Human genetics : prepared by the Standing Medical Advisory Committee.

Human Genetics

Prepared by
The Standing Medical Advisory Committee for
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the Secretary of State for Social Services,
the Secretary of State for Scotland
and the
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DEFINITIONS

Chromosomes —chromophilic bodies within the cell nucleus, visible as homologous pairs in dividing cells. (They consist of a double chain of DNA on a framework of protein.)

Sex-chromosomes—the pair of chromosomes responsible for sex determination (XX in women, XY in men).

Autosomes —chromosomes other than the sex chromosomes.

Gene —the unit of inheritance, occupying a specific site (locus) on a chromosome (it consists of a short segment of DNA coded for the synthesis of a particular polypeptide).

Alleles —alternative forms of a gene which may occupy the same site on homologous chromosomes (only two may be present in any one individual).

Homozygous —having the same allele at a gene locus on each of a pair on homologous chromosomes.

Heterozygous —having different alleles at a gene locus on each of a pair of homologous chromosomes.

Dominant trait —one which is determined by the presence of a gene in heterozygous form.

Recessive trait —one which is determined by the presence of a gene in homozygous form.

Sex-linked trait —one determined by the presence of a gene on the sex chromosomes. In practice such traits are X-linked since none is yet known to be certainly Y-linked.

Trisomy —the presence of one chromosome additional to the normal homologous pair.

Translocation —the transfer of a segment of a chromosome to a site on a different chromosome.

Mosaicism —the presence of more than one cell type in a single individual (for example, an individual may be a mosaic of normal and trisomy 21 cells).

M luced change in a gene or

HUMAN GENETICS

Introduction

1. The memorandum is concerned with the medical implications of human genetics and in particular the role of genetic counselling. It is presented in a simplified form and gives the bare outline of the subject only. The main types of inheritance: dominant, recessive, sex linked (X-linked) are explained. Conditions due to chromosomal abnormalities and those with partial and complex inheritance are discussed. It is intended to alert doctors to the problem of genetic disease in the community and to the number of persons who would find genetic counselling of benefit.

Recent Trends

2. A consequence of the successful control of diseases due to exogenous factors is the increasing relative importance of genetically determined diseases and congenital abnormalities among the remaining causes of death and disease. In 1900 the infant mortality rate was 154 per 1,000 in England and Wales; in 1970 it was 18 per 1,000. In this period the deaths from congenital malformations have shown only a small reduction so that their relative importance is much greater today; whereas in 1900 congenital malformations accounted for 1 in 30 of infant deaths, they account for 1 in 5 today. Further a higher proportion of infants with genetically determined diseases and congenital disorders reach adult life. It is increasingly important that doctors should have a knowledge of medical genetics and should know how to obtain specialist advice. Appendix III of the memorandum gives information, current at the time of issue, about specialist advisory centres. The following paragraphs describe the more important features of medical genetics, and reference is made to some of the common diseases in which heredity plays a significant role.

Genetic Counselling

3. Genetic counselling consists essentially in giving as accurate information as possible to the extent that knowledge permits, on the risks of transmission of inherited or partly-inherited conditions. Family doctors are well placed to undertake simple genetic counselling with supporting specialist help. Routine premarital counselling is not practicable but advice could be given where there is a specific problem. Experience at genetic counselling clinics is that most enquiries come from parents who have had an abnormal and handicapped child and wish to know the risk of recurrence in a subsequent child. Relatives of persons who have had a mental illness, schizophrenia or other psychiatric disorder, often seek advice. Enquirers are often concerned about a high incidence of common disease such as cancer in close relatives. Many of those who come have groundless

fears and an important aspect of genetic counselling is to give reassurance, allay anxiety and dispel any feelings of guilt. Most serious simply inherited conditions are individually rare so that the family doctor is not likely to see many instances. The present trend towards practice in groups serving large populations may, however, afford the interested doctor a greater opportunity to concern himself with such disorders.

4. The formulation of genetic prognosis requires an accurate clinical diagnosis together with adequate information about the family history. The estimation of risk may be very simple or extremely difficult. Sometimes an exact diagnosis, as in phenylketonuria or cystic fibrosis, is all that is needed for a risk estimate. Difficulties arise in conditions which are partially genetic in which the aetiology is not fully understood. In such cases the risk estimates have to be empirical, based on published data, involving a large series of comparable families.

