are normal.

ii Family (7) Cleft lip and multiple malformations

Johanne G. (M.C.H. 161019) was born on February 11, 1958 and hospitalized at The Montreal Children's Hospital for repair of a bilateral cleft lip. She was then referred to the Genetics Department because of her malformation.

Family History (Fig. 34)

Both parents were French Canadian and not related. The father was 31 and the mother 23 years old when the child was born. The proband was the third born in this family. The first one (0-3), a boy, was normal. The second child, (0-4) a girl, died eight hours after birth and had an absence of the nasal bones but was aparently normal otherwise. Following the proband's birth (0-5), the mother had one spontaneous miscarriage (0-6) and three years later a normal girl. Three paternal first cousins had abnormalities of the face. A male (0-9) was treated surgically for an eyelid opening defect. Another boy (0-11) had bilateral cleft lip and palate and absence of the nasal bones. One female (0-12) had an abnormally shaped nose and protruding eyes. The father had fifteen brothers and sisters who were all normal. The mother's relatives were also all normal.

Physical examination (Fig. 35, 36)

The physical examination of the proband revealed a bilateral and complete cleft lip, absence of the nasal bones, and microcephaly. The infant had convulsions. The ears were big and abnormally shaped. The other systems were normal.

FIGURE 34 - PEDIGREE OF FAMILY (7)

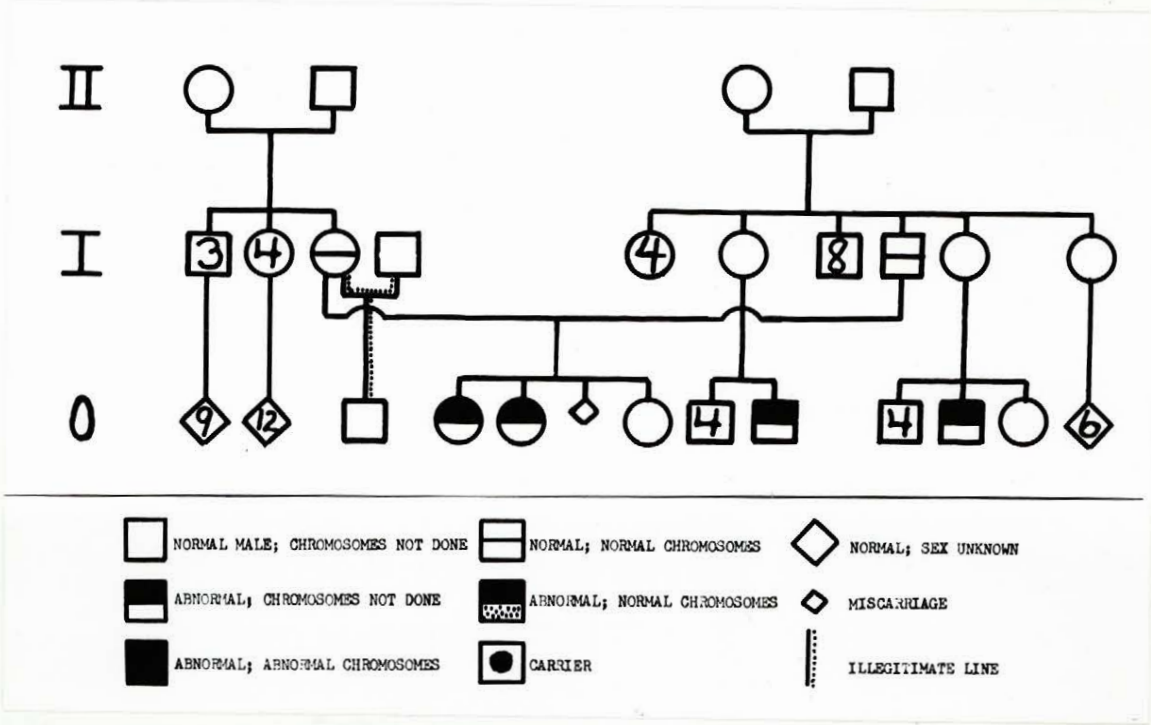


FIGURE 35 - PICTURE OF PROBAND FAMILY (7)

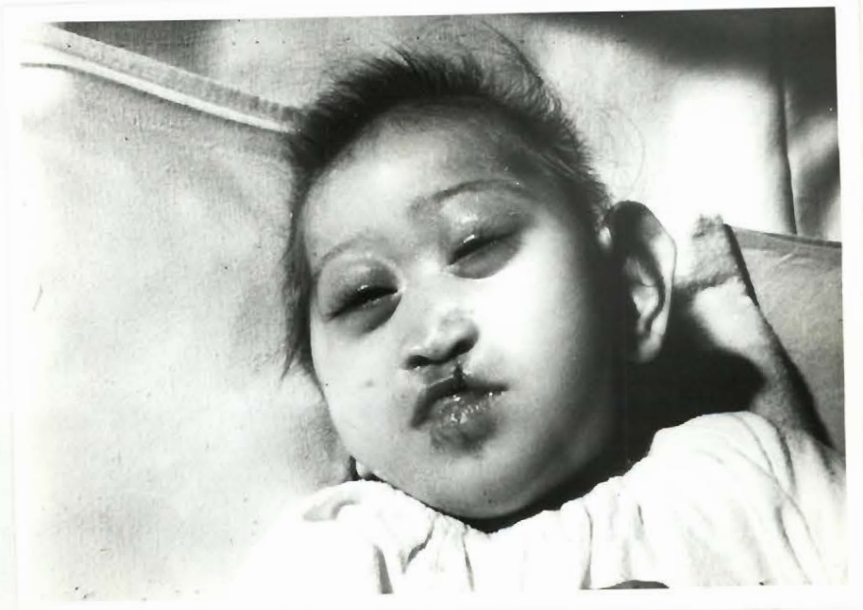
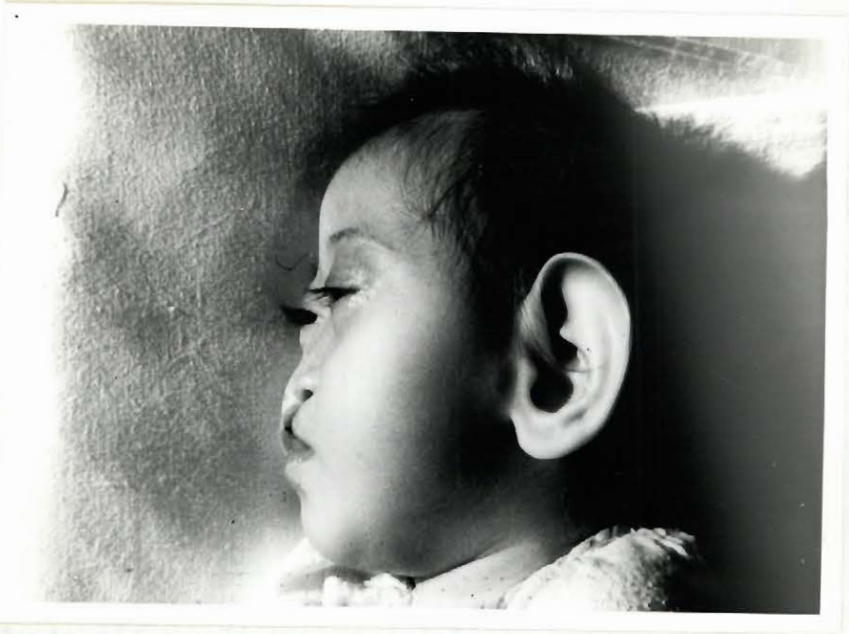


FIGURE 36 - PICTURE OF PROBAND FAMILY (7)

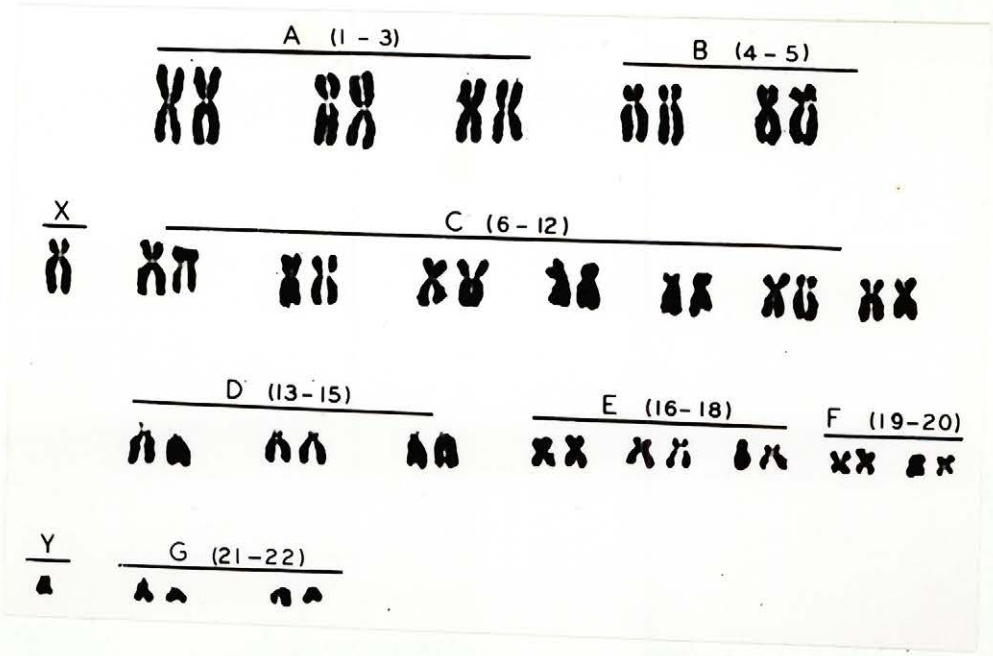


Cytogenetic studies (Fig. 37)

The chromosomal analysis of the two parents failed to reveal the presence of a translocation or even some degree of rearrangement in their chromosomes. The children died before 1959.

Chromosome number	44	45	46	47	48	Poly-ploid	Total
Father	0	0	55	0	0	0	55
Mother	0	0	20	0	0	0	20

FIGURE 37 - KARYOTYPE OF FATHER FAMILY (7)



Final diagnosis

The syndrome described in this female patient and present also in one sib and three first cousins suggested an abnormality of the chromosomes of the D group. However both parents were found to have a normal karyotype. Since the syndrome was not complete one could not expect to find in this case a familial non-disjunction of a deleted chromosome. One is not dealing here with a simple case of cleft lip: the skull is malformed, the ears are abnormal and there is some degree of eye malformation. The children were also mentally retarded, and convulsions and early death were also part of the picture.

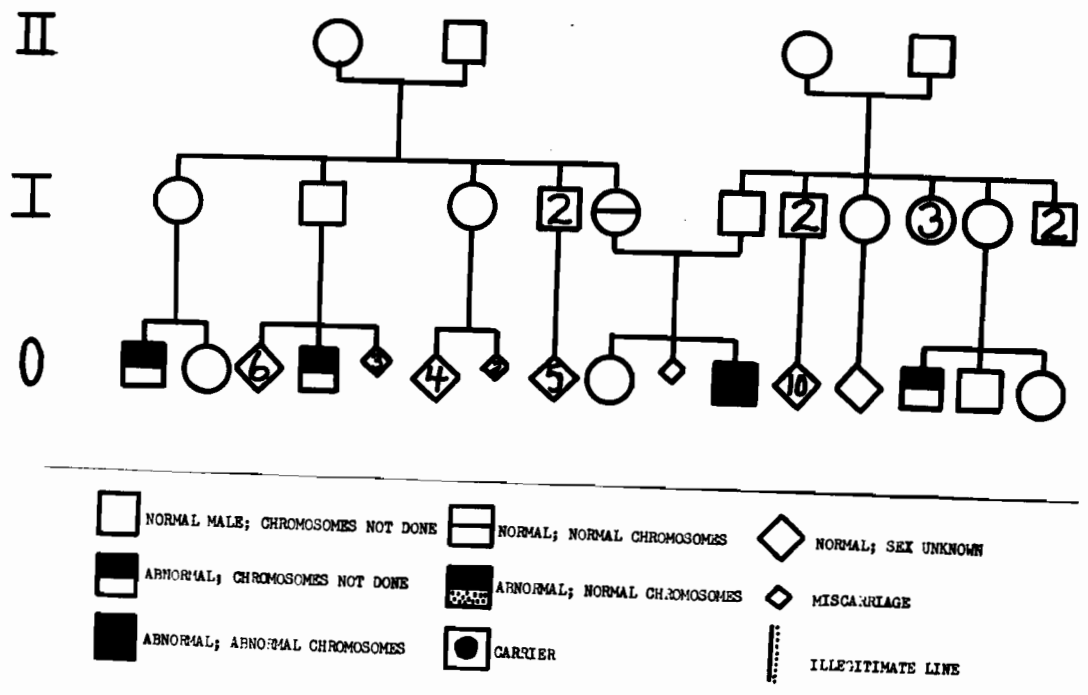
iii Family (8) Multiple malformations of unknown origin

John C. (M.C.H. Gen. C.P. 236) was referred to the Cleft Palate Clinic when he was two years old. At birth the child weighed 4 lbs and had multiple bone anomalies.

Family History (Fig. 41)

The proband (O-11) was the result of a third pregnancy. The first child born to the same parents was a normal girl. The second pregnancy terminated in a sudden abortion (O-10) after two months and a half gestation. The fourth and fifth pregnancies not shown in the pedigree also resulted in miscarriages after respectively two and three months gestation. The father was 40 and the mother 33 at the time of birth of the proband. They were unrelated. The physical examination of the mother revealed a mild micrognathia and slight exophtalmus. The father was normal. One paternal first cousin (O-14) died at birth and was said to have a cleft palate.

FIGURE 38 - PEDIGREE OF FAMILY (8)



Physical examination

The patient had as well as the cleft palate, a dolicocephalic skull, antimongoloid slant of the eyes, a depressed nose bridge, wide spaced eyes, micrognathia, a small mouth, and low shoulders. There was a bilateral dislocation of the hips, limited extension of the arms, accessory nipples and no patellae. The heart was normal on ausculation. The psycho-motor test was borderline. The dermatoglyphics were not done.

Cytogenetic studies

The family was moving to another country when the mother was contacted for chromosomal studies. The patient and the father were already gone. However the studies were done on the mother and she was found to have normal chromosomes.

Final diagnosis

At the age of seven the proband was attending school, and was said to be fairly intelligent. The cleft palate had been repaired and he was still under treatment for his dislocated hips. It is unfortunate that the chromosomal pattern of the child could not be determined. According to the private physician who treated the mother during her pregnancy, she was given estrogenic and corpus luteum hormones since her first two pregnancies resulted in miscarriages. However, those were the only medicaments she received. No final diganosis has been reached in the proband's condition.

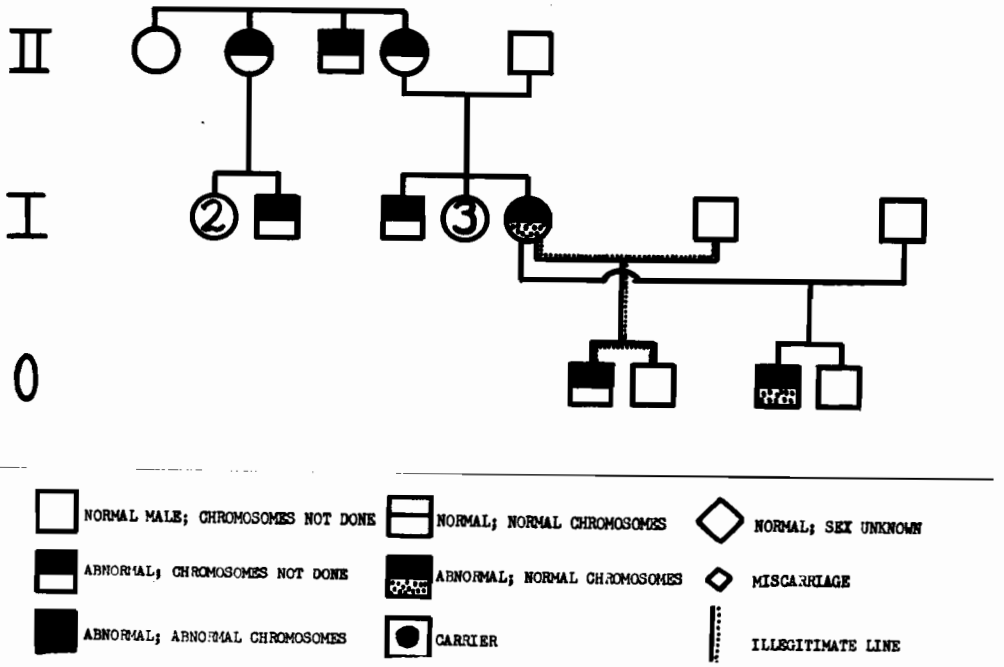
iv Family (9) Congenital cataracts and associated anomalies

Wesley I. (M.C.H. 218290) was born May 20, 1959 and was hospitalized in 1962 for diagnosis and treatment of neurological disorders. At the time of admission the mother stated that the child had frequent episodes during which he showed no coordination of his movements. He was referred to the Genetics Department for cataracts.

Family History (Fig. 39)

The family history is interesting from a point of view of transmission of a hereditary trait. The mother had four children, two of which were adopted by her husband since she had had them before her marriage by another man. The first adopted child (O-1) had cataracts and no other neurological disorder. From the present marriage she had two children. The proband (O-3) is the first one, the other being normal. Both mother and father are English and the rest of the family still lives in England. But the mother's brother (I-3), her mother (II-4), one uncle (II-3), one aunt (II-2) and one first cousin (I-2) were all known to have some eye trouble described by the mother as being cataracts. One could not verify if they had colobomas as well. The mother also claimed that during the gestation of the proband she had vaginal bleeding during the first three months. Incidentally, she had occasional bleeding at the beginning of each pregnancy, except the first one which also resulted in a child with cataracts. She had not been exposed to infectious diseases. She herself had bilateral congenital cataracts, colobomas, and some incoordination of her movements.

FIGURE 39 - PEDIGREE OF FAMILY (9)



Physical examination

The proband, a three-year-old boy appeared mentally retarded and quite inactive at the time of his examination. The eye examination revealed the presence of bilateral congenital cataracts, and a coloboma of the right eye. The palate was high and arched. The microphthalmia was apparent and his ears were rather large and low set. The heart seemed to be normal from the auscultation. The patient could not stand on his feet, and had incoordination of his movements. He was not agitated during the examination. He could recognize his mother, and he cried when she left the room. His vocabulary was limited to a few sounds. He had a left

inguinal hernia repaired in 1961.

Laboratory data

The electroencephalogram showed mild diffuse dysrythmia. The radiological examination showed a dilatation of the collecting system. A cystoscopy revealed the presence of trabeculae in the bladder. There was no aminoaciduria.

Cytogenetic studies (Figs. 40, 41)

A total of 30 cells were analyzed both from the mother's and from the child's peripheral blood cultures. All the cells had a normal complement, except one in the mother in which there was a reciprocal translocation between a member of the A group, a number two, and a member of the D group, a number 13. It is not likely that there is any relation between this incidental finding and the phenotypes of the two patients examined. However the case is mentioned here, since Hirschhorn and Cooper (1961) reported in the Chromosome Newsletter a case in which the phenotype of the patient showed an ocular anomaly and had a reciprocal translocation involving a member of the B group. If one assumes that the mother may be mosaic for the translocation, then the child should present the same anomaly in his chromosomes. Further chromosomal studies will be done later.

FIGURE 40 - MOTHER'S CELL IN METAPHASE SHOWING AN A/D TRANSLOCATION FAMILY (9)

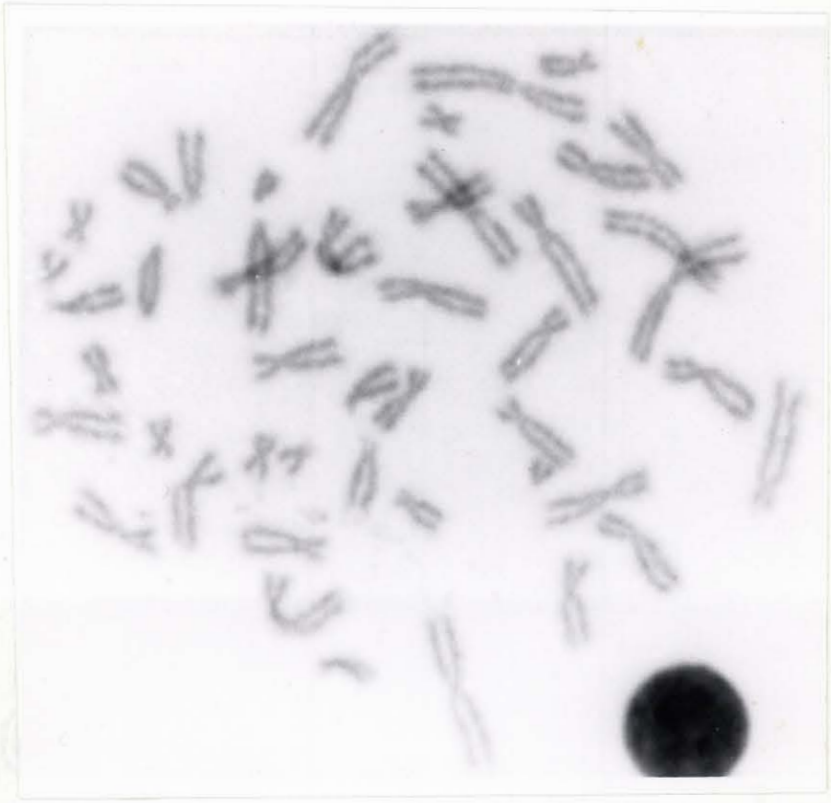
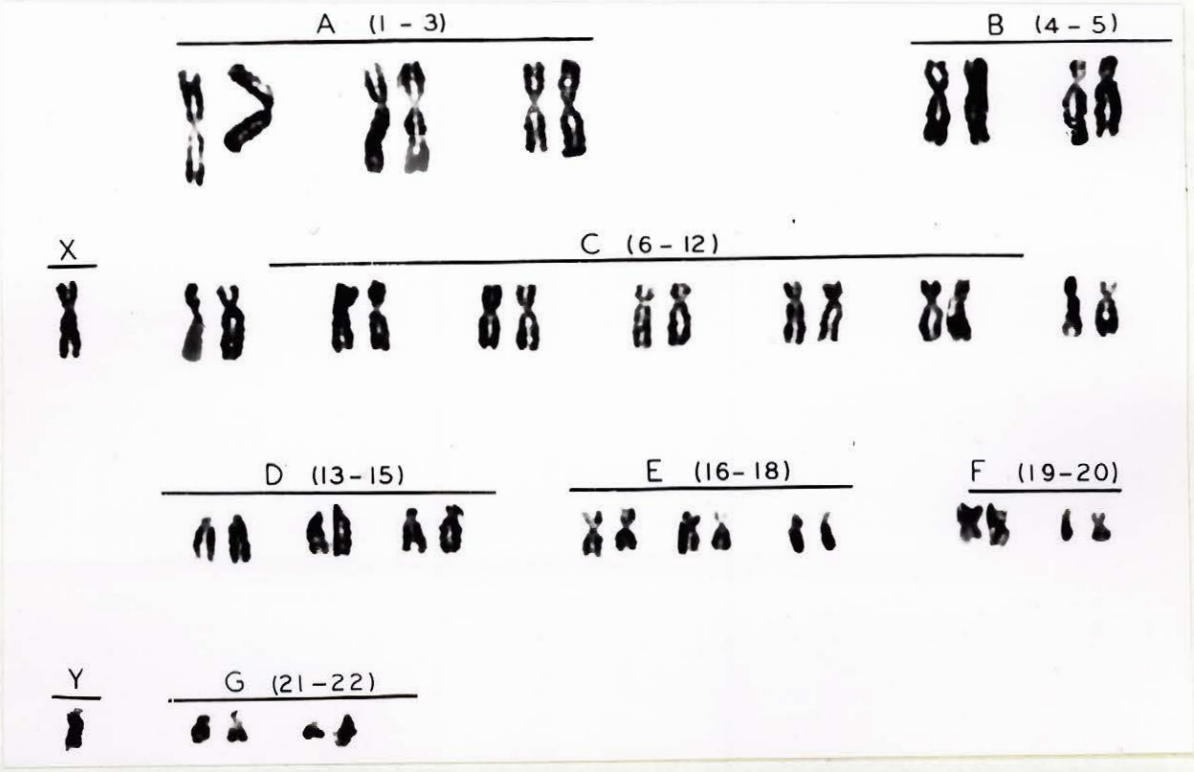


FIGURE 41 - KARYOTYPE OF PROBAND FAMILY (9)



Final diagnosis

A final clinical diagnosis of congenital cataracts due to a dominant gene was made in view of the typical family history. The associated physical anomalies seen in the proband did not seem to be related and were not cytologically induced.

v Family (10) Branchial cyst

Peter M. (M.C.H. 227709) was born on January 20, 1962 and admitted to the Hospital six months later because of a failure to thrive. The patient had a branchial cyst of the left side, and a consultation was sent to the Genetics Department for advice on the incidence of this malformation.

Family History

Both parents were of English origin, unrelated and young at the time of birth of the proband. The mother had been operated for a branchial cyst when she was only a few years of age. The proband was the first born in the family. There was no miscarriage.

Physical examination

The child was premature and weighed only 5 lbs. 12 oz. at birth. His head circumference was 15". He had a patent ductus arteriosus, a branchial cyst and a left hydronephrosis. The intravenous pyelogram also demonstrated a slight uretero-pelvic obstruction. The electroencephalogram was borderline normal. The finger prints were normal.

Cytogenetic studies

The chromosomes of the mother and those of the child were normal. Thirty cells were counted in each case and five were analyzed.

Final diagnosis

A diagnosis of familial branchial cyst was made.

vi Family (11) Cleft lip

Stephen D. (M.C.H. Gen. Dept. CIL 349) was born on September 17, 1957. The patient was referred to the Cleft Palate Clinic of the Montreal Children's Hospital and to the Genetics Department.

Family History

The proband was the first child born to a young mother of 22 and a father of 25 years of age. They were Irish and English respectively, in origin. The mother had a normal pregnancy. One mother's sister also had a daughter affected with a cleft lip and palate.

Physical examination

The birth weight of the child was 9 lbs. He was delivered normally after an uneventful pregnancy. The child was perfectly normal except for the cleft in the left lip. The dermatoglypic studies showed the presence of a loop in the 4th interdigital space on the left hand. He had no high triradius.

Cytogenetic studies

The chromosomes of the mother were examined and found to be normal. Fifty cells were examined. They all had a normal diploid count of 46 chromosomes.

Final diagnosis

The cytogenetic studies were done on the mother in order to exclude any possibility of translocation. Since the two affected children were mentally normal and showed no other physical anomaly, the mother was given a 5% risk of recurrence in future pregnancies. The etiology of the cleft lip seems to be multifactorial. The chromosomal defect, trisomy 13/15

causing the same malformation is accompanied by many other somatic malformations. In this case the patient was perfectly normal otherwise.

vii Case (8) Partial autosomal trisomy

P. Bou. (M.C.H. 230669) a female infant was born on May 5, 1962, and admitted to the Montreal Children's Hospital 6 months later for repair of a cleft palate and clinical evaluation of other congenital anomalies. The treating physician referred the patient to the Genetics Department because of her cleft palate.

Family History

Both parents were French Canadian and unrelated. The mother was 28 and the father 35 years old when the girl was born. They previously had 3 normal boys and 2 normal girls. There was no family history of congenital malformations.

Physical examination and laboratory data

The proband was fairly well developed, considering that she had been fed with some difficulty because of her palate malformation. She had low set ears, a patent ductus arteriosus and an umbilical hernia. An I.V.P. revealed a kidney malformation described as left side hydronephrosis and uretero-pelvic constriction, and a left accessory artery. The skull was flattened on the right. The hemogram showed some degree of anemia secondary to the inadequacy of her diet and to the chronic kidney malformation. There was no sign of mental retardation: on the contrary the girl seemed alert and was responding with a smile to the attention given by the medical staff. The finger prints were normal.

Cytogenetic studies (Figs. 42, 43, 44)

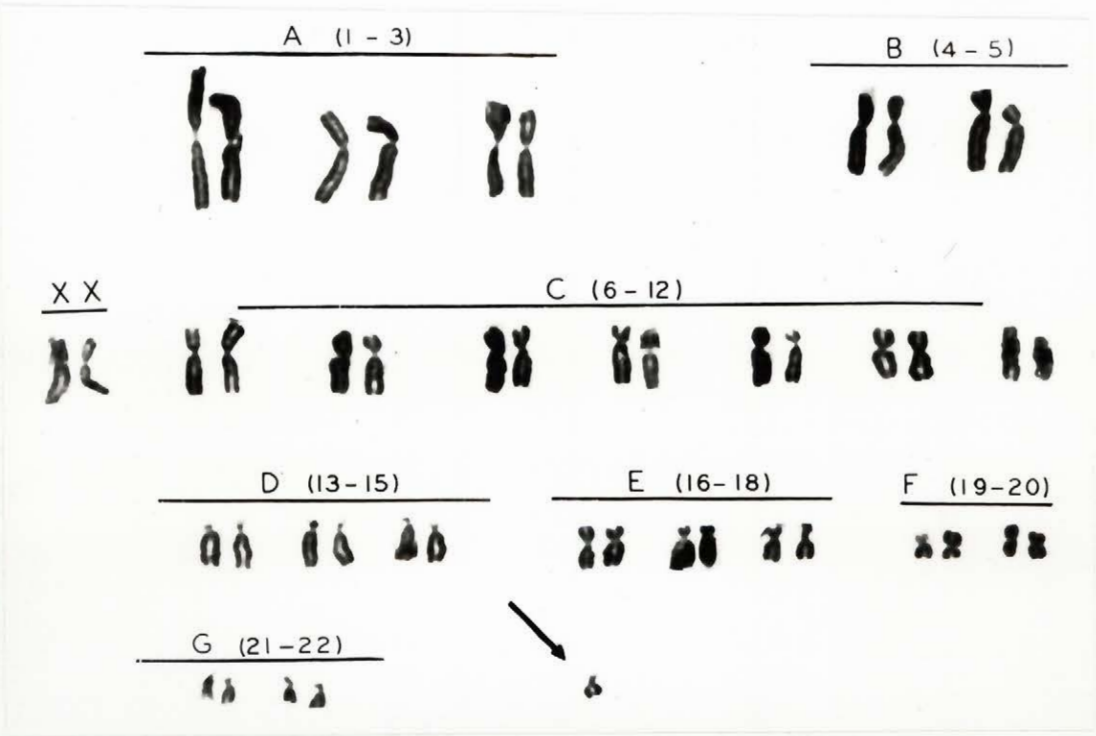
Chromosomal count	44	45	46	47	48	Total
Blood culture (1)	1	0	6	17	0	24
Blood culture (2)	0	0	20	8	0	28
	1	0	26	25	0	52

The extra chromosome found in half of her cells was an abnormal small acrocentric, comparable in size to a number 21 and in shape to a deleted number 13/15, as seen on the karyogram. The possible explanations of this abnormality are of three types:

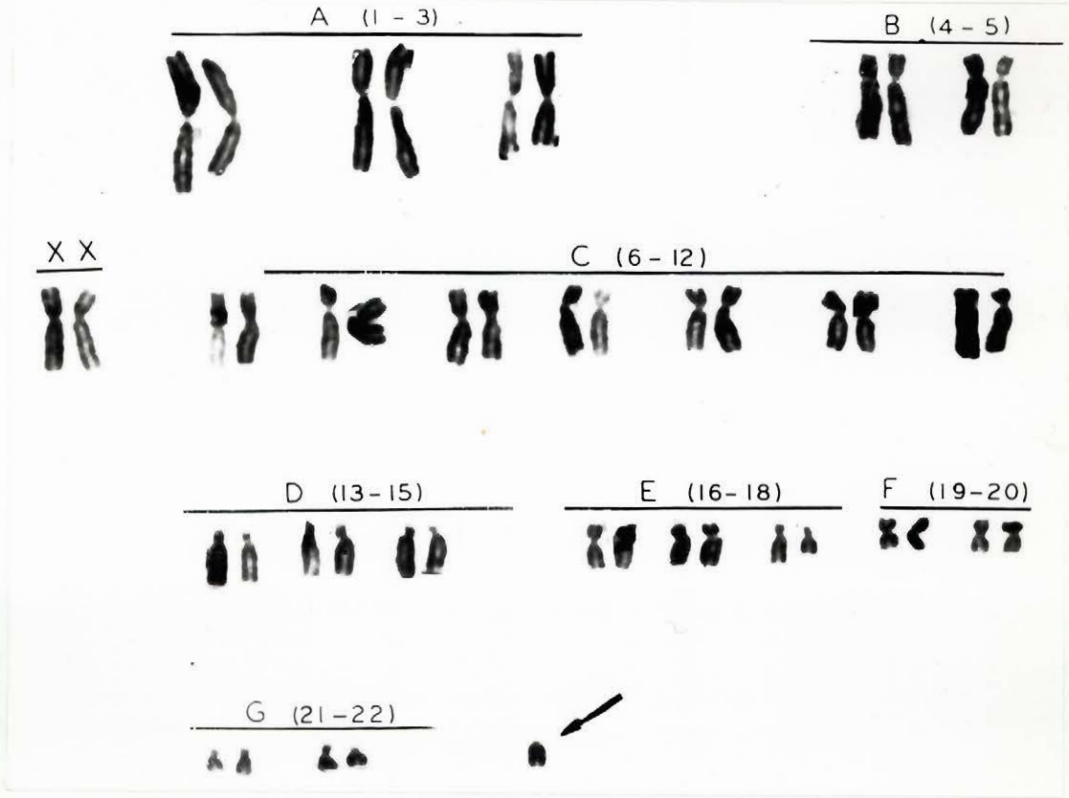
1. The deleted chromosome may belong to another chromosome of the higher groups, and may have arisen from 2 broken chromatids that rejoined to form an extra member. The patient had a chest X-ray before the blood was taken for chromosomal analysis, and this may have been the breaking agent. But it seems unlikely that a chromosome may duplicate without a centromere.
2. The patient may have been trisomic for a member of the D group or the E group, and what one sees now may be the result of the deletion affecting the long arms of this extra chromosome.
3. Finally the abnormality may have taken place in one of the parents. If the event took place during gametogenesis, one could not detect any abnormality in the somatic cells of the parents. But if a reciprocal translocation took place early in the development of the mother or the father, than a chromosomal analysis should reveal the origin of the aberration.

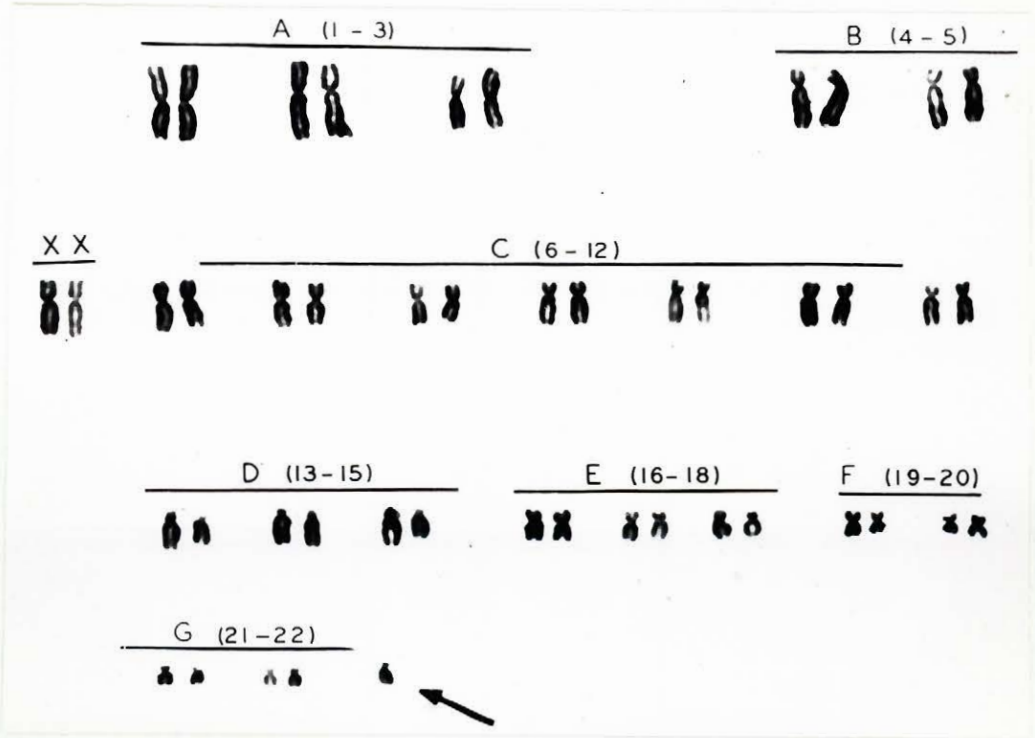
Peripheral blood cultures were done on both parents, and all the cells were found to have 46 chromosomes, and there was no sign of chromosomal rearrangement.

FIGURE 42 - KARYOTYPE OF PROBAND CASE 8



FIGURES 43, 44 - KARYOTYPES OF PROBAND CASE 8





Final diagnosis

This patient represents a case of partial trisomy. The extra abnormal chromosome could be a deleted 13/15 or a deleted 17/18. The physical abnormalities suggest that a member of the D group is involved.

viii Case (9) Partially deleted E chromosome.

Sandra T (M.C.H. 220457) was born on August 30, 1961, and hospitalized one month later for investigation of multiple congenital anomalies including a cleft palate.

Family History

The proband was an illegitimate child of a 19-year-old English mother and a 21-year-old French Canadian father. Very little was known of the two families since the patient was under the care of a foster mother. The mother was an epileptic who had been controlled by anticonvulsive drugs for some time. Both parents were apparently physically normal otherwise, and there was no history of familial defects.

Physical examination

The proband was born after a 12 hour labour. Her birth weight was 3 kg. At six weeks of age the weight of the patient was 3.63 kg. Her head circumference was 14 1/2". Her length was 21". The infant had oblique palpebral fissures, crooked little fingers and one crease only on the left, a protuberant anterior fontanelle, a ptosis of the right eyelid, a haemangioma in the back of the neck and a cleft palate. The foster mother stated that the infant had a poor sucking reflex, and had frequent twitching of the face and limbs. The sagittal suture was one inch wide. At the age of 18 months she could not turn over by herself. She could smile and hold objects in her hands.

Dermatoglyphic studies

The patient had arches on all fingers, high triradius on both hands and equivocal simian creases. There was no tibial arch in the hallucal area of the feet. There was a loop distal on the left foot and a whorl

on the right. The log. index was -2.25, this being considered as the normal limit for mongolism.

Special examinations

The electroencephalogram was abnormal. There was diffuse irregularity of low amplitude, with some epileptiform activity. The skull X-ray showed some immaturity of the vault and definite bulging of the anterior fontanelle. The pneumoencephalogram showed assymetry of the lateral ventricles suggestive of some atrophy of the right cerebrum or a space occupying lesion on the left side of falx. The cerebro-spinal fluid was normal.

Cytogenetic studies (Fig. 45).

The chromosomal studies were done on three occasions and the same results obtained each time.

Chromosome number	44	45	46	47	48	Poly-ploid	Total
Proband 1	0	0	4	0	0	0	4
2	1	0	5	0	0	0	6
3	0	0	47	0	0	0	47

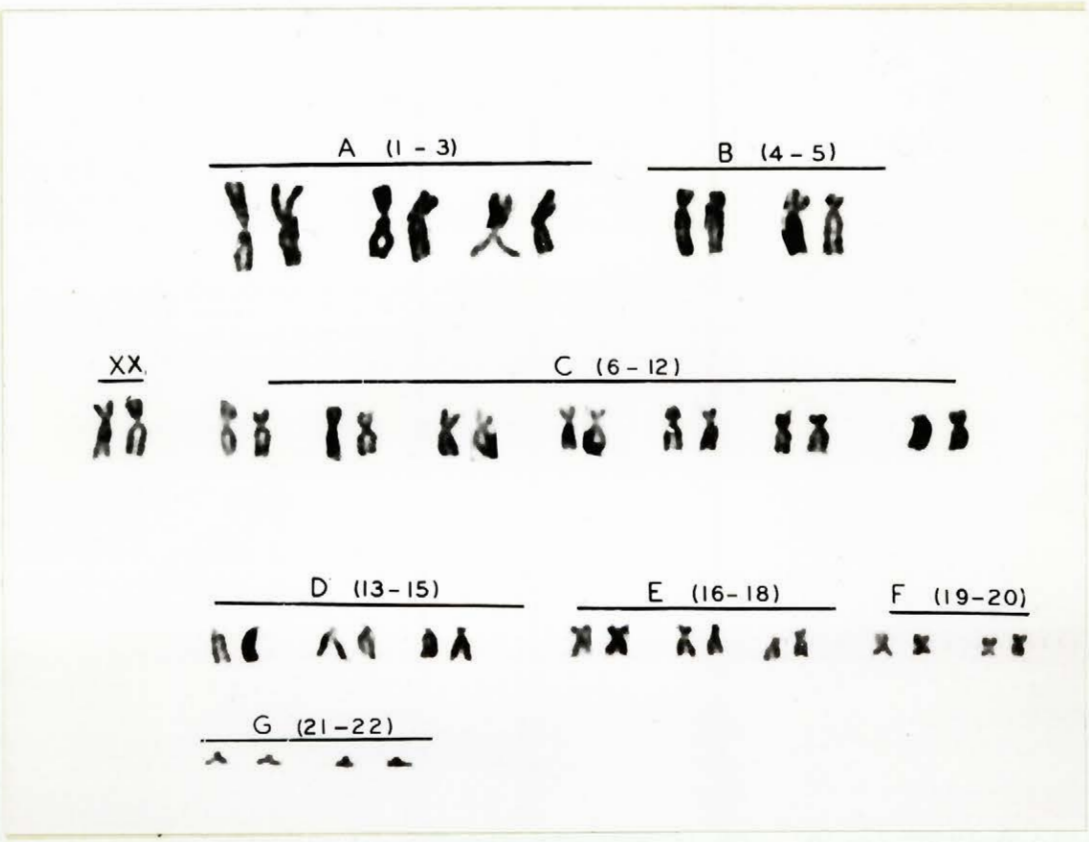
It seemed that one of the E chromosomes 17/18 had a deletion of the short arm. The finding was not typical for every cell analyzed and it was very difficult to make a definite diaghosis. Buccal smears were done on two different occasions and found normal in both instances.

