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PRESUMPTIVE ISO-CHROMOSOMES FOR THE LONG ARM OF X IN MAN ANALYSIS OF FIVE FAMILIES

by

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PRESUMPTIVE ISO-CHROMOSOMES FOR THE LONG ARM OF X IN MAN - ANALYSIS OF FIVE FAMILIES by M. FRACCARO (Euratom), D. IKKOS (Karolinska Hospital - Stockholm), K. KAIJSER (Central Hospital - Eskilstuna), J. LINDSTEIN (Karolinska Hospital - Stockholm) and R. LUFT (Karolinska Hospital - Stockholm).

The cytological study of five female individuals is indicative of the existence in man of iso-chromosomes for the long arm of the X chromosome. Phenotypically these subjects are characterized by primary amenorrhœa, short stature, elevated excretion of gonadotrophins and low excretion of œstrogens in urine.

Laparotomy revealed in two of them gonadal streaks. Analysis of dermatoglyphics showed patterns similar to those found in XO individuals.

The five subjects are sex chromatin positive in buccal mucosa smears and in cultured cells, and drumsticks are found consistently in their neutrophils. The karyotypes of the five patients are consistent in their appearance : in all

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the cells with forty-six chromosomes from different tissues (bone marrow, skin and blood) there are fifteen chromosomes in the 6-12-X group instead of of sixteen, and an extra metacentric chromosome similar to those of pair no. 3. These cells are interpreted as having one normal X chromosome and a presumptive iso-chromosome for the long arm of X. In one or more of the tissues cultured from patients A.S., L.A. and B.J. there is a proportion of cells with forty-five chromosomes and with an XO constitution.

The origin of the iso-chromosomes is thought to be meiotic and paternal. This hypothesis is discussed on the basis of an apparent deficiency of females in the sibships of the patients and of the genetical information provided by the study of the sex-linked Xg blood group system in the family of B.J. This family, in which red-green colour blindness is segregating, provides also evidence that the Xg and the red-green colour blindness loci are located on the short arm of the X chromosome.

Personal, family and laboratory data are provided in Appendices, together with the cytological data and chromosome measurements.

Presumptive iso-chromosomes for the long arm of X in man. Analysis of five families

By J. LINDSTEN,* M. FRACCARO,† D. IKKOS,*‡
K. KAIJSER,§ H. P. KLINGER,‖ AND R. LUFT*

INTRODUCTION

Numerical and structural variations in the X chromosomes, usually ascertained through abnormal phenotypes, are relatively common in man. The study of such changes has important genetical implications since X is the only human chromosome on which genetical markers have been located.

In early 1959 two of us (M.F. and J.L.) examined cytologically a patient with Turner's syndrome selected for chromosome studies by K.K. This female patient, M.A., in the present series, was found to have forty-six chromosomes but an abnormal karyotype with only one presumptive X chromosome and three metacentric chromosomes similar to those of pair no. 3. Subsequently two other females were found of similar phenotype and karyotype. We suggested that these abnormal chromosomes were iso-chromosomes for the long arm of X (Fraccaro, Ikkos, Lindsten, Luft & Kaijser, 1960).

Iso-chromosomes were apparently described for the first time by Håkansson (1933) in wheat. The name and the first comprehensive observations on their origin and behaviour, however, are due to Darlington (1939, 1940a) who described and discussed two new phenomena, misdivision of the centromere and formation of iso-chromosomes. The formal definition of an iso-chromosome implies that it is a metacentric chromosome in which the two arms are mutually homologous. The evidence in favour of the existence of such chromosomes is cytological. The chain of events leading to iso-chromosomes was summarized by Darlington (1939) thus: 'Following misdivision of the centromere at meiosis in diploid and triploid *Fritillaria* new telocentric chromosomes are formed whose broken ends rejoin within the centromere. This type of chromosome is delayed at metaphase and anaphase in the pollen-grain mitotis. It may then either break again at the centromere, or pass without separation to the pole as a new iso-chromosome. The misdivision and the origin of the iso-chromosome are each likely to be important as affecting the genetic structure of the chromosome and the mechanical properties of the centromere.' In discussing the evolutionary implications of these findings Darlington (1940a) pointed out that the effects of misdivision on the mechanical properties of the centromere were likely to be more evident in those sex chromosomes which required, because of peculiarities in reproduction and behaviour, special properties in their centromeres, as in the case of *Sciara* and *Cimex* (Darlington, 1940b).

Iso-chromosomes in wheat have been recently studied by Sears (1952a, b). They are produced mostly at the first division of meiosis, when univalents undergo several types of misdivision, and both telocentric and iso-chromosomes are formed. In this material a high frequency of uni-

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valents is obtained from viable monosomics. It is also considered possible, however, that the iso-chromosomes actually transmitted are not those formed at the first division, which can be lost, but are produced from the telocentrics at some post-meiotic division. On the basis of his observations and analysis of the literature Sears concluded that iso-chromosomes in plants have various origins in different species according to the behaviour and transmission of telocentrics at the different stages of cell division.

Iso-chromosomes in the classical sense are known only in plants. Equal-armed abnormal chromosomes, however, occur in *Drosophila*, a well-known example being the attached *X* of *Drosophila melanogaster* which could be considered, according to White (1959), an iso-chromosome. The mitotic appearance of equal-armed chromosomes obtained by Rasmussen (1960) through radiation-induced rearrangements of the arms of autosomes II and III of *Drosophila melanogaster* has been illustrated by Gerletti & Rasmussen (1962). Iso-chromosomes have hitherto been unknown in mammals.

Following the primary observations of presumptive human iso-chromosomes, similar cases have been observed and reported by several authors, for example, C. E. Ford (personal communication); Jacobs, Harnden, Buckton, Court Brown, King, McBride, MacGregor & Maclean, 1961; Blank, Gordon & Bishop, 1961; Engel & Forbes, 1961; Hamerton, Jagiello & Kirman, 1962; de la Chapelle, 1962. In this paper we present in detail the three cases of presumptive iso-chromosomes mentioned in 1960 and describe two additional patients, one of whom, B.J., has been briefly reported by Lindsten (1961).

<div align="center">METHODS</div>

<div align="center">(i) Clinical investigations</div>

Clinical routine investigations on all patients included X-ray examination of skull, heart and lung and skeletal system, intravenous pyelography and electrocardiography; determinations of serum electrolytes (sodium, potassium, chlorides, bicarbonate) and of blood levels of calcium, inorganic phosphate, alkaline and acid phosphatase, cholesterol; tests of thyroid function; intravenous glucose tolerance test; total serum proteins and electrophoresis of serum proteins, pattern and amount of urinary aminoacids, calcium excretion in urine. Unless otherwise stated in the clinical descriptions to follow, the results of these investigations were in all patients within normal range of variation for adult individuals.

Intelligence was tested with the Wechsler–Bellevue intelligence scale adapted to Swedish circumstances (CVB), and with another test (SRB) composed of three parts: a block test, a reasoning test and a synonym test of multiple choice type.

Colour vision was tested by using the 15th edition of the Ishihara charts and, when possible, an anomaloscope. Hormone titrations in urine were performed by the method of Vestergaard (1951) for 17-ketosteroids, by the method of Norymberski, Stubbs & West (1953) as modified by Appleby, Gibson, Norymberski & Stubbs (1955) for 17-ketogenic steroids, by the method of Klinefelter, Albright & Griswold (1943) for total gonadotrophins, by the method of Brown (1955) as modified by Diczfalusy & Westman (1956) and Brown, Bulbrook & Greenwood (1957) for oestrogens. Blood levels of glucose-6-phosphate dehydrogenase (G-6-PD) were determined by the qualitative method of Glock & McLean (1953).

(ii) *Cytological investigations*

(a) *Dimorphism of interphase nuclei*

Buccal mucosa smears were prepared and stained according to the method of Klinger & Ludwig (1957). Drumsticks of polymorph neutrophils were studied in blood smears stained with May–Grünwald–Giemsa. Sex chromatin in cultured cells was studied by the methods described by Fraccaro & Lindsten (1959).

(b) *Somatic chromosomes*

Long-term cultures of bone marrow and skin cells were prepared according to the methods described by Fraccaro, Kaijser & Lindsten (1960). Cytological preparations from these cultures were made by the acetic orcein squash technique described in the same paper. Skin specimens obtained at a later date were cultured and processed by the method of Hsu & Kellogg (1960), with modifications. Blood cultures were prepared and processed according to the method of Moorhead, Nowell, Mellman, Battips & Hungerford (1960), with modifications.

Chromosome counts, cytological analysis and photographs were made with Zeiss phase-contrast microscopes. Chromosomes were measured as described by Fraccaro & Lindsten (1960).

THE PATIENTS AND THEIR FAMILIES

Relevant personal, family and laboratory data pertaining to these patients and members of their families are given in Appendices 1 and 2.

Blood group and serum protein data are set out in Appendix 3 and quantitative data of dermatoglyphics in Appendix 4. Appendices 5 and 6 show the results of nuclear sexing in buccal mucosa cells and blood polymorph neutrophils. The results of chromosome counts are shown in Appendix 7 and chromosome measurements and indices of selected cells from various patients in Appendix 8. Appendix 9 describes the pedigrees of the five families, illustrated in Fig. 1.

A special investigation on growth hormone levels in four of these patients has been published by Almqvist, Lindsten & Lindvall (1963).

Patient M.A. (Pl. 1 (a))

She was admitted to the Pediatric Department in Eskilstuna in 1950 at the age of 13 because of infantilism and short stature. From 1947 to 1950 she had been treated with thyroid hormone. At the last examination there was dwarfism, slight obesity and lack of secondary sex characteristics. She had broad shoulders and a short neck without webbing, hyperflexible joints and several pigmented moles scattered over her body. No other relevant signs at physical examination. Gynaecological examination revealed a normal clitoris, a very small uterus and no ovaries were palpable per rectum. Roentgen investigations revealed slight cubitus valgus and typical changes of the medial tibial condyle. The IV and V metacarpals, bilaterally, were shorter than normal. She was treated with oestrogens cyclically and this resulted in regular withdrawal bleedings, some breast development and appearance of slight axillary and pubic hair.

One skin biopsy, three bone marrow and three blood specimens were obtained on different occasions for chromosome studies (see Pl. 2). Bone marrow, blood and skin biopsies were obtained from her mother, and blood specimens from her twin sister and her father.
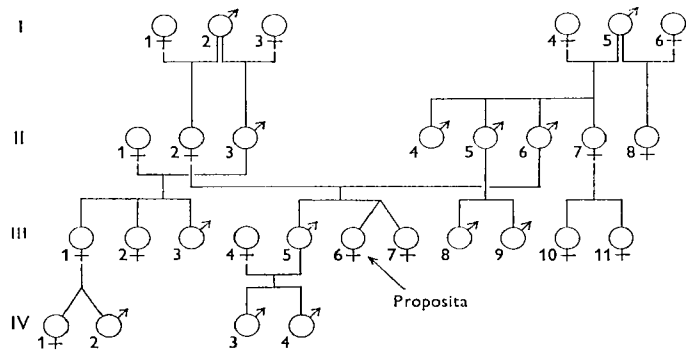
(a) Pedigree of patient M.A.
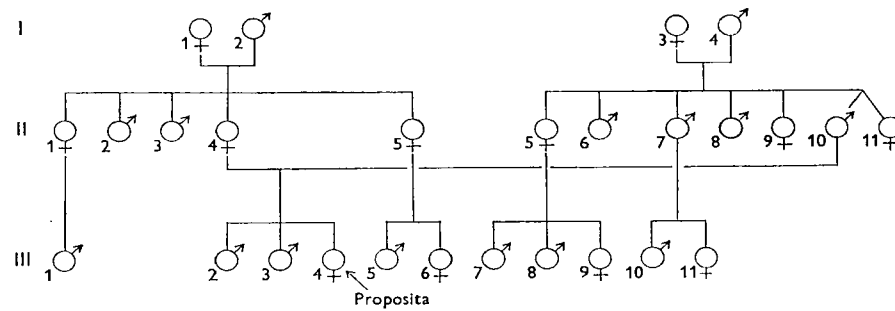
(c) Pedigree of patient L.A.