5. The various types of inheritance and their implications on the risk of recurrence are discussed in greater detail later; the main points in counselling may be summarized as follows:—

Dominant inheritance, if uncomplicated, raise few problems: there is a one-in-two chance that any child of an affected person will be similarly affected.

In recessive inheritance where a couple are known to be carriers because they have already had an affected child the risk is one-in-four that any future child will be similarly affected. Apart from cousin marriages the risk to the children of affected people or to children of their normal sibs is very small.

In sex-linked (X-linked) inheritance, the classical example of which is haemophilia, an affected man cannot transmit to a son. If a woman is heterozygous for an X-linked gene, ie carries the abnormal gene on one of her two X chromosomes, there is a one-in-two chance that her son will be affected or that her daughter will be a carrier. Advances in the detection of heterozygous carriers are improving the reliability of genetic counselling, especially with X-linked conditions.

The advances in human cytogenetics have enabled more accurate guidance to be given about diseases associated with abnormal chromosomes such as Down's Syndrome (Mongolism).

A list of some of the better known dominant, recessive and X-linked conditions is given in Appendix I.

Chromosomes and Genes

6. A human being originates in the union of two gametes, the ovum and the spermatozoon. The nucleus of the human cell contains 23 pairs of chromosomes, one of each pair being derived originally from each parent. As each cell divides, the resultant cells retain the same chromosomal

pattern. An exception to this occurs in the gametes, in which only one set of 23 chromosomes, one from each original pair of chromosomes, is represented (see figure 1). These will join to make up 23 pairs of chromosomes in the newly formed embryo. Each chromosome is divided into loci, which contain the particular gene substance that determines the inherited characteristics of the individual. One pair of chromosomes is associated with sex differences. A female has two X chromosomes and a male one X and one Y chromosome. The remaining 22 pairs are known as autosomes. The 46 chromosomes from a dividing cell (male) are illustrated inside the back cover. An individual's genetic constitution is called his genotype. Occasionally a gene alters, a process known as mutation, and the gene then retains the new characteristic in subsequent cell divisions. As a result of different mutations an individual gene may exist in the population in several different forms, known as alleles.

7. If an individual inherits from each parent the same allelic form of a particular gene he is said to be homozygous for that gene locus; if different alleles are present he is said to be heterozygous. When a particular allele gives rise to an obvious physical characteristic when present in the heterozygote it is said to be dominant, but if the particular characteristic only appears in the individual when he is homozygous for the gene it is said to be recessive.

Dominant Inheritance (see figure 2)

8. Dominant inheritance is due to genes whose effects manifest themselves in the heterozygote. The majority of dominant traits are sufficiently mild in their effects to be transmitted through several generations, but some are severe. Affected persons married to normals have, on the average, affected and normal offspring in equal proportions. The normal children of affected parents when they in turn marry normals have only normal offspring.

9. Simple dominant defects do not always extend backwards indefinitely through the generations; abnormal genes must arise by fresh mutation at some time or other. In dominant inheritance an affected child may thus be born to normal parents and the risk of their subsequent children being affected is extremely small. However, care must be taken in such a situation to distinguish truly dominant defects, for example, classical achondroplasia, from apparently similar defects which may result from other types of inheritance and may carry high risks of recurrence.

10. Patients with dominant conditions of less severity, or those with late onset, will usually have one affected parent. Huntington's Chorea is an example of a severe dominant defect of late onset often transmitted through many generations. It is characterised by disordered and involuntary muscular movements and progressive mental deterioration. The defect does not usually manifest itself until comparatively late in life after the

affected person may have had children. Half the children of the affected person will carry the gene and these in turn will have the opportunity of producing families before the disease becomes manifest.

11. Where a condition is not fully dominant in the sense that it is not always manifest in the heterozygote there may be skipping of generations, which causes problems for counselling.

Recessive Inheritance (see figure 3)

12. Autosomal recessive inheritance is due to genes whose effects manifest themselves clinically only in the homozygote. The affected person must receive the gene for the condition from both parents, for both members of the chromosome pair concerned must carry it and each parent has contributed one chromosome to that pair. Two persons may marry who are normal in appearance but each may be a heterozygous carrier of the gene, for example for albinism, so albinos may appear among their offspring. The number of heterozygotes in the population is very large compared with the number of affected persons, the homozygotes. Individual genes for harmful recessive traits are therefore relatively common; in aggregate there is probably not one of us who does not carry at least one such gene. Few people are unlucky enough to marry a person carrying the same harmful gene, but if they marry a close relative the risk is much increased. Where two carriers of the same gene do marry the proportion of normal to affected children among their offspring is 3 to 1.