Final diagnosis

If the cytological findings represent the true genotype of the patient,

one can state that the patient had an abnormal karyotype. Partial deletions of the autosomal chromosomes have not been described very often in the literature, and the case will be discussed later. The loss of chromosomal material seen in this patient may be responsible for the described physical abnormalities.

FIGURE 45 - KARYOTYPE OF CASE 9



e. Gastro intestinal

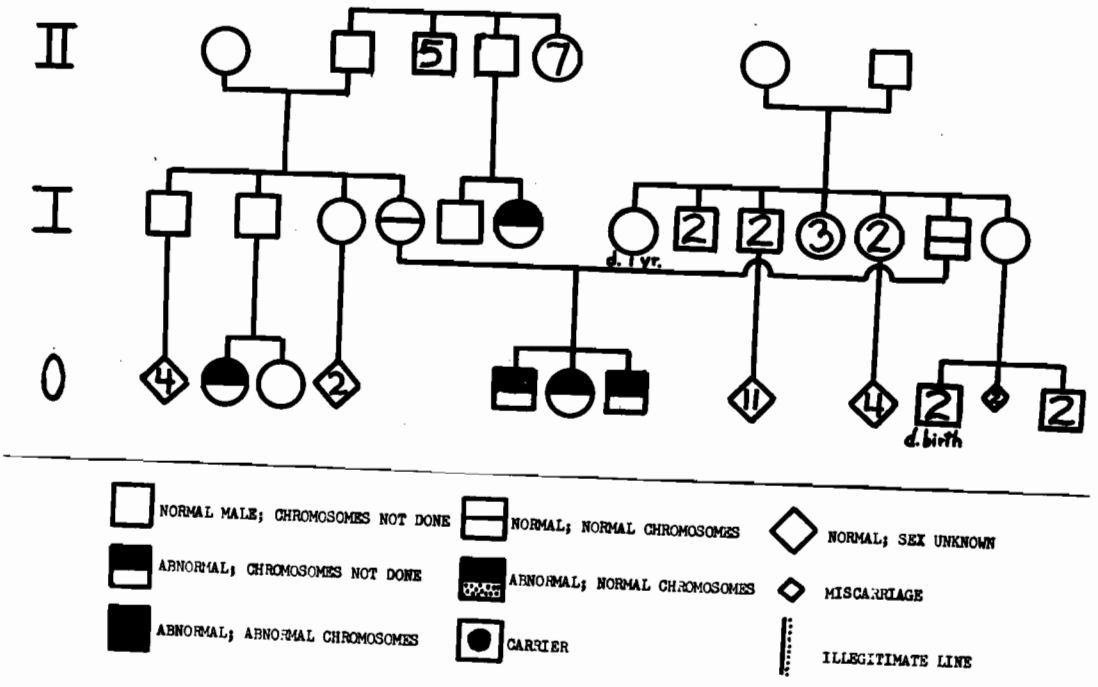
i Family (12) Hirschprung's disease

Mario B. (M.CH. Gen. CD 137) was born on September 23, 1962. His parents were referred for counselling because the boy presented an intestinal aganglionosis and a kidney malformation, and there were two sibs similarly affected.

Family History (Fig. 46)

The parents were French Canadian and unrelated. The father was 36 and the mother 28 when the child was born. The proband (0-7) was the third boy born in the family. The first two (0-5, 0-6) died of intestinal obstruction. Two paternal c ousins were said to be mongoloid. No information is available on them. The pregnancies were uneventful. The mother however stated that she had severe episodes of constipation in the past.

FIGURE 46 - PEDIGREE OF FAMILY 12



Physical examination

The birth weight of the first child was 9 lbs 10 oz. The second weighed 8 lbs 11 oz. Finally the proband's birth weight was 9 lbs 9 oz. They were all full term and delivered normally. They were all diagnosed as having Hirschprung's disease. The proband also had a renal anomaly. The first boy died after one month and the second died after 18 days of life. Apart from the gastro and genito anomalies the presented no other obvious physical anomalies.

Cytogenetic studies

The chromosome studies were done on both parents. On the first examination the father was found to be normal. The mother however presented some chromosomal breaks in a high percentage of her cells.

Chromosome number	44	45	46	47	48	Poly-ploid	Cells with breaks	Total
Mother 1	0	0	60	0	0	0	15	60
Mother 2	0	0	15	0	0	0	0	15
Father 1	0	0	5	0	0	0	0	5
Father 2	1	0	24	0	0	1	0	26

However, the second blood culture done three months later was normal in both parents. No breaks were seen in the mother's cells. The second analysis was done 2 months after the first one and 6 months after the mother had a radiological examination to look for an intestinal anomaly. The origin of the chromosomal breaks may be due to the X-rays or less likely to the culture technique itself since the control tubes did not yield any

chromosomal aberration under the same conditions.

There was no sign of mosaicism or translocation in either one of the examined parents.

Final diagnosis

The condition of the children in this family was described as Hirschsprung's disease. The chromosomal studies done on the parents ruled out the possibility of a parental chromosomal translocation, which could have been responsible for the transmission of the disease. The b reaks found in the first culture of the mother's leucocytes were probably caused by external factors since they had disappeared on the second examination.

ii Family (13) Abnormal G chromosome

Yves T. (M.C.H. 245011) was born on January 16, 1963 in Moncton, New Brunswick, and immediately transferred to the Montreal Children's Hospital because he had an imperforate anus and many other congenital anomalies. He died 21 days later.

Family History

The proband was the first born of a very young mother. She was 20 and her husband 22 when Yves was delivered. The parents were unrelated, and of French Canadian origin. The mother had two sisters who were married. One was 35 years old and had 3 miscarriages and the second was 29 and previously had 4 miscarriages. The father was the only married man in his family.

Physical examination

The following abnormalities were found throughout the physical examination and during the post-mortem: the boy had a malformed skull, micrognathia, low set ears and an haemangioma of the face covering the base of the nose and the forehead. There was marked hypertelorism. The fissures between the lobes of the lungs were abnormally formed. There was a septum primum defect. There was a stenosis of the left uretero-pelvic junction and a right hydroureter and hydronephrosis. The meatus was constricted. The anus was imperforate. The feet showed bilateral talipes equino-varus. The testes were undescended.

The patient had apparent mental retardation and marked failure to thrive. His finger prints showed a high triradius on the left hand, simian creases on both hands but no abnormal pattern in the third interdigital space. The feet were covered with correcting casts at the time of examination, and the soles could not be examined then.

Cytogenetic studies (Figs. 47, 48, 49).

The chromosomal studies were done on the patient and the culture showed an abnormality of the karyotype. The total number of chromosomes was 46, but there was a member of the G group or the Y chromosome from which a segment appeared to be deleted. On the other hand one member of the G group carried on its short arms some extra material equivalent to half the length of a number 21/22. All the cells analyzed showed the same abnormality of the chromosomes.

Chromosome number	44	45	46n	46 abn.	47	48	Total
Proband	0	0	0	60	1	0	61

The parents lived far away and did not accompany their child when he was admitted to the hospital. Their chromosomes should be analyzed in the near future. This may give the answer to the problem seen in the patient, in reference to the origin of the translocated piece.

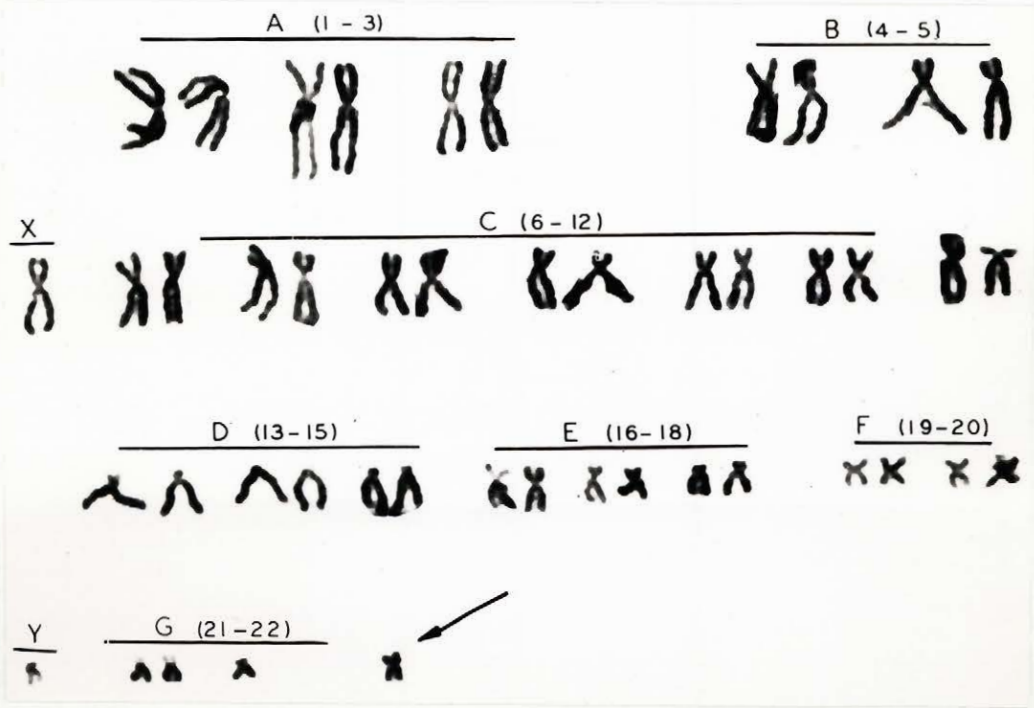
In most of the cells 2 chromosomes of the G group had satellites. The deleted member has never been seen with satellites. None of the cells had 4 satellited chromosomes, which would have been the only way to prove that the translocated chromosome was the Y chromosome. With the cytological information available so far the following conclusions are drawn:

1. The partially deleted chromosome may be a Y chromosome or a member of the G group 21/22.
2. The translocated piece is attached either to a Y chromosome, or a number 21/22.

Vaharu (1961) reported a case of partial Y deletion in which there

was an imperforate anus and malformations of the genito-urinary tract. Since one can identify the Y chromosome without too much difficulty by its general appearance (the Y is bigger and its long arms are closer together than a number 21/22) in the present case one can suggest that the deleted chromosome is the Y chromosome because none of the other four small acrocentrics have the same peculiarity. But variations in size of the Y have been mentioned before and one may be dealing here with a normal variation of a small Y male sex chromosome. If so, the only abnormality left in the karyotype would be the translocated piece from some large chromosome onto a member of the G group, which would be responsible for the phenotype described.

FIGURE 47 - KARYOTYPE OF PROBAND FAMILY 13



FIGURES 48, 49 - KARYOTYPES OF PROBAND FAMILY 13

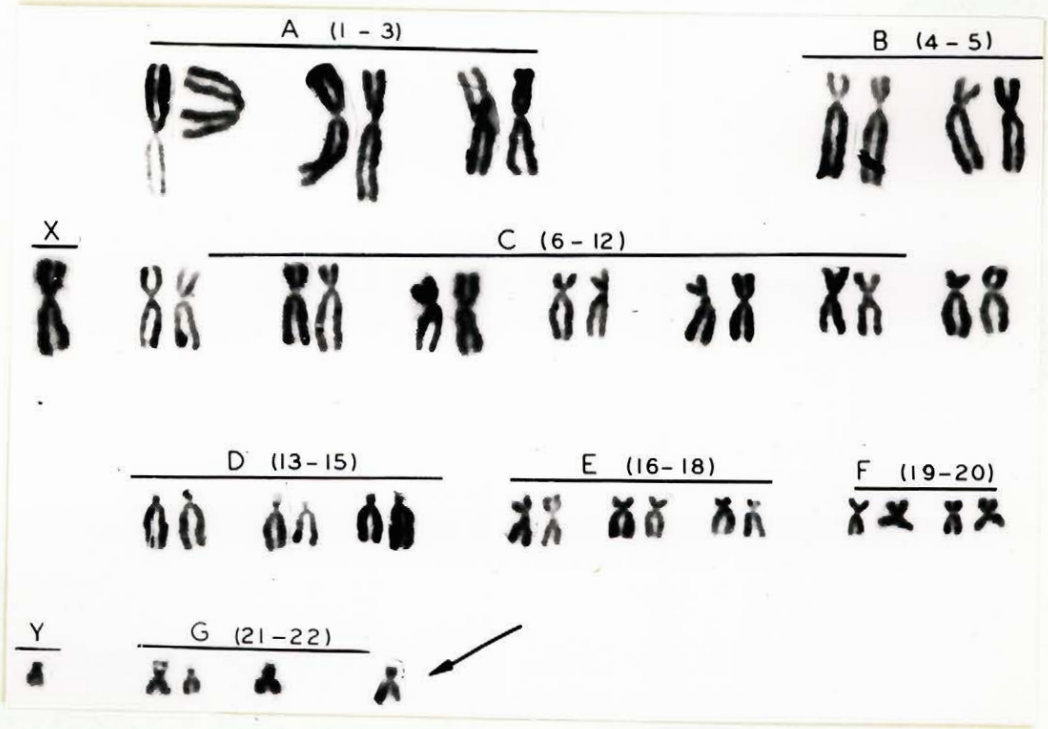


Fig. 48

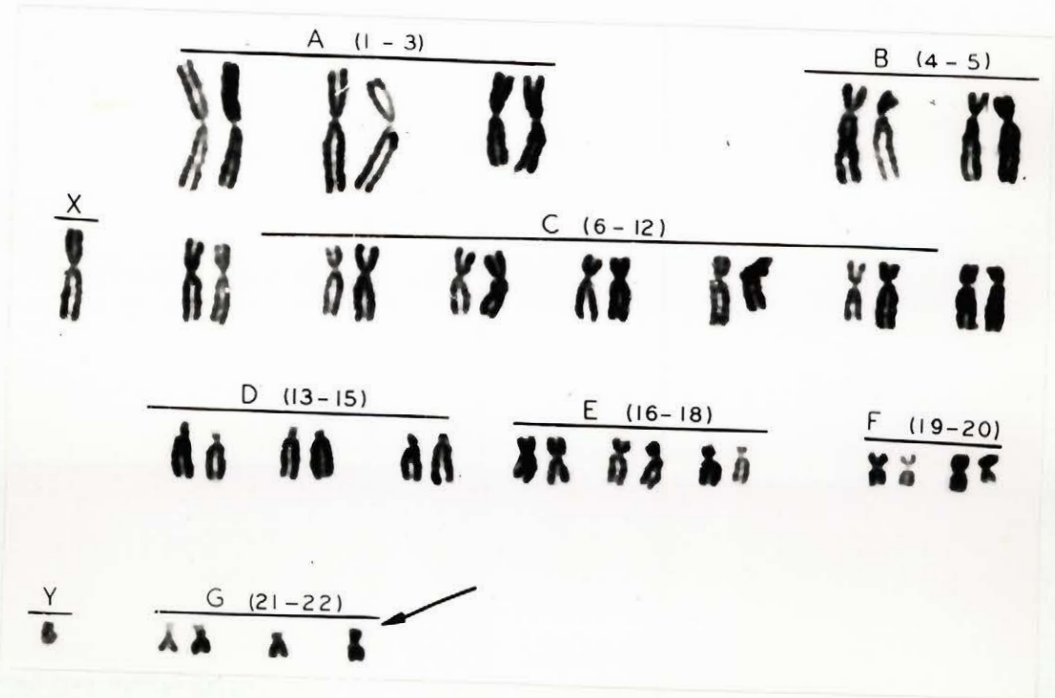


Fig. 49

Final diagnosis

The final diagnosis at death was multiple congenital anomalies of unknown origin. Cytologically the patient had an abnormality which could be described as a translocation which could have originated from a transfer of material from the Y chromosome to a member of the G group. However, it is possible that an unknown chromosome donor was responsible for the presence of extra material on a small acrocentric.

f. Genito-urinary

i Family (14) Familial sexual anomalies

Helene T. (R.V.H. 222511) was born on June 30, 1932. She was referred to the Genetics Department for counselling because she had a large number of miscarriages.

Family History (Fig. 50)

The proband (I-8) was the eighth child of a family of ten children. The parents were unrelated. One brother (I-5) died accidently at the age of four months. Five brothers and sisters had a malformation of the genito-urinary system, as described in Table 7. The patient had 5 miscarriages, each after at least 15 weeks of pregnancy. She also had one ectopic pregnancy that lasted 12 weeks and one hydatiform mole that was removed after 4 1/2 months of evolution.

FIGURE 50 - PEDIGREE OF FAMILY 14

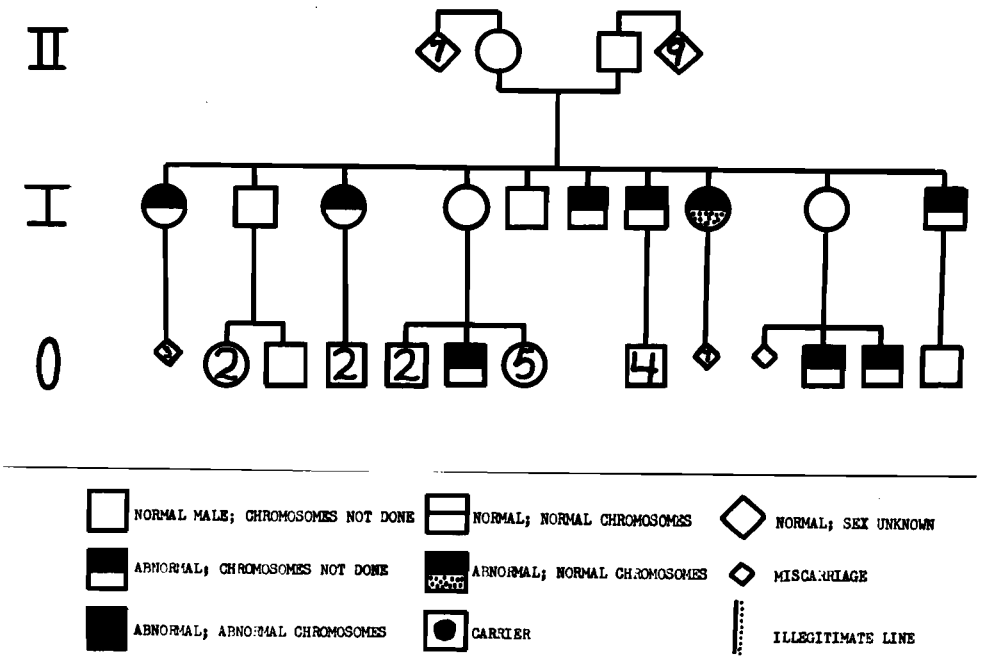


TABLE 7

LEGEND OF PEDIGREE OF FAMILY (14)

I-1	Female with infantile uterus. Had three miscarriages
I-2	Normal male
I-3	Female with double uterus and vagina. Had two children
I-4	Normal female
I-5	Male died at 4 months of age, accidentally
I-6	Male with abnormal sexual organs
I-7	Male abnormal: has three kidneys
I-8	Proband: had 3 miscarriages, one ectopic pregnancy, one mole, and two more miscarriages
I-9	Normal female
I-10	Male with hypospadias

Physical examination

The patient was perfectly normal except for a bifid uterus.

Cytogenetic studies

The chromosomal studies were done on the proband because of the history of familial sexual dysgenesis. The chromosome count was 46, and both XX chromosomes were found to be normal, as far as one can tell.

Final diagnosis

This unusual family, in which both males and females had a dysgenesis in the development of their genito-urinary system strongly suggested at the time of study that one X chromosome could have been involved. But with the actual techniques used for the analysis of the chromosomes many small aberrations of the chromatids may be unseen, and therefore be class-

ified as normal. It may also be a developmental trouble or the result of one rare recessive gene.

ii Family (15) Familial nephropathy

Jean-Claude T. (M.C.H. 100019) was born on February 6, 1949 and hospitalized more than once for treatment of a nephropathy that seemed to have a familial character. The parents were then referred to the Genetics Department for counselling.

Family History

The father was 27 and the mother 20 years old when the child was born. They were both French Canadian. The entire family is now under thorough study from a genetic point of view. Many relatives are affected and the mode of transmission of the disease appears to be autosomal dominant. One older sister presented some hematuria.

Physical examination

The proband presented with polyuria since the age of 5 months. He has had persistent albuminuria and hematuria. The physical examination was entirely negative.

Laboratory data

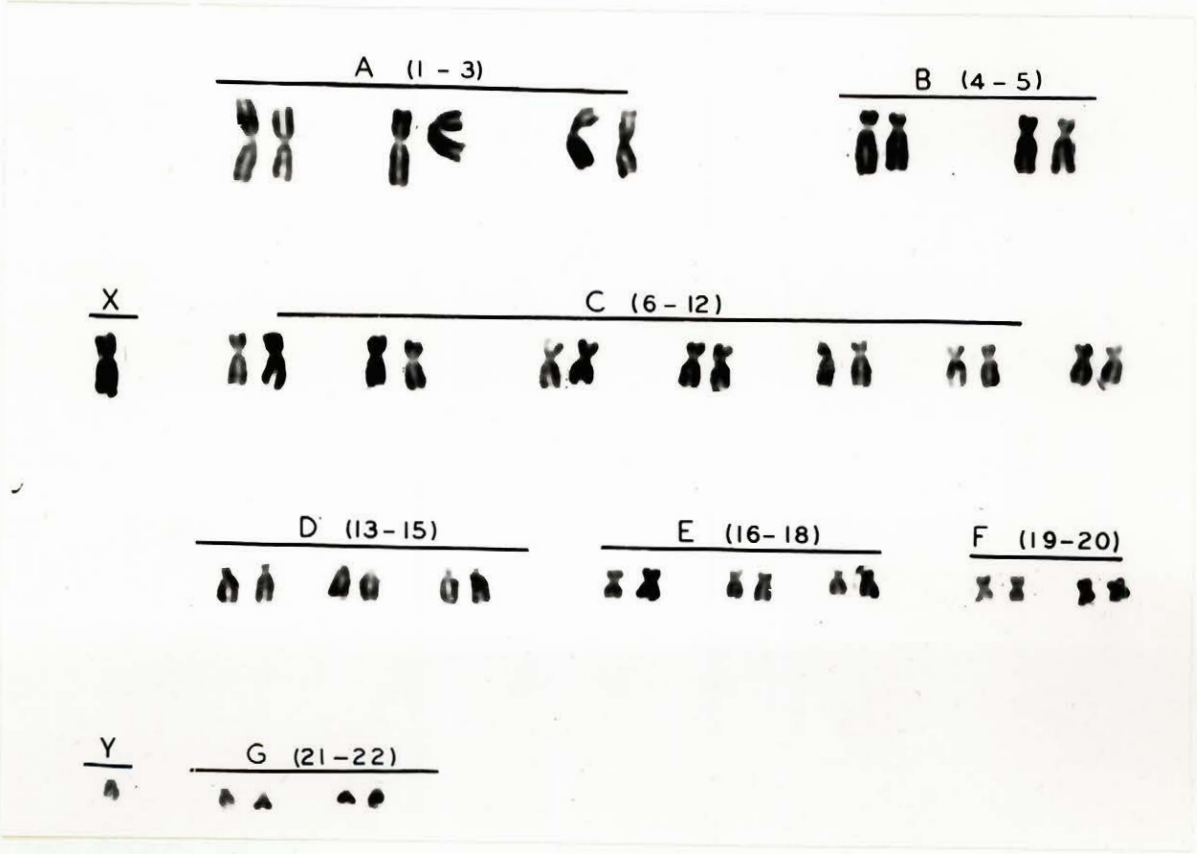
The audiogram was normal. The radiological examinations revealed that the left kidney was smaller than the right. A renal biopsy was done and the reports read as follows: "Subacute or recurrent proliferative glomerulonephritis, and a pathological condition determined by the presence of a glomerulonephritis."

Cytogenetic studies (Fig. 51)

A peripheral blood culture done on the patient showed that the cells in division had a modal count of 46 chromosomes.

Chromosome number	44	45	46	47	48	Poly-ploid	Total
Proband	0	0	50	0	0	0	50

FIGURE 51 - KARYOTYPE OF PROBAND FAMILY 15



Final diagnosis

The cytogenetic studies were done on the above patient because a report from Gagnon (1963) showed that in some patients of the same family there was some evidence of mosaicism in the peripheral blood cultures:

some cells in a percentage varying from 8-15% had an extra chromosome of the F group. Not all the patients had this mosaicism, and an increase in the abnormal cells was seen in more severely affected patients, or in patients in acute crisis.

The proband being normal, the same studies were done on an 18-year-old girl, cousin of the proband, who presented the same symptoms. The results were also normal. Unfortunately the same patients have not yet been examined by Dr. Gagnon. It would be interesting to note if the mosaicism is due to the technique or if the abnormality is present only in a low number of affected people. In this case one could suspect the presence of a familial mosaicism not due to the nephropathy.

iii Family (16) Multiple malformations of unknown origin

Gilbert L. (M.C.H. 193704) a male, was born on October 21, 1959, and admitted to the hospital 7 months later for diagnosis. On admission his condition was named pseudohermaphroditism and his parents were then referred to the Genetics Department for counselling.

Family History (Fig. 52)

The father was 27 and the mother 20 years old when the proband was born. They were both French Canadian and not related. Gilbert was their second child, but the product of a third pregnancy. The first gestation in 1957 resulted in a miscarriage and the second in 1958 resulted in a normal boy. Following the birth of the patient another malformed boy, Rejean, was born in 1961. Finally a normal boy was born in 1963. The mother stated that never during any of her pregnancies had she taken other drugs than common vitamin and mineral pills. One sister of the father (I-6) was mentally retarded and had a mental age of 10, with no mongoloid stigmata. Two first cousins of the proband (O-10, O-12) were also mentally retarded and one of them was known to be mongol.

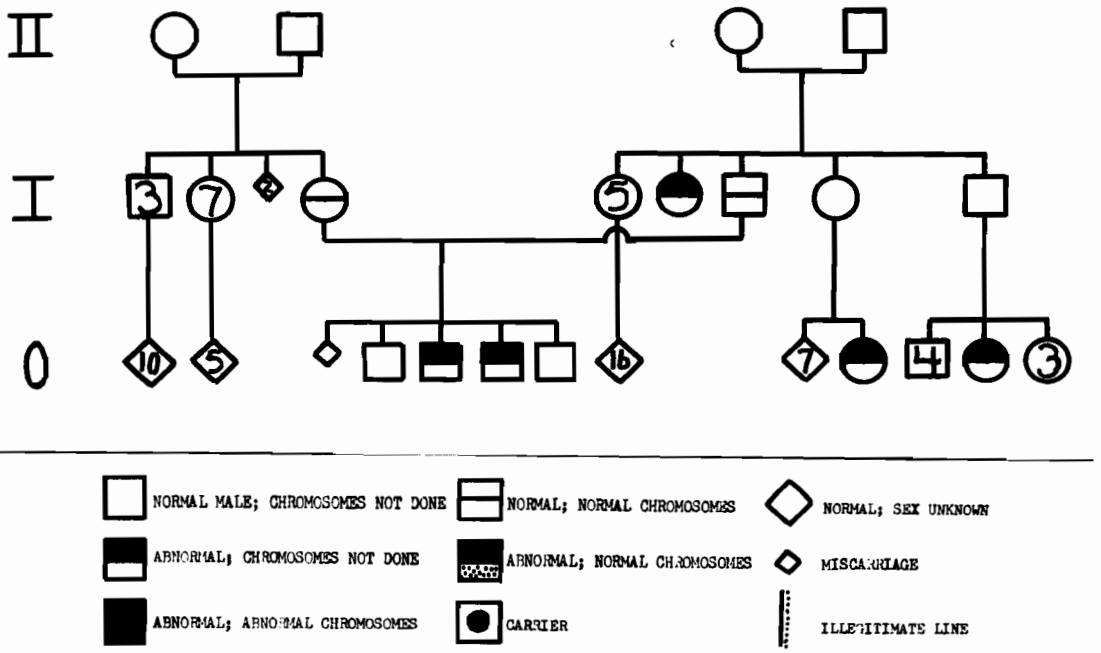
Physical examination (Figs. 53, 54)

The proband was born by breech. His birth weight was 5 lbs, he was mentally retarded and presented failure to thrive. His head circumference was 14 1/2" at 7 months of age. He had a micrognathia, his skull was abnormally shaped, his neck was short, his ears were big and low set. His palate was high and arched. The heart was normal on auscultation. The scrotum was underdeveloped. There was a hypospadias at the base of the penis. One testicle could be felt in the left inguinal canal. No intravenous pyelogram was performed but the treating physician felt that an ab-

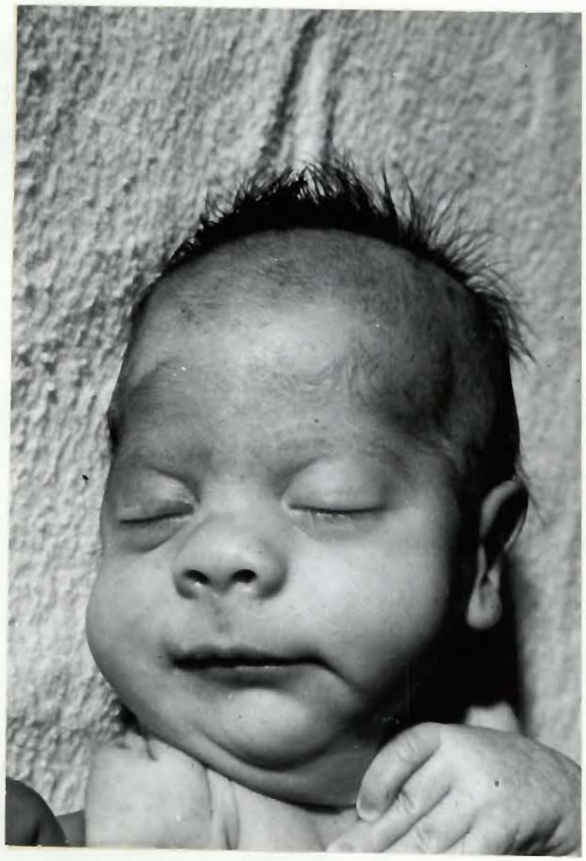
normality of the urinary tract would be suggested as well. There was a syndactyly of the second and third toes on both feet.

Rejean L. (M.C.H. 216287) was born in 1961. His borth weight was 5 lbs 3 oz. His head circumference was 12 1/2". He also had failure to thrive, a microcephalic skull and a high arched palate. The patient was very irritable and mentally retarded. His neck was short. The heart was normal. His liver was slightly enlarged. His ears were normally set. His scrotum was underdeveloped and the right testicle was not descended. There was a hypospadias. On both feet the second and third toes were fused. There were simian creases on both hands. Unfortunately no information is available on the finger prints of the proband. The I.V.P. showed dilatation of the calices and constriction of the bladder neck. Rejean had a bilateral flexion of the second finger over the third.

FIGURE 52 - PEDIGREE OF FAMILY 16



FIGURES 53, 54 - PICTURES OF PATIENT (O-6) FAMILY 16



Cytogenetic studies

A buccal smear was done on both patients and found to be chromatin negative. The chromosomal studies done on the patient (0-6) shortly before death yielded only 4 mitoses which had 46 chromosomes. The studies were done twice on the parents to rule out a translocation. The results were normal in both instances.

Chromosome number	44	45	46	47	48	Poly-ploid	Total
Patient	0	0	4	0	0	1	5
Mother 1	1	0	10	0	0	3	14
Mother 2	0	0	25	0	0	1	26
Father 1	0	0	5	0	0	0	5
Father 2	2	0	26	0	2	3	31

Final diagnosis

The syndrome can be summarized as follows:

1. Prematurity
2. Failure to thrive
3. Mental retardation
4. Microcephaly
5. Abnormal and low set ears
6. High arched palate
7. Genito-urinary malformation
8. Syndactyly.

Since the sex chromatin studies were negative, one could not suspect a sex chromosomal anomaly of the Klinefelter type. However, a Y deletion

could have been present. On the contrary the Y seemed quite large in both the patient (0-6) and the father. In counselling the parents were told that they had a 25% risk of having another malformed child, on the grounds that the abnormality could be due to a recessive gene.

The typical flexion on the second finger over the third seen in the patient (0-6) suggests a relation with the trisomy 17/18. There was no record available on the number of arches on the fingers. However, one is struck by the failure to thrive, the micognathia and the malformations of the genito-urinary tract. The syndactyly is usually seen in the D syndrome.

The cell count being so low on the patient (0-6) it is difficult to rely on the cytological examination for a definite diagnosis. Assuming that both parents had normal chromosomes, the children may have had a partial trisomy or some degree of mosaicism for a D or more likely an E chromosome.

iv Family (17) Triple X female

Phyllis I. (M.C.H. 254058) was born on October 10, 1955. She was admitted to the hospital with her older sister for investigation since both of them were developing too slowly though the proband had precocious secondary sexual characteristics.

Family History

Both parents were in their twenties when their only two daughters were born. They were not related, and there was no history of malformations or retarded growth in the family. Both gestations were uneventful.

Physical examination and laboratory data

The proband's sister (M.C.H. 254057) was born on January 1, 1954. They were hospitalized at the same time and the following was noted at that time. Celia was eight years old and Phyllis seven when the physical examinations were performed.

	Celia	Phyllis
Age	8 years	7 years
Birth weight	6 lbs 3 oz	6 lbs 8 oz
Present weight	16.2 kilos	17.4 kilos
Height	44 inches	42 inches
Albumin	4.54 gms %	4.32 gms %
alpha 1	0.26 "	0.19 "
alpha 2	1.40 "	1.31 "
beta	0.56 "	0.85 "
gamma	0.53 "	1.254 "
17 ketosteroids	1.035 mgm/day	1.254 mgm/day
17 hydroxyketo	5.670 "	5.950 "

Xylose test	normal	normal
Fat absorption test	normal	normal
Bone age	9 years	5-6 years

In the laboratory findings it was noted that the albumin and alpha globulin was above normal in both cases. The beta and gamma globulin were below the normal in Celia. The variation in the bone age is not too significant. The phosphorus values were low in Celia.

The physical examination revealed that both children were small and generally underdeveloped for their age.

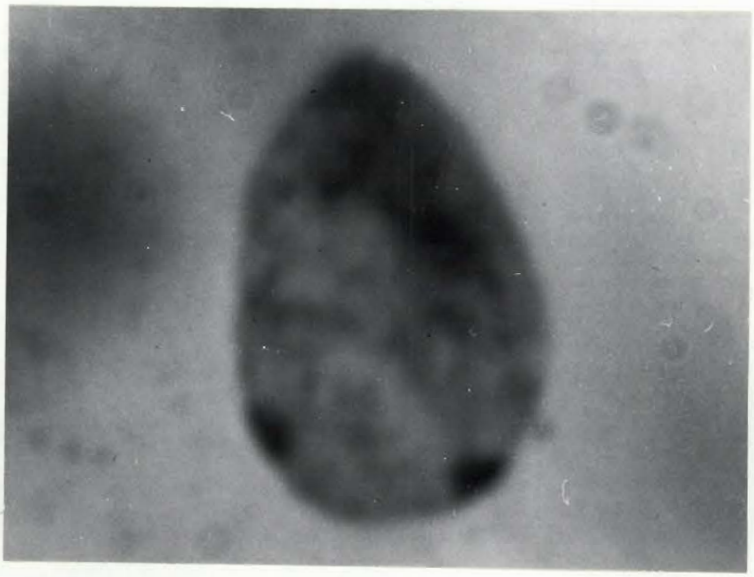
Cytogenetic studies (Fig. 55)

The chromosomal studies were done on the two sisters at the same time. The youngest one, the proband, was found to have an abnormal karyotype, with an extra long submetacentric chromosome. The sex chromatin studies were normal in Celia but showed two chromatin masses in a high percentage of cells of the proband. It was then assumed that the extra chromosome was an X chromosome.

Chromosomal number	44	45	46	47	48	Poly-ploid	Total
Phyllis	0	0	0	48	0	0	48
Celia	0	0	55	0	0	0	55

The parents were not available for chromosomal studies.

FIGURE 55 - SEX CHROMATIN OF PROBAND FAMILY 17



Final diagnosis

A final diagnosis of Triple X was made in the case of the proband. The investigations were not completed at the time of this study and it had been suggested doing chromosomal analysis of more tissues, to rule the mosaicism in both sisters, though the results are quite convincing so far. The normal sister may have been a mosaic in the early stages of her development and may have lost the abnormal trisomic cells, as her sister may have been a true triple X.

v. Case (10) Sexual mosaicism

Deborah D. (M.C.H. 229958) was born on April 20, 1950 and admitted to the hospital at the age of twelve for investigation of a persistent pain in the left groin . During a previous admission at the age of 9 months she had a bilateral inguinal hernial repair.

Family History

There were two other normal sibs in the family. The parents, who were not related, were well at the time the patient was seen and were in their thirties when the patient was born. The family history is negative.

Physical examination (Fig. 56)

The weight of the patient was 50.6 kilos when she left the hospital. The physical examination did not reveal any gross abnormality. She had a small tumor on the right foot which was described pathologically as a benign neuro-epithelial naevus. A vaginal examination was performed: a half inch canal was found ending in a blind end with no cervix. The external genitalia were in the normal limits. During the laparotomy some gonadal tissues were found in the right abdomen and in the left inguinal canal. Both tissues were described as being immature testicular tissues after study of the biopsies. No uterus was found. The testes were left in place.

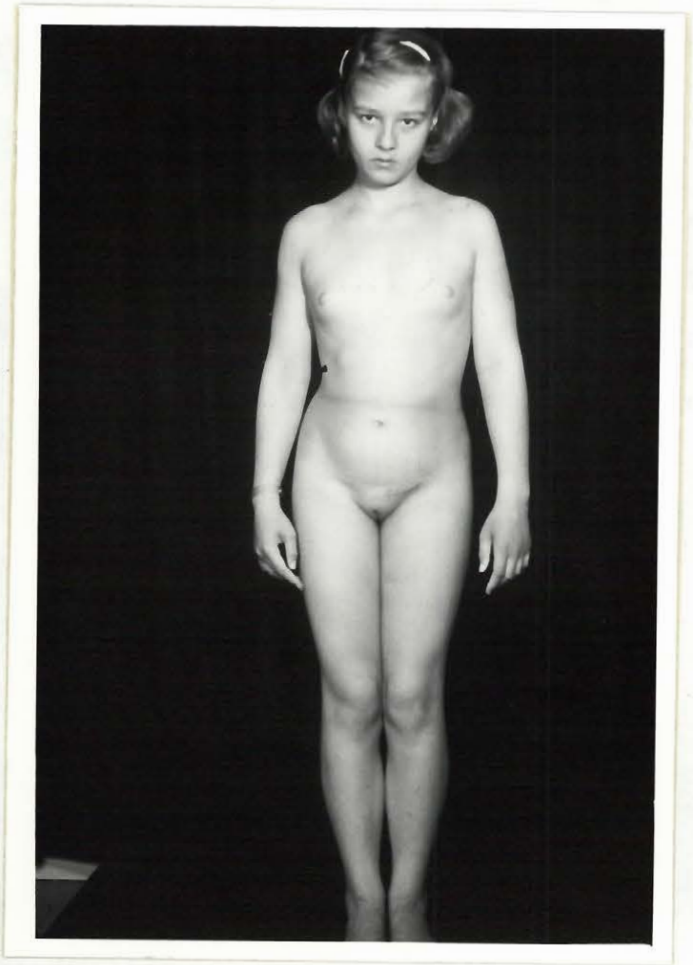
Laboratory data

The radiological examinations, which included an intravenous pyelogram were normal. The FSH was positive at 13 mouse units per 24 hours, it was negative at 52 mouse units, that is considered a high value for her age.

Cytogenetic studies

A buccal smear was done and found negative. The chromosomal studies revealed two types of cells: there was a low percentage of XO cells and mainly XY cells.

FIGURE 55 - PICTURE OF CASE 10



Final diagnosis

A clinical diagnosis of testicular feminization was made. Cytologically the patient is a mosaic XO/XY. The symptoms and physical anomalies found during the different examinations performed, confirmed the fact that the patient was originally a male, but due to the loss of a Y chromosome probably by late non-disjunction, she had severe disturbance of her sexual

development.

vi Case (11) Pseudohermaphroditism

Mark G. (M.C.H. 231173) was born in England on December 20, 1954. The child presented multiple anomalies at birth and he was immediately placed under investigation, and treatment. Four years later the patient came to America with her parents and subsequently was referred to the Montreal Children's Hospital for further assistance. He was seen in the Genetics Department for a sexual anomaly.

Family History

The English parents were unrelated and young at the time of birth of the patient. Mark was the only child born in this family. There was no history of congenital malformation in the other members of each family.

Physical examination

At birth the child presented many anomalies of which the heart malformation seemed to be the most severe. On the other hand the patient also had malformed external genitalia. The medical report obtained from the English hospital states that the sex chromatin of the child was positiveand that they made a boy out of him because it is easier for a man to earn his living. The clitoris was enlarged and opened at the base. There were no testes. The clitoris was transformed into a male urethra and the hypospadias was corrected. No heart surgery was done.

The investigations done in Montreal revealed that the patient had a Fallot tetralogy. The intravenous pyelogram showed a mild hydronephrosis on the left side. The radiological examination of the chest confirmed the diagnosis previously made clinically: the heart was enlarged on the X-ray picture. The boy had a female stature and manners. There was no webbing of the neck and the skeleton structure was normal. His

heart defect was corrected partially. The endocrinological tests confirmed that the boy had a female constitution.