(b) Pedigree of patient A.S.

Key

⊙ Normal colour vision ● Miscarriage

● Abnormal colour vision ⊘ Neonatal death
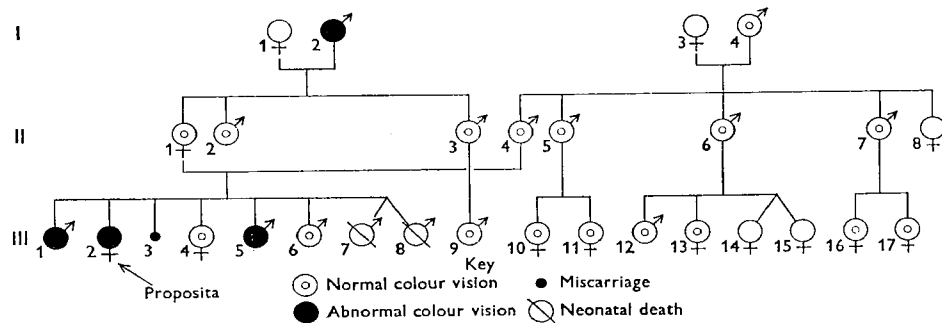
(d) Pedigree of colour blind patient B.J.

(e) Pedigree of patient Y.L.

J. LINDSTEN, M. FRACCARO, D. IKKOS, K. KAIJSER, H. P. KLINGER AND R. LUFT
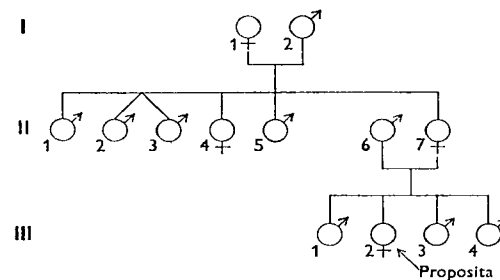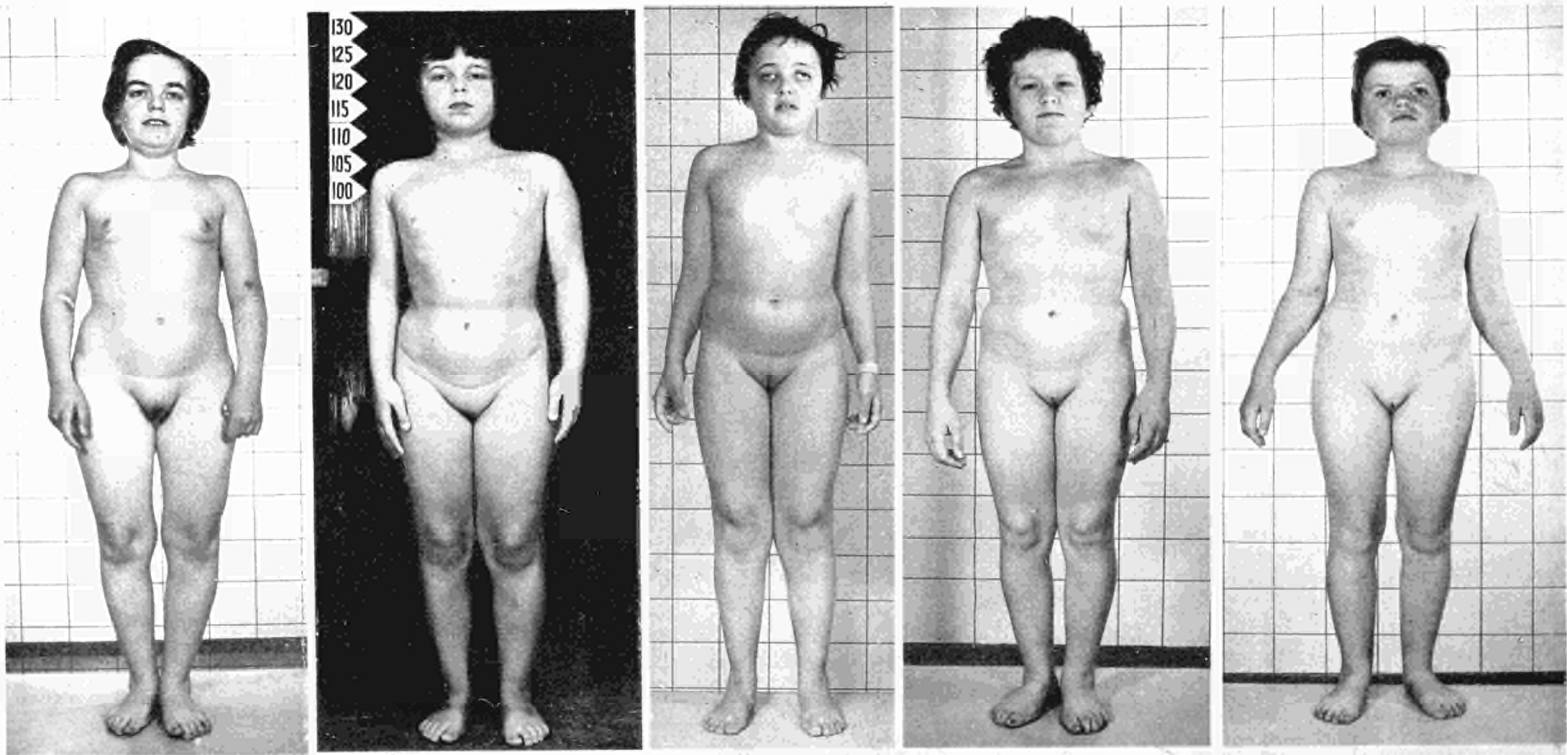
(a) M.A. (25)   (b) A.S. (14)   (c) L.A. (17)   (d) B.J. (17)   (e) Y.L. (16)

Photographs of the patients; ages indicated by numbers in brackets.

Plate 1

(i)
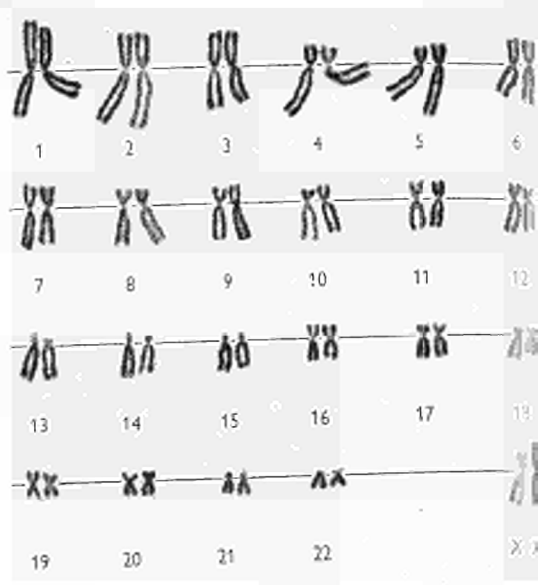
(ii)

(iii)
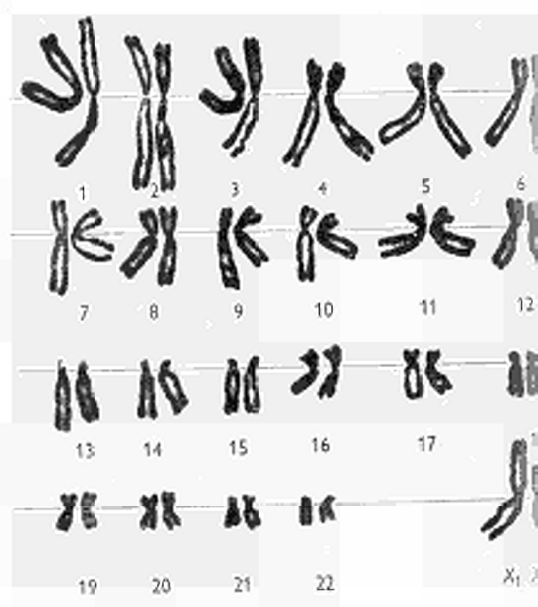
(iv)

Patient M. A: (i) mitotic blood cell; (ii) karyotype; (iii) mitotic bone marrow cell, not treated with colchicine; (iv) karyotype.

J. LINDSTEN, M. FRACCARO, D. IKKOS, K. KAIJSER, H. P. KLINGER AND R. LUFT

Plate 3
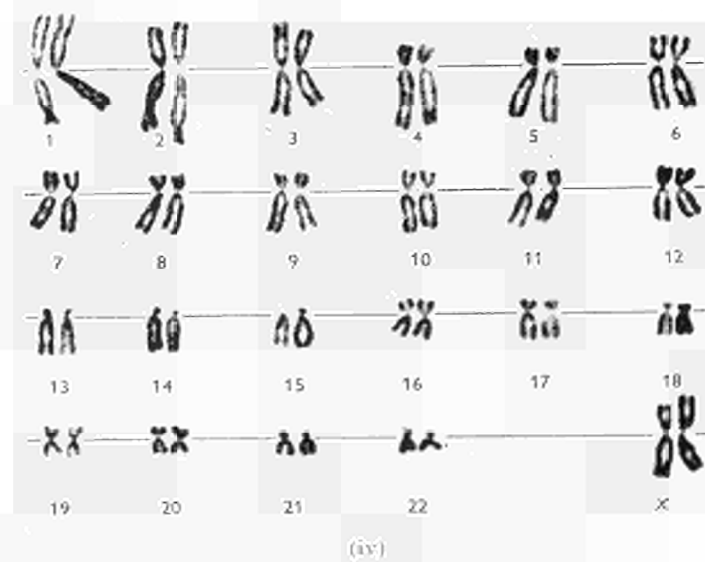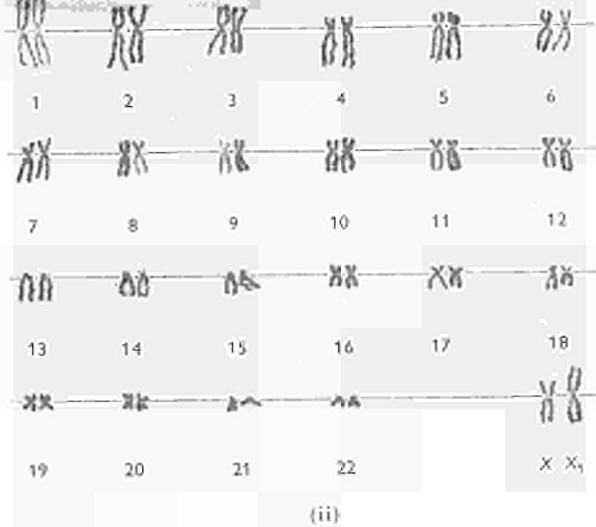
(i) (ii) (iii) (iv)