13. Cystic fibrosis with a frequency of about 1 in 2,000 live births is the commonest serious recessive condition in this country. Phenylketonuria which has a recorded birth frequency of about 1 in 10,000 live births in this country, is, like many other inborn errors of metabolism, also a recessive condition. There is failure to metabolize phenylalanine, but modern treatment by means of a low phenylalanine diet may secure normal development. There are very many recessively inherited conditions but most of them are individually uncommon. The total of recessive disease is, however, substantial.

14. With modern treatments an increasing number of patients with recessive conditions such as cystic fibrosis and phenylketonuria are surviving into adult life. The risks of their children being affected are relatively low, for example about 1 in 40 for women with cystic fibrosis (male patients are sterile).

15. It is characteristic of recessive conditions that they show much variation in birth frequencies between different populations. In Britain sickle-cell anaemia is relatively common in the children of immigrants from the West Indies and West Africa, thalassaemia in the children of immigrants from Cyprus and Malta and Tay-Sach's disease in the Jewish children whose ancestors come from Poland and Lithuania. In contrast cystic fibrosis is a rare disease outside Europe.

Sex-linked (X-linked) Inheritance (see figure 4)

16. In addition to their function in determining sex the sex chromosomes, like other chromosomes, carry genes affecting the structure and function of the individual. Sex-linked inheritance of disease has so far proved always to have been X-linked. The genes carried on the X chromosomes, eg for Duchenne type of muscular dystrophy and haemophilia, are usually recessive. A woman with such a gene on one of her two X chromosomes will not manifest the trait, but if she transmits the gene her sons will be affected. The risk to the sons is 1 in 2 and there is also a risk of 1 in 2 of the daughters being carriers. Over a hundred X-linked conditions are known in man but the great majority are very rare.

17. The classical example of sex linkage is haemophilia, in which the male carries the gene in his one X chromosome. The underlying anomaly is a defect of blood thromboplastin formation due to the deficiency or inactivity of anti-haemophilic globulin. About one boy in 10,000 is born with the disease. In X-linked transmission an affected man cannot transmit to a son. Thus a haemophilic man who marries a normal woman has children all of whom are outwardly normal, but while his sons will all be truly normal his daughters will all be heterozygous and so can transmit to the next generation. In most cases of haemophilia the mother is a heterozygous carrier of the gene but in a proportion of cases the boy is affected as a result of a fresh mutation.

18. There are a few X-linked dominant conditions, an example is hypophosphataemic vitamin D resistant rickets. With this form of inheritance women who are heterozygous for the mutant gene are clinically affected, but usually less severely so than affected men.

Carrier Detection

19. Especially in the case of X-linked recessive disease it is important to know whether the mother of a single affected boy, with no other male relative affected, is a carrier and so at risk of producing further affected sons, or whether her affected son resulted from fresh mutation, when any risk to further sons is negligible. Similarly the sisters, aunts and nieces of affected males will want to know if they are carriers. Increasingly tests for the carrier state are becoming available. In Duchenne muscular dystrophy about 80 per cent of the carriers can be shown to have abnormal enzyme levels in their blood although they show little if any signs of clinical disease. Carrier detection is at present less important in autosomal recessive diseases except where, as in the case of cystic fibrosis in Britain, carriers are relatively common or where cousins with a family history of recessively inherited disease are contemplating marriage. No satisfactory test is yet available for carriers of the gene for cystic fibrosis, but reliable tests are available for a number of less common autosomal recessive disorders such as phenylketonuria and Tay-Sach's disease.

Chromosome Abnormalities

20. In the past decade there have been major advances in the field of human cytogenetics. In 1956 it was shown that the normal human chromosome number was 46 not 48 as had been thought for the preceding thirty years. The application of new techniques to stop cell division at a stage when the chromosomes are clearly visible in the cells of bone marrow, solid tissues and peripheral blood etc has paved the way for recent discoveries which have shown that abnormal chromosomal patterns are associated with specific clinical abnormalities. It is now known that about 1 per cent of all liveborn children and about a quarter of fetuses spontaneously aborted in the first trimester have chromosome abnormalities. As about 15 per cent of all known pregnancies are believed to end spontaneously in first trimester abortion it would seem that about 4 per cent of all zygotes which last long enough to be recognised have chromosome abnormalities.