Cytogenetic studies

The chromosomal studies showed that the boy had an XX sex constitution. The karyotype was normal otherwise. No XY cells were found. No other investigation was done on other tissues to determine if the child was a mosaic. The chromatin studies however, were done on different tissues and were all positive. There was a high percentage of drumsticks in the polynuclear cells. A total of thirty two cells in mitotic metaphase were analyzed and found to have 46 chromosomes and an XX sexual pattern.

Final Diagnosis

The cases of pseudohermaphroditism are always very difficult to determine accurately. In this case it is obvious that the child is a female. No testicular tissue was found. It was said previously that the Y chromosome is strongly male sex determining. The absence of male sex tissue seems to prove that if the child is mosaic, there was no XY cells in the development of the sexual organs.

vii Case (12) Sexual mosaicism

F.X. Des. (Q.M.V.H. 67420) a 66-year-old man was born on June 29, 1896. Both parents were French Canadian. He was hospitalized for cardio-vascular troubles and found to have marked hypogonadism.

Family History

The patient had three normal sisters and one brother also treated for heart trouble at home. One unmarried sister died at the age of 57 of uterine cancer. As far as the patient can recall everyone on both sides of the family seemed to live a normal life and no one was known among the relatives to have congenital malformations. The patient's parents died of heart attacks. The father was 31 and the mother 27 when the patient was born.

Physical examination and medical history

The patient stated that he started to shave when he was 20 years old. Five years later, at the age of 25 he started to gain weight very rapidly and his breasts enlarged markedly. He claimed that he had some genital activity described as libido and nocturnal emissions, as well as short-lived erections. He worked hard all his life, and never worried about getting married or about the fact that he might have been abnormal.

His blood pressure was 170/100. His weight 186 lbs. The head to toe length was 66 inches. His skeleton was of the male type, and he had a marked trunk obesity. The hair distribution was feminine on the pubis. He had none on the thorax. The hair was sparse on the face and he used to shave once a week. His voice was normal, as well as his manner. The inguinal canal was clear on both sides. The penis was infantile, and a hypospadias could be noted at the base of the urethra. There was marked

gynecomastia and the prostate seemed very small if present at all. His thyroid was enlarged.

Laboratory findings

The hemogram, urine examinations and ESR were normal. The uptake of I^{131} was low at 14.6% in 24 hours. The 17 ketosteroids were 16.5 mgms per 24 hours (normal 9-22 mgms/24 hours). The 11 hydroxycorticoids were 4.1 per 24 hours (normal 6-15/ 24 hours).

The radiological examinations revealed that the kidneys were normal, as well as the skull. The radiography of the chest showed a mass in the right upper mediastinal region due to thyroid enlargement with displacement of the trachea.

Cytogenetic studies (Fig. 57)

A buccal smear was done on two different occasions. Cells from both sides of the mouth were examined. Some 25% of the cells were found to have a chromatin mass at the periphery of the nucleus. This was interpreted as a positive sex chromatin. The following counts were found in the cells in division:

	XO	XXY	XY	Total
Proband 1st culture	5	30	65	100
Proband 2nd culture	2	14	25	41
	7	44	90	141

From cultures made from peripheral blood only, the patient was diagnosed as being a mosaic of type XO/XXY/XY.

FIGURE 57 - SEX CHROMATIN CASE 12

Final diagnosis

The phenotype of the patient seemed to be the result of at least one non-disjunction that took place early in his development. It is also possible that this kind of mosaicism arises by the fusion of abnormal parental gametes. The low percentage of XO cells suggests that they may be due only to mitotic cell non-disjunction.

viii Case (13) Sexual mosaicism

Camille M. (M.C.H. 218394) was born on October 15, 1945. He was referred to the Genetics Department during his last hospitalization in 1962. Camille had an abnormal development of the sexual organs, and had been in hospitals many times for investigation and treatment of his condition.

Family History

The parents, who were of French Canadian origin, were third cousins. Camille was the sixth eldest of a family of fourteen. The father was 31 and the mother 23 years old when he was born. No one in the family had a condition resembling the patient's.

Physical examination (Fig. 58)

The patient was an obese and tall 15-year-old boy, very cooperative and alert. His voice was not completely masculine. His head was normal. His breasts were enlarged, but the nipples were small. There was a small phallus, and an opening posterior to the phallus which admitted a small finger to a depth of one inch on either side. A mass could be felt in the left scrotum, which incidentally was bigger than the right. The pubic hair had a female distribution. Both the pubic and axillary hair started to develop early, that is around the age of 11. Some brown pigmentation was present at the upper region of both thighs. The hair was present on the legs but sparse and fine on the rest of the body. His skin was smooth. The bone age was of a normal male.

An exploration of the lower abdomen revealed the presence of a right ovarian tube and ovary and a hemi-uterus, with a small cervix protruding

into the anterior vaginal wall. Pathologically there was a stenosis of the Fallopian tube and failure of luteinization of maturing Graafian follicles.

Laboratory data

An atypical cholinesterase with high activity was demonstrated after the patient had presented prolonged apnea to an ordinary dose of succinylcholine. Studied at the University of Toronto the patient's serum showed the following values: cholinesterase value ..... 146 units

dibucaine number ..... 17.4 units

sodium fluoride ..... 11.3 units.

The excretion of 17 ketosteroids was normal for 24 hours: 10.47 mgms/day.

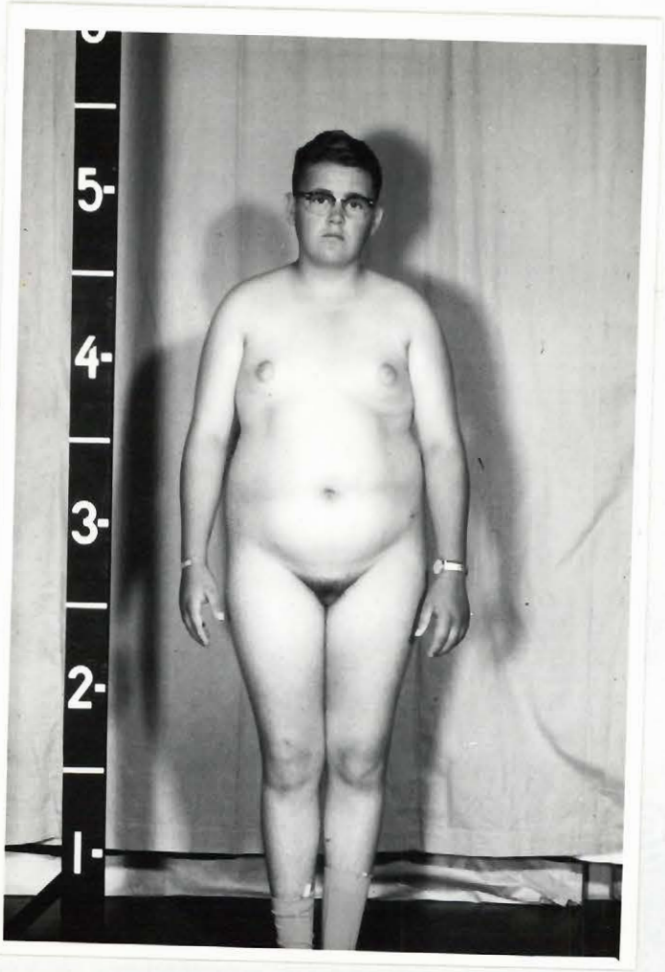
Cytogenetic studies

The blood was drawn twice for chromosomal studies. The count of chromosomes varied from cell to cell. There were cells with 45 chromosomes and some with 46 and 47. The cells with a normal count were of the XY type. The others were of type XO and XXY.

Chromosome number	44	45	46	47	48	Polyploid	Total
Patient	0	10	15	6	0	0	31
Patient	0	5	12	9	0	0	26

The presence of two X's in some of the cells was confirmed by the sex chromatin which was positive. The three different cell lines may have arisen in the egg development following a simple or a double non-disjunction of one cell line.

FIGURE 58 - PICTURE OF CASE 13



Final diagnosis

The patient was a true hermaphrodyte in the sense that he had the two types of gonads present at birth. Cytologically he was a mosaic, with at least three demonstrable cell lines.

ix Case (14) Triple X female with unusual features

O. Ren. (M.G.H. 204231) was referred to our Department when she was 29 years old for cytogenetic studies. Her case was taken into consideration since she presented with unusual features and mainly a complex sexual and gastro-intestinal pathology.

Family History

The patient was interviewed on two different occasions. She stated that her father left home when she was very young and did not get to know him. She was now living with her mother. She had five sisters and one brother all normal and alive. There was no history of consanguinity, or of malformed or retarded relatives on either side of the family. Her mother stated that while she was pregnant and carrying her daughter she felt chronically unwell but denied any specific infectious disease. She pointed out that the delivery was normal after 40 weeks gestation, and that the proband did not show any sign of anoxia. The mother added that during infancy the patient was frequently kept at home because of respiratory infections and general weakness. She was "thin and frail". Her vision was very poor and she also had to take private lessons.

Physical examination (Figs. 59, 60)

The proband was born in 1934. She had her first menstruation at the age of 14, but they have been irregular in recurrence and duration throughout her life. In 1955, she was then 21 years old, she complained frequently of headaches and falls that she attributed to her poor eyesight.

In 1942 she had a tonsillectomy.

In 1955 she had a tendon transplant for the correction of a hammer toe.

Her left ovary was removed since it was cystic. A right para-ovarian cyst was also excised. The appendix was removed. In a subsequent operation her coccyx was removed for coccydinea.

In 1956 the patient was hospitalized for sacral infection, and later for neurosis.

In 1957 the patient received psychotherapy. The medical report stated that the patient had a hysterical personality. She was then complaining of low back pain.

In 1958 the proband had her first operation for congenital bilateral cataracts. There were 5 operations in all of the same type between 1958 and 1962.

In 1959 a bone cyst was removed from her left axilla.

In 1960 hospitalization was required for the investigation of persistent headaches. During the same year she had a laparotomy following a sub-acute abdominal episode. The umbilicus was removed. Subsequently she was treated for a mucomembranous colitis.

In 1961 the patient was treated for tracheal bronchitis and sciatica. A few months later a discoidectomy was performed between L4 and L5.

In 1963 she was finally admitted to the Montreal General Hospital with complaints of weakness and general malaise of 6 months duration. The physical examination revealed a 29-year-old female whose height was 66 inches and weight 87 lbs. The crown to pubis measurement was 31 inches and the pubis to heel 35 inches, so that the upper segment of the body was smaller than the lower segment. Her arm span was 67 inches. She had a prominent forehead, low set ears and no teeth. The face and mandible were asymetrical. Her left pupil was irregular. The fundi could not be visualized clearly because the anterior tissues were cloudly: this was mainly due to the fact

that she had bilateral congenital cataracts, and that the surgical procedures did not remove all the deteriorated tissues. The heart sounds were normal. There was a midline incision on the abdomen. The pubic hair was normally present and there was no gross abnormality of the external genitalia. The vagina could not be visualized, but the uterus seemed very small on rectal examination. Apart from a mild hypoesthesia on the right side below the groin, and on the left side of the skull, the neurological examination was negative. She was allergic to penicillin, chloromycetin, novocaine and atropine.

Laboratory data

The cholesterol, calcium, phosphorus, total proteins, albumin, gamma globulin and alkaline phosphotase values were all normal. There were no urinary **porphyrins** and bilinogen. The hemogram was normal.

Radiology

The X-ray of her skull showed some calcification of the Falx cerebri. The radiological examination of her hands was normal and there was no sign of arachnodactyly.

Dermatoglyphic studies

The log. index obtained by the Walker method for the determination of mongolism was normal at - 5.19. There were no high triradius, simian creases or abnormal configuration of the hallucal area of the foot.

Cytogenetic studies (Figs. 61, 62)

The peripheral blood culture was done on two occasions. The first

examination revealed the presence of 47 chromosomes. But the poor quality of the cells in division raised a doubt about the true chromosomal complement of the patient. The second culture was done two weeks later and at the same time a buccal smear was taken.

Chromosome number	44	45	46	47	48	Poly-ploid	Total
Culture 1	0	0	0	7	0	0	7
Culture 2	0	0	0	15	1	0	16

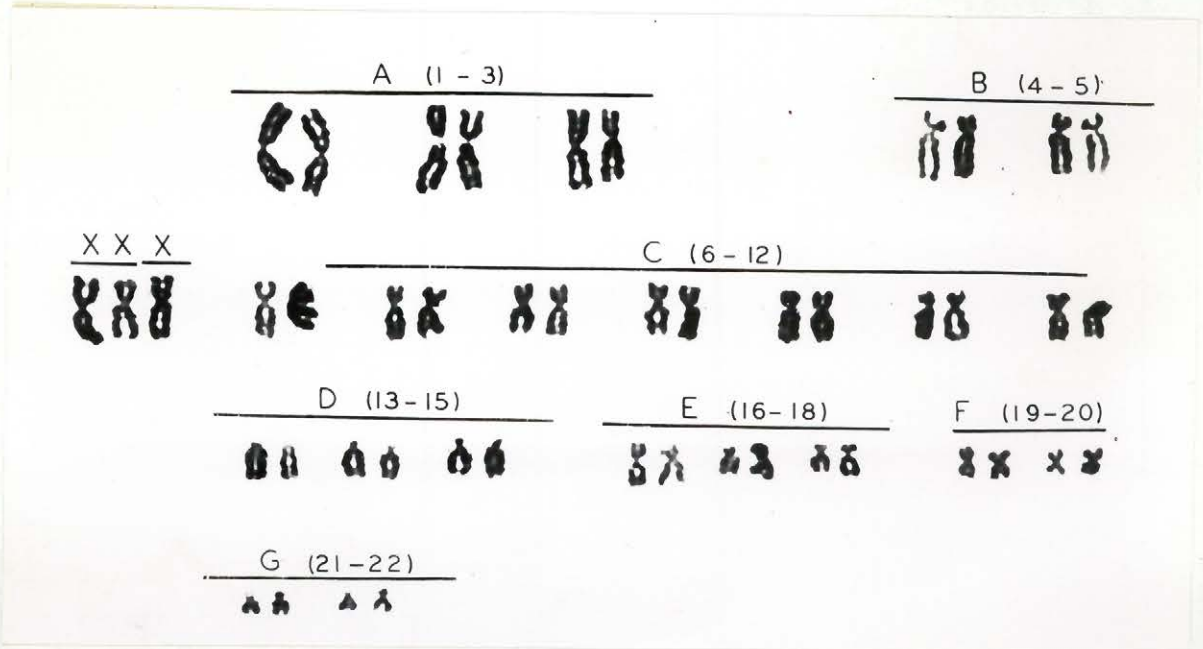
The extra chromosome was identified consistently as being one member of the C group. The sex chromatin studies obtained from the Feulganization of the buccal cells revealed the presence of two masses in 11% of the cells. The remaining number was mostly made up of a single mass at the periphery of the nucleus.

FIGURE 59 - PICTURE OF CASE 14

FIGURE 60 - PICTURE OF CASE 14

FIGURE 61 - SEX CHROMATIN OF CASE 14

FIGURE 62 - KARYOTYPE OF CASE 14



Final diagnosis

One can argue in this case that the phenotype of the patient is not in agreement with the previously described cases of Triple X females, so-called super females. The patient was however selected for chromosomal studies on the grounds that she had ovarian troubles accompanied by what seemed to be a combination of congenital malformations irrelevant to each other. This is what probably brought the physicians in 1959, when she was

25, to make a diagnosis of Marfan's syndrome. But the clinical aspect of the picture does not fit the criteria of dislocated lenses, heart malformation and arachnodactyly. The patient showed cataracts of both eyes without dislocation, her heart was normal and though her arm span was longer than her body height, her extremities, hands and feet were perfectly normal.

The multiple operations she underwent are quite significant. She had a hammer toe, repaired by a tendon transplant, one ovary removed and a cyst removed on the other one. She also had bilateral congenital cataracts and multiple alveolar cysts some of which entered the sinus cavity.

On the cytological grounds the patient can be called a super-female, presenting with atypical features.

x Case (15) XO female

Nancy H. (M.C.H. 189623) a 12-year-old girl, born on February 21, 1952, was seen in consultation because in the past and still occasionally she had vaginal bleeding of unknown origin.

Family History

The proband was the first child of a family of four. She had one brother and two sisters. The father was 26 and the mother 24 at the time of her birth, they were unrelated. The pregnancy was complicated by oedema of hands and feet and vascular hypertension after the 6th month. The same swelling of the extremities was noted in the three subsequent pregnancies. Both parents were in good health and had normal color vision. The family pedigree did not show any relative suffering from congenital malformations.

Physical examination

The patient was previously examined under anesthesia in another hospital because she was presenting with vaginal bleeding. The vagina, uterus and ovaries were described as being present and of normal size. She was seen in the Endocrinological Clinic of the Montreal Children's Hospital for a follow-up and she was found to have a short neck and short stature and to be rather obese. The examination also revealed the presence of moles or naevi on her back, arms and also irregularly on the thorax and lower limbs. The rest of the physical examination was negative, except that she had red-green color blindness.

Laboratory data

There was a marked thrombocytopenia. The urine gonadotrophins were

high at plus 26 mouse units per 24 hours, and the urine estrogens were negative at 10 mouse units per 24 hours. The creatinine was in the normal limits at 0.5 gms per 24 hours. The 17 ketosteroids were normal at 3.465 mgms per 24 hours. The FSH value was positive at 105 mouse units per 24 hours, which is very high.

Cytogenetic studies

The buccal smear done on the child was found to be negative. The chromosomal analysis revealed that the patient had only 45 chromosomes. One member of the C group was missing and it was believed to be an X chromosome.

Chromosome number	44	45	46	47	48	Poly-ploid	Total
Patient	1	27	1	0	0	0	29

Final diagnosis

The final diagnosis in this case was XO female with atypical features. Normally in cases of Turner's syndrom the internal sexual organs are rudimentary. The report on the patient seemed to indicate that the uterus, ovaries and vagina were normal. The presence of abnormal pigmentation consisting of naevi was noted. This sign will be discussed later.

xi Case (16) XO female

Therese M. (M.C.H. 239090) was born after 8 months of gestation in New Brunswick. The infant was transferred to the Montreal Children's Hospital because of failure to thrive, and recurrent vomiting. She was referred to the Genetics Department because of abnormal physical development.

Family History

Both parents were of French Canadian origin and not related. The father was 28 and the mother 24 when the child was born. There were two other sibs in the family, both normal. The mother had had no miscarriage. There was no history of malformation in the family.

Physical examination (Figs. 63, 64)

At the time of examination the patient was lying flat in her bed. At 7 1/2 months of age she could not stand or sit alone. Her scalp veins were dilated. Her neck was short and some webbing could be noted. The palate was high and arched. There was some pitting oedema of the feet and hands. Some degree of limitation existed in the arms. The external genitalia were apparently normal. The head circumference was 17 1/2 inches and the length was 26 inches. The hair line at the base of the skull was straight.

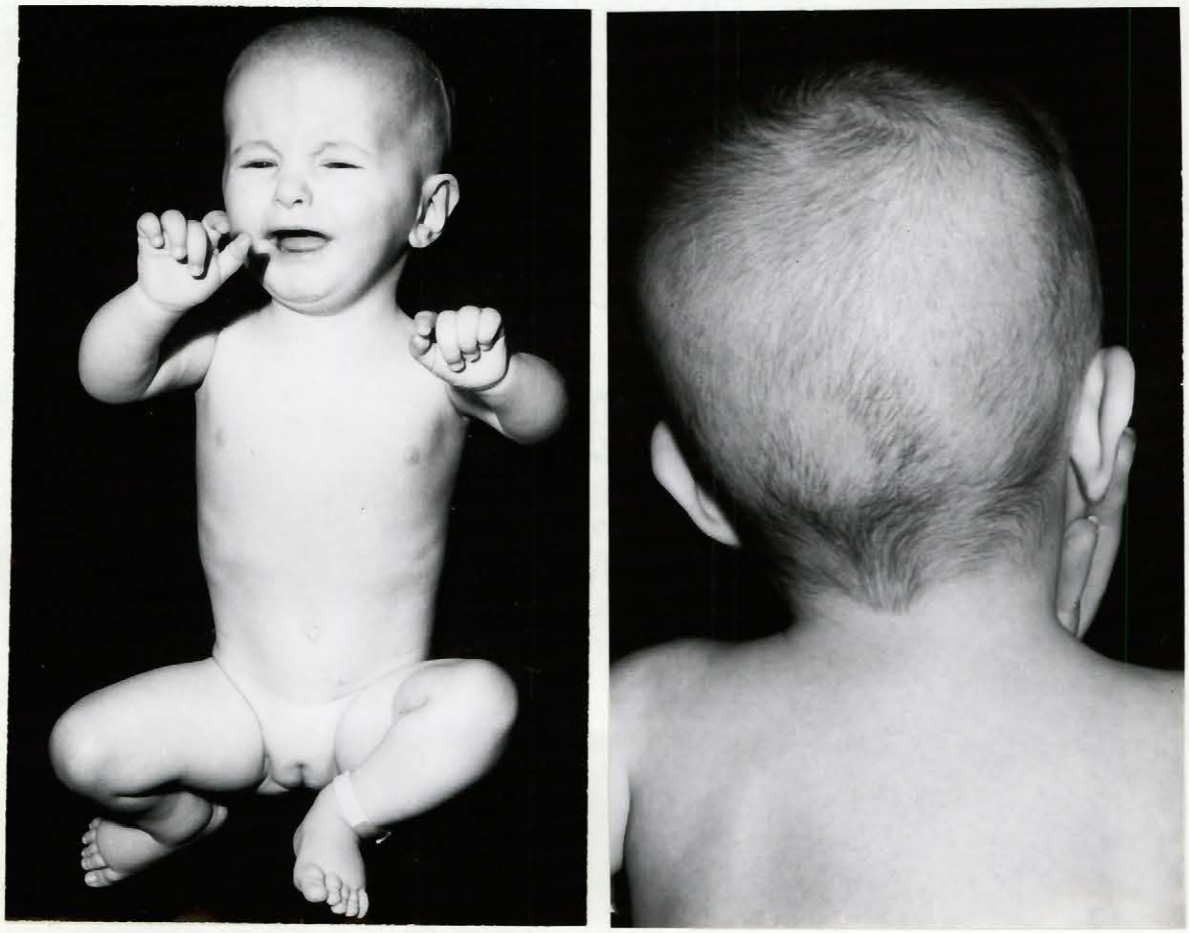
Laboratory data

The radiological examination of the skull and chest revealed no abnormality. The electroencephalogram showed some epileptiform disturbance in the left occipital region.

The FSH was positive at 6 m.u. (normal = 0). The estrogens were at 2.5 micrograms/24 hours (normal =0).

The Cattel's test for mental assessment revealed that the child was at the upper limit of the defective range.

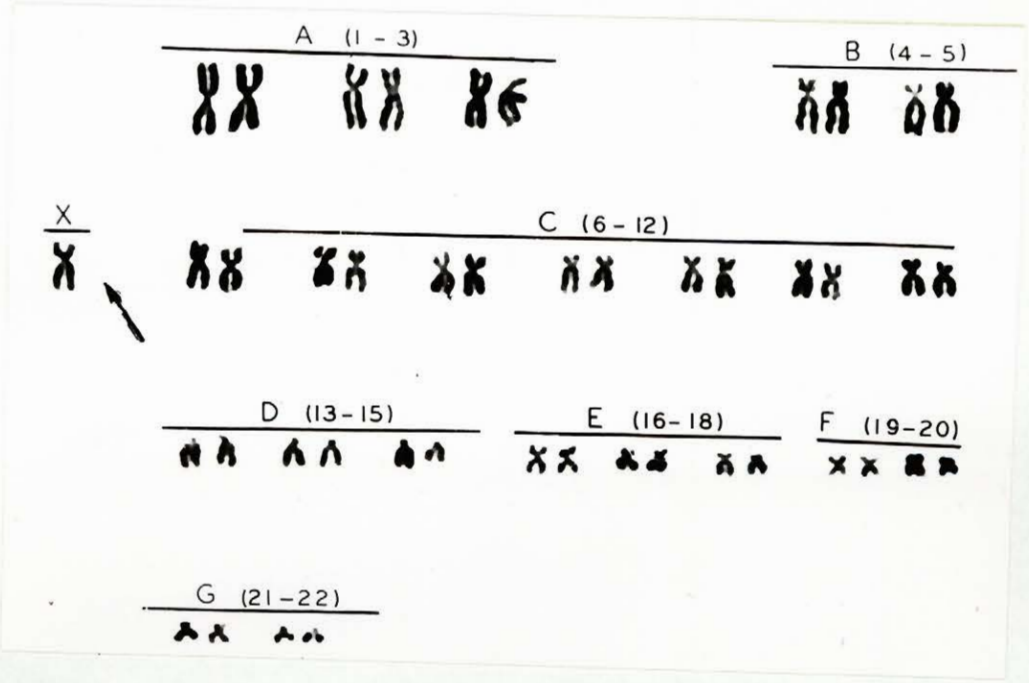
FIGURES 63, 64 - PICTURES OF CASE 16



Cytogenetic studies (Fig. 65)

A buccal smear revealed that the sex chromatin was negative. The chromosomal studies done from culture of peripheral blood leucocytes showed that the patient had only 45 chromosomes in her karyotype. The missing member seemed to be of the size of the C group, and since the chromatin was negative the cytodiagnosis was XO female. Fifty cells were counted and eight of them analyzed.

FIGURE 65 - KARYOTYPE OF CASE 16



Final diagnosis

Usually an XO female will not present anything more than some oedema of the feet at birth, unless the syndrome is accompanied by a severe heart malformation of the coarctation type which, according to Lindsten (1963) is not as common as one would expect, and actually would represent only 10% of the cases.

In view of the cytogenetic findings, this girl represents a case of Turner syndrome and is believed to have in her cells only 45 chromosomes, one sex chromosome being lost most likely in the parental gametes.

g. Mongoloid

i Family (18) Trisomy 21

Gisele St. P. (M.C.H. 118952) was born on December 4, 1954. She had mongoloid features, and she was referred with her parents to the Genetics Department for counselling, because of the history of malformation in the family.

Family History

The mother was 37 and the father 34 years of age when the proband (0-5) was born. The father was of French Canadian origin and the mother of English. The first child born in the family (0-3) died of pneumonia at 11 months of age. The post mortem done at the Royal Victoria Hospital (R.V.H. 21-1-729), revealed a transposition of the great vessels. There was no other apparent congenital anomaly. His birth weight was 9 lbs 10 oz. The mother had some vaginal bleeding during the first few months of her pregnancy. The second child, (0-4) a boy, born on October 12, 1952 weighed 7 lbs at birth, and the pregnancy had been uneventful. His physical examination revealed a reduplication of the 5th finger with webbing of the third and fourth fingers of the same hand, and fusion of the nails. The boy is now 11 and in good health. On her fourth delivery on February 18, 1956, the mother gave birth to a girl of 7 lbs 10 oz. Lorraine, who is still alive and well. Both parents were in good health at the time of examination. One maternal cousin of the father was a mongol. The father had worked as an X-ray technician between 1944 and 1949.

Physical examination

The proband had oblique palpebral fissures, a steep narrow palate, a

furrowed tongue, a flat nose bridge and epicanthal folds. Her irides were blue, she had abnormally shaped ears that were low set, short hands, fingers and toes, a simian crease on the left hand, a crooked fifth finger, a wide-spaced big toe and a heart defect. There was a marked flexibility of the joints, a decreased muscle tone and hoarseness of the voice. The second boy had a crooked little finger on the left hand, short, broad hands, malformed digits and a narrow palate.

Dermatoglyphics (Table 8)

The finger prints revealed that the mother had a loop pattern in both third interdigital spaces. Lorraine had a loop on the right hand. The proband had loops on both hands, but was the only one to have a high triradius.

FIGURE 66 - PEDIGREE OF FAMILY 18

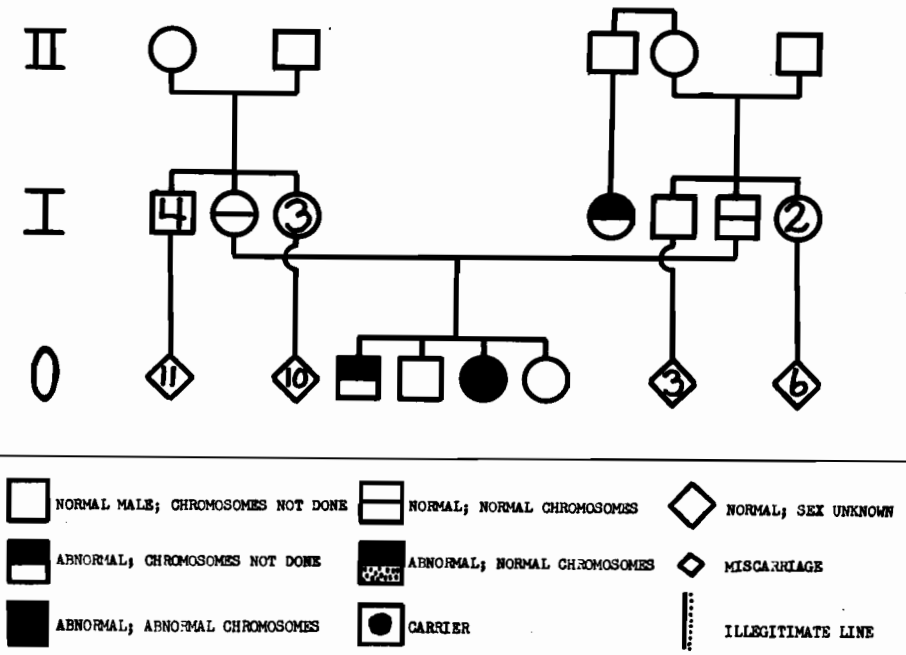


TABLE 8

DERMATOGLYPHICS OF FAMILY 18

	I		II		III		IV		V		±40		3rd interdigit space		Plantar area		Score
	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	
Mother	W	W	W	UL	UL	UL	W	W	UL	UL	-	-	Loop	Loop	SLD	SLD	-0.73
Garry 0-4	W	W	W	W	W	W	W	W	W	W	-	-	-	-	AF	SLD	-3.95
Gisele 0-5	W	UL	UL	UL	UL	UL	W	RL	UL	UL	+	+	Loop	Loop	SLD	SLD	+4.28
Lorraine 0-6	W	W	UL	UL	RL	UL	W	UL	UL	UL	=	-	Loop	-	LLD	LLD	-2.70

LLD - large loop distal
AF - arch fibular
SLD - small loop distal

W - whorl
UL - ulnar loop

Cytogenetic studies

The chromosomes of both parents were found to be normal, fifty cells were counted in each case. No cell was seen in either of them with an extra member of the G group that could suggest a state of mosaicism. The chromosomal pattern of the proband was typical of mongolism with an extra small acrocentric for a total count of 47.

Final diagnosis

The cytogenetic studies suggest that one is dealing with a simple case of nondisjunction. No relation is seen between the fact that the proband had an extra chromosome and the presence of two other children in the family presenting with entirely different anomalies. It was noted that the father had worked as an X-ray technician in the past for a period of five years. Some mutations or chromosomal aberration could have been induced then, but no one has yet demonstrated this hypothesis in man.

ii Family (19) — Familial mongolism due to a 21/21 translocation

Jean P. (M.C.H. 191928) was the youngest child of a family. He was born on October 13, 1956, and was referred for diagnosis to the Department of Genetics of the Montreal Children's Hospital because he had mongoloid features and the history of several similarly affected sibs.

Family History (Fig. 67)

The father was 42 and the mother 36 at the time of birth of the patient. They were both French Canadians and unrelated. Their first child (0-5), a stillbirth, was said to be a male with a mongoloid appearance. The second pregnancy (0-6) resulted in another mongoloid boy. The third pregnancy (0-7) was a spontaneous miscarriage at three months of pregnancy, and the last three (0-8, 0-9, 0-10) were mongoloid males. All pregnancies were uneventful, except the third one which resulted in a sudden miscarriage after a period of one week during which the mother was kept in bed for severe bleeding. The mother was followed regularly during each pregnancy, did not present any excessive vomiting and had no bleeding. There was no history of malformed children on either side of the family.

TABLE 9 - BIRTH ORDER

1.	B.B. Boy (0-5)	9	2	1938	Weight	7.4	Stillbirth. Mongoloid features
2.	Normand (0-6)	10	10	1940		9.0	Alive. Mongol.
3.	Miscarriage (0-7)			1945		-	-
4.	Gaston (0-8)	13	1	1950		8.8	Died 2 d. Heart malformation. Mongol.
5.	Raymond (0-9)	16	5	1955		11.0	Alive. Mongol.
6.	Jean (0-10)	13	10	1956		7.0	Alive. Mongol.

FIGURE 67 - PEDIGREE OF FAMILY 19

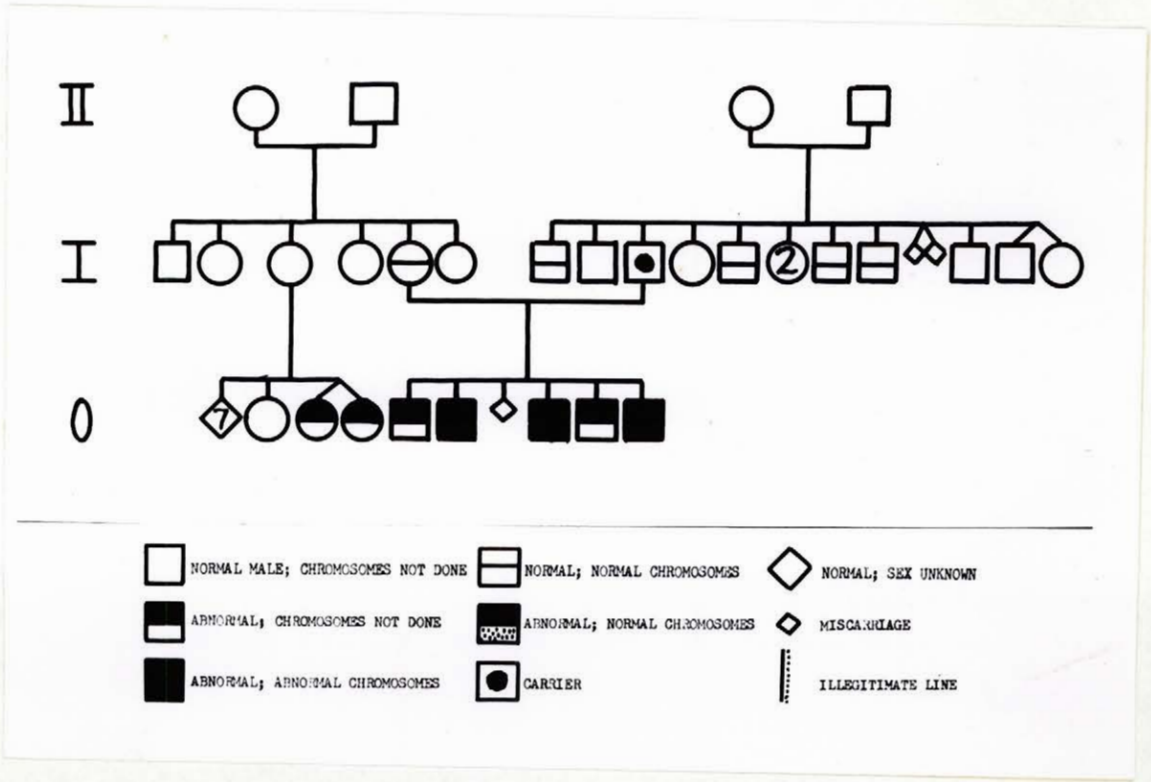


FIGURE 68 - PICTURE OF CHILDREN FAMILY 19

Physical examination (Fig. 68)

	Normand	Raymond	Jean
Head circumference	51 cms	50 cms	47 3/4 cms
Height	155 cms	114 1/2 cms	100 1/4 cms
Ears abnormal (low set)	No	No	No
Brushfield spots	Yes	Yes	Yes
Hypotonia	Yes	Yes	Yes
Epicanthic folds	Yes	Yes	Yes
Depressed nose bridge	No	Yes	Yes
Arched palate	No	Yes	No
Short fingers	Yes	Yes	Yes
5th finger crooked	Yes	Yes	No
# creases 5th finger	2 (R) 2 (L)	1 (L) 2 (R)	2 (L) and (R)
Simian creases	Yes	No	No
Vestigial nails	Yes	Yes	No
Tongue protruding	Yes	Yes	Yes
Mental retardation	Yes	Yes	Yes

The analysis of the finger prints in the parents and the children revealed that neither of the parents had mongoloid patterns, and that the three living children were all in the mongol range except one who was at the lower limit (see Table 10).

The blood group studies are summarized in Table 11.

Electrocardiograms

Electrocardiographic studies were done on the three living children; they showed that Normand has a severe left ventricular hypertrophy, Raymond a normal heart and Jean a left ventricular hypertrophy also.

Cytogenetic studies (Figs. 69, 70, 71, 72)

The chromosomal studies were done on both parents, on the three living children and on four paternal brothers. The father was found to have only 45 chromosomes including one extra metacentric member, the size of a 19/20, and two chromosomes missing in the G group. The mother was normal. All three children had 46 chromosomes one of the G group missing and one extra member like the father's. All four paternal brothers had a normal chromosomal complement.