Patient L. A.: (i) mitotic skin cell; (ii) karyotype. Patient B. J.: (iii) mitotic blood cell; (iv) karyotype.
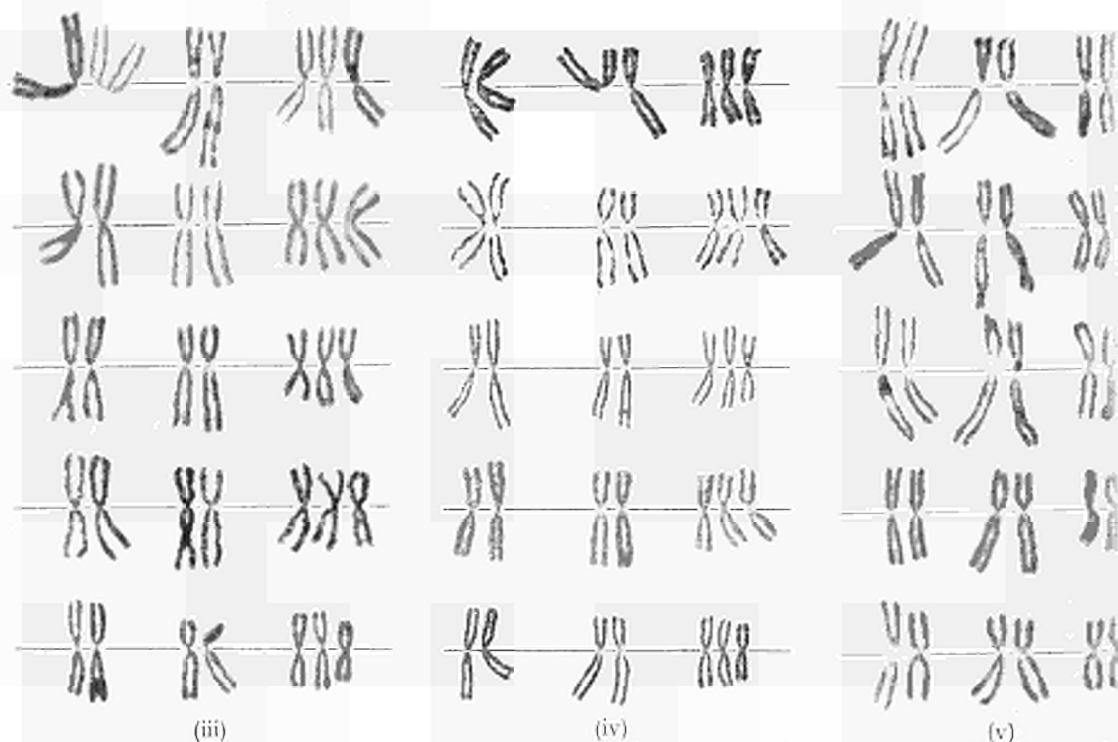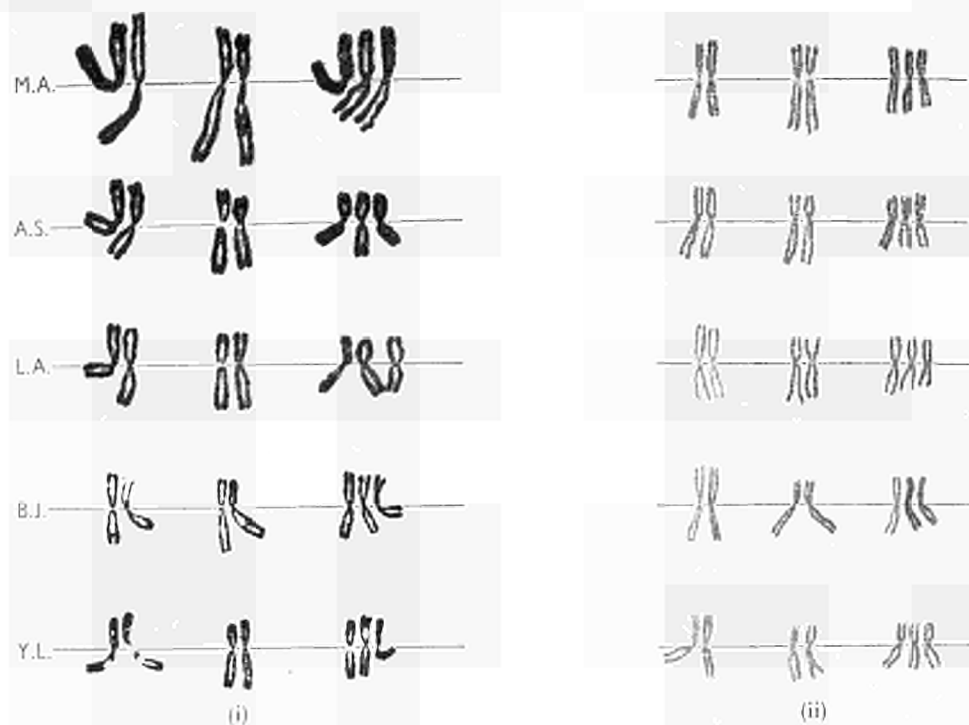
Chromosomes of pairs nos. 1, 2 and 3 with iso-chromosome from (i) five bone-marrow cells; (ii) five skin cells; (iii)–(iv) fifteen blood cells.

J. LINDSTEN, M. FRACCARO, D. IKKOS, K. KAIJSER, H. P. KLINGER AND R. LUFT

Patient A.S. (Pl. 1(*b*))

She was admitted to the Endocrinological Clinic of the Karolinska Hospital, Stockholm, in 1958 at the age of 14 because of infantilism and short stature. She had infantile external genitalia and no breasts, pubic or axillary hair. Gynaecological examination revealed a normal vagina, a small uterus and no ovaries were palpable per rectum. Physical examination revealed dwarfism, broad shoulders, short neck with low implantation of hair and no webbing. She was treated with oestrogens cyclically and this resulted in regular withdrawal bleedings, some breast development and appearance of slight axillary and subnormal amount of pubic hair.

Intravenous pyelography showed a normal urinary tract.

Laparotomy (June 1960) revealed an almost normal-sized uterus and tubes and the presence of bilateral gonadal streaks, 10×2 mm. long. Histological examination of the streaks showed a fibrous tissue reminiscent of ovarian stroma with a rich vascularization and no hilar cells, follicles or corpora lutea.

Specimens were obtained on different occasions for chromosome studies, two of bone marrow, one of blood and one of skin. Blood specimens were obtained from her mother, father, sister and other members of her family.

Patient L.A. (Pl. 1(*c*))

She was born 5 weeks before the expected date of delivery. She walked at 18 months and talked at 2 years of age. She is of short stature. She was referred to the Endocrinological Clinic, Karolinska Hospital, in 1959, aged 17, because of arrested growth in the past 2 years. She complained of primary amenorrhoea.

Physical examination revealed dwarfism; short neck with low implantation of hair but no webbing or cubitus and genu valgi. The external genitalia were infantile and she had no pubic or axillary hair and no breast development. Gynaecological examination revealed a small uterus and no palpable ovaries. A pyelogram showed a double left kidney, pelvis and ureter.

Since 1958 there have been clear symptoms of a slowly progressing cerebellar degeneration characterized mainly by ataxia, dysarthria, and nystagmus. Vision was 0·7 bilaterally and there was a divergent, alternating, cong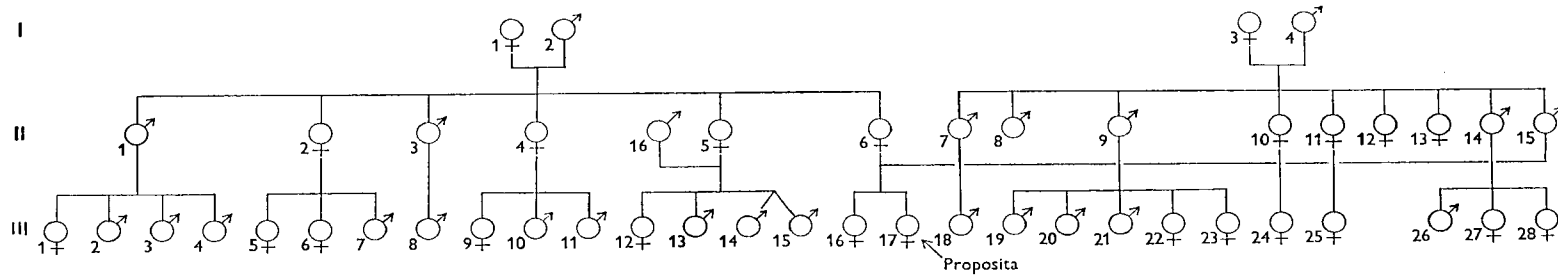enital strabismus. Electrocardiography, electroretinography and electroencephalography gave normal results. Encephalography showed cortical atrophy and no evidence of an expansive process in the posterior fossa of the cranium. Electromyography of the anterior tibial muscles and of the femoral quadriceps gave normal results. Urinary excretion of creatine and creatinine was also normal.

Laparotomy (May 1960) revealed a hypoplastic uterus (1×5 cm.), normal tubes and two vestigial gonadal streaks about 4 mm. long. Histological examination of the streaks revealed vascularized connective tissue of the type usually seen in the interstitial portion of the ovaries and hili. There was a small cluster of hilar cells but no follicles or corpora lutea were seen. One bone marrow, one skin and one blood specimen were obtained for chromosome studies (see Pl. 3(i) (ii)). Blood specimens were obtained from parents and sibs.

Patient B.J. (Pl. 1(*d*))

The patient was admitted to the Endocrinological Clinic in 1960 (Karolinska Hospital), complaining of primary amenorrhoea, infantilism and dwarfism. Physical examination revealed dwarfism, broad shoulders, short neck with low implantation of hair but no webbing or hyper-

flexibility of fingers. External genitalia were infantile; there was no pubic and axillary hair and no breast development. The uterus was found to be small and the ovaries were not palpable. An intravenous pyelogram revealed a cleft left renal pelvis.

She was colour blind (deuteranopic) and colour blindness was found to segregate in the family (see Pedigree, Fig. 1(d) and Appendix 9). Examination showed that eye movements and pupil reactions were normal. Slight convergent strabismus was present on the left side. Light perception was normal. For a short period in the past she had a central scotoma on the left side. Vision: 0·9 right; 0·1–0·2 left. Fundi showed normal appearance of maculae, vessels and papillae.

Her colour vision was tested independently for the two eyes with the Ishihara charts and with an anomaloscope. The result of the test with the charts indicated that the patient was deuteranopic. In the anomaloscope she had a normal Raleigh equation with an increased contrast. It was suspected that the patient had a complicated colour vision defect which warrants further investigation.

She was treated with oestrogens cyclically and this resulted in regular withdrawal bleedings, some breast development and appearance of slight axillary and pubic hair.

Two skin biopsies and one blood specimen were obtained for chromosome studies (see Pl. 3(iii), (iv)).