21. Chromosome abnormalities may be divided into those where the abnormality is of number, usually an extra chromosome, and those of structure where one or more chromosome breaks have determined loss of, or rearrangement of, chromosomal material. The best known of the conditions associated with abnormal chromosome number is Down's Syndrome (Mongolism) which has an incidence of about 1 in 600 livebirths and is responsible for about a quarter of all severely mentally handicapped children of school age. The abnormality usually consists of an extra chromosome identical to the members of the normal pair number 21, so that they have three No 21 chromosomes (trisomy 21) and 47 chromosomes altogether. Here the frequency is closely related to advancing maternal age and the risk of recurrence is usually small, between 1 and 2 per cent. Occasional cases of Down's Syndrome (Mongolism) result from an extra chromosome 21 being attached to another chromosome (translocation). If one or other parent has the attached chromosome the risk of having a second affected child may be greatly increased. Before giving genetic counselling to parents who have had a child with Down's Syndrome (Mongolism) chromosome studies on the patient or parents are appropriate at least where the mother was less than 30 years old when the patient was born.

22. The examination of sex chromosomes has now an essential place in the investigation of primary amenorrhoea, male infertility and intersex states. (If there is doubt about the sex of a newborn infant specialist opinion should be sought immediately). Turner's Syndrome, characterised by undeveloped gonads, short stature, webbing of the neck with a low hairline, often cardiac and other anomalies, results from lack of one sex chromosome, ie there is only one X chromosome present giving a total of 45 chromosomes instead of the natural complement of 46. The incidence of the condition is about 1 in 4,000 female livebirths. These patients often present with amenorrhoea. Klinefelter's Syndrome, which has an incidence of 1 in 1,000 male livebirths, is characterised by underdeveloped testes and

relative absence of facial, axillary and pubic hair. The patients may also be mentally handicapped and show psychological disturbances. Affected individuals have two or more X chromosomes in addition to one Y chromosome. With both these syndromes the risk of recurrence in later children of the parents is small, and the patients themselves are usually sterile. Males with an extra Y chromosome are sometimes intellectually dull and are fertile but appear to have chromosomally normal children.

Possible Pitfalls in Genetic Counselling

23. In giving genetic advice, two by no means uncommon complications must be borne in mind. The first is that occasionally it is found that quite different genes may give rise to the same abnormality. The second, and somewhat similar complication is that sometimes environmental influences may produce effects indistinguishable from those of genes. Both complications are illustrated by retinitis pigmentosa. About 80 per cent of cases are due to recessive genes. Most of the remainder are non-genetic. A small proportion of instances are due to a sex-linked gene or genes, and an extremely small proportion to a dominant gene or genes. It will be realised that these possible complications add greatly to the difficulty of counselling.

Diseases with Partial and Complex Inheritance

24. There are many conditions whose aetiology is not properly understood but is probably multifactorial in the sense that it includes both genetic variation at many gene loci and as yet unknown environmental triggers. The common congenital malformations are examples. A few of these are due to known environmental factors, such as the Rubella virus or the drug Thalidomide. A few are due to single genes of large effect, for example cleft lip of the upper lip with mucous pits of the lower lip, and congenital dislocation of the hip in association with Larsen's Syndrome. Most instances, however, of common malformations, such as spina bifida cystica, cleft lip with or without cleft palate, infantile pyloric stenosis, congenital dislocation of the hip, are multifactorially determined. Brothers and sisters and offspring of most patients with such malformations are affected 30 to 50 times more often than the general population. There is a smaller but still significant increase in the risk to less close relatives, such as nephews and nieces and first cousins. The recurrence risks after a single affected child are, however, usually less than 1 in 20 and so there is no strong indication for family limitation.