Chromosome number	44	45	46	47	48	Poly-ploid	Total
Mother I-5	1	0	25	0	0	0	26
Father I-9	2	60	1	0	0	1	64
I-7	0	0	5	0	0	0	5
I-11	0	0	7	0	0	0	7
I-13	0	0	13	0	0	0	13
I-14	0	0	9	0	0	0	9
Normand	0	0	47	0	0	0	47
Raymond	0	0	50	2	0	0	52
Jean	1	0	60	0	0	0	61

TABLE 10

DERMATOGLYPHICS OF FAMILY 19

	I		II		III		IV		V		±40		3rd interdigit space		Plantar area		Score
	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	
Mother	W	UL	W	TA	UL	UL	UL	UL	UL	UL	-	-	Loop	-			-2.32
Father	UL	UL	W	W	UL	UL	W	W	UL	UL	-	-	-	-	Loop Open Tibial Field		-5.48
Patient I Jean	W	W	UL	UL	UL	UL	RL	W	RL	W	+	+	Loop	-	Large loop distal		+5.90
Patient II Raymond	UL	UL	UL	A	W	A	W	A	RL	RL	+	+	Loop	-	Whorls		+6.11
Patient III Normand	UL	UL	UL	W	UL	UL	UL	W	UL	UL	+	+	Loop	-	Large loop distal		+0.94

RL - radial loop
A - arch
UL - ulnar loop
W - whorl
TA - tented arch

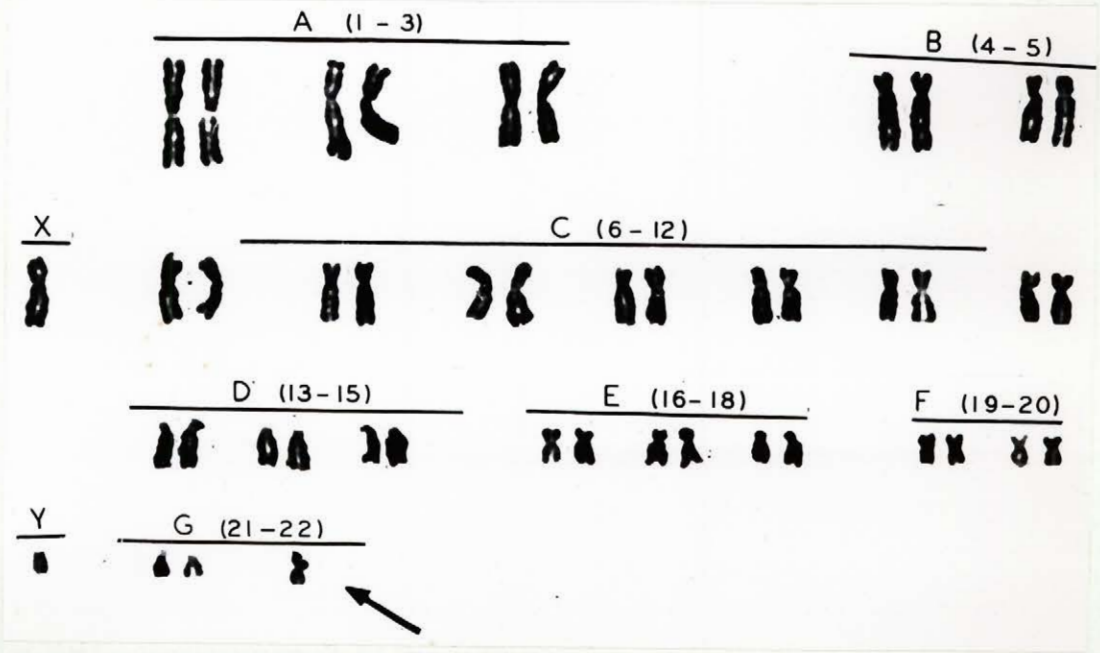
TABLE 11

BLOOD GROUPING FAMILY 19

	ABO			MNS		CDE					Duffy	Kell Cellano		Diagn.
	A	B	A_1	M	N	C	D	E	c	e	Fy	K	k	
Mother	-	-	-	+	+	-	+	+	+	+	+	-		DcE/dce
Father	-	-	-	-	+	+	+	-	+	+	+	-		DCe/dce
Normand	-	-	-	+	+	-	-	-	+	+	+	-		dce/dce
Raymond	-	-	-	-	+	-	-	-	+	+	+	-		dce/dce
Jean	-	-	-	-	+	-	-	-	+	+	+	-		dce/dce

\+ Positive (+) Questionable Positive
\- Negative (-) Questionable Negative

FIGURES 69, 70, 71, 72 - KARYOTYPES OF FATHER AND CHILDREN FAMILY 19



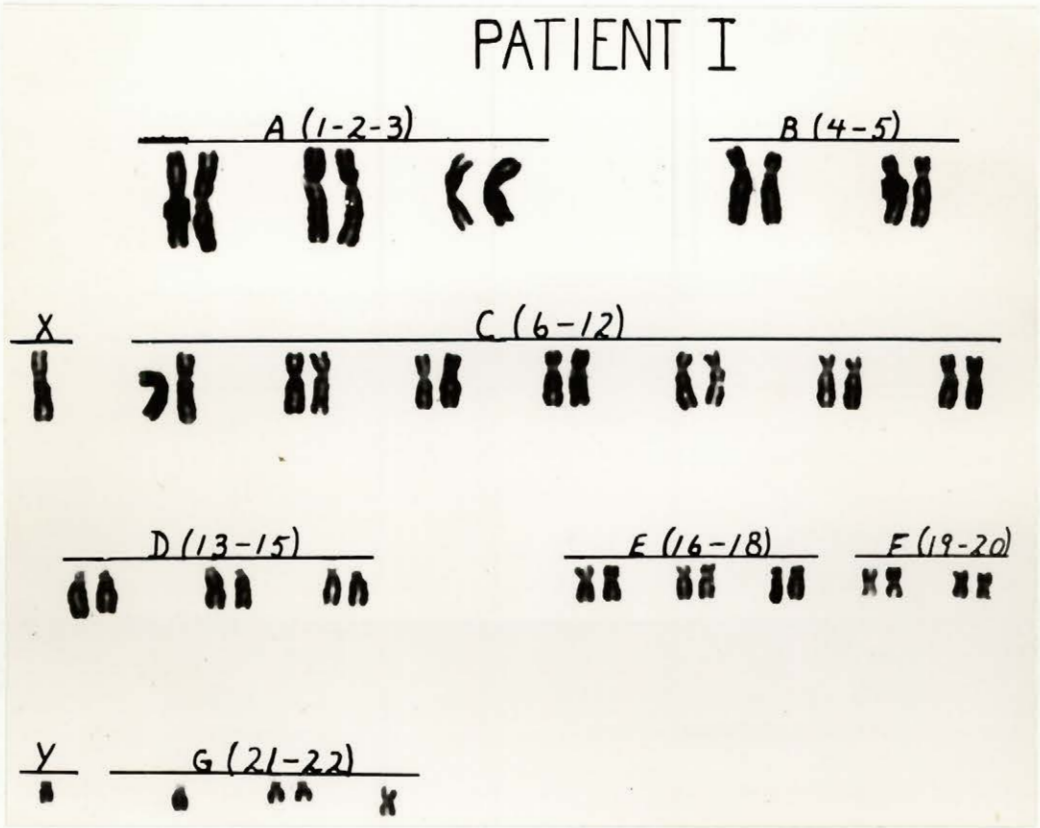


FIGURE 70

PATIENT II

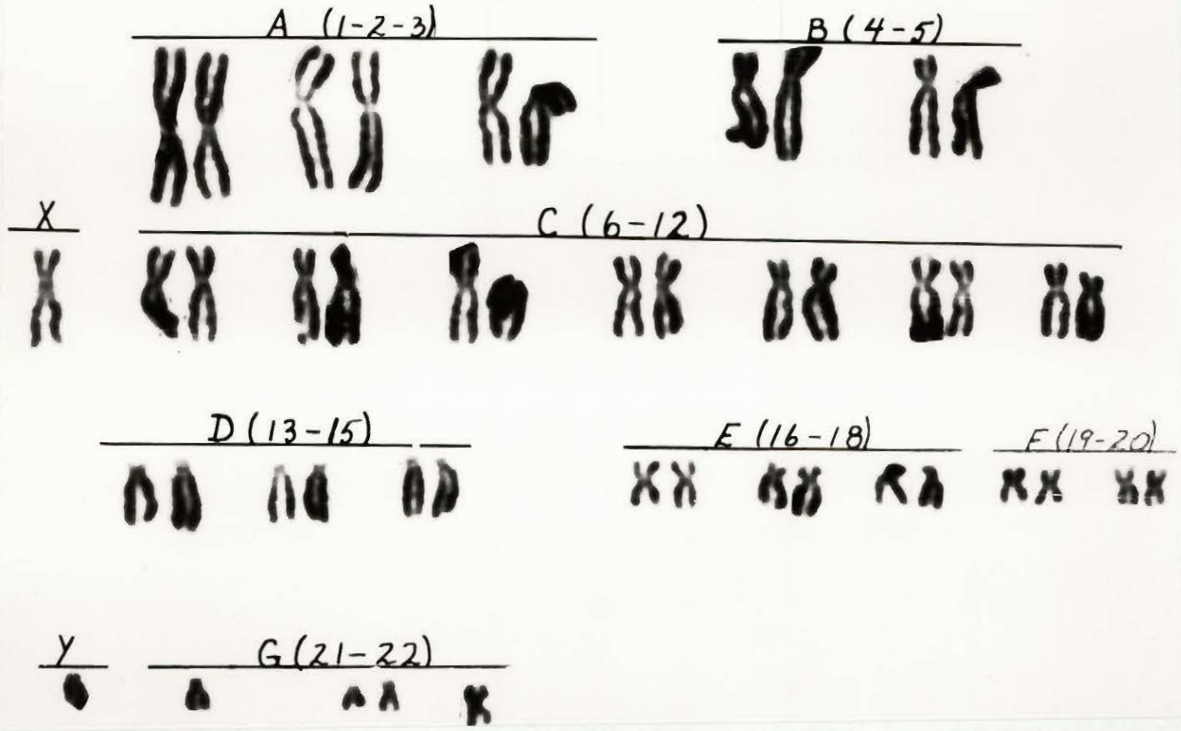


FIGURE 71

PATIENT IIIA

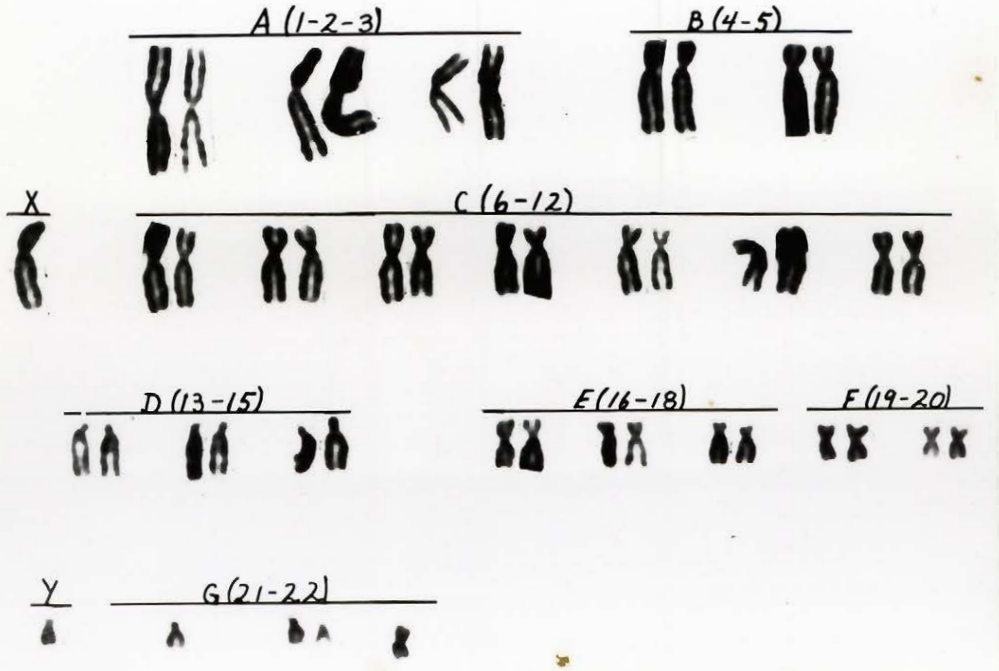


FIGURE 72

Final diagnosis

It is obvious that in the family presently described, the father has a simple translocation involving two members of the G group. Furthermore, since all the children were mongoloid and all three examined had the same chromosomal anomaly, one can assume that the translocation that arose in the father either in his early development or in one of his parents sexual gametes, involved two chromosomes of the same type: that is, two 22 or two 21. It is commonly believed that the chromosome number 21 when present in triplicate, is responsible for the production on mongoloid traits. Another proof of this assumption is based on the fact that all paternal brothers and sisters have normal children, and that the four examined brothers have normal karyotypes. But unless one day one can distinguish for sure the two chromosome pairs of the G group, some doubt will remain concerning the validity of such a statement. In counselling the parents should be aware of the fact that they may never have normal children if one of them is found to have this type of translocation. On the other hand if one normal child was born the chromosomal rearrangement involves one member of each pair and, if segregation were random, the chances of having an abnormal infant would be approximately 25%; there would be 25% chance that the child be a carrier, 25% chance that the child be perfectly normal and 25% chance that the egg would lack one chromosome and not survive.

The blood group studies did not bring any light into the problem of location of the blood group alleles on the autosomes.

Atkins (1962) reviewed the literature on translocations in mongolism and presented a family with three affected children.

iii Family (20) — Familial mongolism due to non-disjunction

Mrs. K. Mac. (M.C.H. Gen. Dept.) was referred for counselling by her private physician because she had three boys and all of them were mongoloid.

Family History (Fig. 73)

The mother was 28 and the father 30 years of age when they had their first child (0-5). Their racial origin was Irish and they were unrelated. Two years later they had another boy (0-3) also a mongol and the following year another mongol boy (0-4) was born. None of the parents suffered from any congenital disorder, or had been treated in hospital for serious physical disorders. The mother first menstruated at the age of 13 and has always had a very regular cycle, lasting 6 days and occurring every 28 days.

The mother stated that she did not feel well throughout the gestations. While pregnant she had to stay in bed for long periods of time, ranging from three to five months and was hospitalized for a few days for the last two pregnancies at the third month of pregnancy for severe uterine bleeding. She was on a severe low calorie diet during each pregnancy around the third month because she used to gain too much weight. The diet consisted of 1,000 calories for the third to the seventh month and 800 calories for the last two months. The three children were born after 8 months of pregnancy. The family history was negative otherwise.

Physical examination (Fig. 74)

The birth weight of the children was as follows: Michael 6.7 lbs, David 5 lbs 8 oz., and James 8 lbs. They all had typical mongoloid features:

brushfield spots, a wide spaced big toe, short fingers and toes and a protruding tongue. The back of the skull was flat. All three of them had mongolian spots on the back. Their necks were short and the skin was loose in that region. There was a marked hyperextensibility of the joints. Michael and David had epicanthic folds. Michael and James had a Grade II systolic murmur heard all over the cardiac region. David also presented a heart murmur heard in the left axillary region. They were all mentally retarded and frequently affected with colds and upper respiratory tract infections. The finger print index showed that they were all in the mongoloid range (Table 12). The parents were normal. The blood group studies were not contributory (Table 13).

FIGURE 73 - PEDIGREE OF FAMILY 20

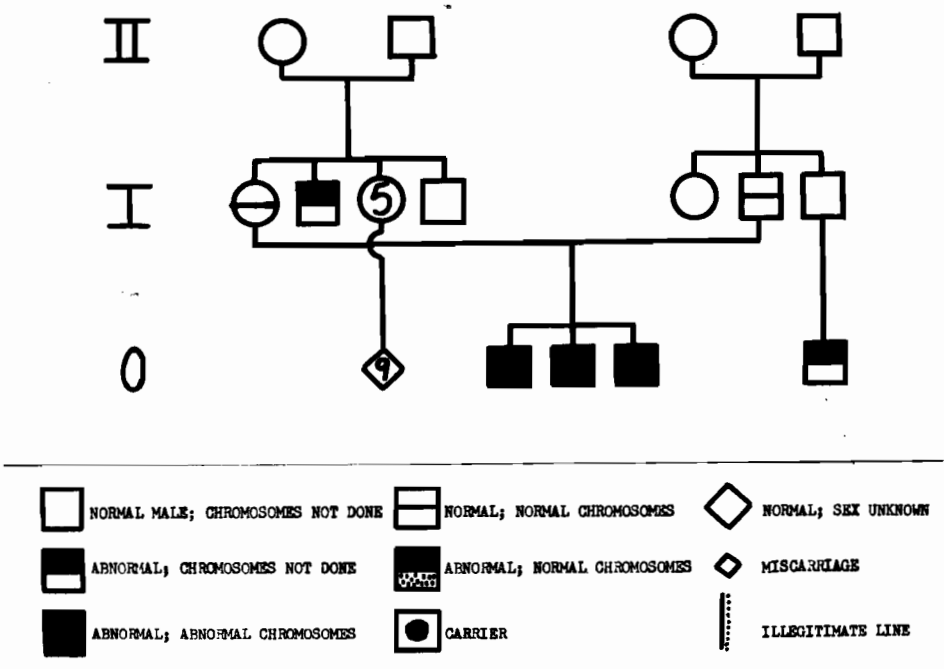


TABLE 12

DERMATOGLYPHICS FAMILY 20

	I		II		III		IV		V		±40		3rd interdigit space		Plantar area		Score
	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	
Mother	UL	W	UL	W	UL	UL	W	W	W	UL	-	-	-	-	Small loop distal		-1.12
Father	W	W	RL	UL	UL	UL	UL	UL	UL	UL	-	-	-	-	Whorls		-5.66
Michael	UL	UL	A	UL	UL	UL	UL	W	W	UL	+	+	Loop	Loop	Small loop distal		3.33
David	UL	UL	UL	UL	UL	UL	UL	A	UL	UL	+	+	Loop	Loop	Arch tibial		7.39
James	UL	UL	UL	UL	UL	UL	A	UL	UL	UL	-	-	Loop	Loop	Arch tibial		4.56

UL - ulnar loop
A - arch
W - whorl

TABLE 13

BLOOD GROUPING FAMILY 20

	ABO			MNS		CDE					Duffy	Kell Cellano		Diagn.
	A	B	A_1	M	N	C	D	E	c	e	Fy	K	k	
Mother	-	+	-	+	-	-	+	-	+	+	+	-	+	Dce/dce
Father	-	-	-	+	-	+	+	-	+	+	+	-	+	DCe/dce
Michael	-	-	-	+	-	+	+	-	+	+	+	-	+	DCe/dce
David	-	-	-	+	-	+	+	-	+	+	+	-	+	DCe/dce
James	-	+	-	+	-	-	+	-	+	+	+	-	+	Dce/dce

\+ Positive (+) Questionable Positive
\- Negative (-) Questionable Negative

FIGURE 74 - PICTURE OF CHILDREN FAMILY 20

Cytogenetic studies (Fig. 75, 76, 77)

Chromosomal studies were done on the three abnormal children and on the two parents. The boys all had an extra small acrocentric chromosome, and the parents had normal karyotypes. There was no sign of translocation or mosaicism in the parents.

Chromosome Number	44	45	46	47	48	Poly-ploid	Total
Mother	0	0	75	0	1	3	79
Father	0	1	52	1	0	1	55
Michael	0	0	0	39	0	0	39
David	0	0	0	40	0	1	41
James	0	1	0	40	0	1	42

FIGURES 75, 76 - KARYOTYPES OF CHILDREN FAMILY 20

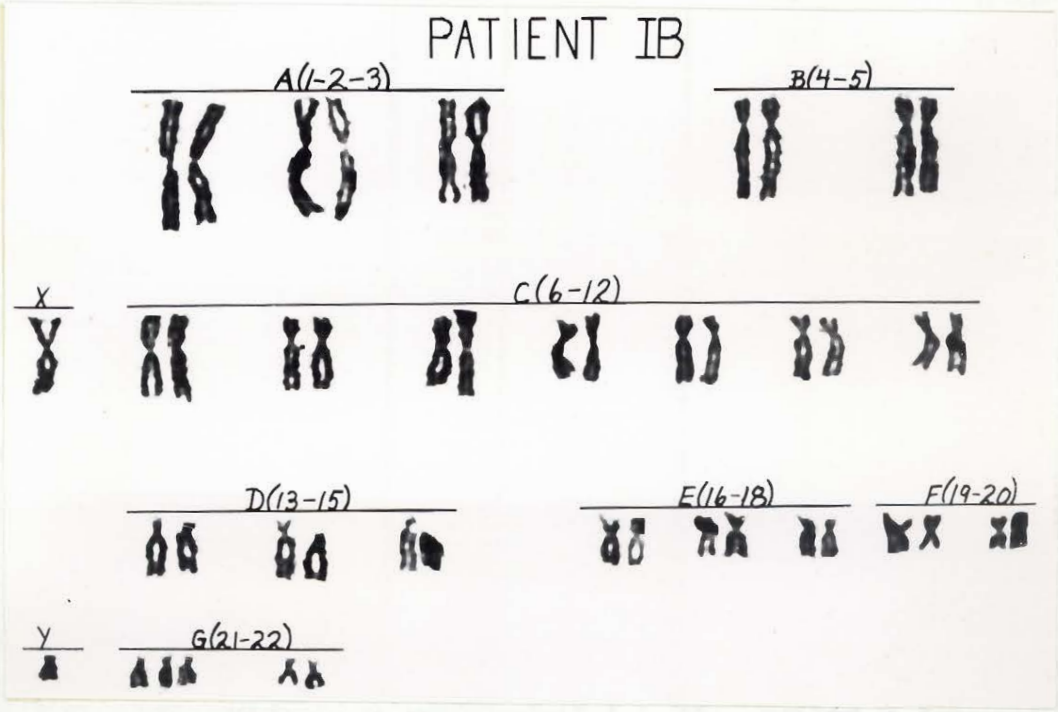


FIGURE 76

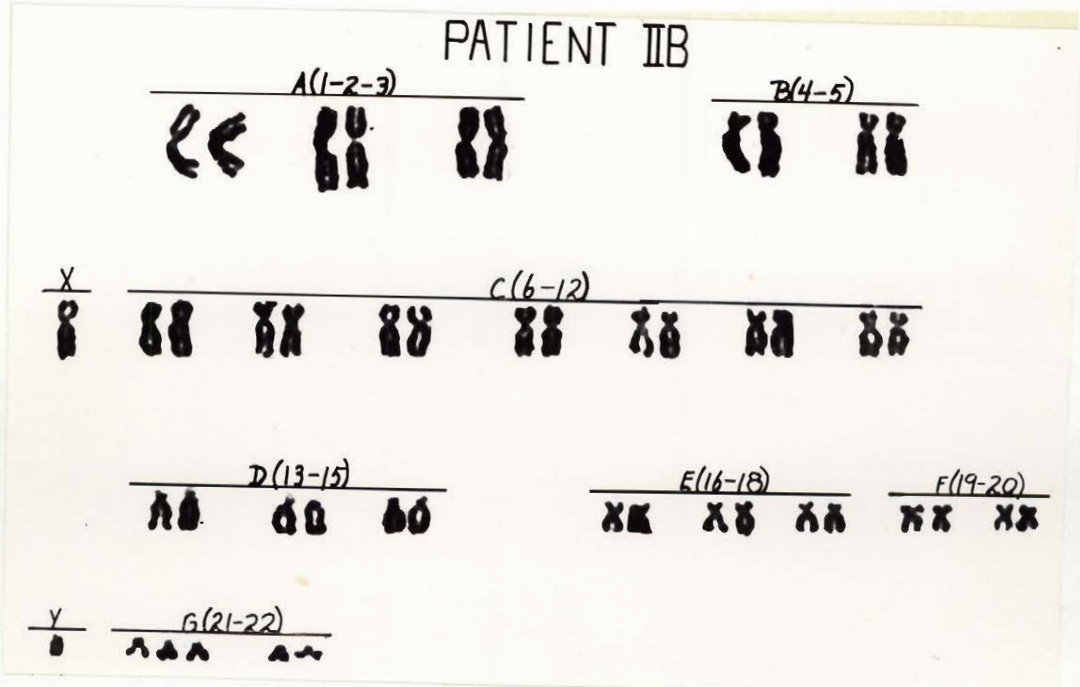
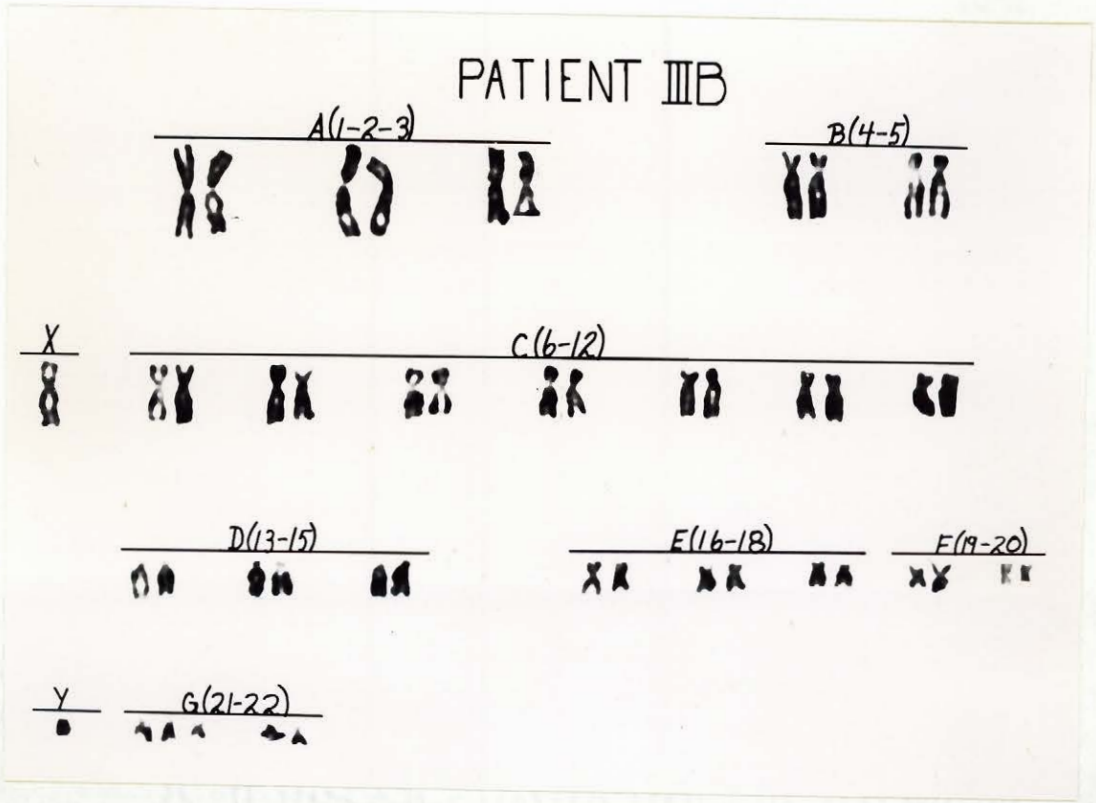


FIGURE 77 - KARYOTYPE OF CHILD FAMILY 20



Final diagnosis

This family represents a case of familial non-disjunction involving a small acrocentric chromosome, and thus producing mongolism. The origin is unknown. The parents of the children have been told after the first and the second pregnancies, by medical people, that the chances of having a normal child were more than excellent.

If the chromosomes had been examined when the first child was born, the same advice would have been given since none of the parents carried a translocation, and they were relatively young at that time.

One should not forget that the mother was confined to bed during all three pregnancies. It seems (assuming the therapy was effective) that she

would have had three miscarriages instead of three viable infants if such a preventative therapy had not been applied. The diet had no influence on the fact that the three boys had an extra chromosome.

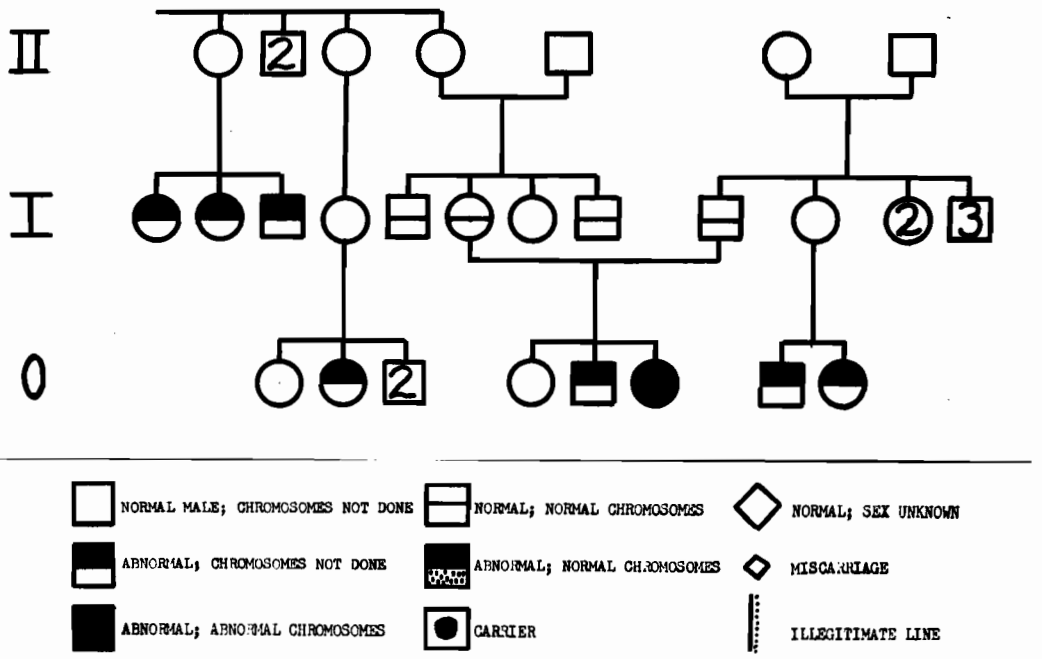
iv Family (21) Partial translocation

Jean Mc. (M.C.H. 235740) was born on February 26, 1960. Being retarded she was admitted to the Montreal Children's Hospital for evaluation and diagnosis of her condition. Since she had a mongol brother, her parents were referred to the Genetics Department for counselling.

Family History (Fig. 78)

The father was Irish in origin and the mother Scottish. They were both 31 years of age when the proband was born. Their first child was a normal girl (0-4) who is still alive. The second pregnancy (0-5) resulted in a mongoloid child. The proband (0-6) was the third and last born in the family. One father's sister had two children (0-8, 0-9) who died shortly after birth and had multiple malformations.

FIGURE 78 - PEDIGREE OF FAMILY 21



Physical examination (a)

The proband who had no mongoloid features, but was a severely mentally retarded was found to have an absence of the corpus callosum. She had been slow in developing since birth, and was hypotonic. She could not recognize her parents. No other abnormality could be detected throughout the physical examination. The mongol boy was operated on for an oesophageal stenosis at birth. He died of internal haemorrhage six months after birth.

Electro-encephalogram

The E.E.G. done on the proband showed evidence of diffuse, slow dysrythmia, the pattern of which was quite suggestive of poor celebral maturation. No epileptiform activity was noted.

Dermatoglyphic studies (Table 14)

The finger prints showed that the mongol child had abnormal patterns characteristic of Down's syndrome. However, the proband and both parents had a normal print configuration.

Physical examination (b)

In the father's sister's family the first child (0-9) was born in 1960 at the Catherine Booth Hospital. The weight of the non-viable female was 2 lbs 7 oz. She had a double spontaneous footling breech. The infant was an anencephalic monster with a meningocoele and a large hematoma.

The second child (0-8) was born after 34 weeks of gestation, and had multiple skeletal anomalies: there was an absence of the 4-12 ribs on the left, and absence of the 8-12 on the right. There was an extreme

kyposcoliosis, and hyperplasia of the pelvic and shoulder blades. There was a massive umbilical hernia, hepatomegaly and a neoplasia of the posterior fossa of the skull.

Cytogenetic studies (Figs. 79, 80, 81, 82)

The cytogenetic studies were done on the proband and on the parents of the two different families. The proband was found to have a partial translocation of a member of the D group. One cell was found in which there was no extra material on the D member but on the other hand it contained a small acrocentric believed to be the translocated piece detached from its recipient. The size of the extra chromosome was slightly smaller than a number 21/22. This is in favour of the real presence of extra chromosomal material on a long acrocentric. All parents were normal.

Chromosome number	44	45	46	47	48	Poly-ploid	Total
Mother a 50	0	0	50	1	0	2	53
Father a 55	0	0	55	0	2	0	57
Proband	0	0	76	1	0	3	80
Mother b 30	0	0	30	0	0	0	30
Father b 34	0	0	34	0	0	0	34
I-5 20	0	0	20	0	0	0	20
I-8 20	0	0	20	0	0	0	20

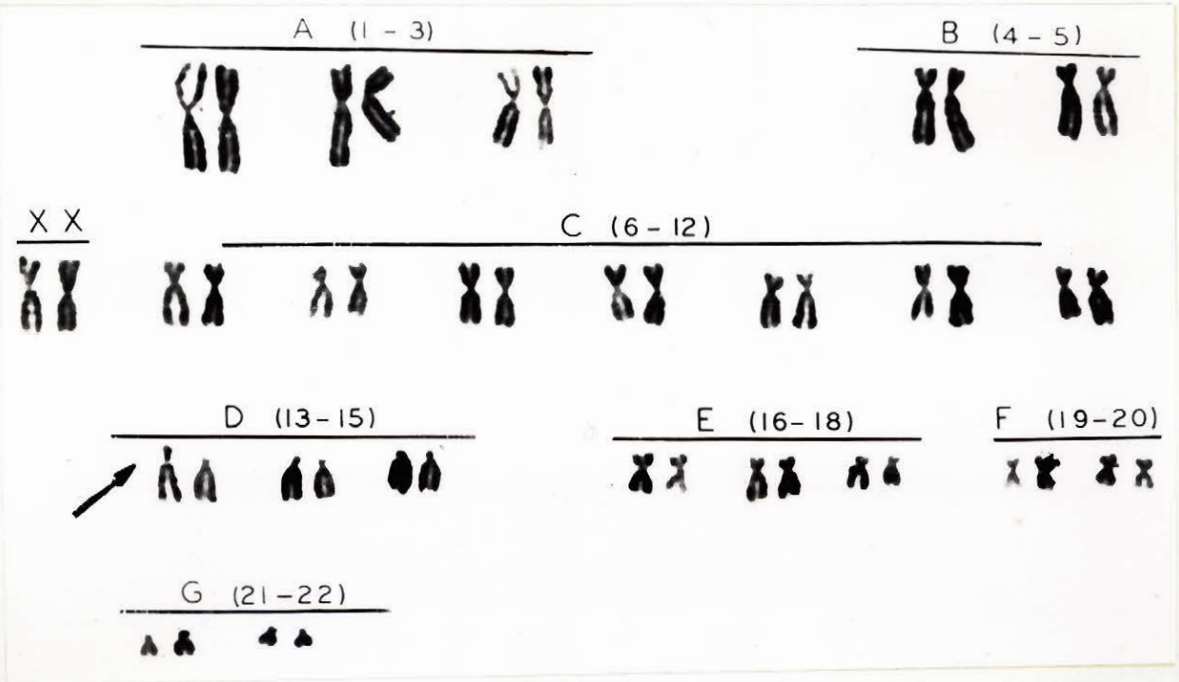
TABLE 14

DERMATOGLYPHICS FAMILY 21

	I		II		III		IV		V		±40		3rd interdigit space		Plantar area		Score
	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	
Mother	W	W	W	W	UL	UL	UL	W	UL	UL	-	-	-	-	Whorl		-5.71
Father	UL	UL	RL	UL	UL	UL	RL	UL	UL	UL	-	-	+	+	Tibial arch		+0.04
Joan O-4	UL	UL	W	UL	UL	W	W	W	UL	UL	-	-	-	-	Small loop distal		-1.16
Jean O-6	W	W	UL	UL	UL	UL	W	W	UL	UL	-	+	-	-	Whorl		-2.72

W - whorl
UL - ulnar loop
RL - radial loop

FIGURES 79, 80 - KARYOTYPES OF PROBAND FAMILY 21



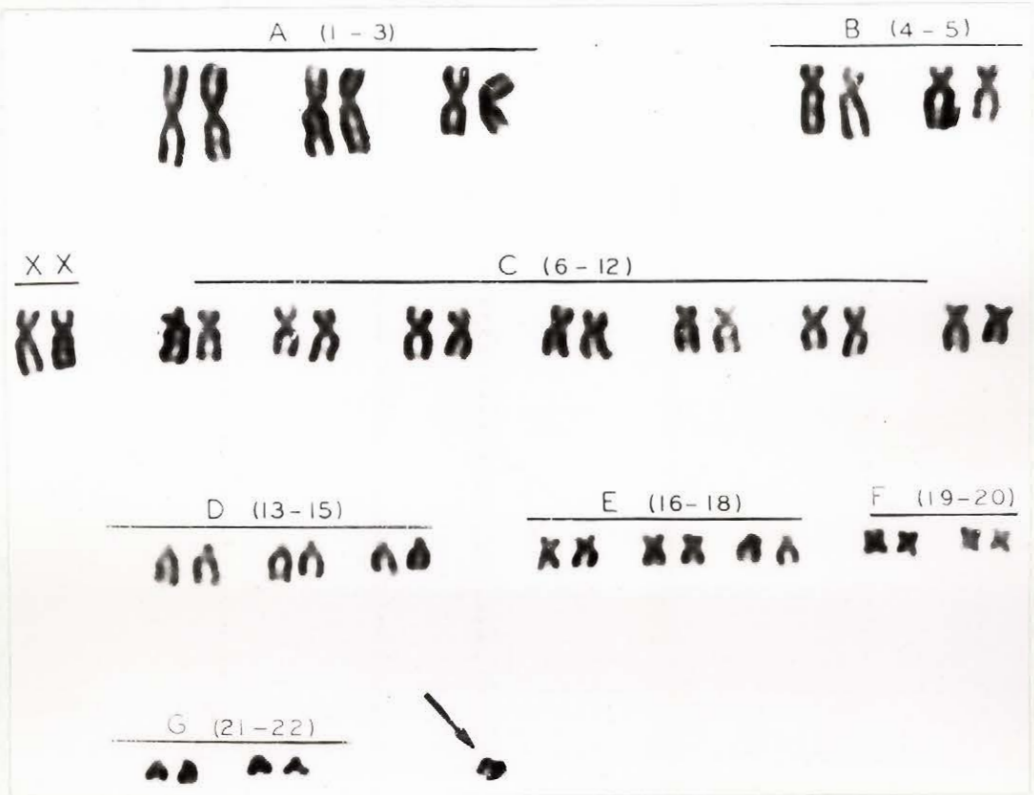


FIGURE 80

FIGURE 81 - KARYOTYPE OF FATHER

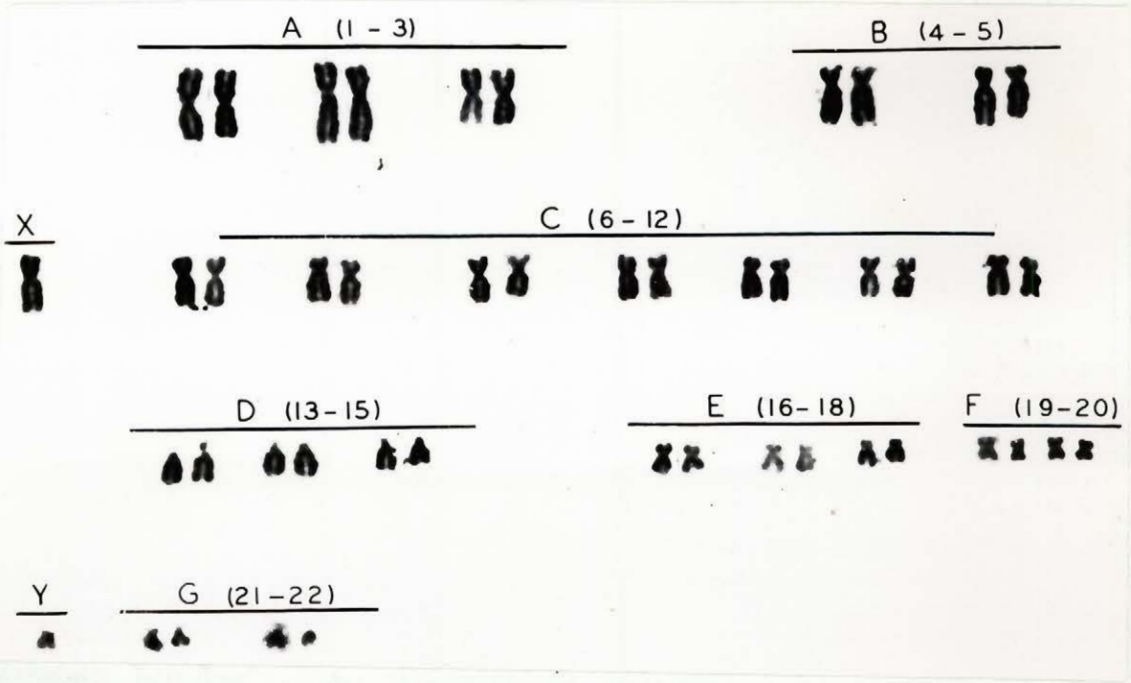
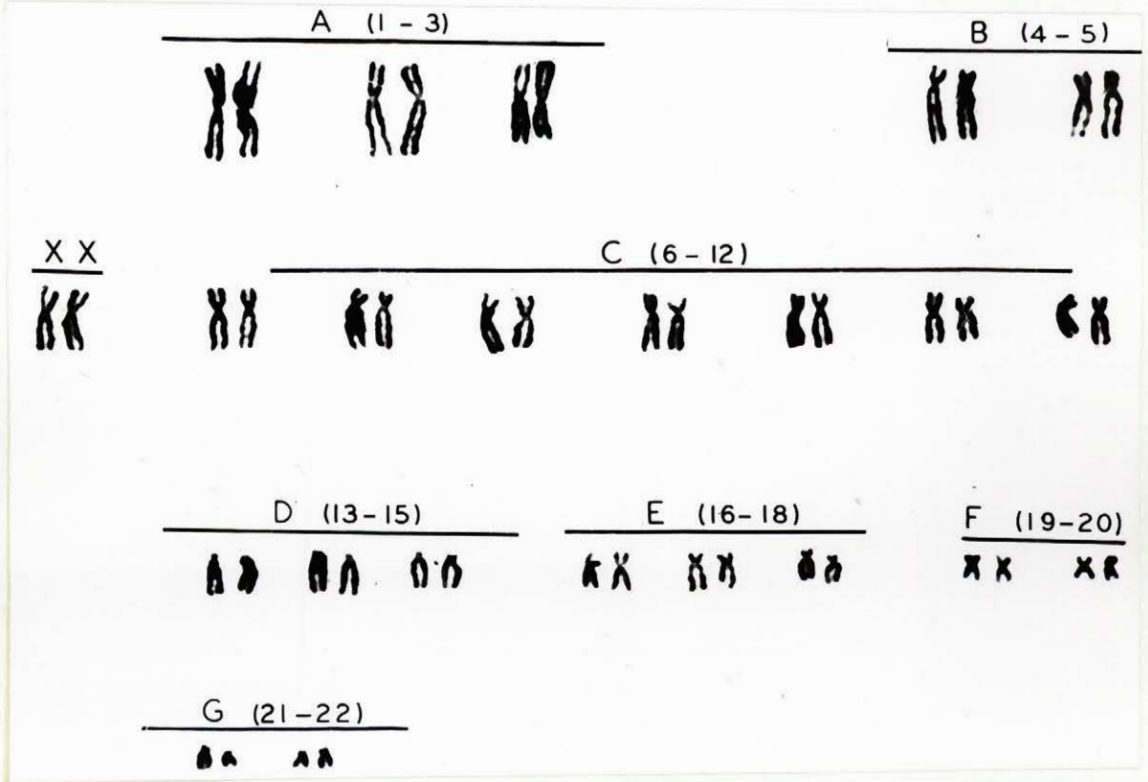


FIGURE 82 - KARYOTYPE OF MOTHER



Final diagnosis

The chromosomal abnormality found in the proband's cells has been described by Patau (1961) in a case of Sturge Weber syndrome. Lejeune (1963) found a family in which one child was mongoloid and the other one was mentally retarded and had an absence of the corpus callosum. This last patient also had a partial translocation to a D chromosome.

Since the anomaly could not be traced in the parents, one can only guess the origin of the extra material. Since one of the sibs was mongol, the translocation may involve a deleted number 21. The deletion may have taken place in the early development of the child or in some of the parental gametes.

v Family (22) Mongolism and other anomalies

Baby girl G. (M.C.H. Gen. Dept. CD84) was born on November 3, 1955 at the Jewish General Hospital with multiple congenital anomalies. The problem was brought to the attention of the Genetics Department of the Montreal Children's Hospital, because the first born of the family was mongoloid.

Family History (Fig. 83)

The father was 28 and the mother 30 years of age when the proband was born. One father's brother (I-7) died at seven months of age: he was premature, deaf and severely retarded. Both proband's parents were physically normal. The paternal ancestry was Roumanian and the maternal Polish. The first pregnancy of the mother resulted in a spontaneous miscarriage (0-3). The following year they had a mongoloid boy (0-4) who died three months later. Their first normal child was a boy. The fourth pregnancy was the proband (0-6) and the fifth a normal child. During the proband's pregnancy she had intermittent bleeding and mild swelling of hands and feet.

Physical examination

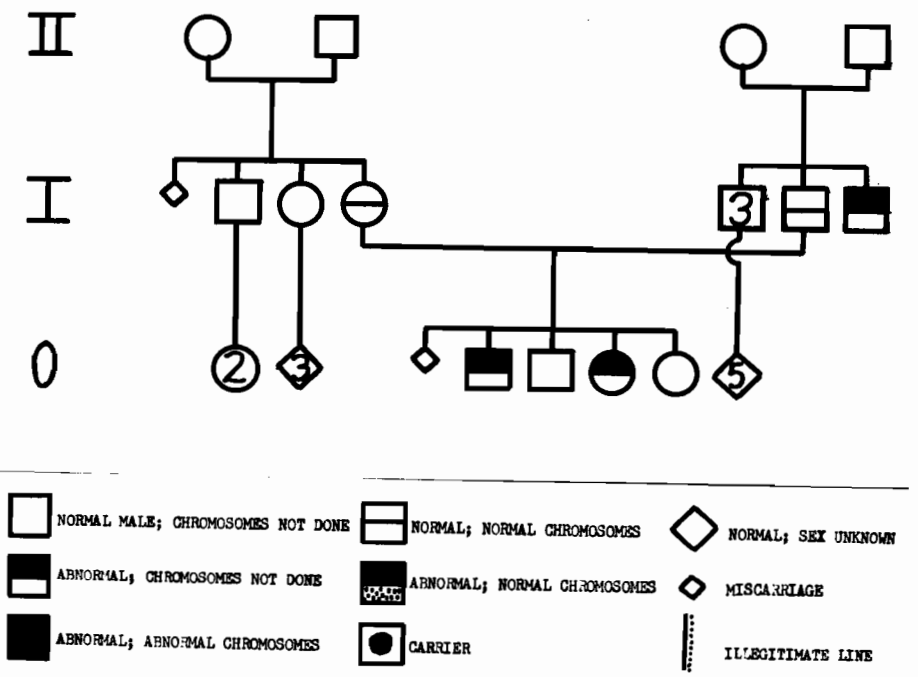
The proband died a few hours after birth. The autopsy report stated that the child had an atresia of the upper third of the oesophagus, fetal pulmonary atelectasis and hyperemia of the leptomeninges. The proband had no mongoloid features.