<center>*Patient Y.L.* (Pl. 1(e))</center>

The patient is of short stature. She walked at two and started school at the usual time. She had never menstruated. Examination showed infantile breasts with no palpable glandular tissue and scanty axillary and pubic hair. She had brittle nails, several pigmented moles and cubitus valgus. At gynaecological examination, the vagina was found to be 6 cm. long and the uterus measured 2 × 0·5 cm. Ovaries were not palpable. Roentgen investigation of the skeleton revealed a coarse bone structure and open epiphyseal zones. There were typical changes of the medial tibial condyles. Three blood specimens and one skin biopsy were obtained for chromosome studies.

<center>DERMATOGLYPHICS</center>

Analysis of the dermatoglyphic patterns on the finger tips and on the palms of the five patients by Prof. L. S. Penrose and Dr Sarah B. Holt led to some interesting conclusions (see Fig. 2). The first is that on the average there is a high degree of pattern intensity on the fingers. As measured by the total ridge count their mean is 174·6; the individual values are all higher than the mean for Swedish females (120·7). On the assumption that the standard deviation of the control sample is about 50·0, this excess of 53·9 above the mean, for five cases, would only be exceeded about once in 100 trials. It is noteworthy that in cases of Turner's syndrome, with XO karyotype, an exactly similar tendency towards increased pattern intensity, as measured by total ridge count, is found.

The second conclusion is that the number of ridges between the triradii a and b on the palms tends to be larger than the average. The mean sum of this value on right and left hands, for the five patients here, is 96·8 as compared with 84·9 for control females. This number also tends to be high in Turner's syndrome where a mean value of 100 is typical.

The third point is that the position of the t-triradius is rather more distal than in the average female hand but not nearly as distal as in cases of mongolism. The mean atd angle, which

measures this peculiarity, summed for both hands, reaches an average of 111·1 as compared with 85·9 for normal control females and 138·7 for mongol females. This tendency, which is far less marked than in mongolism, is also characteristic of palms in Turner's syndrome.

(a) (i) M.A.

(a) (ii) I.A.

(b) A.S.

(c) L.A.

(d) B.J.

(e) Y.L.
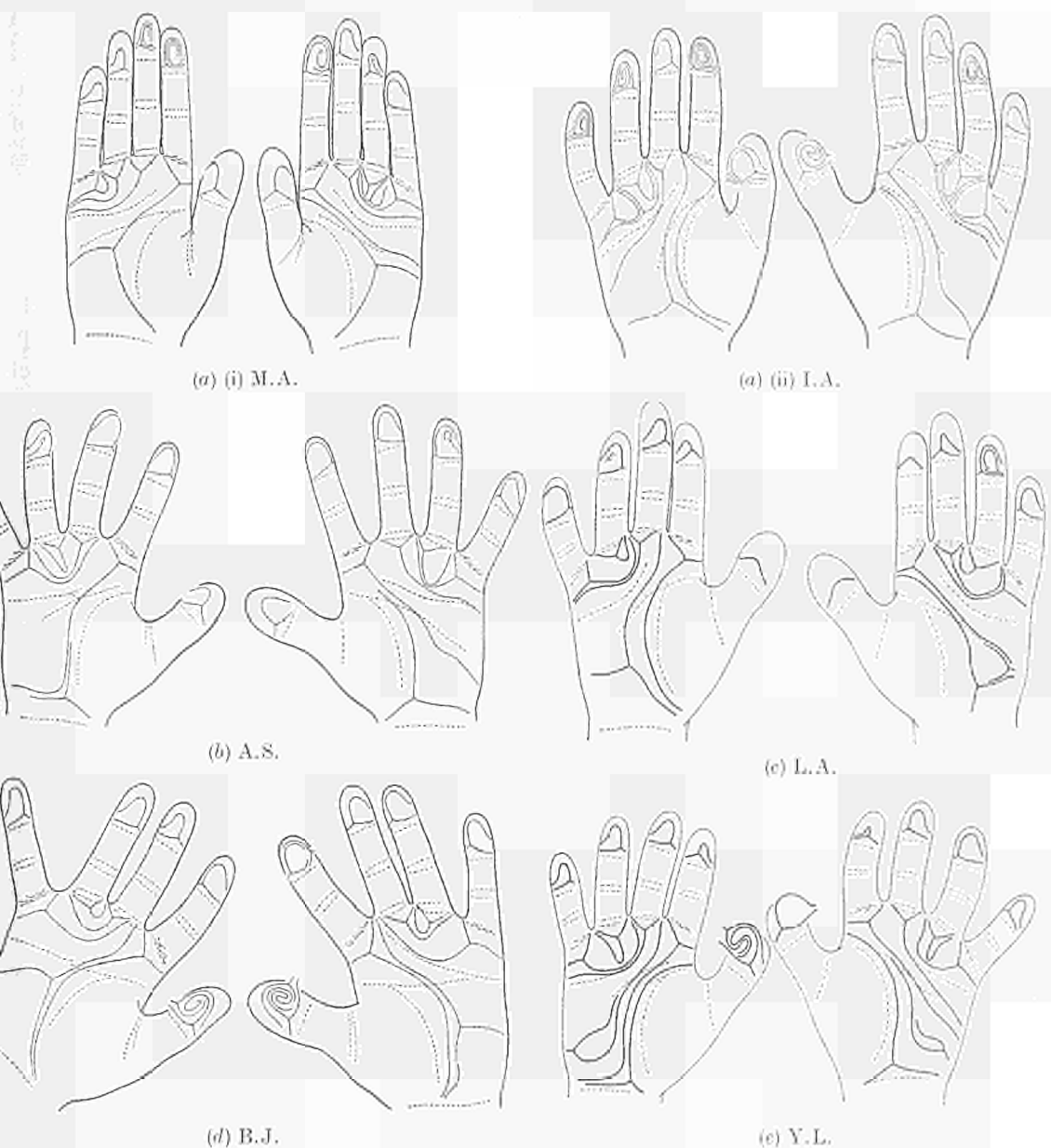
Fig. 2. Dermatoglyphs on the hands of the patients and of I.A., the twin sister of M.A.

It is of interest also to observe that the unaffected twin sister of one of the patients shows quite similar deviations towards the Turner dermatoglyphic pattern type. The significance of this is not clear and it might be a coincidental event since all these features have some genetical background and this might be common to the two sisters in question. Quantitative data are given in Appendix 4.

CYTOLOGICAL FINDINGS

The five patients were consistently sex-chromatin positive in buccal mucosa smears and cultured cells. The result of the enumeration of sex chromatin bodies in buccal mucosa smears from each of the five patients is given in Appendix 5. Drumsticks were consistently found, in varying proportions, in all patients. The proportions found on different occasions are entered in Appendix 6. Occasionally, Barr bodies appeared to be of considerable size and also conspicuous drumsticks were observed at times. Estimates of the DNA content of Barr bodies of the five patients and of suitable controls showed that the sex chromatin bodies of the patients have an average higher content of DNA.

The karyotypes of the five patients were remarkably consistent in their appearance, so that it is possible to make a collective description. In all the cells with forty-six chromosomes from different tissues of the five patients there were fifteen chromosomes in the 6-12-X group, instead of the sixteen found in normal females and an extra chromosome in the 1-3 group. The abnormal chromosome was metacentric and morphologically identical, within the limits of variation commonly found in this type of material, with the chromosomes of pair no. 3. In analysing any cell with forty-six chromosomes it was immediately obvious that there were three 'threes'. This is exemplified by the compositions shown in Pl. 4, in which these three chromosomes have been aligned with each other and with the chromosomes of pairs nos. 1 and 3. It can be seen that the differences in length and centromere position among the three 'threes' are no more apparent than the differences between the individual chromosomes of nos. 1 and 2.

The visual impression is confirmed by the results of the chromosome measurements which are shown in Appendix 8. There are, in each measured cell, three chromosomes which have the relative length and arm ratio of chromosome no. 3. In group 6-12-X we could find only one chromosome which would satisfy our usual morphological criteria for the definition of the X chromosome and we therefore concluded that one X was consistently missing from these cells.

In each preparation from each patient there was a proportion of cells with forty-five chromosomes. In several such cells it was possible to diagnose a random loss of different chromosomes. However, in one or more of the tissue samples cultured from patients A.S., L.A. and B.J. there was a considerable proportion of cells with forty-five chromosomes which consistently lacked one chromosome of the 6-12-X group and in which we could find only one presumptive X.

In conclusion, we interpreted the cells with forty-six chromosomes as having one apparently normal X chromosome and a presumptive iso-chromosome for the long arm of X; the cells with forty-five chromosomes in A.S., L.A. and B.J. were interpreted as XO cells.

All parents and relatives who were cytologically examined had apparently normal karyotypes. These individuals and the result of the analysis of their cells are listed in Appendix 7.

DISCUSSION

(i) *Nature and origin of the iso-chromosome*

The results of the present investigation are suggestive of the existence in man of iso-chromosomes for the long arm of the X chromosome.

Sex chromatin studies and chromosome morphology indicate that the abnormal chromosome is in its entirety or in part composed of X chromosome material. The five patients are consistently sex chromatin positive. It is generally assumed that the sex chromatin body is present

only in those nuclei which contain two or the greater part of two X chromosomes. Unpublished experiments, in which blood cultures of some of our patients have been flash labelled with ³H thymidine according to the method described by Gilbert, Muldal, Lajtha & Rowley (1962), show that the presumptive iso-chromosome is symmetrically 'hot' along its length and behaves as one of two X chromosomes of normal female cells usually does. Further support for the concept that the iso-chromosome is mainly composed of X chromosome material comes from the preliminary experiments on DNA content of sex chromatin body. These observations, however, are not proof that the abnormal chromosome is entirely composed of X chromosome material. According to Ohno (1962) this behaviour would be observed even if the abnormal chromosome were the result of an X-autosome translocation. An X chromosome in the mouse carrying the translocated portion of an autosome was observed by Ohno and this behaved along its full length as would a normal X chromosome.

The clinical picture of the five patients is remarkably uniform, and this suggests a common underlying cause. They all display primary amenorrhoea, short stature, elevated excretion of gonadotrophins and low excretion of oestrogens in urine. In those who have been laparotomized, gonadal streaks were found. These are signs characteristic of Turner's syndrome, which is usually associated with a sex chromosome constitution of the XO type. No instances of mental retardation, webbing of the neck or *coarctatio aortae*, which are sometimes observed in Turner's syndrome, were found in our patients. The only unusual symptoms are the kidney malformation and the central nervous system defect found in patient L.A. It should be noted, incidentally, that central nervous system defect is occasionally found in association with abnormalities of the sex chromosomes (see Indemini & Ammann, 1961). On the whole, the clinical picture of this group of patients is that of Turner's syndrome. The dermatoglyphic patterns also agree with those usually found in Turner's syndrome.

If the abnormal chromosome common to these patients is an iso-chromosome for the long arm of X, its carriers are formally monosomic for the short and trisomic for the long arm of X. Since their phenotype is similar to that of XO individuals it follows that there is no dosage effect for the genes on the long arm of X. An alternative interpretation that cannot be formally excluded is that the XO cell line has been a determining factor in the production of the observed phenotypes.

The abnormal chromosome might theoretically originate from a different mechanism. Thus, duplication, translocation between X and autosome, reciprocal translocation or intrachromosomal rearrangement (chromatid interchange) involving breakage and reunion at points close to the centromere are among the events which could produce such a chromosome. The occurrence in several unrelated patients of an apparently identical abnormal chromosome, however, requires at its origin a mechanism which can occur repeatedly with a uniform final result. Formation of iso-chromosomes by misdivision of the centromere meets this requirement, while each of the alternative explanations requires one or more additional assumptions, e.g. preferential breakage at specific points of the X chromosome (Ford, 1961).