Cytogenetic studies

The chromosomal studies were done on both parents and found normal.

Forty cells were counted in each case. Ten cells were analyzed in the mother and four in the father.

FIGURE 83 - PEDIGREE OF FAMILY 22



Final diagnosis

The possibility for the parents to be carriers of a chromosomal translocation has been ruled out. But since the chromosomal studies on the proband and the mongoloid child could not be done, one cannot assume that the malformed children had normal chromosomes, though one can be quite certain that the mongol child had an extra member of the G group. The coincidence of mongolism and oesophageal atresia should be noted here.

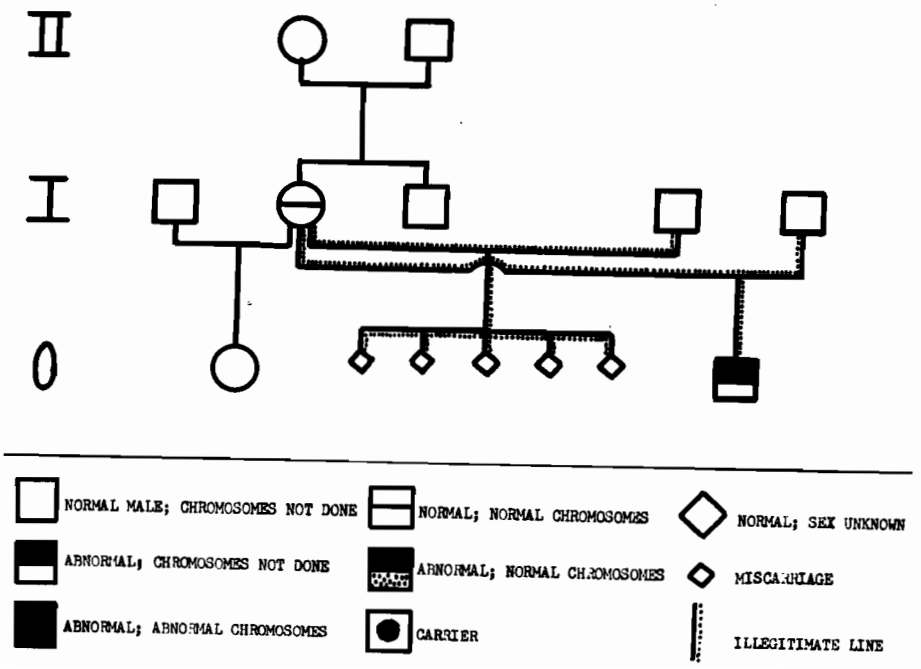
vi Family (23) Mongolism following several miscarriages

Baby boy B. (R.V.H. 307221-1) was born on April 10, 1961, and died two months later. He was referred to the Malformation project of the Royal Victoria Hospital because he had an imperforate anus and mongoloid features.

Family History (Fig. 84)

The mother had seven pregnancies. Only one girl (O-1) is alive and well. Five gestations (O:2, 3, 4, 5, 6) terminated spontaneously in miscarriages. The fathers are unknown, except the first one to whom the mother was legally married and who sired her only normal child. The mother was only 24 when the proband, the product of the last pregnancy was born.

FIGURE 84 - PEDIGREE OF FAMILY 23



Physical examination

The proband's weight at birth was 7 lbs. He had an imperforate anus and typical mongoloid features. His dermatoglyphics were in the mongol range. The mother was physically normal.

Cytogenetic studies

The chromosomes of the mother were examined and found to be normal. All the cells had a total count of 46 chromosomes, and there was no translocation present. The proband died a few hours after birth and chromosomal studies could not be done on him.

Final diagnosis

In view of the important history of miscarriages and the fact that most likely none of the fathers was the same for any of the pregnancies, the cytogenetic studies were done to rule out the possibility of a translocation present in the mother. Her chromosomes being normal, the cause of the abnormal pregnancies remains undetermined, though it is still possible that one is dealing here with a predisposition to non-disjunction which would make the foetuses unviable. Unfortunately the chromosomes of the proband could not be examined.

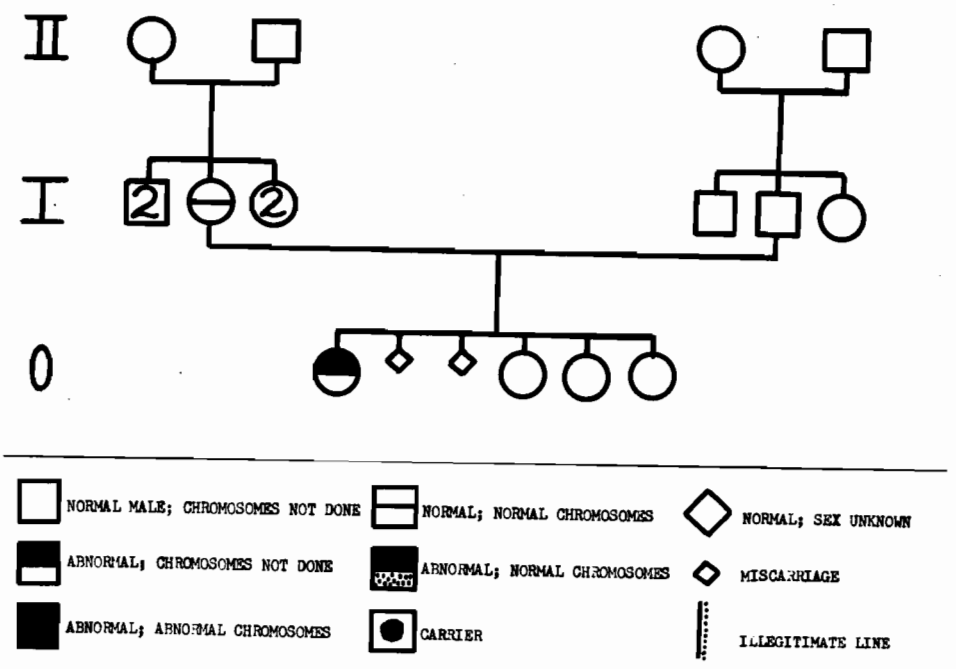
vii Family (24) — Mongolism and abnormal dermatoglyphics in members of the family

Denise R. (M.C.H. Gen. Dept. 41) was born on October 27, 1943. She was diagnosed as a mongol at birth and the mother was referred for counselling to the Genetics Department because she also had two miscarriages and one other mentally retarded child.

Family History (Fig. 85)

The mother was of French Canadian origin and she was only 24 years old when the proband was born. She had her children by three different husbands. During the proband's pregnancy the mother stated that occasionally she had swollen ankles and feet and also severe headaches. The gestation terminated by a breech delivery and the girl weighed 6 lbs 8 oz. One girl (O-6) was said to be mentally retarded.

FIGURE 85 - PEDIGREE OF FAMILY 24



Physical examination

The proband was a typical mongol child. The log. index in the dermatoglyphic score was + 7.51. Her mother was physically normal but had a high triradius on both hands. The mother's sister also had one high triradius (Table 15).

Cytogenetic studies (Fig. 86)

The chromosomes of the mother were examined by means of peripheral blood culture, and found normal. Fifteen cells were analyzed. The children were not available for chromosomal studies.

FIGURE 86 - KARYOTYPE OF THE MOTHER FAMILY 24

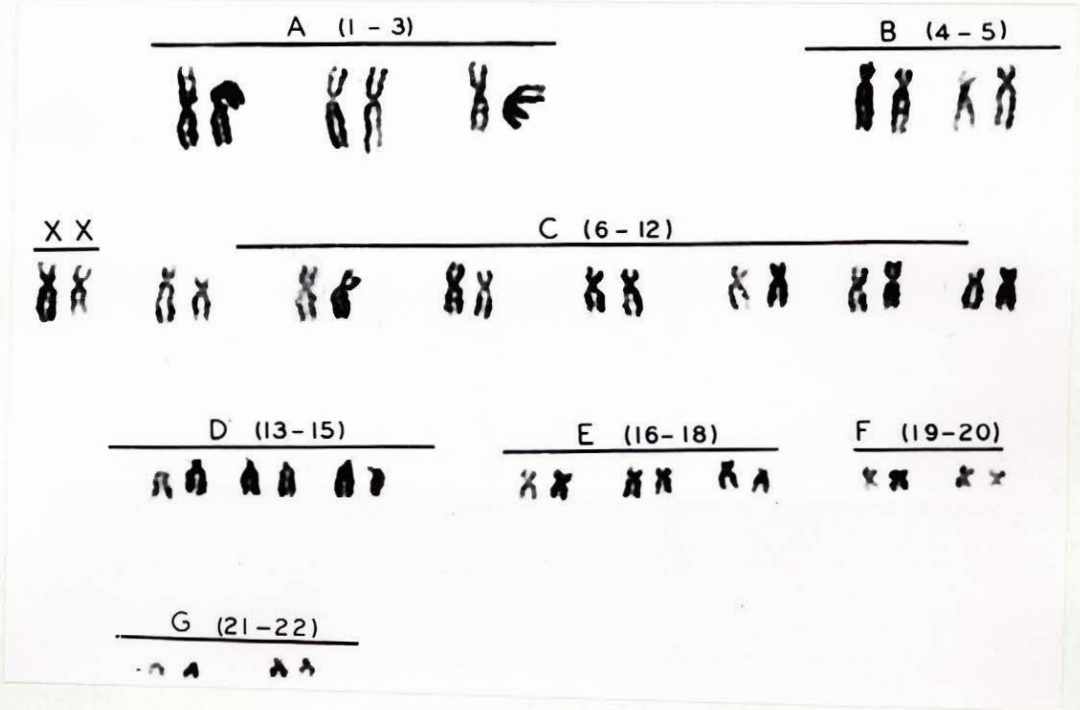


TABLE 15

DERMATOGLYPHICS FAMILY 24

	I		II		III		IV		V		±40		3rd interdigit space		Plantar area		Score
	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	
Mother I-2	UL	UL	A	RL	UL	UL	UL	UL	UL	UL	+	+	Loop		LLD	LT	-1.85
Denise O-1	UL	UL	UL	UL	UL	UL	UL	UL	UL	UL	+	+	Loop		AT	AT	+7.51
Lillian O-3	UL	UL	W	UL	W	UL	UL	UL	UL	W	-	+	Loop		LLD	AF	-1.48
Helen O-4	UL	W	UL	UL	UL	UL	UL	W	UL	UL	-	+	Loop		LF	LF	-1.71

UL - ulnar loop
RL - radial loop
W - whorl

AT - arch tibial
LLD - large loop distal
AF - arch fibular

LF - loop fibular

Final diagnosis

The cytogenetic studies were done on the mother because she had one mongol child, one mentally retarded child and two miscarriages. Her dermatoglyphic studies showed that she also had a high triradius on both hands. Penrose (1954) previously stated that there was a correlation between the location of the triradius in the mongols and that of the mother, and had reported (1960-61) a family where several heterozygus translocations had elevated triradii. In this case the mother had normal chromosomes. The proband was not available for chromosomal studies, but one may conclude that the mother was not responsible if the child was a translocated mongol.

viii Family (25) Familial multiple malformations

Mark B. (M.C.H. 216252) was born on July 4, 1961. His parents were referred for counselling because this child had a ventricular septal defect and they were afraid of having another abnormal infant since one of his first cousins was known to be a mongol.

Family History (Fig. 87)

Both parents were young when the child (0-2) was born. The father was 28 years old and the mother 18. The mother presented some vaginal bleeding, like menstruations at the 8th and 9th months of her pregnancy. One paternal uncle was mongoloid and so was a first cousin of the patient.

Physical examination

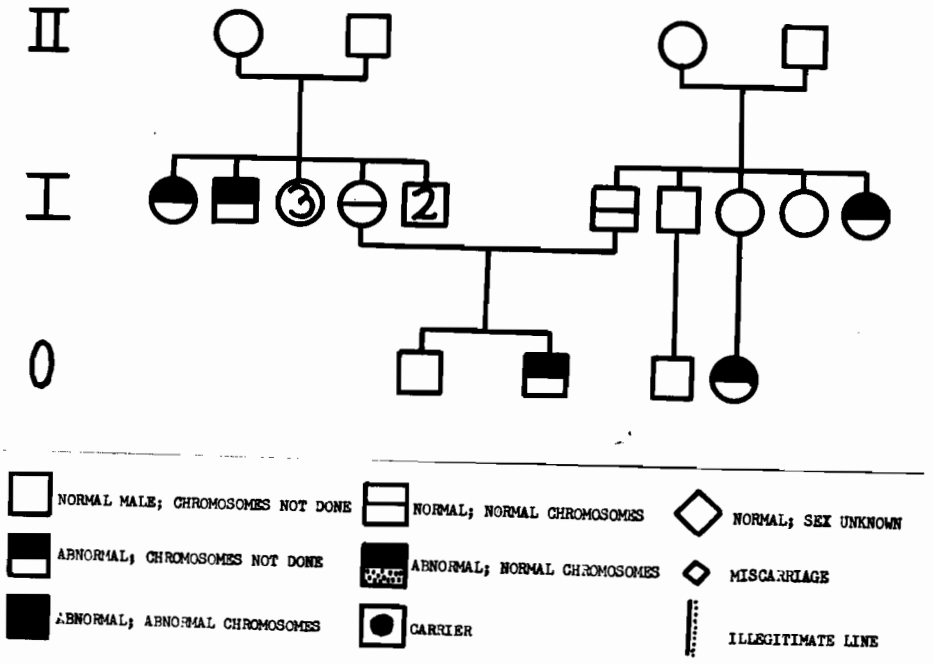
The child weighed 6 lbs 11 oz. at birth. The physical examination revealed a young infant handicapped by a heart malformation described as a ventricular septal defect, but with no other congenital anomaly. His finger prints were normal. On the other hand his first cousin (0-4) was an atypical mongol, presenting with no epicanthic folds, low set ears, mental retardation, crooked little fingers, simian creases on one hand and no brushfield spots. The proband was hypotonic. The log. index of the dermatoglyphic studies was + 0.80. There was no information available on the uncle.

Cytogenetic studies

The chromosomal sutdies were done on the father and the mother of the child affected with a heart malformation, and both of them had a normal karyotype, with no apparent translocation.

Chromosome number	44	45	46	47	48	Poly-ploid	Total
Father	0	0	20	0	0	0	20
Mother	0	0	25	0	0	0	25

FIGURE 87 - PEDIGREE OF FAMILY 25



Final diagnosis

The parents of the mongoloid child objected seriously to having their chromosomes studied, since at the time they were expecting another child, who turned out to be a normal infant. At least the possibility of

a translocation was ruled out in the family seen in consultation. As far as one can be sure, there seems to be no correlation between the two malformed children. The risk of recurrence of a heart malformation is not well known, but it seems to be very low.

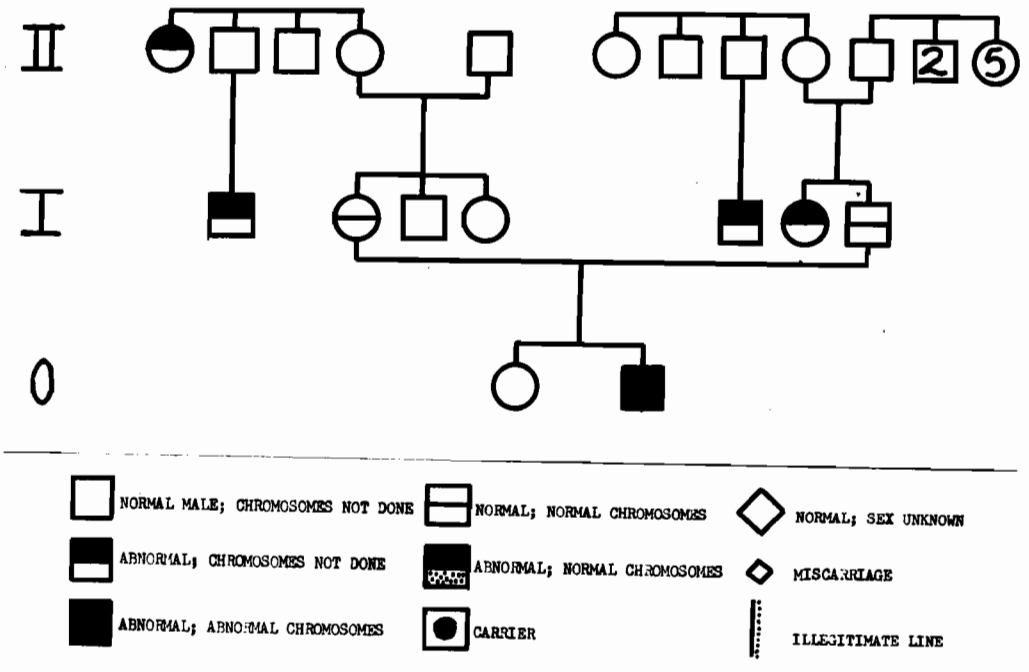
ix Family (26) A case of mongolism with a 21/13 translocation

Baby boy Des, (M.C.H. 244107) was transferred to the Montreal Children's Hospital one month after birth for diagnosis. His mongoloid appearance on one hand and a severe heart defect on the other led the attending physician to suspect that the child had a Down's syndrome. The delivery was uneventful after an uncomplicated pregnancy that lasted 40 weeks.

Family History (Fig. 88)

The boy was the second born to a mother aged 25 and a father of 28, both in very good health, unrelated, and not carriers of any congenital anomaly. The first pregnancy had given a normal girl. On the mother's side one maternal cousin (I-1) is believed to be mentally retarded, while the father's sister (I-6) died shortly after birth. She had a heart defect and was premature. One maternal cousin (I-5) is said to be mongol.

FIGURE 88 - PEDIGREE OF FAMILY 26



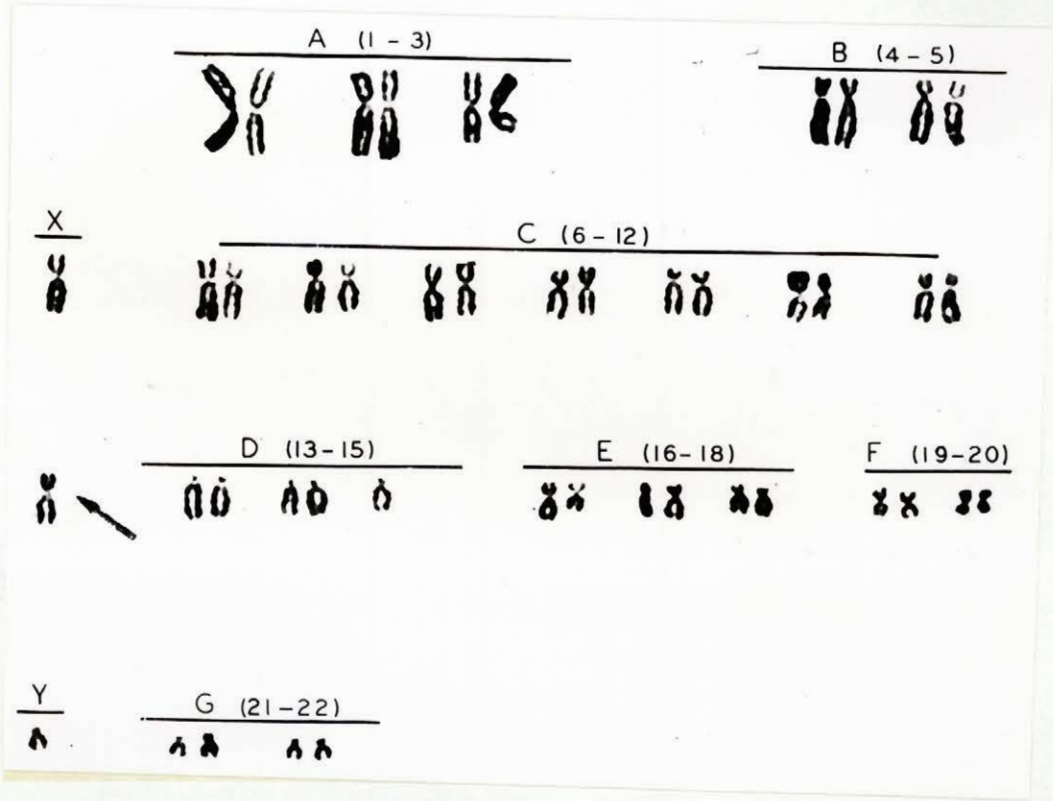
Physical examination

The birth weight of the proband was 5 lbs 7 oz. The patient was receiving oxygen almost constantly at the time of hospitalization. His reflexes were present but of reduced intensity. His tonus was poor. His skin was marbled. He had brushfield spots, low set ears, and a wide space between the first and second toes. Auscultation revealed the presence of a Grade II systolic murmur irradiating towards the carotid. The finger prints revealed a mongol score of + 3.8 for the proband. Neither of the parents had abnormal dermatoglyphic patterns.

Cytogenetic studies (Fig. 89)

The peripheral blood culture made on the proband showed that all the cells analyzed had a total count of 46 chromosomes; however the karyotype was abnormal since there were only 5 members in the D group and an extra member of the C group. This was interpreted as being the result of a G/D translocation. The parents were then examined and both found to have normal chromosomes, and no sign of mosaicism.

FIGURE 89 - KARYOTYPE OF PROBAND FAMILY 26



Final diagnosis

When a patient is carrying a translocation and also has extra chromosomal material, we suspect that one of the parents is carrying the translocation. In the present case one paternal cousin was mongol, and the father's sister died at birth of an undiagnosed cardiovascular malformation. She was also premature. Since that child was born at home and in the country we cannot verify the statement that she was mongoloid. However, since both parents have normal chromosomes the translocation may have taken place during gametogenesis of one of them, or less likely, shortly after conception, thus giving rise to two cell lines of which one failed to develop since it was monosomic.

x Family (27) Absence of corpus callosum

Carol T. (M.C.H. Gen. Dept. CD32) was referred to the Genetics Department with her sister Gail because they both had an absence of the corpus callosum, and were mentally retarded.

Family History

The mother was 28 and the father 35 years of age when Carol was born. They were both English in origin. The first pregnancy resulted in a spontaneous miscarriage. Carol was then born on March 18, 1952. The next child Terry was normal. Gail was born on March 31, 1947. Finally the last pregnancy terminated normally and the mother gave birth to a normal girl Colleen. One paternal uncle was hospitalized in a mental institution for psychotic troubles. Both parents were physically normal and not related.

Physical examination

The proband weighed 3 lbs 4 oz. at birth. She had a pyloric stenosis treated medically. Her sternum was depressed and she looked retarded in the first months of life. Further investigation revealed at the time that the girl had an enlarged clitoris, a deep voice and an absence of the corpus callosum. Her sister was mentally retarded but apart from the absent corpus callosum had no other striking anomaly.

Cytogenetic studies

The chromosome studies were done on the proband and found to be normal. More than forty cells were counted and ten of them analyzed. A special attention was paid to the presence of enlarged satellites on the

long acrocentrics, or the existence of small fragments in the cells in metaphase.

Final diagnosis

A final diagnosis of absence of corpus callosum was made.

xi Case (17) Atypical mongol with mosaicism

Joy W. (M.C.H. 232008) was born on May 28, 1962, after a normal 43 week gestation. The patient was seen by the Genetics Department because she had atypical mongoloid features.

Family History

The 30-year-old mother previously had 4 normal children, two of which required exsanguino transfusions at birth. There was no family history of mongolism. The father was 28 years old and unrelated to the mother.

Physical examination

The birth weight of the child was 3.4 kg. Her bilirubin was 3.25 mgm at birth and went up to 22.8 mgm 96 hours later. She then had an exchange transfusion due to Rh incompatibility. Her head circumference was 33 1/2 cms., her length 51 cms. She had slanted eyes, epicanthic folds, small but normally set ears. Her fifth fingers were short and incurved. She had no brushfield spots. Her heart was normal. At the age of two months the infant seemed retarded. She would not follow a light nor smile. She was hypotonic. She was taken back to the hospital at the age of 6 months, because the mother feared that she could not see, but the ophthalmological examination revealed that everything seemed to be in order. At the age of 15 months she has made great progress, but was still hypotonic. Her intelligence level has improved greatly and the mongoloid signs seemed to have faded.

Cytological examination

The chromosomal studies were done on three separate occasions. The

first time, shortly after birth, the results obtained from the peripheral blood culture showed three types of cells: some cells had 46 chromosomes with a sex pattern of XY, some cells had an XX pattern and finally some had a female constitution plus an extra small acrocentric.

The second culture gave only two types of cells: both of them were female like but some had an extra small acrocentric. It was then believed that the first time some of the cells found in the culture came from the blood donor who was found to be a male on investigation. Those cells had disappeared two weeks after the exchange transfusion, and only the patient's cells were analyzed. But the infant was found to be a mosaic mongol, with a relatively high proportion of aneuploid components. Three months after birth 70% of the cells counted had a normal diploid count and 30% of them were trisomic for a small acrocentric.

Final diagnosis

The final diagnosis was made with reserve and the parents were told that the child would have to be followed very closely since it may happen that her development would be abnormal. Further chromosomal analysis will be done in the near future to check the existence of those abnormal trisomic cells.

h. Skeleton

i Family (28)

Daniel B. (M.C.H. 149515) was born on November 5, 1957. Multiple anomalies were found at birth and the parents were referred to the Genetics Department for advice since he was the third child in the same family born with multiple malformations.

Family History (Fig. 90)

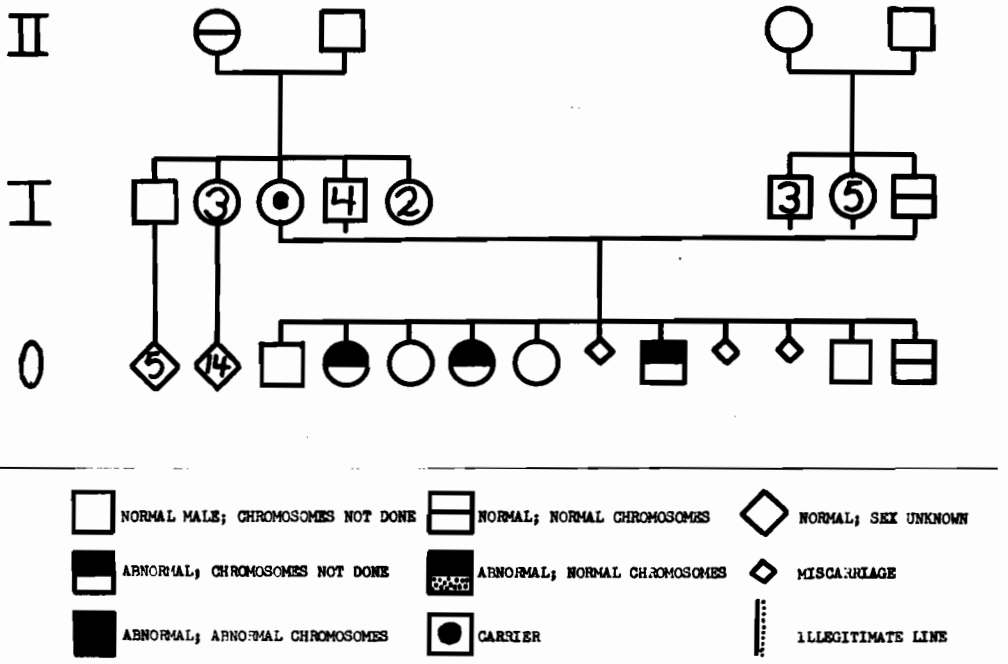
The racial origin of the parents was French Canadian, and they were not related. The father was 28 and the mother 26 when Daniel was born. Up to 1963, the mother had had 11 pregnancies, three of which resulted in spontaneous miscarriages (0:8, 10, 11), three in malformed children (0:4, 6, 9) and five normal sibs. Apart from the miscarriages the periods of gestation were uneventful. One father's sister had two children who died at birth of congenital anomalies (not shown on the pedigree). One had a pyloric stenosis and the other one had a patent ductus arteriosus accompanied by a cleft palate and webbing of the second and third toes. Both parents of the proband were physically normal as well as the parents of the last two children described.

Physical examination (Figs. 91, 92, 93, 94)

In Table 16 the physical examination of the three malformed children is summarized along with a similar case described by Jennings (1961). Pauline was born in 1950 and died 14 months later. Jeannette was born in 1953 and was only 9 months old when she died. The proband died in an institution apparently only a few months after birth. Only the proband was

hospitalized at the Montreal Children's Hospital. The other two children were born and treated in out-of-town hospitals and a post mortem was done on only one of them.

FIGURE 90 - PEDIGREE OF FAMILY 28



FIGURES 91, 92, 93, 94 PICTURES OF PROBAND FAMILY 28

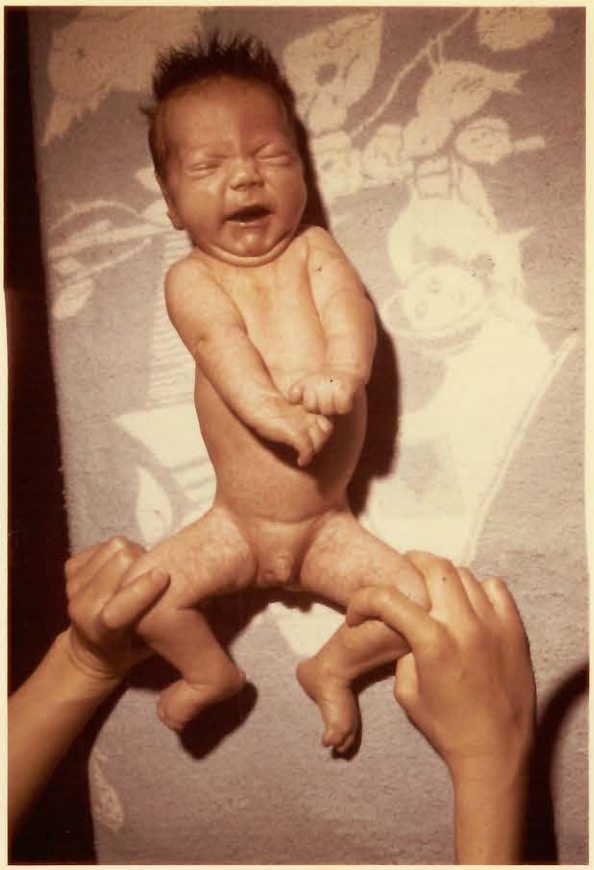


FIGURE 91

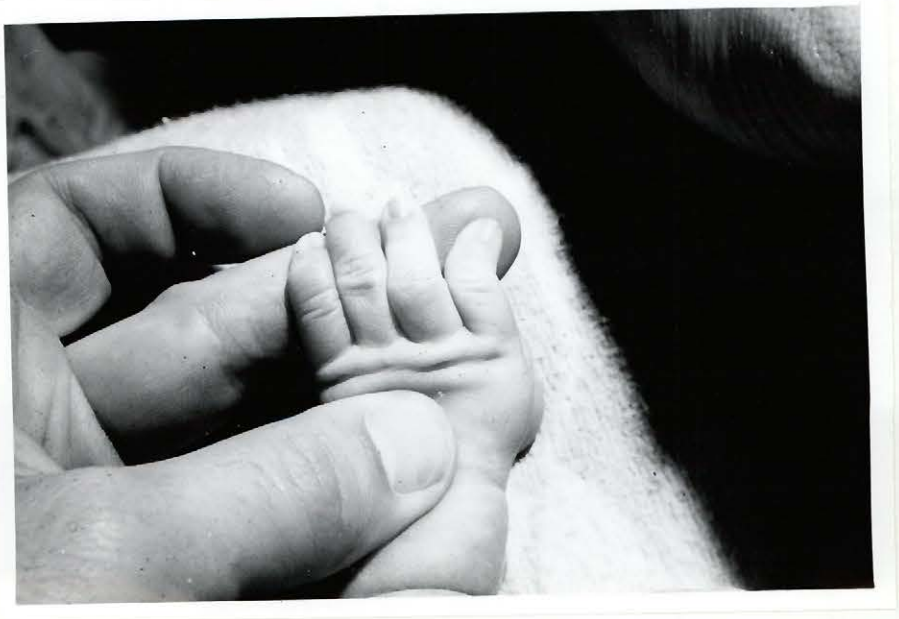


FIGURE 92

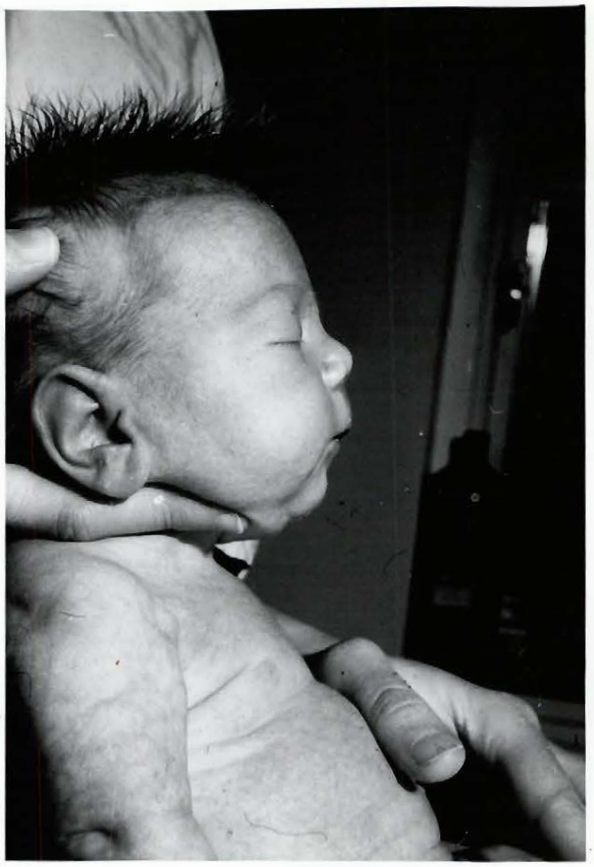


FIGURE 93

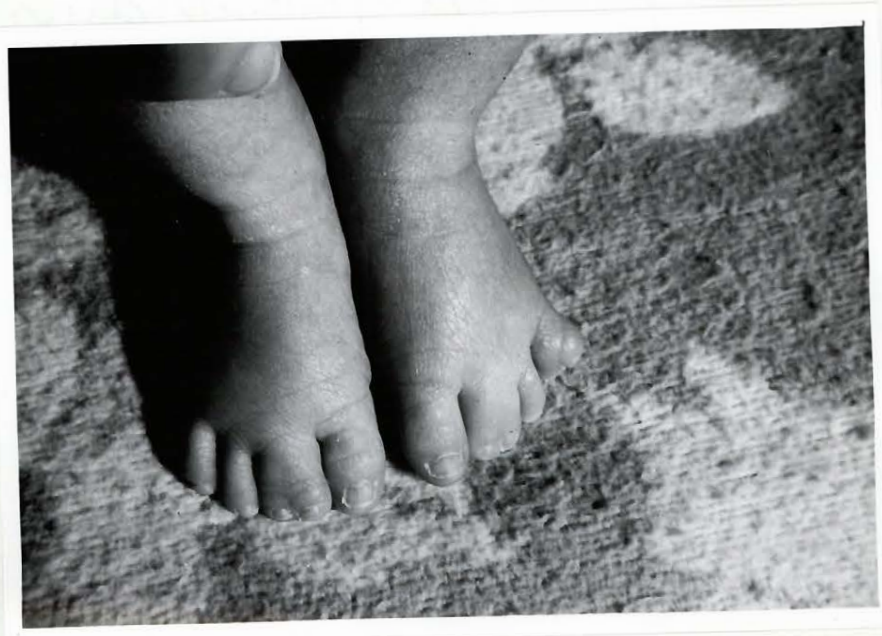


FIGURE 94

TABLE 16

PHYSICAL EXAMINATION OF CHILDREN FAMILY 28

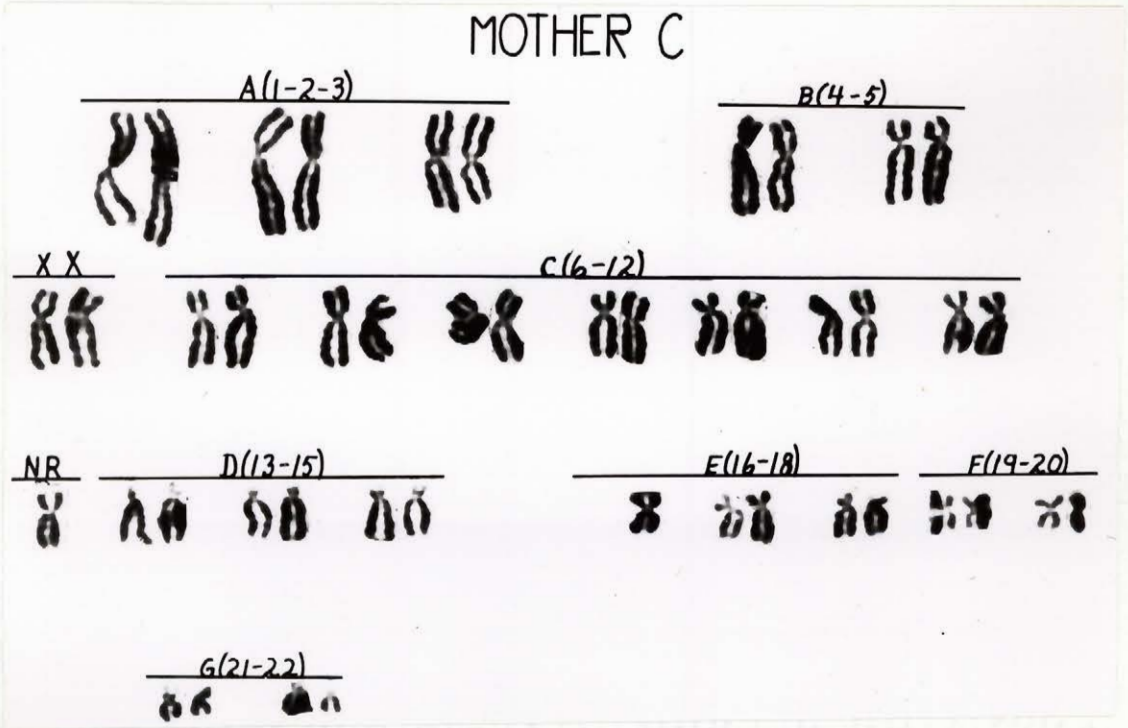
Anomalies	Jennings (1961)	Pauline	Jeannette	Proband
Birth weight	?	7 lbs 4 oz	6 lbs 8 oz	6 lbs 6 oz
Head circumference	?	?	12 1/2"	12 1/2"
Prematurity	+	+	+	+
Mental retardation	+	+	+	+
Epicanthic folds	+	+	+	?
Optic atrophy	?	+	+	+
Hearing loss	+	+	+	+
Malformed ears	+	+	+	+
Cleft palate	+	high	+	very high
Webbed neck	+	+	+	+
Hypotonia	+	+	+	+
Polydactyly	-	?	+	+
Fusion of vertebrae	+	+	-	-
Narrow shoulders	+	+	+	+
Divarication of recti	+	?	+	+
Micrognathia	?	?	+	+
Urinary tract normal	+	+	+	+
GI tract normal	+	?	+	+
Malformed genitalia	+	?	+	+
Normal heart	+	+	+	+
Webbed toes	?	+	+	+
Crooked fingers	?	?	?	+
Talipes equinovarus	+	?	?	+
Skull X-ray normal	+	?	+	+
Poor osseous development	+	+	+	+
Umbilical hernia	?	+	+	+

Cytogenetic studies (Figs. 95, 96, 97)

Since the children died well before chromosomal studies were available, the cytogenetic studies could be done on the parents only. The father was found to have a normal karyotype, as well as the maternal grandmother. The mother however, had 46 chromosomes and an abnormally long number 16 of the E group. The studies were repeated on three separate occasions, and the same results were obtained each time. It was estimated that 60% of her cells had this unusual chromosome. The relative length, centromere index and arm ratio were calculated by the same method used by the Denver group (Table 17a-17b) and the measurements were also made on normal cells of the same mother. In a few cells in which the length of the number 16 was normal, enlarged satellites were noted on one member of the D group. The relative length of the abnormal chromosome placed it within the lower limits of the range of the C group. The chromosome chosen as being the abnormal one was always the smallest found in the C group. The chromosomes of the last child born in this family were examined and found to be normal. The unusual 16 could not be found in any cell.