The iso-chromosomes so far described in plants originated in meiosis. It is conceivable that this applies also to man. If this is so, the origin of the abnormal chromosome is likely to be paternal, since pairing of the sex chromosomes in the male meiosis is such as to favour irregularities in chromosome behaviour. Thus, the sex chromosomes, when observed at diakinesis and first metaphase of primary spermatocytes, are usually associated terminally, but the X and Y are also occasionally seen unpaired and well separated from each other as univalents (Ford &

Hamerton, 1956). It should be stressed that misdivision of univalents is known to be the commonest source of iso-chromosomes in plants (Sears, 1952b).

The presence in some of the patients of a chromosomal mosaic XO/X_I, might be explained by assuming that the occasional iso-chromosome undergoes a mitotic accident which results in its loss and the production of an XO cell line. It is possible, for example, that the new centromere ('isocentromere') may respond quite abnormally to the spindle forces so that loss ensues through lagging. Somatic loss of iso-chromosomes is known to occur with detectable frequency in wheat (Sears, 1952b).

Furthermore, if a telocentric, X_T, produced by misdivision in the male meiosis, is conveyed in a sperm instead of the normal X and effects fertilization, the zygote so produced may have one of several abnormal karyotypes. These are (i) perpetuation of the telocentric, (ii) iso-chromosome formation giving an XO/XX_I mosaic, (iii) loss of the telocentric and formation of an XO individual, (iv) loss of one daughter telocentric giving an XO/XX_T mosaic and (v) formation of the iso-chromosome at a later division resulting in an $XO/XX_I/XX_T$ mosaic.

Theoretically, misdivision of the centromere and formation of iso-chromosomes might also happen at any postzygotic mitosis. From an originally XO zygote would then arise directly either an XO/X_IO or an XO/XX_T mosaic. Conversely, mitotic origin of iso-chromosomes from XX zygotes would give origin to an XO/XX_I or an $XX/XO/XX_I$ mosaic, which must be a very rare event.

No firm conclusion regarding the origin of the abnormal chromosome can be drawn from our present evidences. Although a meiotic origin seems likely it is clear that origin at a mitotic division in the embryo cannot be excluded.

Two ancillary observations support the view that the iso-chromosome in our patients might be of paternal origin, either during spermatogenesis or during cleavage.

(a) Genetical evidence in the family of B.J. where the X chromosome is marked by the Xg blood group system and by colour blindness.

(b) An apparent deficiency of females is observed in the sibships of patients with iso-chromosomes. The five patients have among them ten brothers, counting the like sexed twins of B.J. as one brother, and only three sisters. Adding five other patients (unpublished) with iso-chromosomes the ratio is sixteen males to ten females. The excess of males over females is not significant but, should the trend be confirmed on larger material, it could be explained as the result of the occasional loss of female zygotes because of the contribution of an abnormal X chromosome from the paternal side. Deficiency of females is also observed among the sibs of XO individuals. In this respect it is tempting to postulate the existence on the human X chromosome of a genetic entity reminiscent of the segregation-distorter found by Sandler, Hiraizumi & Sandler (1959) on chromosome II and responsible for meiotic drive in natural populations of *Drosophila melanogaster*. Such a phenomenon could explain the deficiency of females in terms of meiotic drive. A cytogenetic model similar to the one postulated by Sandler *et al.* (1959) could also explain the formation of iso-chromosomes.

(ii) *Iso-chromosomes and the location of the Xg and red-green colour vision loci*

The recent discovery of a sex-linked blood-group system permits the combination of cytological with genetical evidence in the case of abnormalities of the X chromosome, when informative families are involved (Race & Sanger, 1962). The family of B.J. (Fig. 1(d)) is

informative in this respect. The reasons why this and a similar family from another source provide evidence that the Xg locus might be located on the short arm of the X chromosome have been discussed by Lindsten, Fraccaro, Polani, Hamerton, Sanger & Race (1963).

Patient B.J. is Xg (a−), while her mother, father and sibs are all Xg (a+). Normal daughters of Xg (a+) males are Xg (a+). The fact that B.J. is Xg (a−) indicates that her apparently normal X chromosome comes from her mother, who should be therefore heterozygous, Xg^a/Xg. In consequence, the presumptive iso-chromosome should be of paternal origin and should not carry the Xg^a gene. If the cytological interpretation is correct, it follows that the locus should be located on the short arm of X and is missing from the iso-chromosome which is composed of the two long arms of the paternal X. The same argument applies to the red-green colour vision locus.

Inspection of the pedigree shows that at least two of five carriers of the maternal X in the sibship of B.J. represent cross-overs between the Xg and the colour vision locus. This confirms the previous estimates of a high Xg red-green colour vision cross-over rate (Race & Sanger, 1962).

SUMMARY

The cytological study of five female individuals is indicative of the existence in man of iso-chromosomes for the long arm of the X chromosome. Phenotypically these subjects are characterized by primary amenorrhoea, short stature, elevated excretion of gonadotrophins and low excretion of oestrogens in urine.

Laparotomy revealed in two of them gonadal streaks. Analysis of dermatoglyphics showed patterns similar to those found in XO individuals.

The five subjects are sex chromatin positive in buccal mucosa smears and in cultured cells, and drumsticks are found consistently in their neutrophils. The karyotypes of the five patients are consistent in their appearance: in all the cells with forty-six chromosomes from different tissues (bone marrow, skin and blood) there are fifteen chromosomes in the 6-12-X group instead of sixteen, and an extra metacentric chromosome similar to those of pair no. 3. These cells are interpreted as having one normal X chromosome and a presumptive iso-chromosome for the long arm of X. In one or more of the tissues cultured from patients A.S., L.A. and B.J. there is a proportion of cells with forty-five chromosomes and with an XO constitution.

The origin of the iso-chromosomes is thought to be meiotic and paternal. This hypothesis is discussed on the basis of an apparent deficiency of females in the sibships of the patients and of the genetical information provided by the study of the sex-linked Xg blood group system in the family of B.J. This family, in which red-green colour blindness is segregating, provides also evidence that the Xg and the red-green colour blindness loci are located on the short arm of the X chromosome.

Personal, family and laboratory data are provided in Appendices, together with the cytological data and chromosome measurements.

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APPENDIX 1

Personal and family data

Patient. Initials and date of birth	Birth weight (g.)	Birth length (cm.)	Age at last examination	Stature* (cm.)	Pubis to sole measurement (cm.)	Span (cm.)	Weight (kg.)	I.Q.		Parental age	
								CVB†	SRB†	Mother	Father
M.A. (19. ii. 37)	1660	43	25	135 (153·5)	68	132	38	90	102	35	31
A.S. (14. v. 43)	2940	47	18	138 (151·5)	66	135	34	96	100	28	30
L.A. (1. ix. 42)	1980	43	19	141 (152·5)	72	140	40	92	87	35	51
B.J. (5. i. 43)	3090	50	18	139 (152·5)	70	149	44	99	102	25	33
Y.L. (6. iii. 46)	2760	47	16	132 (147)	68	133	34	109	108	23	30

* Lower limit of normal shown in parentheses.

† See text.

APPENDIX 2

Hormone titrations in urine and G-6-PD

Patient	17-Keto-steroids (mg./24 hr.)	17-Ketogenic steroids (mg./24 hr.)	Total gonado-trophins (mu./24 hr.)	Oestrogens before treatment (mu./l.)	G-6-PD levels
M.A.	5·4–6·6	10·2–11·6	> 96	< 10	—
A.S.	3·4–4·8	3·9– 8·6	> 96	< 10	—
L.A.	3·7–9·6	6·7–18·5	> 96	< 20	Normal
B.J.	2·5–5·3	7·0–12·1	> 53	< 10	Normal
Y.L.	2·5–3·8	5·8– 7·9	< 6·5	< 10	Normal

APPENDIX 3

Blood group, haptoglobins and serum group data

Patient and Family	ABO	MNS	P	Rhesus	Kell	Duffy	Lewis	Xg	Hp	Gc	Gm
M.A. (pedigree *a*)											
III.6*	A₁	NSNs	+	R₁R₁	−	a+	a−	a+	1·1	2·1	a−
III.7†	O	NsNs	+	R₁r	−	.	.	a+	.	.	.
II.2‡	O	NsNs	w	R₁R₁	−	a+	a−	a+	2·1	2·1	a+
II.6‡	A₁	NSNs	w	R₁r	−	a+	a−	a−	1·1	.	.
A.S (pedigree *b*)											
III.17*	A₁	MMS	−	R₁r	−	a+	a−	a−	.	2·1	a+
III.16†	A₁	NNS	.	R₁r	−	.	.	a+	.	.	.
II.6‡	O	MNS	−	r r	−	a+	a−	a+	2·1	1·1	a+
II.15‡	A₁	MNS	.	R₁R₁	−	.	.	a−	.	.	.
L.A. (pedigree *c*)											
III.4‡	A₁	MNS	+	R₂r	−	a+	a−	a+	2·1	2·1	a−
III.2†	A₁	MMS	.	R₁r	−	.	.	a+	.	.	.
III.3†	A₁	MNS	.	R₂r	−	.	.	a+	.	.	.
II.4‡	A₁	MNS	.	R₁R₂	−	.	.	a+	.	.	.
II.12‡	O	MNS	+	R₁r	−	a+	a−	a−	2·2	2·2	a−
Y.L. (pedigree *d*)											
III.2*	O	MsMs	−	R₁r	−	a+	a+	a−	2·1	2·1	a+
III.1†	A₁	MSMs	−	R₁r	−	.	.	a+	.	.	.
III.3†	A₁	MsMs	+	r r	−	.	.	a+	.	.	.
III.4†	A₁	MSMs	w	r r	−	.	.	a+	.	.	.
II.7‡	A₁	MSMs	−	r r	−	a−	a−	a+	2·2	2·1	a+
II.6‡	A₁	MSMs	+	R₁r	−	.	.	a−	.	.	.
II.2	A₁	MNS	.	R₂r	−	.	.	a+	.	.	.
II.3	A₁	MNS	.	R₂R₂	−	.	.	a+	.	.	.
II.1	A₁	MsNs	.	r r	−	.	.	a+	.	.	.
II.5	A₁	MsNs	.	R₂r	−	.	.	a+	.	.	.
I.2	O	MMS	.	R₂r	−	.	.	a+	.	.	.
B.J. (pedigree *e*)											
II.2*	O	NSNs	−	R₁r	−	a+	a−	a−	1·1	2·1	a+
II.1†	O	MSNS	−	R₁r	−	.	.	a+	.	.	.
III.4†	O	MSNS	−	R₁r	−	.	.	a+	.	.	.
III.5†	O	MSNS	w	R₁R₁	−	.	.	u+	.	.	.
III.6†	O	MSNS	w	R₁r	−	.	.	a+	.	.	.
II.1‡	O	NSNS	+	R₁R₁	−	.	.	a+	1·1	2·2	.
II.4‡	O	MSNs	+	R₁r	−	.	.	a+	.	.	.
I.4	A₁	MSMs	−	r r	−	.	.	a−	.	.	.
II.3	A₁	MSNS	+	R₁R₁	−	.	.	a+	.	.	.
II.2	O	MNSs	+	R₁R₂	−	.	.	a+	.	.	.
III.9	O	MNSs	+	R₁R₁	−	.	.	a+	.	.	.