Chromosome number	44	45	46	46*	47	48	Poly-ploid	Total
Mother	1	0	36	78	0	0	0	115
Father	0	1	30	0	0	0	0	31
Child 0-13	0	0	30	0	0	0	0	30
MGM II-1	0	0	40	0	0	1	1	42

FIGURES 95, 96, 97 - KARYOTYPES OF MOTHER FAMILY 28



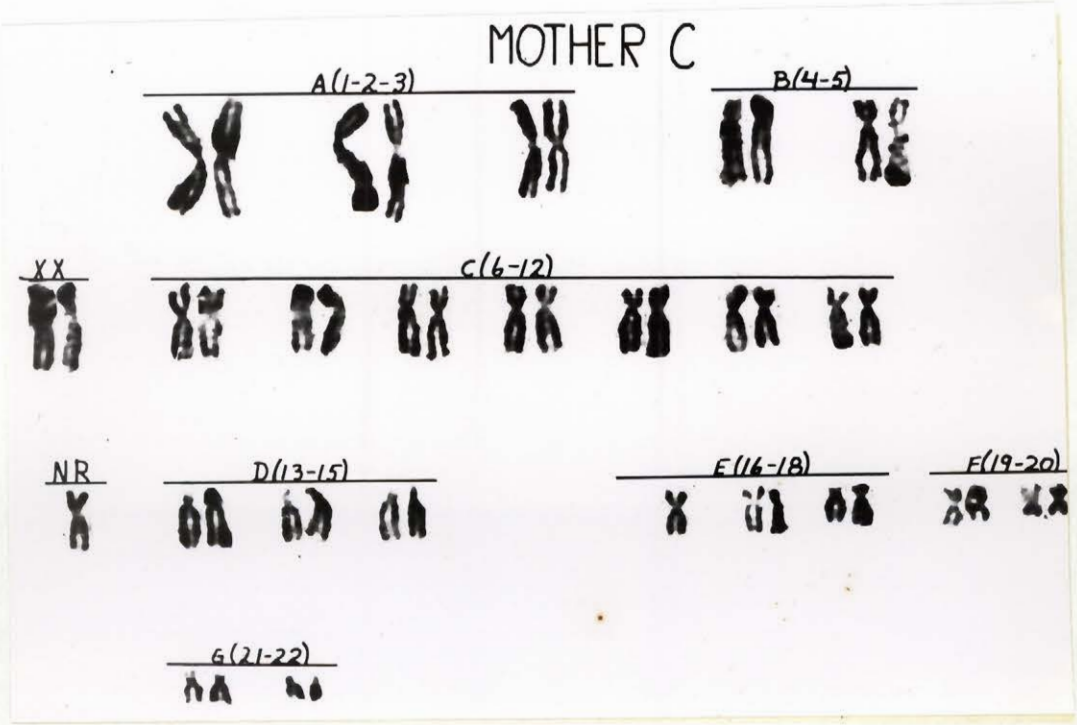


FIGURE 97 - KARYOTYPE OF MOTHER FAMILY 28

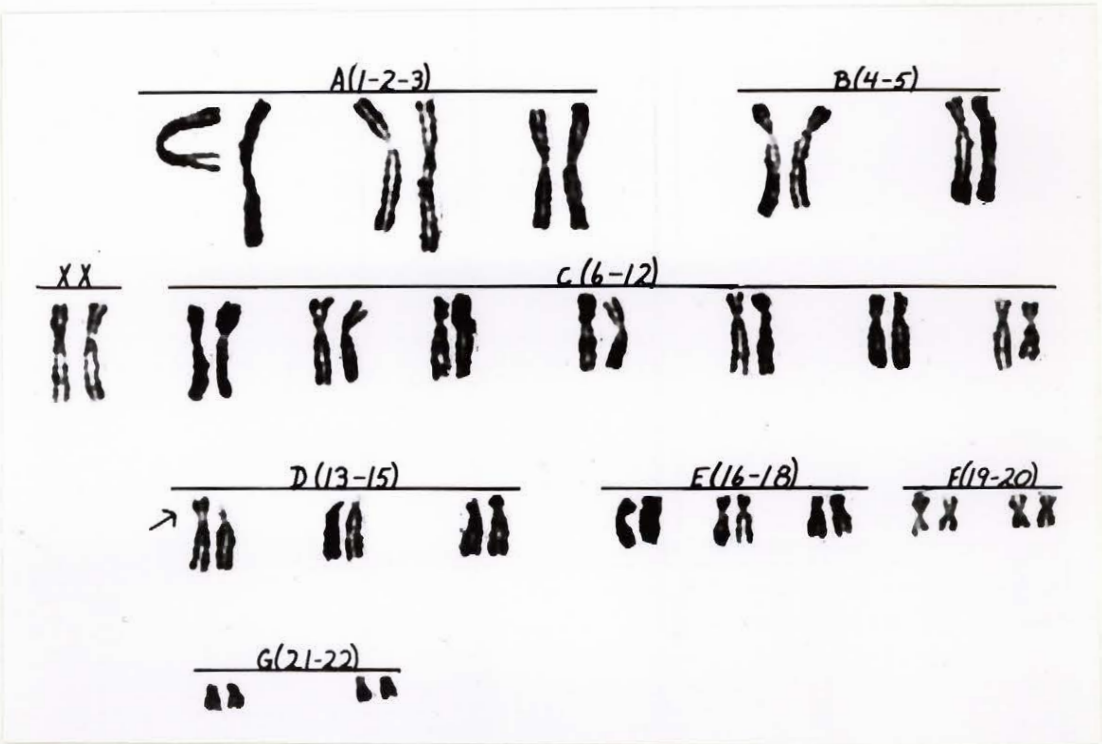


TABLE 17

RELATIVE LENGTH OF CHROMOSOMES IN MOTHER FAMILY 28

Chromosome Number (Denver)	Cell number																								Range
	Abnormal																Normal								
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	1	2	3	4	5	6	7	8	
1	87	88	93	85	80	84	83	86	80	84	80	85	87	92	85	78	80	85	90	88	87	81	92	86	78-93
2	83	79	86	77	80	84	80	84	80	81	87	81	83	80	85	85	81	85	75	75	87	88	82	86	75-88
3	66	69	73	64	69	71	71	72	68	66	70	66	69	78	60	70	66	71	67	67	71	73	69	67	64-78
4	70	69	63	64	63	63	63	60	64	70	63	66	67	74	60	66	72	68	59	67	66	66	69	67	59-74
5	66	59	63	64	63	63	63	55	64	62	63	55	58	68	60	59	72	61	63	60	66	63	55	62	55-72
x	58	56	57	57	63	59	60	62	56	59	62	62	55	62	60	55	57	57	63	60	58	60	55	57	55-63
6	54	52	47	53	59	55	56	53	56	59	52	55	53	57	51	51	57	54	55	53	58	57	51	48	47-59
7	54	49	47	53	49	50	48	48	56	48	49	51	51	48	51	47	45	47	47	53	59	51	51	48	45-56
8	46	46	43	46	49	50	48	48	48	48	49	48	47	48	51	51	48	44	47	49	46	47	46	48	44-51
9	50	49	47	42	45	46	48	46	48	48	45	44	45	44	51	43	42	47	51	46	46	44	46	43	42-51
10	50	46	47	42	45	42	40	46	44	48	45	44	44	44	51	47	42	47	43	46	46	47	42	43	40-51
11	46	46	43	46	42	42	48	43	44	40	42	44	44	40	47	43	42	47	43	49	46	44	42	43	40-49
12	42	39	43	42	38	38	39	43	40	43	42	44	40	40	43	43	42	44	39	39	37	41	41	43	37-44
13	32	40	33	32	35	35	36	40	36	33	35	37	34	35	34	31	36	34	31	32	32	31	32	38	31-40
14	29	33	33	32	31	34	32	31	32	29	31	33	30	31	30	27	30	30	31	28	32	32	32	34	27-34
15	25	26	27	32	31	29	32	26	28	29	28	29	27	21	25	27	27	27	31	28	29	25	32	24	21-32
16	29	29	27	31	35	29	32	29	28	29	28	29	25	26	30	31	33	30	35	35	29	28	37	24	24-37
17	25	26	27	32	31	29	32	26	28	29	28	29	33	21	25	31	27	28	31	28	25	28	28	33	21-33
18	21	26	23	28	28	25	24	26	24	22	24	29	29	21	30	31	27	24	27	28	25	28	28	24	21-31
19	21	23	23	25	24	21	24	24	24	22	24	22	25	21	25	27	24	20	19	25	21	22	23	19	19-27
20	21	20	20	25	21	21	24	21	24	22	21	18	24	17	21	23	24	27	23	18	21	19	23	19	17-27
21	16	16	17	18	14	17	16	17	12	15	17	15	18	13	13	16	18	17	16	14	12	13	14	14	12-18
22	12	13	13	14	10	13	8	14	16	11	14	11	13	13	13	16	12	10	12	11	8	10	9	14	8-16
NR	37	39	33	39	42	38	36	41	36	40	38	40	40	39	43	39									33-43

TABLE 18

CENTROMERE INDEX, ARM RATIO FAMILY 28

			Centromere Index		Arm Ratio	
			16	42	16	NR
		1	36	42	1.5	1.6
		2	35	27	1.9	2.6
		3	50	25	2	3
	ABNORMAL	4	46	35	1.1	1.9
		5	50	28	2.0	2.5
CELL NUMBER		6	41	38	1.4	1.6
		1	35		1.9	
	NORMAL	2	29		2	
		3	47		1.3	
	RANGE		29-50	25-42	1.1-2	1.6-3
	DENVER RANGE		31-42		1.4-1.8	
	JENNINGS RANGE					1.8-3

Final diagnosis

Jennings in 1961 and Carr in 1963 reported similar cases in which there was an unusually long chromosome of the E group, identified as a number 16. Jennings (Table 16) found the same abnormality in a 13-year-old girl. Carr's case is still under investigation (1963 P.C.), but the author found the same abnormality in normal sibs, which seems to indicate that the presence of the abnormal chromosome may be compatible with a normal phenotype.

The following explanations are considered in the explanation of the abnormally long chromosome:

1. A normal variation of one of the members of the homologous pair involved.
2. A duplication of the long arms of the chromosome.
3. A reciprocal translocation between a member of the D group and an E chromosome which took place late in the development of the mother and was transmitted to some of the children.

It is merely a coincidence that similar abnormalities of the phenotype were found in a patient in Australia and that the same chromosomal aberration was present in the patient as well as in our case where the mother is mosaic for the aberration and gave birth to three abnormal children. Jennings (1962) had not yet located the parents of the institutionalized child in order to do cytogenetic studies on them.

If the chromosome 16 is really involved in a duplication or a reciprocal translocation, the risk for the mother giving birth to an abnormal child or a miscarriage may be as high as 50%, or less if the abnormality is compatible with a normal life as demonstrated by Carr, assuming that the abnormality has the same origin.

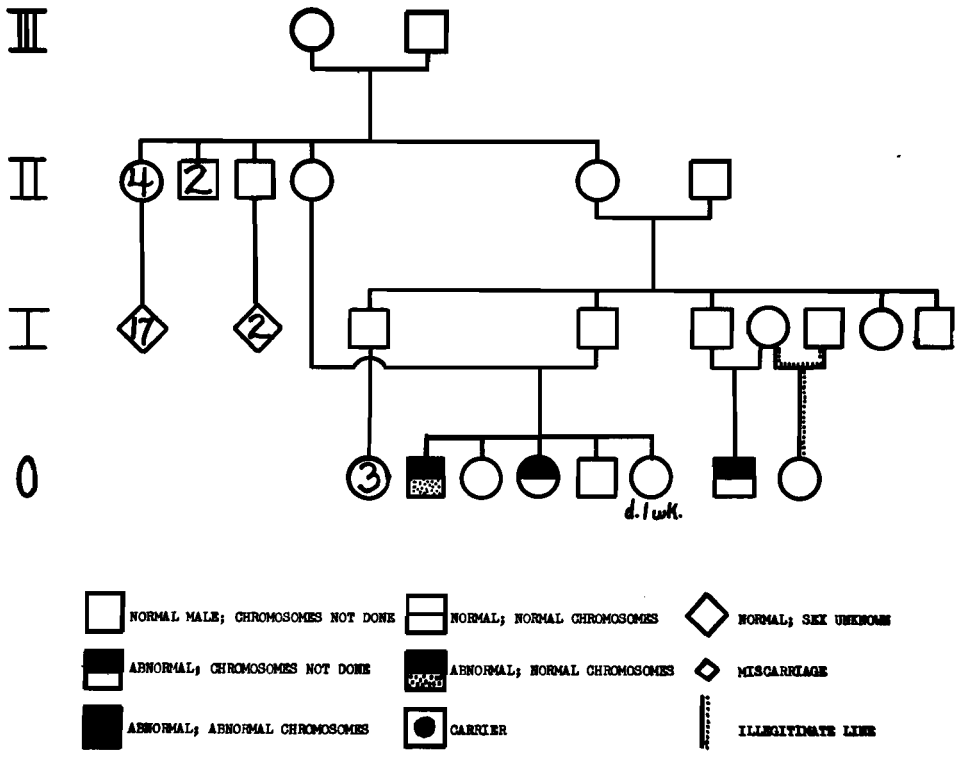
ii Family (29)

Vincent B. (C.M.H. 95057) was born on April 16, 1950 after 28 to 32 weeks of gestation. It was a breech delivery and the birth weight was 2,150 gms. The proband had multiple malformations. He was then referred to the Genetics Department for diagnosis.

Family History (Fig. 98)

The father was 27 years old and the mother 22 when the child (O-1) was born. There was at the time no family history of congenital malformations. Both parents were of Italian origin. The parents were related, the mother having married her nephew. The pregnancy was uneventful except for severe vomiting experienced by the mother especially in the first trimester.

FIGURE 98 - PEDIGREE OF FAMILY 29



Physical examination (Figs. 99, 100)

The physical examination revealed at the time of birth marked cyanosis of the extremities. The child had blond hair, a depressed nose bridge, a pigeon chest, dislocation of the elbows, finger, hips and knees. The sclerae were clear, and the eyes found normal on ophtalmological examination. The fontanelles were normally open. The tongue was protruding. On auscultation a harsh systolic murmur could be heard which suggested a severe heart malformation. There was some hepatomegaly. The child was hypotonic. The finger prints were normal.

Dentition

The dental examination revealed congenitally missing lower cuspids. The teeth were proportional in size to the general development of the oral structure. The mandible was overdeveloped or the premaxilla underdeveloped.

Radiology.

The X-rays showed no evidence of any dwarfing or increase in width or shift of ends of bones. The muscles were underdeveloped. The long bones were long and thin. There was radiological dislocation of elbows, shoulders, hips, hands and knees. The X-ray of the hands demonstrated a rudimentary sixth finger between the index and middle finger of the right hand.

Laboratory data

The usual laboratory examinations were done and no abnormal results were noted. The blood Kahn was negative.

The proband's sister (O-3) was born at the Royal Victoria Hospital. She died four hours after birth. She was described at birth as being a premature newborn. The delivery was normal. The child had mongoloid features, clubbing of feet and hands, a patent foramen ovale and an interventricular septal defect.

The proband's sister (O-5) was also born at the Royal Victoria Hospital and lived only one week. The cause of death was unknown.

FIGURES 99, 100 - PICTURE OF PROBAND FAMILY 29

AT BIRTH

FIGURE 99

AT AGE SIX

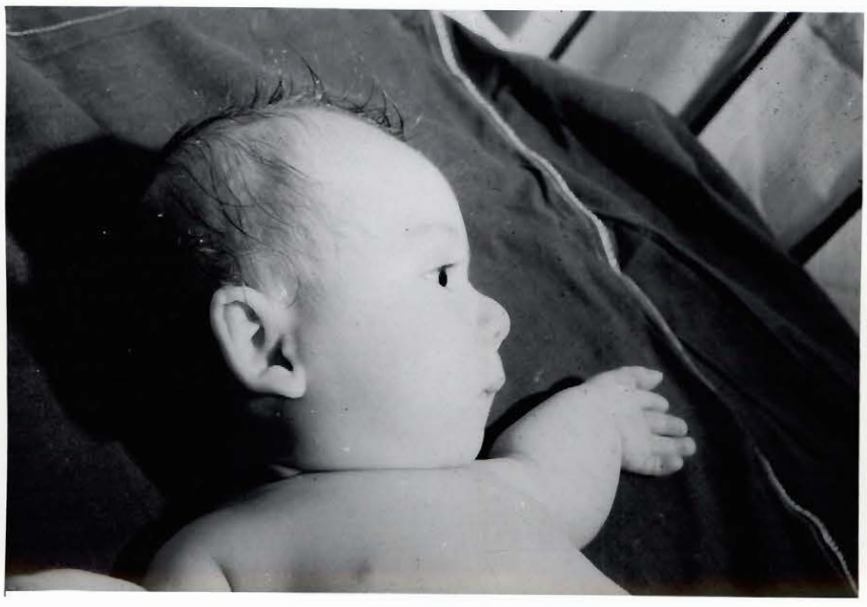
FIGURE 100

The proband's first cousin, J.B. (0-9) was born on April 2, 1956 at the Royal Victoria Hospital. The mother had a normal delivery after an uneventful pregnancy that lasted 40 weeks. The mother had no miscarriages previously, and this was her first pregnancy.

Physical examination (Figs. 101, 102)

The physical examination at the time of birth revealed a short neck, flattening of the right occipital bone, deformities of hands and fingers, sub-luxation and dislocation of hips and knees. Both feet were in equino-cavo-varus position. The eyes and ears were normal. There was no evidence of heart defect. The hair and eyes had a normal pgimentation. An electro-encephalogram done at the age of 5 1/2 months of age showed minimal evidence of focal abnormality in the right temporo-parietal area. A psychological test revealed that the child's intelligence was in the normal range. The finger prints were normal.

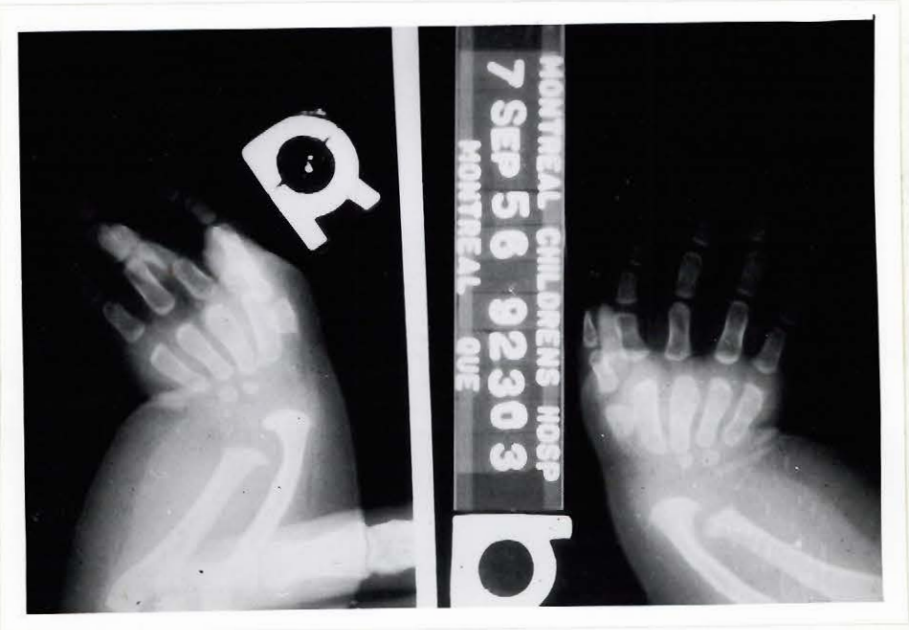
FIGURE 101 - PICTURE OF PATIENT (0-9) FAMILY 29



Radiology

The radiological examination revealed shortening of the long bones, with proximal radio ulnar dislocation bilaterally and subluxation at the distal radio ulnar joint, with ulnar deviation of the wrist and joint. There was absence of the lower femoral epiphysis bilaterally. The infant had bilateral talipes equinovarus with metatarsus adductus, and bilateral subluxation of both hips.

FIGURE 102 - RADIOLOGICAL PICTURES OF PATIENT O-9



Cytogenetic studies

Blood was taken for chromosomal studies in 1962 from the proband, and the same analysis was repeated again after three months to exclude any possibility of mosaicism. All the cells examined had a normal diploid count of 46, including normal sex chromosomes of XY type. There was no evidence of translocation or deletion.

Final diagnosis

A final diagnosis of multiple malformations of unknown origin was made. The case will be discussed later.

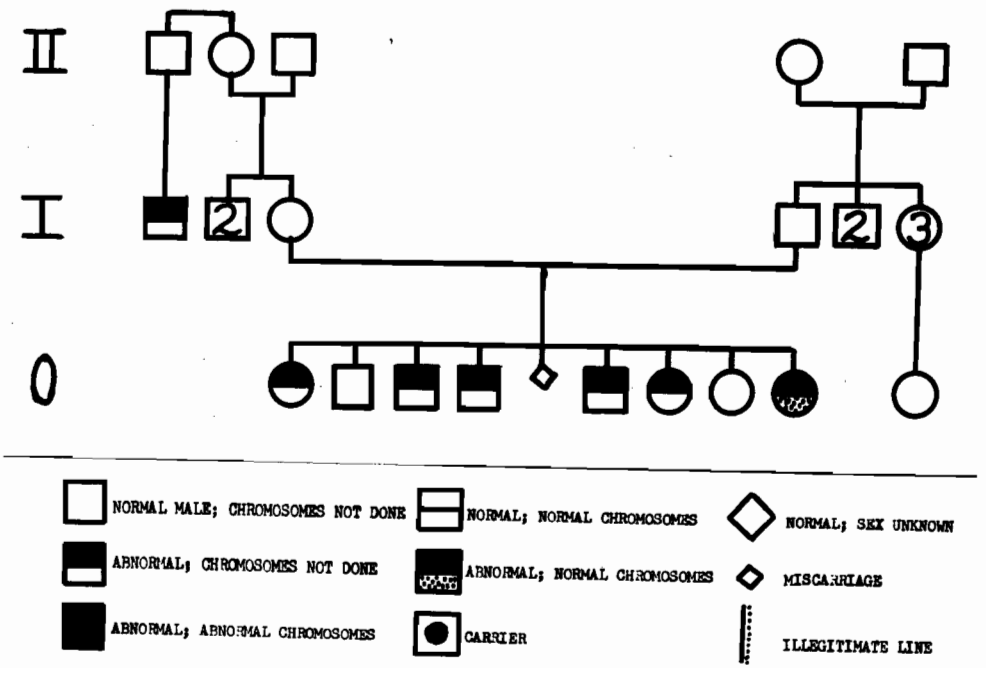
iii Family (30)

Jacques L. (M.C.H. 147412) was born on February 12, 1957. The proband was the third child in the same family born with multiple bone anomalies. The parents were then referred to the Genetics Department for counselling.

Family History (Fig. 103)

Both parents were French Canadians and quite young at the time of birth of the patient: the father was 24 and the mother 21 years old. One maternal uncle (I-1) had a cleft palate. Both parents were physically normal and of average intelligence. They were not related. The mother had nine pregnancies one of which resulted in a spontaneous miscarriage (O-5). Six children had malformations of the skeleton. The proband (O-4) had a breech delivery.

FIGURE 103 - PEDIGREE OF FAMILY 30



Physical examination and medical history (Figs. 104, 105)

(O-1) Francine (M.C.H. 116905) was born on April 4, 1955 and placed in an institution where she died six months later. She had long curved fingers, a cystic lesion of the left pinna, an absence of the uvula, bilateral dislocation of the hips, a lumbo-sacral lordosis and hypoplasia of the left thoracic pedicles. The pregnancy was uneventful.

(O-2) Jean-Pierre (M.C.H. 148566) was born on January 4, 1956. The pregnancy was complicated with severe vomiting that lasted 7 months. The patient had no physical anomalies but an electroencephalogram done after an episode of convulsions revealed some subcortical disturbance. One should note that the child was born after only 8 months of gestation, and the birth weight was 3 lbs 9 oz.

(O-3) Proband. The physical examination at birth revealed that the patient had crooked fingers, a flat facies, very short bones, hypermobility of the joints, a torticollis and limited motion of the fingers and toes.

(O-4) Andre (M.C.H. 161690) was born on July 1, 1958. His birth weight was 3,080 gms. His head circumference was 34 cms. The patient had a club foot and was suspected of being mentally retarded. In the following months the bone anomaly was corrected and the child seemed to develop slowly. At the age of five the mother claimed that her child was normal. However, a physician saw the patient and thought that the boy was at the lower limit of normal intelligence.

(O-5) Miscarriage.

(0-6) Baby boy (Ste. Jeanne d'Arc Hospital) died 5 hours after birth. The patient was premature, being born after only 30 weeks of gestation. The malformations were not described at the time. There was a mention that the child was anophthalmic.

(0-7) Baby girl died shortly after birth in 1961.

(0-9) Francine (M.C.H. 242794) was born in 1960, and lived only a few days. Her birth weight was 1,644 gms. She had an haemangioma of the left lid and left thigh. Both feet were clubbed, her ears were low set and abnormally formed. She also had a cyst on the left ear that was filled with sero-sanguinous fluid. Her palate was high and arched.

The symptoms described in these patients may be summarized in a broad way since all the sibs did not have exactly all the same malformations at the same time:

1. Flat facies
2. Broad nose bridge
3. Malformed ears
4. Multiple skeleton anomalies including shortening of the bones, hip dislocation, and crooked fingers.
5. Apparent mental retardation
6. Micrognathia
7. Palate malformation

FIGURES 104, 105 - PICTURES OF PROBAND FAMILY 30

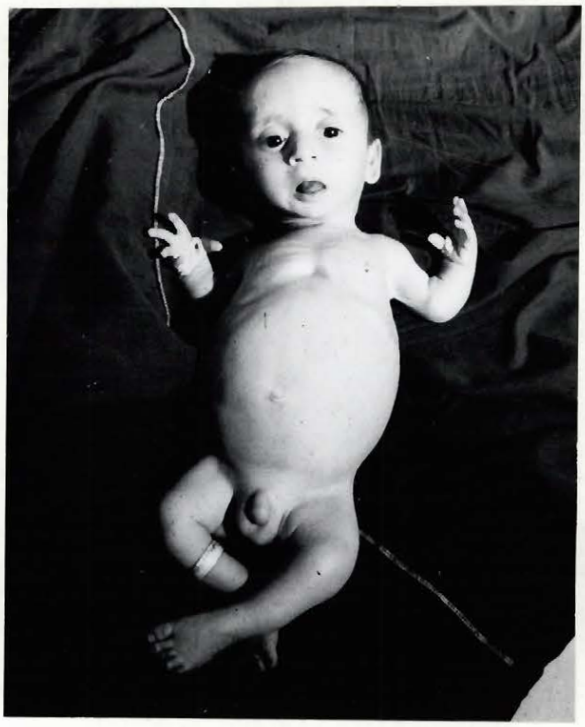


FIGURE 104

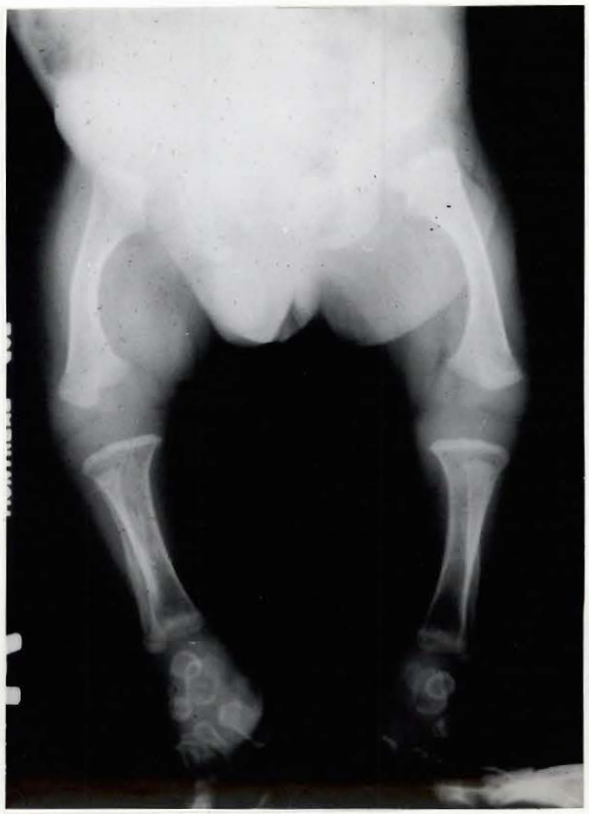


FIGURE 105

Laboratory data

The laboratory investigations were all in the normal limits.

Cytogenetic studies

The chromosomal studies were done on patient (0-9) on two different occasions and the results were considered normal. There was no extra material and the chromosomes did not show any sign of translocation. A total of 90 cells were counted and more than 20 were analyzed.

Final diagnosis

A final diagnosis of multiple malformations of unknown origin was made.

C. PATIENTS WITH ABNORMAL PHENOTYPE AND NORMAL KARYOTYPES

Fifty patients who had physical anomalies of unknown origin and no family history of congenital malformations were found to have normal karyotypes. In Table 19B the anomalies of those patients are described in relation to the anatomical system. For example: prognathism or micrognathia will go under mandible, cataracts or brushfield spots are entered under eyes.

In Table 19A the main systems involved are given in order of importance. An average of 4.1 different types of systems were affected for all patients. In only one patient out of 50 as many as nine systems were involved. The significance of these findings will be discussed later.

TABLE 19A

		Patients
1.	Mental impairment	21
2.	Ears	18
3.	Skeleton	18
4.	Height	15
5.	Cardio-vascular	13
6.	Eyes	12
7.	Genito-urinary	12
8.	Weight	12

TABLE 19B — PATIENTS OF PRESENT STUDY WITH ABNORMAL PHENOTYPES AND NORMAL KARYOTYPES

DEFECT	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	TOTAL
Cardio-vascular												+								+	+	+			+				+						+	+	+		+	+									+	13
Central nervous system																															+	+										+					+			5
Dermatoglyphics			+					+																									+																	3
Ears			+					+				+	+	+	+			+	+								+			+				+			+	+	+								+	+	+	18
Endocrine	+		+							+	+	+																																							6
Epicanthic folds																																																			0
Eyes				+	+				+									+		+									+	+			+				+												12
Face									+				+	+	+			+		+							+											+												9
Failure to thrive							+												+	+	+																														4
Gastro-intestinal																									+																										1
Genito-urinary						+	+							+					+				+			+											+	+												12
Haemangioma																			+			+																+												5
Height	+	+	+				+	+		+				+					+		+								+					+															15
Hematopoietic				+													+							+																		+	+		+							6
Hernia							+									+							+																												7
Hypogonadism	+										+	+				+							+		+		+																								8
Mandible					+		+	+													+												+			+														6
Mental impairment			+				+	+	+		+	+		+	+					+				+		+	+		+					+		+			+										21
Muscle																+																						+												3
Neck												+																																							3
Palate and Lips				+		+			+												+								+	+							+		+									8
Skeleton			+	+				+	+	+			+					+		+	+	+													+	+	+												18
Skin																																			+															3
Skull													+										+		+										+															7
Weight		+	+					+		+	+	+							+		+								+																					12
TOTAL	4	3	7	2	3	1	8	6	6	3	4	6	4	5	3	3	1	4	6	6	7	3	4	1	4	2	3	2	5	6	1	1	4	6	3	4	6	5	6	1	1	9	3	7	2	2	3	6	7	6	205 $\bar{X}$: 4.0

IV DISCUSSION

A. STUDY OF CHROMOSOMAL ANOMALIES

a. Blood dyscrasia

In the present study, one familial type of blood dyscrasia was investigated in Family 1 and no chromosomal anomaly was found. Though the patient presented some minor physical anomalies, they were not present in the other affected relatives and one should not expect to find a chromosomal defect responsible for the syndrome. Special attention was paid to partial deletions of chromosomes and mosaicism. Two other families with more than one member affected with a similar type of anemia were studied and also found to have a normal chromosomal pattern, as suspected.

No familial anemia has yet been found to be caused by an inherited chromosomal rearrangement. One could however mention the abnormally long X chromosome described by Elves and Israels (1962) in an haemophiliac patient who also had other physical anomalies. Bottura et al (1961), German et al (1961) and Bernirschke et al (1962) described patients presenting a syndrome called Waldenstrom's macroglobulinemia, of which one feature is a severe anemia. Their cases independently showed the presence in a low percentage of the cells of an extra long chromosome, having a variable position of the centromere, but longer than members of the A group. It is still not clear whether the biochemical abnormality is a cause or a result of the chromosomal aberration. It does not appear to be familial.

Various chromosomal aberrations have been described in cases of malignant diseases, but the only consistent chromosomal anomaly seems to be

the one related to the chronic myeloid leukaemia (Nowell and Hungerford, 1960).

b. Cardio-vascular

1. The E syndrome

In the group of cardio-vascular defects, four cases of E syndrome are described, one of which is a partial trisomy inherited through a maternal D/E translocation, (Brodie and Dallaire, 1962).

The clinical picture associated with the trisomy for an E chromosome, as described by Smith et al (1962), includes mental retardation, hypertonicity, flexion of the second finger over the third, low set and malformed ears, small mandible, failure to thrive, dorsi-flexion of the great toes, patent ductus arteriosus, interventricular septal defect, umbilical and/or inguinal hernia. Crawfurd (1961) and German (1962), also reported cases of the E syndrome confirming those findings.

The E group comprises the chromosomes nos. 16-17-18, but so far only one of the last two has been found to correspond to the above picture when present in triplicate. Which one is still a matter of dispute. This relatively new syndrome has been fairly well documented in the past three years, despite the fact that the affected children die very early in life and that the incidence of the syndrome is quite low.

In the present study the following anomalies were noted as being undescribed yet: in Case 2 and the proband of Family 3 the second finger is rotated on itself instead of being flexed. The pathological examination revealed an abnormal rotation of the cartilage of the terminal phalanx. In Case 1 there was a side-to-side ileo-caecal junction, in Case 2 both the small and the large bowels had a common mesentery, there was a deficiency

in the costo-cartilages of the first ribs, the uterus was unicornuate and the Fallopian tube was blind.

The dermatoglyphic studies revealed in Cases 1 and 2 a total of 10 arches on all fingers and on the toes as well. The proband in Family 3 had a total of 5 arches on his hands. These findings are in agreement with Uchida and Soltan (1963) report on the abnormal dermatoglyphic patterns found in autosomal trisomies.

Out of the three cases due to a primary non-disjunction one mother was 26; the others were over 37 years of age when the patient was born. Hecht (1963) in a review study of the E syndrome found that there was a marked increase in maternal age. Ferguson-Smith (1962) noted that the mean age at the time of death is 90 days; in this study the mean age was 83 days for three patients, no follow-up record is available on the fourth one.

Hecht (1963) found that the sex ratio was 2.7:1 in favour of females. In our study the three cases of non-disjunction involved females only, while the E syndrome originating from a translocation was a boy. No explanation is apparent for the disturbed sex ratio in this autosomal trisomy.

The proband of Family 4 was discharged from the hospital with a diagnosis of chondrodystrophia calcificans and a normal karyotype. The high number of arches on the fingers (6), the flexion of the second toe over the third bilaterally as well as the micrognathia and the kidney anomaly were suggestive of an E syndrome. However, in chrondrodystrophia calcificans, the skeleton anomalies are numerous, and may be associated with other congenital defects: Fraser and Scriver (1954) reported that heart malformations, mental deficiency, cataracts, shortening of the limbs and contractures of the major joints have been found to accompany the syndrome, which according to the authors is probably due to a recessive gene.

2. The D syndrome

The D syndrome as mentioned in the introduction, can be due to a primary non-disjunction or a translocation. In Case 5 there was an extra member in the D group. The patient had no cleft palate or hare lip, but an abnormal configuration of the root of the nostrils. The other features were all typical of the syndrome as reported by Ellis and Marwood (1961), Lubs et al (1961), Patau et al (1961), Conen et al (1962) and Northcutt (1962). In addition to our case and the ones cited in the introduction, Ferguson-Smith (1961) and Townes (1962) described patients with normal palate and lips. Smith (1963) reviewed the syndrome and stated that variations may exist between cases but usually one finds: mental retardation, deafness, seizures, an eye anomaly, maldevelopment of the nose and mouth, abnormal finger nails, polydactyly, haemangioma and heart anomaly. Miller and co-workers (1963) described one patient with absent olfactory bulbs and tracts, and hypoplasia of the optic nerve and eye. The authors conclude that there is some evidence that the D trisomy is an important etiologic factor in arhinencephaly.

c. Central nervous system

The proband in Family 5 had a spina bifida aperta and multiple malformations. Three sibs also had a severe anomaly of the spine. Sorsby (1953) states that spina bifida is often associated with other defects and may also be familial. Miller and co-workers (1962) have found that the frequency of vertebral and rib anomalies was no higher in parents of children with spina bifida than that in controls. On the other hand Fraser (1961) had previously suggested that spina bifida aperta is not determined by a single mutant gene but is etiologically heterogeneous, and that there is an

increased incidence of related malformations among sibs of affected people. The multiplicity of defects found in the proband of Family 5 suggested a chromosomal anomaly. However, the results were within the normal limits.

In Case 7 no definite diagnosis has been reached in the course of hospitalization, and the post-mortem unfortunately could not be done.

d. Cervico-cephalic

In Families 6, 7 and 8 the formation of the median face is involved. One should suspect the presence of an extra D chromosome since the children also had other skeleton anomalies. However the chromosomal studies done on the parents did not show a translocation. One can then assume that either there is a partial translocation which is unrecognizable because of its size and its location, or that the children were trisomic for an extra member of the D group due to a familial non-disjunction. One fact arguing against this possibility is that the majority of the children did not suffer from a heart defect, and as far as one can tell, there was no eye anomaly. The fact that the clinical features are somewhat dissimilar in the three families raises the question of whether they represent variations of the same syndrome or etiologically different anomalies.

In Case 8 the presence of extra chromosomal material in a high proportion of the cells analyzed brings up the problem of partial trisomies and mapping of the chromosomes. In 1961, Patau proposed a method for mapping the E and D chromosomes. This was based on the assumption of a linear order of loci which in triplicate would produce individual features of the syndrome. If so, it should be possible to arrange the features themselves in an order such that in cases where two or more features were missing, they would always be adjacent ones. In Table 20 the anomalies involved in

the syndrome are listed by order starting below the centromere. So far most of the partial trisomies have been cited in relation to translocations of acrocentric chromosomes i.e. 13/15 and 21/22. Very few translocations were reported that involved one acrocentric chromosome and a non-acrocentric or two sub or metacentric members.

In Case 8 as mentioned above there is an extra chromosome believed to be paritally deleted comparable in size to members of the G group that could be either a partially deleted 13 or 17. The patient had a cleft palate, abnormal ears, a malformed skull, a kidney and a heart anomaly. Since the cleft palate is usually seen in the D syndrome and the kidney anomaly is a feature of the trisomy 17/18, while the other anomalies are common to both autosomal defects, one cannot be sure of the origin of the aberrant chromosomal material. The patient described in this work has had surgical correction of her heart defect and seemed to develop fairly well on her discharge from the hospital both physically and mentally, though she showed a marked delay in her general development. A further assessment may prove that she is mentally normal and that the extra chromosomal material being either a deleted D or E is lacking a major portion of the short and long arm responsible for the mental impairment.

The chromosomal map suggested by Patau is a step forward towards the need for identification of the different anomalies caused by abnormalities in specific chromosomes. One notes however, that in the D chromosome description the polydactyly which seems to accompany most of the 13/15 trisomies, is missing; in the E chromosome map syndactyly of the second and third toes is included though it is rarely seen in that syndrome and the kidney defect is not mentioned though it is nearly a constant feature of the syndrome. In Family 1 one has reason to believe that the short arms of a

TABLE 20

PROPOSED MAP OF D AND E CHROMOSOMES (AFTER PATAU)

CHROMOSOMES	
13/15 CENTROMERE	17/18 CENTROMERE
SEIZURES	FLEXION OF FINGERS
DEAFNESS	I.v. septal defect
Hypertonicity	HYPERTONICITY
Hemangiomata	Dorsiflexion of big toes
MENTAL RETARDATION	Short sternum
Retroflexion of thumbs	Small pelvis
Simian creases	FAILURE TO THRIVE
High axial triradius	Patent ductus arteriosus
EYE DEFECT	Prominent occiput
Cubitus valgus	MENTAL RETARDATION
CLEFT PALATE	Loose skin folds
	Syndactyly 2nd and 3rd toes
	Inner epic. folds
	Eventr. of diaphragm
	SMALL MANDIBLE
	Ing. and/or umb. hernia
	EARS LOW SET AND MALFORMED

17/18 are missing in the child: the flexion of the second finger over the third is not present either in the patient. In Table 20 the locus for the flexion of the fingers is located very close to the centromere. Our case therefore supports Patau's hypothesis, if one assumes that not only the short arm but a small segment of the long arm of the translocated 17/18 is missing.

However, in Case 8 the syndrome cannot be applied to any of the two maps: which suggests that either the maps are not correct or that the extra chromosomal material does not come from D or E members. Uchida (personal communication) found a partial trisomy 13 or 17 in a child who had a cleft palate and other anomalies. Gustavson et al (1962) found an abnormal small acrocentric chromosome in two sisters who were mentally retarded, had a severe motor impairment hypotonia, microcephaly hearing trouble, a cleft palate, low set ears, micrognathia and flexion of the fingers and hands. One of the patients also had an anal stenosis. In the D syndrome the palate is usually involved and it is tempting to attribute the extra chromosomes to that group in those cases, but unless there was a considerable rearrangement in the D chromosome preceding the deletion, the syndromes described would not be compatible with the map.

In Case 9 the patient, a female infant, was found to have a partial deletion of the short arms of one of her chromosomes 17/18. Thieffry et al (1963) reported what they thought was the first case of an autosomal deletion causing malformations in the patient: the boy had mental retardation, hypertelorism, strabismus, low set ears, antimongoloid slants of the eyes, incurved fifth fingers and syndactyly of the third and fourth toes. His finger prints were normal. Miller (personal communication) is now studying a child presenting hydrocephalus, cataracts, congenital dis-

location of the hips, retarded bone age, abnormally placed toes, prominent scalp veins and a heart malformation. The syndrome described here corresponds quite well to the syndrome described in Case 9. The mongoloid appearance of the children and the intracranial pressure seem to be part of the complex syndrome, and it is interesting to note that Miller's patient also has a deletion of the short arms of a 17/18.

This chromosomal abnormality, not involving extra material but rather a loss of chromatin, seems to have a response in the phenotype of the carrier, and more attention should be focused on the relatively short chromsomes in the future in order not to overlook such features, which may become very important in the study of congenital malformations related to cytogenetic aberrations.

e. Gastro-intestinal

In Family 12 three male children died in early infancy. All three of them had Hirschprung's disease, involving most or all of the large bowel. There was no family history of the disease and the parents were not related. The cytogenetic studies done on the father and mother on two separate occasions failed to show evidence of a constant chromosomal abnormality.

The genetics of Hirschprung's disease, a rare condition, has been reviewed by Sorsby (1953). There was no indication of an increased incidence of associated malformations. The preponderance of boys was 12.3:1 in a group of 40. There is a familial tendency for the disease to occur more frequently in sibships where there is one affected sib already. No mechanism of transmission has yet been described.

Yntema and Hammond (1954) have suggested that pathologically Hirschprung's disease is caused by some interference with the migration of neuro-

blasts from the lower cranial and upper cervical neural crest to the gut wall. Bodian and Carter (1963) have provided more reliable figures from a large family study. They classified the patients into those having a long affected segment of bowel and those with a short affected segment. The incidence of the disease for all varieties was between 1/2000 and 1/10,000 births, and the sex ratio was 3.6 in favour of males. The maternal age and the birth order seemed to have no effect in their 203 families. The associated malformations were analyzed and found to be more or less coincidental. They were: mongolism, pyloric stenosis, occipital encephalocoele, mental retardation, cleft palate, deafness and cataract. The consanguinity rate was not elevated. The authors mentioned that there was still no satisfactory hypothesis concerning the genetic factors predisposing to the disease. It was interesting, however, that the familial tendency was strongest in the long group.

In Family 13 the proband had multiple malformations involving the cardio-vascular and skeleton systems, as well as the gastro-intestinal tract. His karyotype showed a partially deleted Y and abnormally long short arms on a member of the G group. One of these chromosomal aberrations described in this case has been partly reported by Van Wijck (1961) who found in a mentally retarded child the presence of extra material on the short arms of a 21/22 considered by the author to be the short arms of a 17/18. Carr (1963) also reported the presence of long short arms on a chromosome 21 of a patient. Vaharu (1961) described a girl who had an enlarged phallus, was mentally retarded, had low set ears and micrognathia. Her feet were pronated. The sex chromatin was negative and she had 46 chromosomes including one X chromosome and one fragment interpreted as a

deleted Y chromosome. Conen (1961) found a girl with an enlarged clitoris, a negative sex chromatin and mosaicism in her chromosomes. She had cells with 45 chromosomes (XO), and 46 including a small fragment also interpreted as being a deleted Y chromosome.

Muldal and Ockey (1961) reported a familial transmission of a deleted Y chromosome in males having hypospadias and low gonadotrophin level. In the present case both abnormalities: the Y deletion and the G translocation are found. The hypothesis of an attached portion of the long arms of a Y chromosome onto a 21 or 22 is compatible with these observations. If the small size of the Y chromosome represents a normal variation of that gonosome, then we may have a duplication of the short arms of a G chromosome or less likely an inversion since the long arms of the aberrant chromosome do not seem to have lost any material.

Schmid (1962) recently reported a familial abnormality of one of the G chromosomes found in a study of families with a high incidence of miscarriages. The father was a carrier of the elongated G chromosome and had a normal karyotype otherwise. One other member of this family was also a normal carrier of this abnormal chromosome. One has then good reasons to regard this cytogenetic abnormality as a possible cause for familial malformations.

f. Genito-urinary

Among the patients ascertained through a suspected malformation of the genito-urinary tract, eight out of eleven had an abnormal gonosomal configuration among which there were three XO individuals (Cases 15, 16, and Case 6 described in the cardio-vascular defects). There were also two XXX individuals (Proband Family 17 and Case 14), two mosaics (Cases

11 and 12) and two patients presenting a sex reversal, whose phenotypes did not correspond to their genotypes. It was stated in the Introduction that various anomalies of sex chromosomes may happen by single or double non-disjunction in the gametes or the foetus itself. The XXY, XXXY, and XXXXY patients were described.

One is struck in the XO and XXX patients by the lack of obvious anomalies. In the infant the Turner syndrome is characterized by some oedema of the lower limbs, a failure to thrive, a cubitus valgus, and a straight hair line in the back of the neck. The heart anomaly is seen in only 20% of the cases (Lindsten, 1963). In the super female or triple X the physical signs are usually less pronounced though Case 14 is exceptional in this regard. Normal growth development is one of the chief signs which is also present in many syndromes not related to sex chromosome anomalies. Jacobs (1961) had found a high percentage of X chromosome anomalies among women with primary amenorrhea. The minimal frequency was as high as 43% in a selected group of patients presenting with primary amenorrhea.

The study of sexual anomalies constitutes a chapter in itself which is beyond the terms of reference of this thesis. The lack of obvious anomalies in some syndromes (Cases 15, 16), the complexity in others (Cases 13, 14), the undefined roles of X and Y chromosomes place these sexual anomalies in a group quite different from the autsomal syndromes G, D and E. The random inactivation of one X chromosome in the normal female, the appearance of somatic anomalies when one X is missing in the XO female, and the small differences existing between the XXY, XXXY and XXYY syndromes make one wonder if the expression of the abnormal genotype is not related to unknown mechanisms regulating both the X and Y chromosomes.

Doctor Barr concluded a paper (New York, 1963) on the properties of the sex chromosomes by stating that the X chromosome has several special

characteristics, and that the understanding of these characteristics is essential for the recognition of their role in the production of congenital malformations.

g. Mongoloid

1. Down's syndrome

Down (1866) published a classification of the idiots and described a syndrome in which the affected members had a mongoloid appearance. Today the term mongolism is widely used while referring to patients with the extra chromosomes 21, but there is a tendency to encourage people to mention Down's syndrome instead of mongolism. As previously stated, mongols have an extra small acrocentric chromosome, either separate to give a total number of 47 chromosomes, or fused onto another chromosome (translocation) to give a total of 46 chromosomes.

In Families 18, 20, 22, 23, 24, 25 and in Case 17, non-disjunction of a member of the G group was responsible for the syndrome produced. In Families 19, 21, 26 a translocation was present.

The case reported (Hall, 1962) as being a mongol with a normal karyotype did not have all of the typical mongoloid features; even if clinically the patient can be considered to have Down's syndrome, it is most likely that he has some extra chromosomal material translocated to a larger chromosome and hence unrecognizable. Richards (1962) and Schmid et al (1961) also referred to cases of mongolism with normal chromosomes, but here again the information was not convincing.

Fraser, as reported by Warkany (1960), proposed the theory that a chromosomal rearrangement may produce some minor stigmata of mongolism and also increase the probability of non-disjunction of the chromosomes involved (No. 21).

the trisomic condition producing the full blown syndrome. This would explain why minor stigmata appear in the near relatives of mongoloids (if this is indeed the case).

Cummins (1943, 1950) opened the door for the use of finger prints in the diagnosis of Down's syndrome. The method used for dermatoglyphic studies (Walker, 1957), has proven to be accurate in ten cases of mongoloid children reported here and nine others not included in the study, who had an extra chromosome. The high number of ulnar loops on the fingers, the high triradius, the simian crease, the third interdigital space pattern and also the hallucal area configuration were found to be typical of mongoloid children and to be present in most of the cases.

Penrose's (1954) suggestion that the mothers of mongoloid children have a high triradius more often than other mothers has been contradicted by Carter (personal communication) and Fraser (personal communication) who recently completed a large study of prints of parents and mongoloid children. However, one should not forget that if the mother is mosaic for the extra member of the G group that causes mongolism, she may present abnormal prints. On the other hand since one believes with reason that the abnormal print figures found in Down's syndrome originate from the extra chromosomal material, then the accidental non-disjunction of an acrocentric in a sexual gonad or even in the first cleavages of the egg itself, should not in any circumstances reflect on the parental palm prints.

In Family 24, the mother and two other relatives of the affected child had a high triradius but the chromosomal pattern of the mother was normal. The position of the triradius may then be inherited as a mendelian trait, unrelated to the trisomy. In Family 19 the father is a carrier but his hand and foot prints were normal. In Family 20, none of the parental prints

suggested the presence of an extra chromosome, or some etiologic relation with the children's condition.

The blood group studies were done in two large families (19 and 20) and have not brought any light on the location of the ABO locus. Shaw et al (1962) and Shaw (1962) had previously proposed that the locus was near the centromere of chromosome 21 but Chown and Lewis (1963) have some evidence that this hypothesis may not be correct, the discrepancy in blood types being due to selection from cultural groups where women tend to continue having children relatively late in life.

In this study the mongoloid children were selected because of familial recurrence, and the mean age of the mothers is not over 30 years of age. In cases of translocation one should not expect an increase in maternal age.

The occurrence of mongolism and other anomalies in members of the same family has been described by Bernirschke et al (1962). The tendency to non-disjunction of non-specific chromosomes in the same family has been verified in the past by Therman et al (1961) who found a D syndrome and XO female in the same sibship, by Wright et al (1963) who described a trisomy 21 and a Klinefelter, and Ellis (1963) who found a mongol and a Turner syndrome .

Leukaemia has not been found in the families described in this work. The association of leukaemia and mongoloid children is well known however. Before the discovery of the extra chromosome in mongolism, Kiwit (1959) and Merrit (1956) found an increased incidence of leukaemia among mongoloid children. German et al (1962) reported a family in which the mother was a carrier of a D/G translocation and one mongoloid child had leukaemia and a total of 46 chromosomes.

The problem of risk of recurrence of mongolism in a given family depends on many factors. Among these factors one should consider first of all the

mechanism of production of the syndrome, the age of the mother and incidence of other malformations due to non-disjunction in that family.

Carter and Evans (1961) in a large study of 642 index patients found that for mothers under 25 years of age the risk is 50 fold the one for the general population, that it decreases to 25 fold for mothers between the ages of 25 to 34, and that it is the same as that in the general population for mothers over the age of 35. Hamerton and co-workers (1961) in a cytogenetic study of families in which there was a familial incidence of the syndrome, showed that for mothers under the age of 25, translocations are responsible for a large part of the recurrence of the syndrome, and that in cases of familial primary non-disjunction there must be an inherited predisposition to non-disjunction or the occurrence of trisomy 21 mosaicism in one or other of the parents.

Sergovich (personal communication) is presently studying cytogentically a group of mongoloid children especially selected because of the young age of the mother and/or for the high incidence of recurrence of the syndrome or miscarriages in the family. The findings show that in mongols of young mothers a translocation is present in 5% of the patients and that only once in a hundred patients is one of the parents found to be a carrier.

In Family 20, the mother was in her early twenties when the first two mongoloid children were born. At that time without chromosomal facilities the physician could not suspect a translocation and since the mother was young she was told that the chance of recurrence of the syndrome was very low. The third child born when the mother was still in her twenties also had mongoloid features. All three of them had an extra small acrocentric for a total count of 47 chromosomes. Both parents had a normal karyotype. No explanation for this unusual occurrence is apparent.

In Family 19, even if chromosomal studies had been available, one could not have been sure whether the translocation involved a 21/22 or a 21/21, since there is no way of telling the difference between the two by the usual methods. But the parents could have been aware of the high risk of recurrence of the syndrome in subsequent offspring. They had five mongoloid children and one miscarriage, and this is why a 21/21 translocation is the more likely interpretation.

Is it possible to find a Down's syndrome with apparently normal chromosomes? Clarke (1961) studied the case of an intelligent girl presenting some mongoloid features who turned out to have a normal chromosomal count in her lymphocytes, but two types of cells in tissue culture. Fitzgerald (1961) reported a case of mosaicism in a 51-year-old man having normal cells and cells with an extra small acrocentric. Shortly after, Gustavson (1961) also reported a case of mosaicism in a mongoloid child who had three types of cells: some with 46, some with 47 and others with 48 chromosomes. In the last karyotypes a member of the F group was extra as well as a small 21/22.

Nichols (1962) published the case of a child presenting typical mongoloid features and having a high proportion of cells with 47 chromosomes, with trisomy 21, in both his blood and tissue cultures. Blank (1962) studied the chromosomes of a mother who gave birth to a mongoloid child. The mother had some abnormal trisomic cells while her child was fully trisomic for a member of the G group.

In Case 17 the female infant had two types of cells some trisomic for an extra 21 and some normal, on the second blood exmaination: the first culture yielded cells of three different categories. The third type of cells found probably originated from the male blood donor, who gave his blood for the exchange transfusion. The clinical picture is in favour of a case of

mosaicism: the patient had some mongoloid features but lacked many stigmata specific to mongolism.

The chemical disturbances in mongoloid children have been studied in the past few years. Sobel et al (1958) in an extensive study and review of the literature reported that the absorption of Vitamin A is slower in mongoloid infants. The authors also described low serum calcium values, decreased serum albumin and increased gamma globulin in these patients. Nelson confirmed (1961) the elevation of gamma globulin protein and decreased albumin in these children. The author also found an increase in the lipoprotein fraction except in the second decade of life.

Trubowitz et al (1962) and Alter et al (1962) found high levels of alkaline phosphatase in leucocytes of mongoloid children. King et al (1962) repeated the experiments in individuals of both sexes and of various ages and his results confirmed the previous findings.

A short letter by Brandt (1962) mentioned the possibility that the genetic locus of the galactose-1-phosphate-uridyl-transferase activity may be on the chromosome 21 since mongols have a higher mean value than normal controls. Lawler in the same issue number criticized the previous reports attributing the alkaline phosphate locus to the chromosome causing the Down's syndrome when present in triplicate, since there is evidence that the high levels of enzyme found in mongols may be attributed to the frequent occurrence of infections, and the lower levels in chronic granulocytic leukaemia to the presence of immature cells.

2. Absent corpus callosum

The literature on absence of the corpus callosum has been reviewed by Carpenter and Druckemiller (1953). In the same year Van Epps reported

twelve cases, two of which had a cleft palate and lip. Bell and Van Allen (1959) described a case of absence of corpus callosum associated also with a cleft lip and palate, absence of the nose, proptosis and low set ears. Michaux et al (1959) also reported the history of a child that had absence of the corpus callosum, a short neck, a malformed skull, microophthalmia, polydactyly of feet, severe mental retardation, hypospadias, absence of the scrotum, hypotrophy of the penis, supernumerary nipple on the left, short fingers and simian creases. Bonvini and Kehgayan (1960) reported a mentally retarded child, with a malformed skull and absence of the corpus callosum.

Since the report by Naiman and Fraser (1955) of two cases of agenesis of the corpus callosum in sibs, no mention has been made of the possible genetic factor involved in the production of the syndrome. It seems evident that the abnormality is often associated with other somatic anomalies, mainly of the skull. Gruneberg (1952) described in the mouse a mechanism by which the hydrocephalus is responsible for the defect. Hicks (1953) demonstrated that irradiation may induce the defect in the offspring of treated rats.

In humans, the problem is complex: the cases reported by Michaux have the features of a D syndrome, others may be partial trisomies. It would be valuable in the cases of autosomal trisomies to determine the incidence of agenesis of the corpus callosum. In Family 21 the first child was mongoloid, and the second was severely retarded and had an absence of the corpus.callosum. The cytogenetic studies showed a partial translocation to a D chromosome. On the other hand one of the patients reported by Fraser and Naiman was studied cytogenetically (Family 27) and no demonstrable chromosomal abnormality was found. However, this does not exclude the possibility of an extra

chromosome material undetectable by our present means. Lejeune (personal communication) found a family in which the first child had mongoloid features and the second had an agenesis of the corpus callosum and a partial translocation to a D chromosome, which supports the present findings.

h. Skeleton

In Family 28, two girls and one boy presented similarities in their malformations: they all had malformed ears and skull, haemangioma, a heart defect, poly- and syndactyly, an eye anomaly and a palate abnormality. They were also mentally retarded. The mother had three miscarriages. None of the patients were still alive at the time chromosomal studies could be done. The last child born in the family had a normal karyotype and chromosome 16 was of normal length. The syndrome as described previously in this work has many of the D syndrome abnormalities. The mother being mosaic for an abnormal member of the E group (no. 16), she still may have a normal phenotype, like the mothers who have an extra chromosome in some of their cells and can produce full mongols. Until more information is published, one cannot be sure whether the chromosomal aberration is related to the clinical disease, but it seems likely that the mother is carrying a 16/13 translocation and that she has a high risk of having another malformed child.

In 1959, Larsen described a new syndrome present in six cases studied over a short period of years. This syndrome seems to involve the major joints of the upper and lower extremities, the feet, hands and face. The following features seem to be frequent components of the disease:

a - bilateral anterior dislocation of the tibiae on the femora.

b - antenatal dislocation of both hips.

c - bilateral equinovarus and equinovalgus. Deformities of the feet.

d - bilateral dislocation of the elbows.

e - long and cylindrically shaped fingers.

f - thumbs usually spatulated.

g - hypertelorism.

h - flattened nose bridge.

i - occasional association of heart and palate defects.

j - normal dentition.

k - occasional failure of spinal separation.

l - normal intelligence.

In the six different families reported by Larsen all the sibs were normal. Furthermore the muscular biopsies done on the patients were all normal. Since Larsen's publication on the syndrome involving bone and joints the literature did not mention instances of those anomalies again.

Assuming that the two families (29, 30) reported here are variants of the same condition, one can state that the syndrome is familial, can affect both males and females and does not seem cytogenetically controlled. Though there is some degree of consanguinity in one of the families (29), it does not seem responsible for the occurrence of the malformations since one of the affected cousins was not related to the proband. With some degree of variation Larsen's description of the syndrome seems to be quite complete.

B. CYTOGENETICS OF MULTIPLE MALFORMATIONS

1. Discrimination of cases with chromosomal aberrations by clinical features

On theoretical grounds it is to be expected that when a whole chromosome or section of chromosome is present in excess, or missing, the resulting phenotype will demonstrate widespread anomalies involving many organ systems. To investigate this question, tables have been prepared listing the types of anomalies and systems involved in the present series of cases with autosomal anomalies (Table 22) or sex chromosome anomalies (Table 23) or normal chromosomes (Table 19) as well as cases selected from the literature with multiple malformations and normal chromosomes (Table 21). Table 23 also includes selected cases of sex chromosome aberrations from the literature (Jacob and Strong, 1959; Carr, D.H., 1961; Ferguson-Smith et al, 1960; Carr et al, 1961; Barr et al, 1962).

It seems evident that both in the present study (Table 19) and in the literature (Table 21) all the cases with no chromosomal anomaly have a low number of systems affected, that is, less than 10 out of 25, or less than 40%, while most of the sexual and autosomal anomalies are above this average. The following means and ranges were found for each category.

	Mean	Range
1. Cases of present study with normal chromosomes	4.0	1-9
2. Cases from literature with normal chromosomes	3.7	1-7
3. Patients with anomalies of gonosomes	11.5	8-13
4. Patients with anomalies of autosomes	15.4	12-20
5. All cases with normal chromosomes	3.85	1-9
6. All cases with abnormal karyotypes	13.45	8-20

It may be argued that the cases from the literature were not examined as carefully for certain relevant features (e.g. dermatoglyphics) as those

TABLE 21 CASES WITH NORMAL KARYOTYPES FROM THE LITERATURE

DEFECT	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	TOTAL
Cardio-vascular	+											+						+									+								+				5
Central nervous system								+				+						+											+										4
Dermatoglyphics																											+												1
Ears				+		+		+			+	+					+									+							+	+			+		10
Endocrine															+																								1
Epicanthic folds											+					+																						+	3
Eyes								+			+	+										+																+	5
Face				+									+		+	+										+			+		+			+				+	9
Failure to thrive																			+		+																	+	3
Gastro-intestinal											+						+				+								+		+	+					+		7
Genito-urinary												+																	+								+		3
Haemangioma			+																				+																2
Height	+	+						+																															3
Hematopoietic														+									+																2
Hernia																																							0
Hypogonadism		+						+	+												+					+								+			+		7
Mandible							+												+	+						+													4
Mental impairment		+	+	+	+	+			+				+			+		+				+							+	+	+	+		+				+	16
Muscle																+																					+		2
Neck	+							+			+																+						+	+		+			6
Palate and Lips								+	+	+		+								+											+	+	+	+	+	+			12
Skeleton									+		+	+		+		+	+	+	+	+	+				+				+				+		+	+	+	+	19
Skin								+	+															+	+					+				+						6
Skull									+							+			+																				28
Weight		+						+																															2
TOTAL	3	4	2	3	2	8	4	5	2	2	7	5	3	1	3	6	3	4	4	3	4	2	2	3	1	5	2	1	6	3	4	3	6	5	4	3	5	7	140

$\bar{X}$: 3.7

TABLE 22 AUTOSOMAL ABERRATIONS

DEFECT	F18 G	F19 G	F19 G	F19 G	F20 G	F20 G	F20 G	F26 G	F2 E	C1 E	C2 E	E3 E	C5 D	TOTAL
Cardio-vascular		+		+		+		+	+	+	+	+	+	9
Central nervous system	+	+	+	+	+	+	+	+	+	+	+	+	+	13
Dermatoglyphics	+	+	+	+	+	+	+	+	+	+	+	+	+	13
Ears	+	+	+	+	+	+	+	+	+	+	+	+	+	13
Endocrine	+	+	+	+	+	+	+	+	+	+	+	+	+	13
Epicanthic folds	+	+	+	+	+	+	+	+					+	9
Eyes	+	+	+	+	+	+	+	+					+	9
Face	+	+	+	+	+	+	+	+	+	+	+	+	+	13
Failure to thrive									+	+	+	+		4
Gastro-intestinal									+	+	+	+		4
Genito-urinary									+	+	+	+		4
Haemangioma													+	1
Height									+	+	+	+		4
Hematopoietic														0
Hernia									+	+	+	+	+	5
Hypogonadism	+	+	+	+	+	+	+	+		+	+	+		11
Mandible									+	+	+	+		4
Mental impairment	+	+	+	+	+	+	+	+	+	+	+	+	+	13
Muscle	+	+	+	+	+	+	+	+	+	+	+	+		12
Neck	+	+	+	+	+	+	+	+	+	+	+	+	+	13
Palate and Lips	+		+					+	+	+	+	+	+	8
Skeleton			+	+					+	+	+	+	+	7
Skin													+	1
Skull	+	+	+	+	+	+	+	+	+	+	+	+	+	13
Weight									+	+	+	+	+	5
TOTAL	13	13	14	14	12	13	12	14	19	20	20	20	17	201

$\bar{X}$: 15.4

TABLE 23 SEX CHROMOSOME ANOMALIES

DEFECT	C6 XO	C15 XO	C16 XO	F17 XXX	C14 XXX	1 XXY	2 XYY	3 XXYY	4 XXXY	5 XXXX	6 XXXXY	7 XXXXY	TOTAL
Cardio-vascular	+							+				+	3
Central nervous system					+	+		+			+		4
Dermatoglyphics	+	+	+										3
Ears	+					+		+	+	+	+	+	7
Endocrine	+	+	+	+	+	+	+	+	+	+	+	+	12
Epicanthic folds													0
Eyes		+			+		+		+	+	+	+	7
Face	+			+	+	+	+	+	+	+	+	+	10
Failure to thrive			+										1
Gastro-intestinal			+		+								2
Genito-urinary	+	+	+	+	+	+		+	+		+	+	10
Haemangioma													0
Height	+		+	+	+	+		+	+	+	+		9
Hematopoietic								+					1
Hernia						+	+				+		3
Hypogonadism	+	+		+	+	+		+	+	+	+	+	10
Mandible					+		+						2
Mental impairment	+			+		+		+	+	+	+	+	8
Muscle			+		+			+	+	+	+	+	7
Neck	+	+	+	+					+	+		+	7
Palate and Lips			+			+							2
Skeleton		+	+		+	+	+	+	+	+	+	+	10
Skin		+					+				+	+	4
Skull		+		+	+	+	+	+	+	+	+	+	10
Weight		+	+		+	+	+			+	+		7
TOTAL	10	10	11	8	13	13	9	13	12	12	15	13	139 X: 11.5

in the present study. Nevertheless, the values obtained are not significantly different (3.7 vs. 4.0) and any bias of this kind must therefore be small. It can therefore be concluded that a patient who has less than 9 of the selected abnormal characteristics is unlikely to have an autosomal trisomy, and that a patient with more than 9 abnormalities is likely to be chromosomally abnormal.

There is some suggestion that mosaics, cases of partial trisomies and partial deletions of chromosomes fall between the values for cases with normal chromosomes and those with abnormal karyotypes. In Case 8, who was mosaic for a partial deletion, the patient showed some delay in her somatic and psycho-motor development. She had a cleft palate, malformed ears, a kidney malformation, an umbilical hernia and a malformed skull. Approximately eight systems were affected, a value intermediate between the two means 4 and 13.

In Family 28 one suspects that the malformed children (who had multiple somatic anomalies and could not be examined cytogenetically) had a chromosomal anomaly transmitted by the mother, who had a high proportion of abnormal cells and was normal. They had more than 10 affected systems. Even the proband of Family 13 who had a possible partial deletion of the long arm of the Y chromosome and a translocation onto a G group, has a score that falls in the chromosomal anomaly group. In Families 6, 7, and 8, with normal chromosomes and cervico-cephalic defects, less than 8 systems were affected and the possibility of mosaicism is ruled out on the grounds that more than one child had a typical syndrome in the same family; mosaicism for one chromosome in the parental gametes should have induced a full trisomy in the offspring and hence over 40% of affected systems.

Values for the sex chromosome anomalies are somewhat lower than those for autosomal anomalies. This is not surprising; the X and Y chromosomes

are mainly sex determining though they contain some loci involving somatic tissues: it is then expected that the malformations induced should involve mainly the gonadal functions. This is most evident in XO and XXX cases where a diagnosis is made quite often on the grounds of primary amenorrhea in Turner females (XO) or abnormal growth development in super females (XXX).

In autosomal trisomies it appears that the presence of extra material will produce mental impairment if all the cells of the body contain an aneuploid complement. In sexual anomalies of type XXXXY the genetic imbalance is probably more severe than in cases of XO women and hence may be responsible for a greater variety of malformations in the individual, as in the autosomal defects.

2. Discrimination of chromosomal aberrations from normal variations

In the study of cytogenetic aberrations two questions arise that are of great importance: first how one recognizes a variation of the normal karyotype as being an aberration and second how many subjects are carriers of a chromosomal anomaly that remains unknown because of lack of examination? One should face the fact that without proper knowledge of the normal variations in human genotypes it is quite difficult to be always sure of their significance. For example, shortly after the discovery of the first chromosomal anomaly, DeCarli (1960) reported a trisomy for an autosome of the group 6 to 12. Today this report is considered as being a triple X case, presenting with a low double chromatin mass count, which is not unusual. Dobson (1961) described two sibs affected with convulsions and presenting abnormal secondary constrictions probably originating from reciprocal translocations. These secondary constrictions however, are currently seen in normal subjects, and have been described in the past as normal configuration

of chromosomes (Ferguson-Smith et al, 1962).

As mentioned before, simple translocations or reciprocal translocations may be present in a subject and cause very little disturbance in the phenotype since there is very little loss in the chromatin material. The difficulty in diagnosing these cases comes from the fact that it is impractical to do chromosomes studies routinely, and since the patients present very few malformations they are not likely picked up as good candidates for chromosomal studies. Moorehead (1961) found a family in which the mother had 45 chromosomes and a D/G translocation. Four of her children were also carriers. A fifth child was a trisomic mongol. The carriers all turned out to be retarded and have a speech defect. The author discussed the probability that the small loss of material originating from the translocation may be responsible for the mental impairment seen in the children. But if so, why is the mother not similarly affected?

Vislie (1962) found an interesting familial transmission of a D/E translocation in a mother of two mentally retarded children who had an extra chromosome of the size of the G group for a total count of 47, including the translocated chromosome. The mother had a D and an E missing and two new chromosomes resulting from the rearrangement: one of the size of the C group and one small acrocentric. The mother herself was normal. Mercer (1962) studied a 12-year-old boy who presented with a speech defect, abnormal ears and a short neck. He found 45 chromosomes in the child and a D/A translocation (13/2). The problem of cytogenetically induced malformations then seems very complex. In some cases the loss of chromatin material seems to affect the carrier while in many instances the carriers are found by accident, or because one offspring had a translocation and enough extra chromosomal material to produce a full syndrome.

3. Chromosomes of abortusses

Finally one can mention that studies are now under way to determine the incidence of chromosomal abnormalities among cases of spontaneous abortions. Carr (1963, and personal communication) has found as many as 20% abnormalities in the culture tissues of rejected embryos. The chromosomal abnormalities found in Carr's work are mainly trisomies of E and D group and XO embryos. Two triploid cases were found. If one assumes that the trisomies for larger autosomes are not viable and occur at the same frequency as the ones for the smaller chromosomes, the incidence of cytogenetic aberrations in spontaneous abortions from the first day of conception to the end of the second trimester could be as high as 50%. In this type of study one should then expect to find also cases of monosomy produced by carriers of translocations.

C. ROLE OF CHROMOSOMAL ABERRATIONS IN FAMILIAL MALFORMATIONS

A total of thirty families in which there was more than one child affected with multiple malformations or one affected child and at least one miscarriage were studied. Seventeen cases presenting multiple malformations of unknown origin were also studied cytogenetically since they had syndromes resembling the familial anomalies, and hence could bring some light to the understanding of the mechanism of production of congenital malformations.

Out of the thirty families six presented a chromosomal rearrangement that could be transmitted through a carrier and therefore be familial. Those families were: 2, 5, 19, 21, 26, 28. In one family (20) in which there were three mongoloid children, no translocation could be found, but mosaicism in the gonads could not be ruled out. Alternatively it may be a

case of genetic predisposition to non-disjunction. In our Families 7, 8, 9 and 22, as the children were already dead and only the parents were examined, one cannot rule out the possibility of partial trisomy or translocation in the affected children or that a translocation may have taken place in the gonads and not be seen on routine tissue examinations.

The proportion of rearrangements is then six out of 30, or 20% of the families that showed a chromosomal aberration not resulting from the primary non-disjunction. In two cases the relation of the chromosomal aberration to the children's defects was doubtful: they were Families 21 and 28. In Family 21, the same abnormality has now been described in the literature (Jennings, 1961 and Carr, 1963). The patients have multiple skeletal anomalies, mental retardation, eye and ear defects. One could not be sure of the importance of the unusually long number 16 unless another child born with the malformations were found to have the same chromosomal defect as the one found in a certain proportion of the mother's cells. Gagnon (personal communication) claims that he has also found an affected boy with the same autosomal defect and unusual malformations of the skeleton and mental retardation.

It would seem, therefore, that translocations are an important cause of familial multiple malformations.

No systematic studies have been done in the past among a series of families presenting with the criteria used in this survey. It appears that this way of screening for chromosomal anomalies seems to be fairly good. Seventy more families will be studied in our laboratory in the next few years to get a more reliable figure of incidence, by bringing the total number of families to 100.

One can then state that certain criteria are of great importance in the study of chromosomal aberrations in familial and isolated types of malform-

ations. These are:

1. The number of anatomical systems affected

2. The specificity of the syndrome in autosomal aberrations.

It has been demonstrated without too much doubt by the reported cases and the controls from the literature that the number of systems affected in known chromosomal anomalies is large and that affected children with a normal karyotype fall into a group almost entirely separable from the cytogenetic aberrations by the number of systems affected.

Each of the well known syndromes, trisomies 21, 13 and 17, have very specific characteristics. The problem of mosaicism however, may produce results in conflict with the principle: that is, in the case of mosaicism in mongolism and possible mosaicism in the other two trisomies which are not well documented yet. The dermatoglyphic studies have proven to be of great value in the diagnosis of those syndromes and should be considered as one of the most important factors in the diagnosis of trisomies. Suggestions have been made in the past two years that D and E syndromes may have normal karyotypes but in many instances the cases studied were not typical; that is, they lacked one or more anomalies or had normal print configurations.

In sexual anomalies as one has seen, the patients (XO or XXX) may look quite normal in the pre-adolescent period. They are picked up now since medical people are more aware of the fact that aberrations are almost always linked with an abnormal growth development. The sex chromatin is a very useful tool for diagnosis and is used more frequently than heretofore in clinics. The rarity of the XXXX and XXXXY types of anomalies has made the study of these syndromes more difficult. However, when present they should be diagnosed more easily since they present more severe anomalies in XXXXY.

The most common sexual anomalies, XO, XXY, XXX and the mosaics as well

as XY females with abnormal sexual development and males with XX sex chromosomes are compatible with a fairly normal life compared to E and D syndromes for which the average life expectancy is below four months of age.

The reported families will be followed as well as the isolated cases described in this work. When available, biochemical and additional cytogenetic studies will be done. The problem of mosaicism will be given more attention and use will be made of the clinical and laboratory findings in the screening of patients for chromosomal studies.

SUMMARY

Since the discovery of an extra chromosome present in Down's syndrome (mongolism), chromosomal aberrations have been recognized as an important cause of multiple malformations. More recently it was discovered that translocations may result in familial trisomy syndromes. This study was undertaken to investigate the importance of such translocations as a cause of familial multiple malformations.

Families ascertained through the files of the Department of Medical Genetics or on the wards of The Montreal Children's Hospital, where there was more than one member affected with multiple malformations, or one affected individual and a high incidence of miscarriages, were studied cytogenetically.

Among the thirty families ascertained by these criteria, there were six families in which a chromosomal rearrangement was found in the proband or in one of the parents studied cytogenetically by means of peripheral blood cultures or bone marrow cultures. Thus, in about 20% of the cases a chromosomal aberration other than a primary non-disjunction may be responsible for the familial syndrome.

The families as well as isolated contributory cases were divided into eight groups referring to the main physical anomaly for which they were referred to the Department of Medical Genetics.

From the study of these cases new findings in human cytogenetics were described. These include the maternal transmission of an E syndrome, a child trisomic for part of a D or E chromosome, a case of partial deletion of short arms of chromosome 17/18, two cases of partial translocation to acrocentric chromosomes (T/13-T/21) and an unusual syndrome believed to be

related to an abnormally long E chromosome number 16.

The clinical variations within the known trisomies were considered and new features were described; namely the rotation of the index finger and the side-to-side ileo-caecal junction in the E syndrome. The importance of the dermatoglyphics has been discussed as part of the syndrome due to an aberrant karyotype and not present in the normal carrier who has very little or no change in his phenotype.

It was possible to draw up a list of abnormal features that would discriminate patients with chromosomal aberrations from other types of multiple malformations; patients with an autosomal abnormality had an average of 15.4 abnormal features, while those with normal chromosomes had a mean of only 3.9.

It is demonstrated that familial multiple malformations accompanied or not by a high incidence of miscarriages should be studied cytogenetically, since an appreciable percentage of them are likely to be parental in origin and hence be of great importance in counselling.

BIBLIOGRAPHY

Allerhand, J., Karelitz, S., Isenberg, H.D., Penbharkkul, S., Ramos, A. The lacrymal proteins in Down's syndrome (Mongolism). J. of Pediatrics, 62: 235, 1963

Alter, A.A., Lee, S.L., Purfoar, M., Dobkin, G. Leucocyte alkaline phosphatse in mongolism: a possible chromosome marker. J. Clin. Invest., 41: 1341, 1962

Anders, G., Prader, A., Hauschteck, E., Schaerer, K., Siebenmann, R.E., Heller, R. Multiple sex chromatin and complex chromosomal mosaic in a boy with idiocy and multiple abnormalities. Helv. Paediat. Acta., 15: 515, 1960

Arnold, J. Beobachtungen uber Kerntheilungen in den Zellen der Geschwulste., Virchow's Arch., 78: 279, 1879

Atkins, L., O'Sullivan, M.A., Pryles, C.V. Mongolism in three siblings with 46 chromosomes. New Eng. J. Med., 266: 631, 1962

Atkins, L., Rosenthal, I.M. Multiple congenital abnormalities associated with chromosomal trisomy. New Eng. J. Med., 265: 314, 1961

Aula, P., Hjelt, L., Kauhtio, J. Chromosomal investigation in congenital malformations. Ann. Paediat. Fenn., 7: 206, 1961

Axelrad, A.A., McCulloch, E.A. Obtaining suppressions of animal cells in metaphase from cultures propogated on glass. Stain Technol., 33: 67, 1958

Baikie, A.G. Polymorph alkaline phosphatase and genes on the mongol chromosome. Lancet, ii: 937, 1962

Baikie, A.G., Court Brown, W.M., Jacobs, P.A., Milne, J.S. Chromosome studies in human leukaemia. Lancet 11: 425, 1959

Barr, M.L., Bertram, E.G. A morphological distinction between neurons of the male and female and the behaviour of the nucleolar satellite during accelerated nucleoprotein synthesis. Nature, 163: 676, 1949

Barr, M.L. Some properties of the sex chromosomes and their bearing on normal and abnormal development. Paper presented at the Second International Conference on Congenital Malformations, New York, July 1963

Barr, M.L., Carr, D.H., Pozsonyi, J., Wilson, R.A., Dunn, H.G., Jacobson, T.S., Miller, J.R. The XXXXY sex chromosome abnormality. J. Can. Med. Assn., 87: 891, 1962

Bearn, A.G., German, J.L. 3rd. Chromosomes and disease. Sci. Amer., 205: 66, 1961

Bell, W.E., Van Allen, M.W. Agenesis of the Corpus Callosum with associated anomalies. Neurology, 9: 694, 1959

Bender, M.A. X-ray induced chromosome aberrations in normal diploid human tissue cultures. Science, 126: 974, 1957

Bender, M.A., Gooch, P.C. Somatic chromatic aberrations in normal and irradiated humans. Rad. Res., 14: 451, 1961 (Abstract)

Bender, M.A., Gooch, P.C. Persistent Chromosome aberrations in irradiated human subjects. Rad. Res., 16: 44, 1962

Berg, J.M., Kirman, B.H. Risk of dual occurrence of mongolism in sibships. Arch. Dis. Childhood, 36: 645, 1961

Bernirschke, K., Brownhill, L., Hoefnagel, D., Allen, F.H. Langdon Down anomaly (mongolism) with 21/21 translocation and Klinefelter's syndrome in the same sibship. Cytogenetics, 1: 75, 1962

Bernirschke, K., Brownhill, L., Ebaugh, F.G. Chromsomal abnormalities in Waldenstrom's macroglobulinaemia. Lancet, 1: 594, 1962

Biesele, J., Schmid, W., Hao Lee, C., Smith, P.M. Translocation between acro-

centric chromosomes in a 46 chromosome mongoloid and his 45 chromosome mother. Amer. J. Hum. Genet., 14: 125, 1962

Biesele, J.J., Schmid, W., Lawlis, M. Mentally retarded schizoid twin girls with 47 chromosomes. Lancet, i: 403, 1962

Blank, C.E. Chromosome abnormality in mongolism. Proc. Roy. Soc. Med., 55: 475, 1962

Blank, C.E., Gemmell, E., Casey, M.D., Lord, M. Mosaicism in a mother and mongol child. B.M.J., ii: 378, 1962

Bleyer, A. Indications that mongoloid imbecility is a gametic mutation of degressive type. Amer. J. Dis. Childhood, 37: 342, 1934

Bodian, M., Carter, C.O. A family of Hirschsprung's disease. Ann. Hum. Gen., 26: 261, 1963

Bodmer, W.F. Effects of maternal age on the incidence of congenital abnormalities in mouse and man. Nature, 190: 1134, 1961

Bonvini, E., Kehgayan, E. Un caso di agenesia del Corpo Calloso. Minerva Pediatrica, 12: 1501, 1960

Book, J.A. Chromosomal variations in man and their clinical significance. Uppsala LakForen. Forh., 64: VII-VIII, 1959

Book, J.A., Fraccaro, M., Lindsten, J. Cytogenetical observations on mongolism. Acta Paediat., 48: 453, 1959

Book, J.A., Santesson, B. Malformations in man associated with triploidy (69 chromosomes). Lancet 1: 858, 1960

Book, J.A. Mongolism and other conditions associated with chromosome variations. Uppsala LakForen. Forh., 65: I, 1960

Book, J.A., Gustavson, K.A., Santesson, B. Chromosomal abnormality in a mongolism-like syndrome. Acta Paediat., 50: 240, 1961

Book, J.A., Santesson, B., Zetterquist, P. Association between congenital

heart malformation and chromosomal variations. Acta Paediat., 50: 217, 1961

Book, J.A., Santesson, B., Zetterquist, P. Translocation heterozygosity in man. Lancet, i: 167, 1961

Bottura, C., Ferrari, I., Veiga, A.A. Chromosomal abnormalities in Waldenstrom's macroglobulinaemia. Lancet I: 1170, 1961

Boyd, E., Buchanan, W.W., Lennox, B. Damage to chromosomes by therapeutic doses of radioiodine. Lancet, I: 977, 1961

Brandt, N.J. Genes on the mongol chromosome. Lancet, ii: 837, 1962

Bray, F.P., Mukherjee, B.B. A chromosomal anomaly in an infant with a degenerative disease of the central nervous system. J. Ped., 62: 230, 1963

Breg, W.R., Miller, O.J., Schmickel, R.D. Chromosome studies in Mongolism with particular reference to translocation. Amer. J. Dis. Children. 102: 578, 1961

Brittingham, T.E. Observations on mechanism and prevention of non-specific agglutination of leucocytes. Proc. Soc. Exp. Biol. & Med., 99: 252, 1958

Brodie, H.R., Dallaire, L. The E syndrome (trisomy 17-18), resulting from a maternal chromosomal translocation. J. Can. Mes. Assn., 87: 559, 1962

Bruun Peterson, G., Therkelsen, A.J. Observations on satellited human chromosomes. Lancet, i: 1229, 1961

Buckton, K., Jacobs, P., Court Brown, W.M., Doll, R. A study of the chromosome damage persisting after X-ray therapy for ankylosing spondylitis. Lancet, II: 676, 1962

Butler, L.J., Franse, N.E., Russel, A., Sinclair, L. A chromosomal aberration associated with multiple congenital anomalies. Lancet,ii: 1242, 1962

Carr, D.H. Chromosomal abnormalities and their relation to disease. J. Can. Med. Assn., 88: 456, 1963