Key: w = weakly positive; * = proposita; † = sib; ‡ = parent.

APPENDIX 4(a)

Dermal ridge counts on fingers

		Digits					
Subject	Hand	V	IV	III	II	I	Totals
M.A.	Left	12/0	12/0	13/11	12/14	20/0	160
	Right	18/0	11/0	16/0	20/12	24/0	
I.A.*	Left	16/11	15/13	13/0	6/13	15/21	164
	Right	18/0	14/10	14/0	18/0	22/12	
A.S.	Left	23/0	23/0	26/0	21/0	20/0	226
	Right	23/0	28/0	17/0	0/24	21/0	
L.A.	Left	23/0	18/3	17/0	14/0	0/0	128
	Right	24/0	18/16	14/0	0/0	0/0	
B.J.	Left	20/0	20/0	15/0	21/0	21/18	193
	Right	20/0	19/0	15/0	21/19	21/13	
Y.L.	Left	14/0	18/0	15/0	0/5	26/18	166
	Right	19/0	18/0	19/0	0/4	28/0	

Key to figures: **23**/0 indicates a radial count of 23 and an ulnar count of 0 ridges; **18**/3 indicates a radial count of 18 and an ulnar count of 3 ridges. The total count is the sum of the figures in heavy type. When both radial and ulnar counts are zero, 0/0, the pattern is an arch; when one count is zero the pattern is a loop, **23**/0 shows an ulnar loop, 0/**23** would show a radial loop; when neither count is zero, **18**/3, the pattern is a whorl. The larger number for each finger is used for the total count.

* I.A. is twin of M.A.

APPENDIX (4b)

Configuration of the dermal ridges on palms

	a-b ridge count			Maximal *atd* angle		
Subject	Left	Right	Total	Left	Right	Total
M.A.	50	45	95	65°	60°	125°
I.A.	54	55	109	60°	49°	109°
A.S.	48	48	96	39°	44°	83°
L.A.	51	44	95	57°	50°	107°
B.J.	48	53	101	82°	67°	149°
Y.L.	40	38	78	44°	47°	91°

APPENDIX 5

Sex chromatin incidence per 100 *nuclei of buccal mucosa in different samples from the same smear*

		No. of Barr bodies			
Patient	Sample	0	1	2	Not classifiable
M.A.	I	41	53	.	6
	II	36	57	3	4
	I	33	61	.	6
A.S.	II	69	26	.	5
	III	92	4	.	4
L.A.	I	30	64	.	6
	II	37	59	.	4
	III	46	51	.	3
	IV	38	58	.	4
B.J.	I	42	53	.	5
	II	51	43	.	6
Y.L.	I	50	45	.	5
	II	56	40	.	4
	III	36	58	.	6

APPENDIX 6

Prevalence of drumsticks in the blood neutrophils on different occasions

Patient	Total drumsticks/neutrophils				Totals	Percentage of drumsticks
M.A.	91/161	22/500	26/310	30/500	87/1471	5·9
A.S.	26/300	25/500	—	—	51/800	6·4
L.A.	5/316	15/500	10/500	—	30/1316	2·3
B.J.	12/500	3/160	—	—	15/660	2·3
Y.L.	16/500	15/500	—	—	31/1000	3·1

APPENDIX 7

The result of chromosome counts

Key: BM = bone marrow; S = skin; B = blood; + = cytological preparations made with the acetic-orcein squash method; X_I = iso-chromosome.

Subject (pedigree no. and position)	Type of culture		Date of culture	Number of chromosomes					Sex chromosome
				$\leqslant 44$	45	46	$\geqslant 47$	Total	
Patient M.A.	BM+	I	18. iv. 59	7	6	36	3	52	X_I
(a. III, 6)	BM+	II	26. iv. 59	2	2	9	3	16	X_I
	BM	III	8. i. 60	.	.	13	.	13	X_I
	S		9. vi. 62	.	1	102	.	103	X_I
	B	I	5. i. 61	3	1	41	.	45	X_I
	B	II	30. iii. 61	.	.	47	.	47	X_I
	B	III	5. vi. 62	3	9	72	.	84	X_I
Mother	BM+		2. ii. 60	1	.	5	.	6	XX
(a. II, 2)	S+		2. ii. 60	1	.	7	.	8	XX
	B		26. ix. 61	.	1	55	.	56	XX
Father (a. II, 6)	B		31. i. 62	1	3	27	.	31	XY
Sister (a. III, 7)	B		31. i. 62	1	1	48	.	50	XX
Patient A.S.	BM+	I	3. vi. 60	6	8	38	4	56	XO/X_I
(b. III, 17)	BM+	II	19. xii. 60	.	1	18	.	19	X_I
	S+		3. vi. 60	1	2	25	3	31	X_I
	B	I	2. iv. 61	1	13	32	.	46	XO/X_I
	B	II	v. 62	4	33	24	.	61	
Mother (b. II, 6)	B		3. iv. 61	2	2	39	.	43	XX
Father (b. II, 15)	B		3. iv. 61	1	2	48	.	5	XY
Sister (b. III, 16)	B		3. iv. 61	3	2	35	.	40	XX
b. III, 13	BM+		30. xi. 60	.	2	30	.	32	XY
	B		26. v. 61	2	1	53	.	56	XY
b. II, 5	B		20. i. 61	2	1	42	.	45	XX
b. II, 16	B		26. v. 61	.	3	50	.	53	XY
Patient L.A.	BM+		vii. 60	5	1	27	.	33	X_I
(c. III, 4)	S		10. v. 62	5	27	59	.	91	XO/X_I
	B		13. v. 62	5	41	54	.	100	XO/X_I
Mother (c. II, 4)	B		13. v. 61	2	5	89	.	96	XX
Father (c. II, 14)	B		13. v. 61	1	1	50	.	52	XY
Brother (c. III, 2)	B		13. v. 61	1	2	51	.	54	XY
Brother (c. III, 3)	B		13. v. 61	3	1	27	.	31	XY
Patient B.J. (d)	S	I	28. i. 61	7	3	38	.	48	X_I
	S	II	26. v. 62	7	31	28	.	66	XO/X_I
	B		20. i. 62	3	26	71	.	100	XO/X_I
Patient Y.L. (e)	B	I	27. ii. 61	.	.	48	.	48	X_I
	B	II	8. i. 62	2	.	38	.	40	X_I
	B	III	29. vi. 62	.	1	49	.	50	X_I
	S		30. x. 62	9	6	86	.	101	X_I

APPENDIX 8

Relative length (first column) and arm ratio (second column) of the individual chromosomes of selected cells from the five patients. Chromosomes marked (X) are presumptive X's and those marked (× ×) presumptive no. 6. Key: BM = bone marrow cells not treated with colchicine; B = blood cells treated with colchicine.

Patient M.A.

Chromosome no.	BM 1		BM 2		BM 3		B 1		B 2	
1	4·26	1·08	4·62	1·13	3·92	1·02	4·73	1·02	4·45	1·01
	4·16	1·04	4·28	1·01	4·62	1·04	3·74	1·05	3·94	1·11
2	3·84	1·70	4·23	1·61	4·17	1·76	3·92	1·64	3·78	1·76
	4·12	1·65	3·78	1·35	4·46	1·45	3·59	1·60	3·58	1·55
3 or iso-chromosome	3·56	1·03	3·29	1·06	3·19	1·04	3·25	1·07	3·41	1·16
	3·21	1·20	3·46	1·14	3·59	1·13	3·18	1·14	3·34	1·04
	3·20	1·07	3·06	1·06	3·08	1·02	3·97	1·00	3·23	1·04
4 or 5	2·91	3·12	3·25	2·40	3·30	2·58	3·08	2·02	3·25	2·78
	3·09	3·16	2·98	2·50	3·07	2·73	2·92	2·40	3·20	2·71
	2·88	2·49	3·03	2·61	2·80	2·36	2·85	2·53	2·85	2·38
	2·91	2·46	3·07	2·94	2·93	2·48	2·67	2·52	2·76	2·61
× ×	2·85	1·85	2·67	1·79	2·73	1·75	2·74	1·52	2·92	1·55
× ×	2·73	1·95	2·59	1·70	2·79	1·78	2·72	1·58	2·88	1·60
X	2·25	1·98	2·54	1·39	2·78	1·72	2·70	1·60	2·46	1·59
7–12	2·75	1·66	2·62	1·67	2·48	1·60	2·57	1·60	2·37	2·38
	2·72	1·67	2·62	1·61	2·42	1·59	2·57	1·48	2·30	2·36
	2·51	1·61	2·41	2·09	2·26	3·17	2·45	1·66	2·28	2·25
	2·38	1·66	2·29	2·23	2·36	2·56	2·36	1·51	2·28	2·25
	2·21	2·14	2·22	2·19	2·30	1·19	2·42	2·00	2·34	1·89
	2·24	2·17	2·21	2·28	2·29	1·75	2·29	2·02	2·27	1·93
	2·26	2·70	2·14	2·02	2·15	2·06	2·28	2·37	2·32	1·44
	2·18	2·51	2·27	1·82	2·23	2·13	2·24	2·16	2·27	1·46
	2·13	1·54	2·16	2·58	2·07	2·32	2·28	1·88	2·27	1·80
	2·30	1·63	2·23	2·94	2·09	2·20	2·09	1·54	2·21	1·90
	2·08	2·05	2·14	1·51	2·13	1·55	1·10	2·56	2·18	1·53
	2·29	2·08	2·07	1·54	2·00	1·58	1·96	2·13	2·13	1·33
13, 14 or 15	1·75	4·33	1·63	4·52	1·68	5·68	1·81	5·11	1·88	4·63
	1·55	4·52	1·74	5·13	1·79	7·90	1·76	5·29	1·77	5·73
	1·63	5·70	1·63	5·27	1·54	5·38	1·72	4·20	1·70	5·06
	1·65	5·48	1·54	6·22	1·60	5·12	1·68	5·38	1·63	4·81
	1·64	7·46	1·60	5·00	1·52	7·88	1·57	4·94	1·58	4·00
	1·63	6·09	1·56	4·87	1·54	7·50	1·50	6·00	1·56	5·85
16	1·48	1·54	1·58	1·63	1·57	1·44	1·65	1·70	1·63	1·38
	1·58	1·55	1·49	1·57	1·56	.	1·55	1·24	1·34	1·24
17	1·62	1·71	1·48	1·98	1·40	2·11	1·73	1·76	1·55	1·93
	1·80	.	1·56	2·07	1·44	2·00	1·43	1·81	1·42	1·76
18	1·25	2·22	1·26	2·45	1·26	3·67	1·32	1·96	1·35	2·08
	1·25	2·81	1·36	2·11	1·24	2·65	1·25	1·92	1·35	2·08
19 or 20	1·11	1·17	1·13	1·18	1·18	1·03	1·39	1·15	1·28	1·15
	1·19	1·33	1·04	1·32	1·14	1·19	1·27	1·20	1·28	1·15
	1·02	1·15	1·11	1·00	1·12	1·43	1·25	1·11	1·20	1·27
	1·12	1·09	0·93	1·15	1·04	1·42	1·14	1·16	1·05	1·40
21 or 22	0·91	2·75	0·85	3·24	0·84	3·20	0·96	2·22	0·83	2·62
	0·92	2·62	0·85	3·00	0·83	2·76	0·84	2·25	0·81	3·18
	0·78	2·73	0·67	2·35	0·70	3·38	0·81	2·60	0·81	2·54
	0·68	2·05	0·72	2·81	0·82	3·32	0·78	2·62	0·79	3·09

APPENDIX 8 (cont.)

Chromosome no.	Patient L.A. B1		B2		B3		Patient B.J. B1		B2	
1	4·03	1·05	4·17	1·06	4·49	1·13	4·37	1·10	4·25	1·03
	3·97	1·07	3·67	1·05	3·64	1·06	4·31	1·00	4·20	1·10
2	4·04	1·65	3·70	1·43	4·37	1·66	4·59	1·66	4·27	1·65
	3·88	1·61	3·61	1·52	4·13	1·35	4·01	1·52	4·11	1·55
3 or iso-chromosome	3·33	1·09	3·17	1·15	3·12	1·10	3·47	1·06	3·40	1·03
	3·27	1·12	3·10	1·10	3·11	1·05	2·98	1·04	3·09	1·13
	3·09	1·00	2·79	1·08	3·06	1·25	2·92	1·06	2·91	1·08
4 or 5	3·05	2·51	3·17	3·02	3·23	2·51	3·17	2·58	3·12	2·73
	2·99	3·02	3·05	2·53	3·09	2·46	3·01	2·58	2·98	2·63
	2·94	2·47	2·85	2·67	2·85	2·47	2·94	2·69	2·74	2·15
	2·88	2·41	2·82	2·26	2·79	2·52	2·80	2·65	2·71	2·50
× ×	2·91	1·65	2·82	1·66	2·68	1·74	2·74	1·70	2·87	1·62
× ×	2·80	1·63	2·74	1·79	2·62	1·61	2·70	1·73	2·67	1·59
X	2·51	1·52	2·50	1·55	2·48	1·50	2·70	1·73	2·87	1·54
7–12	2·43	1·79	2·64	1·64	2·54	1·52	2·40	1·76	2·53	1·96
	2·40	1·80	2·49	2·57	2·51	1·68	2·36	1·67	2·40	2·10
	2·44	2·18	2·40	2·10	2·40	1·86	2·35	1·74	2·40	1·57
	2·29	2·39	2·37	2·06	2·30	2·18	2·33	1·39	2·37	1·58
	2·37	1·84	2·19	2·27	2·24	2·16	2·35	2·31	2·34	1·79
	2·36	1·75	2·22	1·44	2·17	2·12	2·26	2·06	2·27	1·66
	2·28	2·32	2·21	1·47	2·16	2·10	2·29	1·92	2·21	1·98
	2·07	2·07	2·21	1·96	2·17	1·89	2·17	2·13	2·09	2·17
	2·25	1·81	2·18	2·17	2·16	1·53	2·23	2·60	2·11	1·85
	2·07	1·97	2·16	1·84	2·10	2·29	2·20	2·47	1·10	1·88
	2·17	1·35	2·13	1·86	2·01	2·04	2·05	1·53	2·03	2·15
	2·04	1·14	2·64	1·53	2·52	1·54	1·99	1·55	2·01	2·13
13, 14 or 15	1·92	4·60	1·76	5·94	1·80	5·05	1·74	4·90	1·88	6·80
	1·78	4·57	1·71	7·24	1·70	5·00	1·73	6·31	1·85	5·05
	1·76	6·70	1·65	5·53	1·69	5·61	1·61	6·27	1·75	6·79
	1·67	6·30	1·62	4·45	1·54	5·81	1·59	8·00	1·66	5·06
	1·65	6·20	1·58	6·57	1·50	4·89	1·56	7·83	1·61	4·56
	1·52	6·39	1·56	4·25	1·43	4·94	1·48	4·82	1·58	5·53
16	1·64	1·92	1·64	1·29	1·70	1·50	1·53	1·64	1·69	1·56
	1·53	1·48	1·55	1·60	1·50	1·52	1·52	1·36	1·42	1·32
17	1·44	2·28	1·59	1·68	1·59	2·00	1·61	2·11	1·43	1·70
	1·43	2·13	1·56	2·09	1·45	1·83	1·52	2·32	1·27	2·16
18	1·44	2·32	1·43	2·43	1·38	2·03	1·37	2·32	1·42	3·00
	1·24	2·60	1·40	2·03	1·23	2·03	1·17	2·11	1·26	2·39
19 or 20	1·32	1·24	1·42	1·21	1·30	1·24	1·25	1·13	1·26	1·29
	1·12	1·21	1·36	1·07	1·22	1·15	1·22	1·24	1·22	1·00
	1·18	1·34	1·33	1·07	1·22	1·35	1·12	1·45	1·10	1·27
	1·10	1·18	1·25	1·33	1·16	1·28	1·06	1·06	1·05	1·17
21 or 22	0·94	3·10	0·98	2·30	0·99	1·92	0·91	2·88	0·10	2·44
	0·92	2·64	0·98	2·88	0·88	3·43	0·86	3·14	0·97	3·00
	0·80	2·33	0·83	2·73	0·85	3·29	0·75	2·99	0·93	2·22
	0·73	3·00	0·82	3·23	0·84	3·21	0·74	2·57	0·74	2·54

APPENDIX 8 (cont.)

Patient A.S.

Chromosome no.	BM1		BM2		BM3		BM4		BM5	
1	4·24	1·13	4·05	1·09	3·77	1·12	3·93	1·03	3·97	1·13
	3·81	1·10	4·68	1·23	4·30	1·18	5·08	1·09	3·94	1·03
2	3·88	1·58	3·80	1·59	3·73	1·36	3·94	1·78	3·52	1·39
	3·55	1·57	3·89	1·44	3·77	1·28	3·46	1·65	3·91	1·46
3 or iso-chromosome	3·60	1·04	3·44	1·15	3·32	1·06	3·05	1·03	3·37	1·10
	2·96	1·19	3·37	1·10	3·10	1·06	3·30	1·01	3·43	1·06
	3·04	1·02	3·37	1·02	2·74	1·04	2·92	1·15	2·98	1·25
4 or 5	2·76	2·72	3·17	3·98	3·08	2·25	3·08	2·78	3·01	2·54
	2·91	2·45	3·15	2·68	3·10	1·84	2·97	3·23	2·98	2·43
	2·96	2·14	2·95	2·55	3·14	2·43	2·87	2·27	2·99	2·59
	2·61	2·19	3·02	2·51	2·87	2·48	2·97	2·38	2·75	2·73
× ×	2·86	1·49	2·95	1·72	2·67	1·37	2·71	1·74	2·89	1·72
× ×	2·96	1·64	2·85	1·72	2·74	1·55	2·65	1·72	2·72	1·72
X	2·12	2·32	1·84	1·25	2·26	1·74	2·52	2·10	2·08	1·35
7–12	2·58	1·81	2·49	1·63	2·46	1·58	2·65	1·68	2·45	1·50
	2·66	1·81	2·60	1·64	2·46	1·49	2·59	1·70	2·63	1·48
	2·45	1·53	2·40	1·97	2·22	2·18	2·44	1·55	2·47	1·70
	2·58	1·46	2·38	2·05	2·42	2·14	2·20	1·56	2·37	1·50
	2·50	2·16	2·44	1·57	2·24	1·55	2·25	1·88	2·29	1·80
	2·38	2·00	2·25	1·41	2·13	1·43	2·36	1·85	2·32	2·09
	2·15	1·71	2·17	2·07	2·17	2·36	2·25	2·06	2·27	1·67
	2·25	1·59	2·27	2·05	2·17	2·36	2·15	2·21	2·31	1·66
	2·27	1·87	2·13	2·02	2·17	1·88	2·19	1·51	2·22	2·09
	2·12	1·96	2·12	2·11	2·10	1·93	2·22	2·31	2·11	2·14
	2·20	1·46	2·01	2·98	2·21	3·56	2·01	1·74	2·01	2·73
	2·10	1·48	2·23	2·61	2·03	2·14	2·23	1·80	2·24	2·43
13, 14 or 15	1·76	4·75	1·68	4·12	2·46	1·58	1·76	5·11	1·91	5·16
	1·69	4·50	1·73	4·07	1·85	2·48	1·98	6·75	1·80	5·11
	1·69	5·00	1·65	6·28	1·76	3·45	1·79	3·67	1·75	3·28
	1·74	5·80	1·55	5·47	1·76	5·16	1·60	5·25	1·85	4·95
	1·76	4·31	1·60	6·94	1·67	3·65	1·50	4·22	1·65	6·21
	1·58	3·77	1·56	6·75	1·65	3·38	1·64	4·72	1·52	5·64
16	1·56	1·44	1·56	1·48	1·65	1·63	1·53	1·67	1·78	1·37
	1·56	1·54	1·55	1·51	1·85	1·19	1·63	1·62	1·67	1·49
17	1·64	1·78	1·41	2·29	1·52	1·83	1·45	1·76	1·52	1·66
	1·69	2·00	1·35	2·15	1·49	1·86	1·53	1·74	1·65	1·89
18	1·43	3·00	1·41	2·50	1·36	2·45	1·42	2·42	1·37	2·36
	1·30	2·92	1·27	2·74	1·24	2·63	1·28	2·81	1·24	2·80
19 or 20	1·18	1·09	1·11	1·05	1·15	1·16	1·10	1·09	1·10	1·31
	1·18	1·42	1·09	1·05	1·20	1·09	1·07	1·03	1·18	1·40
	1·00	1·05	1·02	1·25	1·15	1·37	1·04	1·32	1·11	1·00
	1·15	1·05	1·10	1·23	1·09	1·35	1·09	1·15	1·08	1·28
21 or 22	0·82	1·91	0·79	1·86	1·04	2·22	1·02	1·91	0·98	2·75
	1·00	2·00	0·91	2·27	1·06	1·19	0·85	2·12	1·00	2·59
	0·82	2·20	0·82	2·42	0·81	2·75	0·88	2·24	0·69	1·63
	0·84	2·30	0·79	2·94	0·90	2·13	0·85	1·94	0·90	2·44