Carr, D.H. Chromosome studies in abortuses and stillborn infants. Lancet, II: 603, 1963

Carr, D.H., Barr, M.L., Plunkett, E.R. An XXXX sex chromosome complex in two mentally defective females. J. Can. Med. Assn., 84: 131, 1961

Carr, D.H., Barr, M.L., Plunkett, E.R. A probable XXYY sex determining mechanism in a mentally defective male with Klinefelter's syndrome. J. Can. Med. Assn., 84: 873, 1961

Carpenter, M.D., Durchemiller, W.H. Agenesis of corpus callosum diagnosed during life. Review of literature and presentation of two cases. A.M.A. Arch. Neurol. and Psychiat., 69: 305, 1953

Carter, C.O., Evans, M.A. Risk of parents who have had one child with Down's syndrome (mongolism) having another child similarly affected. Lancet, II, 785, 1961

Carter, C.O., Hamerton, J.L., Polani, P.E. Gunalp, A., Weller, S.D.V. Chromosome translocation as a cause of mongolism. Lancet, II: 678, 1960

Charles, D.R. The spatial distribution of crossovers in X chromosome teterads of Drosophila Melanogaster. J. Genetics, 36: 103, 1938

Chen, H.P., Palmer, G.M. A method for isolating leucocytes. Amer. J. Clin. Path., 30: 567, 1958

Chown, D., Lewis, M. ABO blood groups of mongols. J. Can. Med. Assn., 89: 906, 1963

Chu, E.H.Y., Giles, N.H. Qualitative and quantitative analyses of X-ray induced human chromosome aberrations in cultures of normal diploid somatic cells. Genetics, 44: 503, 1959

Chu, E.H.Y., Giles, N.H., Passano, K. Types and frequencies of human chromosome aberration induced by X-rays. Proc. Nat. Acad. Sci., 47: 830, 1961

Clarke, C., Wedwards, J.H., Smallpeice, V. 21 trisomy/normal mosaicism. Lancet, I: 1028, 1961

Conen, P.E. Chromosome damage in an infant after diagnostic X-irradiation. Lancet, II: 47, 1961

Conen, P.E., Lansky, G.S. Chromosome damage during nitrogen mustard therapy. Brit. Med. J., 2: 1055, 1961

Conen, P.E., Bailey, J.D., Allemang, W.H., Thompson, D.W., Ezrin, C. A probably partial deletion of the Y chromosome in an intersex patient. Lancet, II: 294, 1961

Conen, P.E., Phillips, K.G., Maunter, L.S. Multiple developmental anomalies and trisomy of a 13/15 group chromosome (D syndrome). J. Can. Med. Assn., 87: 709, 1962

Conen, P.E., Bell, A.A., Rance, C.P. A review of chromosomal studies in the diagnosis of mongolism. J. Paed., 60: 533, 1962

Conen, P.E., Bell, A.G., Aspin, N. Chromosomal aberration in an infant following the use of diagnostic X-rays. Pediatrics, 31: 72, 1963

Crawfurd, M. D'A. Multiple congenital anomaly associated with an extra autosome. Lancet, II: 22, 1961

Crawfurd, M. The chromosomes in congenital anomalies of infancy. Heredity, 17: 143, 1962

Cummins, H., Midlo, C. Finger prints, palms and soles. The Blakiston Co., Philadelphia, Pa., 1943

Cummins, H., Talley, C., Platou, R.V. Palmar dermatoglyphics in mongolism. Pediatrics, 5: 241, 1950

Dalgaard, O.Z. Bilateral Polycystic Disease of the Kidneys. E. Munksgaard, Copenhagen, 1957

Dearing, W.H. The material continuity and individuality of the somatic chromosomes of ambystoma tigrinum with special reference to the nucleolus as a chromosomal component. J. Morphol., 56: 157, 1934

De Carli, L., Nuzzo, F., Chiarelli, B., Poli, E. Trisomic condition of a large chromosome in a woman with mongoloid traits. Lancet, II: 130, 1960

Delhanty, J.D.A., Shapiro, A. An unusual acrocentric found in a case of iodiocy with microphtalmia. J. Ment. Defic. Res., 6: 38, 1962

Denver Group: A human chromosome study group. A proposed standard of nomenclature of human mitotic chromosomes. Supplement to Cerebral Palsy Bulletin, 2: No. 3, 1960

De Robertis, E.D.P., Nowinski, W.W., Saez, F.A. General Cytology. W.B. Saunders Co., Philadelphia, Pa., 3rd Ed. 1960

Dobson, R. Ohnuki, Y. Chromosomal abnormalities in a child with a convulsive disorder. Lancet, II: 627, 1961

Down, J.L.H. Observations on an ethnic classification of idiots. Clin. Lect. & Report, Lond. Hosp., 3: 259, 1866

Dunn, H.G., Ford, D.K., Auersperg, N., Miller, J.R. Benign congenital hypotonia with chromosomal anomaly. Amer. J. Dis. Child., 102: 734, 1961

Eagle, H. Amino acid metabolism in mammalian cell cultures. Science, 130: 432, 1959

Edwards, J.H. Chromosome analysis from capillary blood. Cytogenetics, 1: 90, 1962

Edwards, J.H., Harnden, D.G., Cameron, A.H., Crosse, V.M., Wolff, O.H. A new trisomic syndrome. Lancet, I: 787, 1960

Edwards, J.H., Young, R.B. Chromosome analysis from small volumes of blood. Lancet, II: 48, 1961

Ek, J.I., Falk, V., Bergman, S., Reitalu, J. A male mongoloid with 46 chromosomes. Lancet, II: 526, 1961

Ellis, J.R., Marwood, J.C. Autosomal trisomy syndromes. Lancet, II: 263, 1961

Ellis, J.R., Marshall, Ruth, Penrose, L.S. An aberrant small acrocentric. Ann. Human Genetics., 26: 77, 1962

Ellis, J.R., Marshall, R., Normand, I.C., Penrose, L.S. A girl with triploid cells. Nature, 198: 411, 1963

Elves, M.W., Israels, M.C.G. An abnormal chromosome in a haemophiliac with congenital abnormalities. Lancet, II: 909, 1962

Epps, E.F. van Agenesis of the corpus callosum with concomitant malformations including atresia of the foramens of Luschka and Magendie. Amer. J. Roentgenol., 70: 47, 1953

Fanconi, G. Die Mutationstheorie des Mongolismus, Schweiz. Med. Wchnschr., 69: 995, 1939

Ferguson-Smith, M.A. Trisomy of a large chromosome. J. Amer. Med. Assn. 175: 414, 1961

Ferguson-Smith, M.A. Chromosome abnormalities as a cause of human infertility. Fertility and Sterility, 13: 34, 1962

Ferguson-Smith, M.A. Abnormal sex ratio in the autosomal trisomy syndromes. Lancet, II: 992, 1962

Ferguson-Smith, M.A., Johnston, A.W., Handmaker, S.D. Primary amentia and micro-orchidism associated with an XXXY sex chromosome constitution. Lancet, II: 184, 1960

Ferguson-Smith, M.A., Johnston, A.W. Chromosome abnormalities in certain

diseases of man. Ann. Internal Med., 53: 359, 1960

Ferguson-Smith, M.A., Handmaker, S.D. Observations on the satellited human chromosomes. Lancet, II: 1362, 1961

Ferguson-Smith, M.A., Ferguson-Smith, M.E., Ellis, P.M., Dickson, M. The sites and relative frequencies of secondary constrictions in human somatic chromosomes. Cytogenetics, 1: 325, 1962

Fitzgerald, P.H. A possible supernumerary chromosome associated with dystrophia myotonica. Lancet, II: 456, 1962

Fitzgerald, P.H., Lycette, R.R. Mosaicism involving the autosome associated with mongolism. Lancet, II: 212, 1961

Fleming, W. Ueber die Chromosomengahalbleim Menschen. Anat. Anz., 14: 171, 1898

Ford, C.E. Human cytogenetics its present place and future possibilities. Amer. J. Hum. Gent. 12: 104, 1960

Ford, C.E., Hamerton, J.L. The chromosomes of man. Nature, 178: 1020, 1956

Ford, C.E., Hamerton, J.L. A colchicine hypotonic citrate, squash sequence for mammalian chromosomes. Stain Technol., 31: 247, 1956

Ford, C.E., Jacobs, P.A., Lajtha, L.G. Human somatic chromosomes. Nature, 181: 1565, 1958

Ford, C.E., Jomes, K.W., Miller, U. Mittwoch, U., Penrose, L.S., Ridler, M., Shaprio, A. The chromosome of a patient showing both mongolism and the Klinefelter syndrome. Lancet, I: 709, 1959

Ford, C.E., Jomes, K.W., Polaňi, P.E., de Almeida, J.C., Briggs, J.H. A sex chromosome anomaly in a case of gonadal dysgenesis (Turner's syndrome). Lancet, I: 711, 1959

Forssman, H., Lehmann, O. Chromosome studies in eleven families with mongolism in more than one member. Acta Paed., 51: 180, 1962

Fraccaro, M., Gemgell, C.A., Lindsten, J. Plasma level of growth hormone and chromosome complement in four patients with gonadal dysgenesis (Turner's syndrome). Acta Endocrinol., 34: 496, 1960

Fraccaro, M., Kaijser, K., Lindsten, J. Chromosomal abnormalities in father and mongol child. Lancet, I: 724, 1960

Fraccaro, M., Kaijser, K., Lindsten, J. A child with 49 chromosomes. Lancet II: 899, 1960

Fraccaro, M., Lindsten, J. A child with 49 chromosomes. Lancet, II: 1303, 1960

Fraccaro, M., Klinger, H.P., Schutt, W. A male with XXXXY sex chromosomes. Cytogenetics, I: 53, 1962

Fraser, F.C. Genetics and congenital malformations. In Progress in Medical Genetics. A.G. Steinberg, Ed., Grune & Stratton, New York, 1961

Fraser, F.C., Scriver, J.B. A hereditary factor in chondrodystrophia Calcificans congenita. New Eng. Med. J., 250: 272, 1954

Fraser, J.H., Boyd, E., Lennox, B., Dennison, W.M. A case of XXXXY Klinefelter's syndrome. Lancet, II: 1064, 1961

Freese, E.E., Bautz, E., Freese, E.B. The chemical and mutogenic specificity of hydroxylamine P.N.A.S., 47: 845, 1961

Freese, E., Bautz-Freese, E., Bautz, E. Hydroxylamine as a mutogenic and inactivating agent. J. Mol. Biol., 3: 133, 1961

Gagnon, J., Katyk-Longtin, N., Groot, J.A., Barbeau, A. Double trisomie autosomique a 48 chromosomes (21 et 18). L'Union Med. Canada, 90: 1, 1961

Gagnon, J., Archambault, L., Laberge, E., Katyk-Longtin, N. Partial trisomy 18 caused by insertion or translocation 4/18. Un. Med. Canada, 92: 311, 1963

Gagnon, J., Archambault, L., Ducharme, J.R., Katyk-Longtin, N. Resultats preliminaires d'une famille affectee de nephropathie. Revue Can. de Biologie, 22: 133, 1963

Garrod, A.E. Inborn Errors of Metabolism. 2nd Ed. H. Frowde & Hodder & Stoughton, London. 1923

Gates, R.R. Double structure of chromosomes. Nature 140: 1013, 1937

Gates, R.R., Pathak, G.N. Chromosome structure. Nature 142: 157, 1938

Genest, P., Auger, C. Observations on the technique for the study of human chromosomes by the culture of leucocytes from peripheral blood. Can. Med. Ass. J., 88: 302, 1963

German, J.L., Biro, C.E., Bearn, A.G. Chromosomal abnormalities in Waldenstrom's macroglobulinemia. Lancet, II: 48, 1961

German, J.L., Demay, A.P., Bearn, A.G. Inheritance of abnormal chromosome in Down's syndrome (mongolism) with leukaemia. Amer. J. Hum. Genet., 14: 31, 1962

German, J.L., Rankin, T.K., Harrison, P.A., Donovan, D.T., Hogan, W.J., Bearn, A.G. Autosomal trisomy of a group 16-18 chromosomes. J. Paed., 60: 503, 1962

Gray, J.E., Mutton, D.E., Ashby, D.W. Pericentric inversion of chromosome 21. Lancet, I: 21, 1962

Gromults, J.M., Hirschhorn, K. Satellites of acrocentric chromosomes. Lancet, II: 54, 1962

Grouchy, de J. see Thieffry.

Grouchy, de J., Lamy, M. Study of human chromosomes from blood leucocytes. Rev. Franc. Etud. Clin. Biol., 6: 825, 1961

Grouchy, De J., Klotz, H.P., Massin, J.P., Chimenes, H., Nathan Kahn, J. A recent case of XX/XO in a case of Turner's syndrome. Sem. Hop. Paris, 38: 3205, 1962

Grouchy, de J., Job, J.C., Cukier, J. Asymmetrical male pseudohermaphroditism and XY/XO mosaic. Rev. Franc., Etud Clin. Biol., 8: 379, 1963

Grumbach, M., van Wijck, J.J., Wilkins, L. Gonadal dysgenesis with androgenic manifestations in the tall eunochoid female. J. Clin. Endocr., 16: 235, 1955

Gruneberg, H. The Genetics of the Mouse. Martinus & Nijhoff, The Hague, 1952

Gustavson, K.H. Chromosomal translocation in a mongoloid girl with some atypical features. Acta Paediatrica, 51: 337, 1962

Gustavson, K.H., Ek, J.I. Triple stem line mosaicism in mongolism. Lancet, II: 319, 1961

Gustavson, K.H., Hook, O. The chromosomal constitution of the Sturge-Weber syndrome. Lancet, I: 559, 1961

Gustavson, K.H., Hagberg, B., Finley, S., Finley, W.H. An apparently identical extra autosome in two severely retarded sisters with multiple malformations. Cytogenetics, 1: 32, 1962

Hall, B. The chromosomal constitution of the Sturge-Weber syndrome. Lancet, I: 559, 1961

Hall, B. Down's syndrome (mongolism) with normal chromosomes. Lancet II 1026, 1962

Hall, B. Down's syndrome (mongolism) with normal chromosomes. Lancet I: 947,1963

Hamerton, J.L., Briggs, S., Gianelli, F., Carter, C.O. Chromosome studies in detection of parents with high risk of second child with Down's syndrome. Lancet II: 788, 1961

Hamerton, J.L., Cowie, V.A., Gianelli, F., Briggs, S.M., Polani, P. Differential transmission of Down's syndrome (mongolism) through male and female

translocation carriers. Lancet, II: 956, 1961

Hamerton, J.L., Steinberg, A.G. Progeny of D/G translocation, heterozygotes in familial Down's syndrome. Lancet, I: 1408, 1962

Hampar, B., Ellison, S.A. Chromosomal aberrations induced by an animal virus. Nature, 192: 145, 1961

Hanhart, E., Delhanty, J.D.A., Penrose, L.S. Trisomy in mother and child. Lancet, I: 403, 1961

Harnden, D.G. Abnormalities of chromosome constitution and defects of sex development. Proc. Roy. Soc. Med., 53: 493, 1960

Hastings, J., Freedman, S., Rendon, O., Cooper, H.L., Hirschhorn, K. Culture of human white cells using differential leucocytes separation. Nature, 192: 1214, 1961

Hauschka, T.S., Hasson, J.E., Goldstein, M.N., Koepf, G.F., Sandberg, A.A. An XYY man with progeny indicating familial tendency to non-disjunction. Amer. J. Hum. Genet., 14: 22, 1962

Hayashi, T., Hsu, T.C. Chao, D. A case of mosaicism in mongolism. Lancet, I: 218, 1962

Hayward, M.D., Bower, B.D. Chromosomal trisomy associated with Sturge-Weber syndrome. Lancet, II: 844, 1960

Hayward, M.D., Bower, B.D. The chromosomal constitution of the Sturge-Weber syndrome. Lancet, I: 558, 1961

Hecht, F., Bryant, J.S., Motulsky, A.G., Giblett, E.R. The no. 17-18 (E) trisomy syndrome. J. of Pediat., 63: 605, 1963

Heitz, E. Uber Totale und partielle somatische Heteropyknose sowie strukturelle Geschlechtschromosomen bei Drosophila fumelis. Z. Zellforsch., 20: 237, 1933

Herschberg, S.M. Damage to chromosomes by therapeutic doses of radio-iodine. Lancet, II: 104, 1961

Hertig, A.T., Rock, J. Abortive human ova and associated endometria. In Menstruation and Its Disorders, pp. 96-137. Charles C. Thomas, Springfield. 1950

Hicks, S.P. Developmental malformations produced by radiation. Am. J. Roentgenol., 69: 272, 1953

Hsu, T.C. Mammalian chromosomes in vitro. The karyotype of man. J. Hered., 43: 167, 1952

Hsu, T.C., Somers, C.E. Effect of 5-bromodeoxyuridine on mammalian chromosomes. P.N.A.S., 47: 396, 1961

Hungerford, D.A., Donnelly, A.J., Nowell, P.C., Beck, S. The chromosome constitution of a human phenotypic intersex. Amer. J. Hum. Genet., 11: 215, 1959

Ilberry, P.L.T., Lee, C.W.G., Win, S.M. Incomplete trisomy in a child exhibiting minimal stigmata. Med. J. of Australia, July 29, 1961

Inhorn, S.L. The cytogenetics of congenital anomalies. Wis. Med. J., 60: 559, 1961

Ising, U., Levan, A. The chromosomes of two highly malignant tumors. Acta Path. Microbiol. Scand., 40: 3, 1957

Jacobs, P.A., Baikie, W.M., Court Brown, W.M., Strong, J.A. The somatic chromosomes in mongolism. Lancet, I: 710, 1959

Jacobs, P.A., Baikie, A.G., Brown, W.M., McGregor, T.N., Maclean, N., Harnden, D.D. Evidence for the existence of the human "super female". Lancet, II: 425, 1959

Jacobs, P.A., Strong , J.A. A case of human intersexuality having a possible XXY sex determining mechanism. Nature, 183: 302, 1959

Jacobs, P.A., Court Brown, W.M., Doll, R. Distribution of human chromosome counts in relation to age. Nature, 191: 1178, 1961

Jacobs, P.A., Harnden, D.G., Bucktae, K.E., Borwn, W.M., King, M.J., McBridge, J.A. MacGregor, T.N., Maclean, N. Cytogenetic studies in primary amenorrhoea. Lancet, I: 1183, 1961

Jenkins, R.L. Etiology of mongolism. Am. J. Dis. Child., 45: 506, 1933

Jennings, A.N., Turner, B., Dulk, G.M. den, Stapleton, T. A self-perpetuating ring chromosome. Med. J. Aust., 49: 56, 1962

Jennings, A.N., Turner, B. Autosomal chromosomal anomalies. Med. J. Aust., Nov. 18, p. 830, 1961

Kaplan, H., Vaharu, I., Voorhess, M.L., Gardner, L.I. Chromosome analysis in a case of orofacial digital syndrome. New Eng. J. Med., 266: 774, 1962

King, M.J., Gillis, E.M., Baikie, A.G. The polymorph alkaline phosphatase in mongolism. Lancet, II: 661, 1962

Kiwit, W., Good, R.A. Simultaneous occurrence of leukaemia and mongolism: report of a nation wide survey. J. Dis. Child., 94: 289,1957

Kodani, M. The supernumerary chromosome of man. Amer. J. Hum. Genetics, 10: 125, 1958

Lanman, J.L., Sklain, B.S., Cooper, H.L., Hirschhorn, K. Klinefelter's syndrome in a ten-month-old mongolian idiot. New. Eng. J. Med., 263: 887, 1960

Larsen, J.L., Scottstaedt, E.R., Bost, F.C. Multiple congenital dislocations associated with characteristic facial abnormality. J. Ped., 37: 574, 1960

Lawler, S.D. Genes on the mongol chromosome. Lancet II: 837, 1962

Lehmann, O., Forssman, H. Chromosomes in the Sturge-Weber Syndrome. Lancet, II: 1450, 1960

Lehmann, O., Forssman, H. Klinefelter's syndrome and mongolism in the same person. Acta Paediat., 49: 536, 1960

Lehmann, O., Forssman, H. Familial mongolism with chromosomal translocation also observed in normal boy member. Acta Paed., 51: 6, 1962

Lejeune, J. Le mongolisme maladie chromosomique. La Nature, 3296: 522, 1959

Lejeune, J. Personal communication, 1963

Lejeune, J., Gauthier, M., Turpin, R. Etude des chromosomes somatiques de neuf enfants mongoliens. C.R. Acad. Sci.,Paris, 248: 1721, 1959

Lejeune, J., Turpin, R., Gauthier M. Le mongolisme, maladie chromosomique (trisomie). Bull Acad. Nat. Med., 143 (11 and 12): 256, 1959

Lejeune, J., Turpin, R., Gauthier, M. Le mongolisme premier exemple d'abberration autosomique humaine. Annales de Genetique, 1: 41, 1959

Lejeune, J., Turpin, R. Chromosomal aberrations in man. Amer. J. Hum. Genet., 13: 175, 1961

Lenz, W. The effect of parental age and birth order on pathological conditions in the child. Acta Genet., 9: 249, 1959

Leon, N., Epps, D.R. Becak, M.L., Becak, W. Discrepancies between bone-marrow and peripheral blood chromosomal constitution. Lancet, II: 880, 1961

Levan, A. Self perpetuating ring chromosome in two human tumours. Hereditas, 42: 366, 1956

Levine, S. Magnetic techniques for in vitro separation of leucocytes. Science, 123: 185, 1956

Li, J.G., Osgood, E.E. A method for the rapid separation of leucocytes and nucleated erythrocytes from blood or marrow with a phytohemagglutinin from red beans (Phaseolus Vulgaris). Blood, 4: 670, 1949

Lindsten, J. The Nature and Origin of X-chromosome Abberrations in Turner's Syndrome. Almquist and Wiksell, Stockholm, Goteborg, Uppsala, 1963

Lindsten, J., Tillinger, K.G. Self perpetuating ring chromosome in a patient with gonadal dysgenesis. Lancet, I: 593, 1962

Lonsdale, D. Factor stimulating cell division. Lancet, II: 434, 1961

Lubs, H.A., Koenig, E.U., Brant, I.K. Trisomy 13-15: A clinical syndrome. Lancet, II: 1001, 1961

MacKinney, A. et al. Kinetics of leucocytes proliferating in vitro. Clin. Res., 9: 163, 1961

Maclean, N., Harnden, D.G., Court Brown, W.M. Abnormalities in sex chromosome constitution of new born babies. Lancet, II: 406, 1961

Maclean, N., Mitchell, J.M., Harnden, D.G., Williams, J., Jacobs, P.A., Buckton, K., Baikie, A.G., Court Brown, W.M., McBride, J.A., Strong, J.A., Close, H.G., Jones, D.C. A survey of sex chromosome abnormalities among 4,514 mental defectives. Lancet, I: 289, 1962

Makino, S., Nishimura, I. Waterpreatment squash technique. Stain Technol., 27: 1, 1952

Makino, S., Sasaki, M. A study of the somatic chromosomes in the Japanese. Jap. J. Genet., 35: 228, 1960

Makino, S., Sasaki, M. Chromosome constitution in the normal human subjects and in one case of true hermaphroditism. Proc. Jap. Acad., 36: 156, 1960

Makino, S., Tonomura, A., Matsunaga, E. Chromosomes studies in ten cases of mongolism (preliminary report). Proc. Jap. Acad., 36: 12, 1960

Makino, S., Kikuchi, Y., Sasaki, M., Sasaki, Motomomichi, Yoshida, M. A further survey of the chromosomes in the Japanese. Chromosoma (Ber.) 13: 138, 1962

Makino, S., Honda, T., Mitani, M. Chromosomes studies in children with Down's syndrome and their parents. Proc. Jap. Acad., 38: 47, 1962

Makino, S., Sasaki, M.S., Kajii, T. Chromosome studies in eight cases of human congenital disease. Proc. Jap. Acad., 38: 166, 1962

Makino, S., Honda, T., Kajii, T. Chromosome studies in twelve cases of congenital diseases. Proc. Jap. Acad., 38: 356, 1962

Makino, S., Yoshida, M.C., Mitani, M. Chromosome studies in ten cases of human congenital diseases. Proc. Nat. Acad., 38: 356, 1962

Marshall, R., Capon, B. Factor stimulating cell division in cultured leucocytes. Lancet, II: 103, 1961

Mazutani, M., Ohnuki, Y., Nakanishi, Y.H., Pomerat, C.M. Changes in modal values of chromosomes after irradiation of human amnion cells. Proc. Conf. on Research on Radio-therapy of Cancer (Amer. Cancer Soc.) p. 51 1961

McClintock, B. The production of homozygotes deficient tissues with mutant characteristics by means of the aberrant mitotic behavior, or ring shaped chromosomes. Genetics, 23: 315, 1958

McCulloch, C., Hunter, W.S. A search for ocular anomalies in persons with abnormal numbers of sex chromosomes. J. Can. Med. Assn., 86: 14, 1962

McDonald, Alison D. Congenital defects associated with prematurity. Arch. Dis. Childhood, 37: 277, 1962

Mellman,W.J., Kelvit, H.D., Moorhead, P.S. Studies on phytohaemagglutinin-stimulated leukocyte cultures. Blood, 20: 103, 1962 (Abstract)

Mercer, R.D., Darakjian, G. Apparent translocation between chromosome 2 and an acrocentric in group 13/15. Lancet II: 784, 1962

Merrit, D.H., Harris, J.S. Mongolism and acute leukemia: report of 4 cases. J. Dis. Child., 92: 41, 1956

Michaux, L., Duche, D.J., Feld, M. Syndrome multimalformatif avec agenesie du Corps Calleux et atrophie cerebrale diffuse par anoxie neo-natale. Arch. Francaises de Pediatrie, 16: 949, 1959

Miller, J.Q., Picard, E.H., Alkan, M.K., Warner, S., Gerald, Park S. A specific congenital brain defect (arhinencephaly) in 13-15 trisomy. New Eng. Med. J., Jan, 1963

Miller, O.J., Breg, W.R., Schmickel, R.D., Tretter, W. A family with an XXXXY male, a leukaemic male, and two 21-trisomic mongoloid females. Lancet, II: 78, 1961

Miller, J.R., Fraser, F.C., MacEwan, D.W. The frequency of spina bifida occulta and rib anomalies in the parents of children with spina bifida aperta and meningocoele. Amer. J. Hum. Gen., 14: 245, 1962

Mittwoch, U. Properties of X chromosome. Lancet, II, 880, 1961

Morgan, L.V. A close X chromosome in Drosophila Melanogaster Genetics, 18: 250, 1933

Moorhead, P.S., Mellman, W.J., Battips, D.M. Human autosomal anomalies in a sibship of six. Genetics, 45: 1001, 1960 (Abstract)

Moorhead, P.S., Nowell, P.C., Mellman, W.J., Battips, D.M., Hungerford, D.A.

Chromosome preparations of leukocytes cultured from human peripheral blood. Exp. Cell Res., 20: 613, 1960

Moorhead, P., Mellman, W.J., Wenar, C. A familial chromosomal translocation associated with speech and mental retardation. Amer. J. Hum. Genet., 13: 32, 1962

Muldal, S. Trisomy and group V. Lancet II: 879, 1961

Muldal, S., Ockey, C.H. The "double male": a new chromosome constitution in Klinefelter's syndrome. Lancet II: 492, 1960

Muldal, S., Ockey, C.H. Muscular dystrophy and deletion of Y chromosome. Lancet II: 601, 1961

Muller, H.J. Artificial transmutation of the gene. Science, 66: 84, 1927

Naiman, J., Fraser, F.C. Agenesis of the Corpus Callosum. A.M.A. Arch. Neurol. Psychiat., 74: 182, 1955

Nelson, T.L. Serum protein and lipoprotein fractions in mongolism. A.M.A. J. Dis. Child., 102: 369, 1961

Nelson, W.E. Ed. Textbook of Paediatrics, 7th Ed. W.B. Saunders, Philadelphia 1959

Nichols, W.W., Levan, A., Hall, B., Ostergren, G. Measles associated chromosome breakage. Preliminary communication. Hereditas, 48: 367, 1962

Nichols, W.W., Coriell, L.L., Fabrizio, D.P.A., Bishop, H.G., Boggs, T.R. Mongolism with mosaic chromosome pattern. J. Paed., 60: 69, 1962

Northcutt, R.C. Multiple congenital anomalies in a Negro infant with 13-15 trisomy. Southern M.J., 55: 385, 1962

Nowakowski, H., Leng, W., Bergman, S., und Reitalu, J. Chromosomenbefunde beim echten Klinefelter-Syndrom. Acta Endocrin., 34: 483, 1960

Nowell, P.C. Phytohemagglutinin: an initiator of mitosis in cultures of normal human leucocytes. Cancer Res., 20: 462, 1960

Nowell, P.C., Hungerford, D.A. Chromosome studies on normal and leukemic human leukocytes. J. Nat. Cancer Inst., 25: 85, 1960

Ohno, S., Trujillo, J.M., Kaplan, W.D., Kinosita, R. Nucleolus organizers in the causation of chromosomal anomalies in man. Lancet, II: 123, 1961

Painter, T. Studies in a mammalian spermatogenesis. II. The spermatogenesis of man. J. Exper. Zool., 37: 291, 1923

Painter, T. The sex chromosomes of man. Am. Nat., 58: 506, 1924

Patau, K. The identification of individual chromosomes especially in man. Amer. J. Hum. Genet., 12: 250, 1960

Patau, K., Smith, D.W., Therman, E., Inhorn, S.L., Wagner, H.P. Multiple congenital anomaly caused by an extra autosome. Lancet, I: 790, 1960

Patau, K., Therman, E., Inhorn, S.L. Picken, B.F. The cytogenetics of the Sturge-Weber syndrome. Abstract, Mtg. Amer. Soc. Hum. Genet., 14: 1961

Patau, K., Therman, E., Smith, D.W., Demars, R.I. Trisomy for chromosome No. 18 in man. Chromosoma (Berl.), 12: 280, 1961

Patau, K., Therman, E., Smith, D.W., Inhorn, S.L. New cases of D 1 trisomy in man. Hereditas, 47: 239, 1961

Patau, K., Therman, E., Inhorn, S.L., Smith, D.W., Ruess, A.L. Partial trisomy syndromes: an insertion as cause of the OFD syndrome in mother and daughter. Chromosoma, 12: 573, 1961

Patau, K., Therman, E., Smith, D.W. Partial trisomy syndromes and the mapping of trisomy loci. Proc. 2nd International Conf. of Human Genetics, (1961) Rome, 1963

Pathak, G.N., see Gates, R.R.

Penrose, L.S. The relative effects of paternal and maternal age in mongolism. J. Genet., 37: 219, 1933

Penrose, L.S. The distal triradius "t" on the hands of parents and sibs of

mongol imbeciles. Ann. Hum. Genet., 19: 10, 1954

Penrose, L.S. Chromosomes and disease. Trans. Med. Soc. London, 76: 64, 1960

Penrose, L.S. Mongolism. Brit. Med. Bull., 17: 239, 1961

Penrose, L.S. Mongolism, clinical aspects of genetics. Pitman Medical Pub. Co. Ltd., 1961

Penrose, L.S., Ellis, J.R., Delhanty, J.D.A. Chromosomal translocations in mongolism and in normal relatives. Lancet, II: 409, 1960

Penrose, L.S., Delhanty, J.D. Triploid cell cultures from a macerated foetus. Lancet, I: 1261, 1961

Polani, P.E., Briggs, J.H., Ford, C.E., Clark, C.M., Berg, J.M. A mongol girl with 46 chromosomes. Lancet, I: 721, 1960

Puck, T.T. Action of radiation on mammalian cells. Proc. Nat. Acad. Sci., 44: 772, 1958

Puck, T.T. Action of radiation on mammalian cells. III Relationship between reproductive death and induction of chromosome anomalies by X-irradiation of euploid human cells from human and animal subjects. J. Exp. Med., 108: 945, 1958

Puck, T.T., Cieciura, S.J., Robinson, A. Action of X-rays on mammalian cells. II Survival curves of cells from normal human tissues. J. Exp. Med., 106: 485, 1957

Renton, P.H., Stratton, F., Bateman, A.J. Genes on the mongol chromosome. Lancet, II: 727, 1962

Richards, B.W., Stewart, A. Mosaicism in a mongol. Lancet, I: 107, 1962

Rosanoff, A.J., Handy, L.M. Etiology of mongolism. Am. J. Dis. Chil., 48: 764, 1934

Rothfels, K.H., Siminovitch, L. An air drying technique for flattening chromosomes in mammalian cells grown in vitro. Stain Technol., 33: 73,

1958.

Ruchnagel, D.L., Neel, J.V. The hemoglobinopathies. Prog. in Med. Genetics., 1: 158, 1961

Ruess, A.L., Pruznasky, S., Lis, E.F., Patau, K. The oro-faciadigital syndrome: a recently identified congenital disease apparently associated with a previously unidentified chromosomal abnormality. Amer. J. Dis. Child., 102: (4), 586, 1961

Ruess, A.L. Pruzansky, S., Lis, E.F., Patau, K. The oral facial digital syndrome: a multiple congenital condition of females with associated chromosomal abnormalities. Pediatrics, 29: 985, 1962

Sasaki, M. Observations on the modification in size and shape of chromosomes due to technical procedure. Chromosoma, 11: 514, 1961

Sasaki, M., Makino, S. The chromosomal constitution of a human hermaphrodyte. Tex. Rep. Biol. Med., 18: 493, 1960

Schmid, W. A familial chromosome abnormality associated with repeated abortions. Cytogenetics, 1: 199, 1962

Schmid, W., Lee, C.H., Smith, P.M. At the borderline of mongolism. Report of a case with chromosome analysis. Am. J. Ment. Defic., 66: 449, 1961

Schmid, W., Hatfield, D. Normal karyotype/translocation mosaic. Cytogenetics: 1: 210, 1962

Schull, W.J., Neel, J.V. Maternal radiation and mongolism. Lancet, I: 537, 1962

Shaw, M.W. Familial mongolism. Cytogenetics, 1: 141, 1962

Shaw, M.W., Gershowitz, H. A search for autosomal linkage in a trisomic population: blood group frequencies in mongols. Amer. J. Hum. Genet., 14: 317, 1962

Shiwago, P.I., Andres, A.H. Die Geschlechtschromosomen in der Spermatogenese

des Menschen. Z. Zellforsch., 16: 413, 1932

Skoog, J.H., Beck, W.S. Studies in the fibrinogen and phytohemagglutinin methods of isolating leucocytes. Blood, 11: 436, 1956

Slizynski, B.M. The pachytene stage in mammalian oocytes. Nature, 189: 683, 1961

Smith, D.W., Patau, K., Therman, E., Inhorn, S.L. The No. 18 trisomy syndrome. J. Paed., 60: 513, 1962

Smith, D.W., Patau, K., Therman, E., Inhorn, S.L. A new autosomal trisomy syndrome: multiple congenital anomalies caused by an extra chromosome. J. Paed., 57: 338, 1960

Smith, D.W., Patau, K., Therman, E. The 18 trisomy syndrome and the D 1 trisomy syndrome. Amer. J. Dis. Child., 102: (4), 587, 1961

Smith, D.W., Patau, K., Therman, E. Autosomal trisomy syndromes. Lancet, II: 211, 1961

Smith, D.W., Patau, K., Therman, E., Inhorn, S.L., DeMars, R.I. The D1 syndrome. J. Paed., 62: 326, 1963

Sobel, A.E., Straguella, M., Sherman, B.S., Elkan, B., Morgenstern, S.W., Marius, N., Meijel, A. Vit. A absorption and other blood composition in mongolism. Amer. J. Ment. Defic., 62: 642, 1958

Somers, C.E., Hsu, T.C. Chromosome damage induced by hydroxylamine in mammalian cells. P.N.A.S., 48: 937, 1962

Sorsby, A. Ed. Clinical Genetics. Butterworth & Co., London. 1953

Stern, C. The chromosomes of man. J. Med. Educ., 34: 301, 1959

Stewart, J.S.S. Mechanisms of non-disjunction in man. Nature, 194: 258, 1962

Stewart, J.S.S., Sanderson, A. Chromosomal aberration after diagnostic X-irradiation. Lancet, I: 978, 1961

Sturdevant, A.H. The effects of unequal crossing over at the bar locus in Drosophila. Genetics., 10: 117, 1925

Therman, E., Patau, K., Smith, D.W., Demars, R.I. The D trisomy syndrome and XO gonadal dysgenesis in two sisters. Amer. J. Hum. Gen., 13: 193, 1961

Thieffry, S., Arthuis, M., Grouchy, J. de, Lamy, M., Salmon, C. Deletion des bras courts d'un chromosome 17-18: dysmorphies complexes avec oligophrenie. Arch. Francaises de Pediatrie., 20: 740, 1963

Tjio , J.H., Levan, A. The chromosome number of man. Hereditas, 42: 1, 1956

Tjio, J.H., Puck, T.T. Genetics of somatic mammalian cells. J. Exp. Med., 108: 259, 1958

Tjio, J.H., Puck, T.T. The somatic chromosomes of man. Proc. Nat. Acad. Sci., 44: 1229, 1958

Tjio, J.H., Puck, T.T., Robinson, A. The human chromosomal satellites in normal persons and in two patients with Marfan's syndrome. Proc. Nat., Acad. Sci., 46: 532, 759, 1960

Tjio, J.H., Whang, J. Chromosome preparation of bone marrow cells without prior in vivo culture or in vivo colchicine administration. Stain Technol., 37: 17, 1962

Tough, I.M., Buckton, K.E., Baikie, A.G., Court Brown, W.M. X-ray induced chromosome damage in man. Lancet, II: 849, 1960

Townes, P.L., Dehart, G.K., Hecht, F., Manning, J.A. Trisomy 13/15 in a male infant. J. Paed., 60: 528, 1962

Trentin, J.J., Yabe, Y., Taylor, G. Tumor induction in hamsters by human adenovirus. Proc. Amer. Assn. Cancer Res., 3: 369, 1962

Trujillo, J.M., Stenius, C., Ohno, S., Novack, J. Translocation heterozygosity in man. Lancet, I: 560, 1961

Turner, B., Jennings, A.N., Den Dulk, G.N., Stapleton, T. A self-perpetuating ring chromosome. Med. J. Aust., Jul. 14, 1962

Turner, B., Jennings, A.M. Trisomy for chromosome No. 22. Lancet II: 49, 1961

Turpin, R., Caratzalli, A., Mlle Rogier, H. Premier Congres de la Federation Internationale Latine des Societes d'Eugenique, pp. 154. Masson et Cie. Ed., Paris, 1937

Turpin, R., Lejeune, J., Lafourcade, Gauthier, M. Aberrations chromosomiques et maladies humaines. La polydyspondylie a 45 chromosomes. C.R. Acad. Sci., Paris, 248: 3636, 1959

Turpin, R., Lejeune, J. Chromosome translocations in man. Lancet, I: 616, 1961

Uchida, I., Curtis, E. A possible association between maternal radiation and mongolism. Lancet, II: 848, 1961

Uchida, I., Patau, K., Smith, D.W. The dermal patterns of the new autosomal syndromes. Abstracts. 31st Ann. Mtg. Soc. Pediat. Res., 131: 1961

Uchida, I.A., Soltan, H.C. Evaluation of dermatoglyphics in medical genetics. Pediatrics of N. Amer., 10: 409, 1963

Vaharu, T., Patton, R.G., Voorhess, M.L., Gardner, L.I. Gonadal dysplasia and enlarged phallus in a girl with 45 chromosomes plus fragment. Lancet, I: 1351, 1961

Vislie , H., Wehn, M., Brogger, A., Mohr, J. Chromosome abnormalities in a mother and two mentally retarded children. Lancet, II: 76, 1962

Walker, N.F. The use of dermal configurations in the diagnosis of mongolism. J. Pediat., 50: 19, 1957

Walker, N.F. The use of dermal configurations in the diagnosis of mongolism. Pediat. Clin. of N. Amer., 5: 531, 1958

Walker, S., Harris, R. Investigation of family showing transmission of a 13/15 chromosomal translocation (Denver classification). Brit. Med. J., II: 25, 1962

Wang, H.C., Melnyk, J., McDonald, L.T., Uchida, I.A., Carr, D.H., Goldberg, B. Ring chromosomes in human beings. Nature, 195: 733, 1962

Warkany, J. Etiology of mongolism. J. Pediat., 56: 412, 1960

Warkany, J., Kalter, H. Congenital malformations. New Eng. J. Med., 265: 993, 1961

Warkany, J., Rubinstein, J.H. Etiology of the Sturge-Weber syndrome with chromosome analysis of a case. J. Maine Med. Assn., 53: 76, 1962

Wijck, J.A.K. van, Stolte, L.A.M., Kersel, H.S.A.M. van, Tijdink, G.A.J. A trisomic child of a hyperthyroid mother. Lancet, I: 887, 1961

Wijck, J.A.K. van, Tijdink, G.A.J., Stolte, L.A.M. A case of partial trisomy. Lancet, II: 1454, 1961

Williamson, S.M. The leucocyte method for the study of human chromosomes. Can. J. Med. Techn., 24: 13, 1962

Witschi, E. Overripeness of the egg as a cause of twinning and teratogenesis: a review. Can. Res., 12: 763, 1952

Woodruff, M.F.A., Fox, M., Bukton, K., Jacobs, P. The recognition of human blood chimaeras. Lancet, I: 192, 1962

Wright, S.W., Day, R.W., Mosiee, H.D., Koons, A., Mueller, H. Klinefelter's syndrome, Down's syndrome (mongolism) and twinning in the same sibship. J. Pediat., 62: 217, 1963

Yntema, C.L., Hammond, W.S. The origin of intrinsic ganglia of trunk viscera from vagal neural crest in the chick embryo. J. Comp. Neurol., 101: 515, 1954

Zellweger, H., Mikamo, K., Abbo, G. An unusual translocation in a case of mongolism. J. Pediat., 62: 235, 1963

Zellweger, H., Mikamo, K. Autosomal cytogenetics. Helvet. Paediat. Acta., 16: 670, 1961