APPENDIX 8 *(cont.)*

	Patient Y.L.					
Chromosome no.	B1		B2		B3	
1	3·99	1·09	4·04	1·02	4·33	1·02
	3·60	1·00	3·88	1·07	4·15	1·00
2	4·07	1·56	3·88	1·58	3·89	1·52
	4·05	1·49	3·71	1·54	3·71	1·49
3 or	3·36	1·09	3·10	1·06	3·13	1·03
iso-chromosome	3·20	1·03	2·96	1·03	3·07	1·04
	3·13	1·15	2·92	1·12	2·82	1·02
4 or 5	3·31	2·48	2·96	2·38	3·19	2·38
	3·18	2·46	2·94	2·36	3·19	2·43
	3·17	2·71	2·90	2·23	2·75	2·57
	2·77	2·45	2·79	2·35	2·72	2·52
× ×	2·84	1·70	2·75	1·36	2·45	1·74
× ×	2·77	1·82	2·72	1·38	2·70	1·45
X	2·64	1·78	2·69	1·48	2·61	1·51
7–12	2·41	1·45	2·50	1·50	2·73	2·11
	2·40	1·60	2·48	1·59	2·46	2·30
	2·44	1·65	2·60	2·13	2·40	2·46
	2·30	1·69	2·31	2·36	2·26	2·15
	2·36	2·20	2·29	2·06	2·30	1·98
	2·31	2·28	2·27	2·30	2·30	1·98
	2·15	1·98	2·27	1·66	2·36	1·24
	2·10	2·05	2·23	1·89	2·24	1·55
	2·15	1·91	2·23	1·97	2·40	1·77
	2·12	1·72	2·23	1·89	2·20	1·49
	2·17	1·69	2·21	1·72	2·28	1·95
	1·99	1·62	2·10	1·52	2·17	2·54
13, 14 or 15	1·79	4·95	1·71	5·83	1·89	4·92
	1·69	5·44	1·67	3·44	1·78	5·38
	1·64	4·88	1·63	6·09	1·72	8·21
	1·64	5·67	1·58	4·84	1·58	4·95
	1·51	4·75	1·58	4·43	1·48	5·94
	1·43	4·44	1·54	5·17	1·46	6·86
16	1·69	1·51	1·71	1·34	1·76	1·44
	1·67	1·31	1·58	1·24	1·44	1·57
17	1·44	2·03	1·52	1·96	1·57	2·11
	1·43	1·81	1·52	1·92	1·27	1·86
18	1·41	2·58	1·29	2·26	1·46	2·24
	1·39	2·54	1·29	2·30	1·26	2·52
19 or 20	1·23	1·27	1·44	1·03	1·37	1·15
	1·21	1·18	1·44	1·36	1·20	1·09
	1·18	1·25	1·33	1·13	1·10	1·13
	1·13	1·16	1·29	1·25	1·03	1·20
21 or 22	1·02	2·10	1·21	3·33	0·93	3·38
	0·90	2·67	0·96	2·83	0·85	3·00
	0·87	1·94	0·94	2·46	0·83	3·80
	0·76	2·83	0·88	3·20	0·73	4·50

APPENDIX 9

Description of the pedigrees (Fig. 1)

Index no.	Sex	Year of birth	Living or dead (age at death)	Parents	Notes
					Family M.A., (*a*)
I. 1	F	—	l	—	—
I. 2	M	—	d	—	—
I. 3	F	—	d	—	—
I. 4	F	—	d	—	—
I. 5	M	—	d	—	—
I. 6	F	—	—	—	Had children. Number and sex unknown
II. 1	F	—	l	—	—
II. 2	F	1901	d (61)	I. 1, 2	Menarche at 17 years. Short stature (149 cm.). Pubis to sole: 87 cm. Span: 150 cm. Died after long spell of paresis of the legs. No post-mortem. Normal female karyotype
II. 3	M	—	l	I. 2, 3	—
II. 4	M	—	l	I. 4, 5	—
II. 5	M	—	l	I. 4, 5	—
II. 6	M	1905	l	I. 4, 5	Normal male karyotype
II. 7	F	—	l	I. 4, 5	—
III. 1	F	—	l	II. 1, 3	—
III. 2	F	—	l	II. 1, 3	Had one child. Sex unknown
III. 3	M	—	l	II. 1, 3	—
III. 4	F	—	l	—	—
III. 5	M	1932	l	II. 2, 6	—
III. 6	F	1937	l	II. 2, 3	Proposita. Presumptive iso-chromosome
III. 7	F	1937	l	II. 2, 6	Dizygotic twin of III. 6. Menarche at 13 years. Birth weight 2300 g.
III. 8	M	—	l	II. 5	Married. No children. Average stature
III. 9	M	—	l	II. 5	Average stature
III. 10	F	1946	l	II. 7	Average stature
III. 11	F	1950	l	II. 7	Average stature
IV. 1	F	1953	l	III. 1	Twin
IV. 2	M	1933	l	III. 1	Twin
IV. 3	M	1958	l	III. 4, 5	—
IV. 4	M	1959	l	III. 4, 5	—
					Family A.S., (*b*)
I. 1	F	—	d (85)	—	—
I. 2	M	—	d (75)	—	—
I. 3, 4	F, M	—	d, d	—	—
II. 1	M	—	d (38)	I. 1, 2	Died of ileus
II. 2	F	—	l	I. 1, 2	—
II. 3	M	—	d (52)	I. 1, 2	—
II. 4	F	—	l	I. 1, 2	—
II. 5	F	1910	l	I. 1, 2	Normal karyotype
II. 6	F	1913	l	I. 1, 2	Menarche at 15 years. Normal karyotype
II. 7	M	—	d (67)	I. 3, 4	Died of cancer of the prostate
II. 8	M	—	l	I. 3, 4	Married. No children
II. 9	M	—	l	I. 3, 4	—
II. 10	F	—	l	I. 3, 4	—
II. 11	F	—	l	I. 3, 4	—
II. 12	F	—	l	I. 3, 4	Married. No children
II. 13	F	—	l	I. 3, 4	—
II. 14	M	—	l	I. 3, 4	—

APPENDIX 9 (cont.)

Index no.	Sex	Year of birth	Living or dead (year at death)	Parents	Notes
II. 15	M	1915	l	I. 3, 4	Normal karyotype
II. 16	M	. .	l	—	Normal karyotype
III. 1 to 7	—	. .	l	II. 1, II. 2	No direct information
III. 8	M	1943	l	II. 3	—
III. 9	M	1938	l	II. 4	—
III. 10	M	1942	l	II. 4	—
III. 11	F	1944	l	II. 4	—
III. 12	F	1936	l	II. 5, 16	—
III. 13	M	1942	l	II. 5, 16	Delayed puberty. Adrenal insufficiency. Testicular biopsy (1962): normal spermatogenesis. Normal karyotype. Normal palm prints
III. 14, 15	MM	1945	l	II. 5, 16	Twins
III. 16	F	1941	l	II. 6, 15	Menarche at 15 years. Normal karyotype
III. 17	F	1943	l	II. 6, 15	Proposita. Presumptive iso-chromosome
III. 18 to 28	—	—	l	—	No direct information. No major abnormalities reported

Family L.A., (c)

Index no.	Sex	Year of birth	Living or dead (year at death)	Parents	Notes
I. 1	F	—	d (76)	—	—
I. 2	M	—	d (55)	—	Died of heart attack
I. 3	F	—	d	—	—
I. 4	M	—	d	—	—
II. 1	F	—	l	I. 1, 2	—
II. 2, 3	M	—	l	I. 1, 2	Both married late. No children
II. 4	F*	1906	l	I. 1, 2	Menarche at 15 years. Threatened abortion at 5th month when pregnant with proposita
II. 5	F	—	l	I. 1, 2	—
II. 6	F	—	l	I. 3, 4	—
II. 7	M	—	d	I. 3, 4	Died young, accidentally
II. 8	M	—	l	I. 3, 4	—
II. 9	M	—	l	I. 3, 4	Married late. No children
II. 10, 11	F	—	l	I. 3, 4	—
II. 12	M	1891	l	I. 3, 4	Normal karyotype
II. 13	F	—	d (7 d)	I. 3, 4	Twin of II. 12. Died at age of 1 week
III. 1	M	—	l	II. 1	—
III. 2	M	1937	l	II. 4, 12	Healthy. Normal karyotype
III. 3	M	—	l	II. 4, 14	Healthy. Normal karyotype
III. 4	F	1942	l	II. 4, 14	Proposita
III. 5	M	—	l	II. 5	Reported normal
III. 6	F	—	l	II. 5	Reported normal
III. 7, 8	M	—	l	II. 6	Reported normal
III. 9	F	—	l	II. 6	Reported normal
III. 10	M	—	l	II. 8	Reported normal
III. 11	F	—	l	II. 8	Reported normal

Family B.J., (d)

Index no.	Sex	Year of birth	Living or dead (year at death)	Parents	Notes
I. 1	F	—	d (68)	—	Died of heart attack
I. 2	M	—	d (68)	—	Reported to be red-green colour blind. Accidental death
I. 3	F	—	d (35)	—	Died of pneumonia
I. 4	M	—	l	—	Normal colour vision (Ishihara)
II. 1	F	1917	l	I. 1, 2	Menarche at 15 years. Healthy. Normal colour vision (Ishihara and anomaloscope). Sex chromatin positive

APPENDIX 9 *(cont.)*

Index no.	Sex	Year of birth	Living or dead (age at death)	Parents	Notes
II. 2	M	1919	l	I. 1, 2	Married, no children. Normal colour vision (Ishihara)
II. 3	M	1923	l	I. 1, 2	Normal colour vision (Ishihara)
II. 4	M	1910	l	I. 3, 4	Normal colour vision (Ishihara and anomaloscope). Healthy. Sex chromatin negative
II. 5	M	1915	l	I. 3, 4	Reported to have normal colour vision
II. 6	M	1918	l	I. 3, 4	Reported to have normal colour vision
II. 7	M	1920	l	I. 3, 4	Reported to have normal colour vision
II. 8	F	—	d (22)	I. 3, 4	Died of brain tumour
III. 1	M	1941	l	II. 1, 4	Colour vision abnormal: deuteranope (Ishihara and anomaloscope)
III. 2	F	1943	l	II. 1, 4	Proposita. Colour vision abnormal: deuteranope. Presumptive iso-chromosome
III. 3	—	—	—	II. 1, 4	Miscarriage 3rd month
III. 4	F	1948	l	II. 1, 4	No menarche yet. Normal colour vision (Ishihara and anomaloscope)
III. 5	M	1950	l	II. 1, 4	Colour vision abnormal: deuteranope (Ishihara and anomaloscope)
III. 6	M	1955	l	II. 1, 4	Normal colour vision (Ishihara and anomaloscope)
III. 7, 8	MM	—	dd	II. 1, 4	Twins. Both died at delivery. No external malformation
III. 9	M	1954	l	II. 3	Normal colour vision (Ishihara)
III. 10	F	1946	l	II. 5	Reported normal colour vision
III. 11	F	1950	l	II. 5	Reported normal colour vision
III. 12	F	1951	l	II. 6	Reported normal colour vision
III. 13	M	1957	l	II. 6	Reported normal colour vision
III. 14, 15	FF	1959	ll	II. 6	Twins
III. 16	F	1953	l	II. 7	Reported normal colour vision
III. 17	F	1955	l	II. 7	Reported normal colour vision

Family Y.L., *(e)*

Index no.	Sex	Year of birth	Living or dead (age at death)	Parents	Notes
I. 1	F	1893	l	—	—
I. 2	M	1890	d (67)	—	—
II. 1	M	1913	l	I. 1, 2	—
II. 2	M	1915	l	I. 1, 2	Dizygotic twin of II. 3
II. 3	M	1915	l	I. 1, 2	Dizygotic twin of II. 2
II. 4	F	1918	l	I. 1, 2	—
II. 5	M	1921	l	I. 1, 2	—
II. 6	M	1916	i	—	Sex chromatin negative
II. 7	F	1923	l	I. 1, 2	Menarche at 12 years. Sex chromatin positive
III. 1	M	1944	l	II. 6, 7	Healthy
III. 2	F	1946	l	II. 6, 7	Proposita. Presumptive iso-chromosome
III. 3	M	1950	l	II. 6, 7	Healthy
III. 4	M	1953	l	II, 6, 7	Healthy