A list of recurrence risks for some common conditions is given in Appendix II

25. A number of the common diseases both of childhood and of adult life also show family patterns which suggest that genetic factors are playing

some part in their causation, though it is difficult to disentangle the influence of common family environment. The excess frequency in close relatives is usually not great. Thus the incidence of duodenal ulcer in brothers of affected men is rather less than three times the general population frequency. From the point of view of the individual enquirer family histories of common diseases tend to be overvalued, both by doctors and patients, and what is needed is reassurance. The enquirer who is worried about an apparently high family concentration of this or that condition is more likely to suffer from quite different things and to die of quite a different disease. To give an example, patients are often worried by a high incidence in the family of deaths from cancer. Yet, with exceedingly rare exceptions, such as multiple polyposis of the colon and rectum, the incidence of cancers in close relatives of those affected is either very little raised, or there may be no evidence of any increase at all. Such patients can be assured that the apparent high concentration is a coincidence, and with so common a group of conditions will often happen purely by chance.

Mental Handicap and Mental Illness

26. Severe mental handicap is produced by a number of pathological conditions of varied aetiology, often not specifically known, affecting the brain during intra-uterine life or in infancy. Some of those known or understood are specific genetic syndromes with appropriate risks of recurrence, for example Down's Syndrome mentioned in paragraph 21 and phenylketonuria mentioned in paragraph 13. Where two parents have had a child with severe mental handicap, the cause of which cannot be found, the risk of recurrence is not high and is of the order of 3 to 5 per cent.

27. Mental illness is common. For schizophrenia the best estimate of incidence which can be obtained is about 0.8 per cent, i.e. nearly 1 person in a hundred may be expected to develop the condition at some stage in his or her life, both sexes being equally affected. In manic-depressive psychosis the incidence is somewhat similar though females predominate. Although heredity is recognised as an important aetiological factor in both these disorders, the mode of transmission remains uncertain. For both disorders both polygenic inheritance and single gene inheritance (with reduced and variable penetrance), have been postulated. The distinction is not easily made with conditions which have an incidence of nearly 1 per cent in the population. In both illnesses the expectation of occurrence is increased in relatives in proportion to the degree of their relationship to a proband and usually for the same type of mental illness. In both schizophrenic and manic depressive psychosis the risk of brothers, sisters or children developing these complaints is about 10 times greater than in the general population. With neuroses and personality disorders the part played by genetic factors is even more obscure. While it is almost certain that some form of hereditary predisposition is important, it seems at

present to be impossible to disentangle the influence of environmental factors from heredity.

Epilepsy

28. The risk of epilepsy appearing in children varies according to the cause of the epilepsy in the prospective parent. Where no specific cause of the epilepsy is recognised the overall risk to children of affected persons is about 1 in 30 or about three times the risk in the general population.

Consanguineous Marriages

29. Consanguinity is of chief importance in relation to recessive inheritance. As already mentioned, we all carry a number of genes for harmful recessive conditions. Where parents are related the chance of a child being homozygous for some such gene is increased in proportion to the closeness of the parental relationship. However, even with first cousin marriages, provided that there are no relatives who have suffered from recessive traits, the overall risk of a child having a serious condition, not necessarily of recessive inheritance, is only about doubled relative to the risk to the offspring of unrelated spouses. If there are doubts as to whether a disease of recessive inheritance which has occurred in anyone in the family, and particularly in the child of a cousin marriage, is recessive, specialist advice should be sought.

Pre-natal Diagnosis

30. In a few instances where the fetus is genetically at risk it is now possible to determine accurately whether the fetus is affected or not. The method involves obtaining a specimen of the amniotic fluid by suprapubic aspiration at about the 15th week of pregnancy and then culturing the cells for chromosome examination or examining the cells or fluid for specific enzyme deficiencies. The technique is only at an early stage of development, but in the hands of those with experience and the appropriate facilities the risks to mother and fetus are minimal. The method is reliable for the diagnosis of chromosome anomalies and, in laboratories with adequate experience, for a small but increasing number of inborn errors of metabolism. The procedure is at present appropriate where there is a known high risk of a detectable abnormality, for example where the mother carries a chromosome translocation giving a high risk of Down's Syndrome (Mongolism) in the child, or the parents have had one child with Tay-Sach's disease where there is a 1 in 4 risk of recurrence. The procedure should not be carried out unless the parents are agreed that they would like the pregnancy to be terminated if the fetus is found to be abnormal. Pilot surveys are now being carried out to see if the test is appropriate for moderate risk situations, for example in pregnancies where the mothers

are over 40 years of age and have about 1 in 50 chance of major chromosome anomaly in the fetus. It is also possible to sex reliably a fetus from the amniotic cells and this may have practical application where the mother is a carrier for a serious X-linked recessive condition and there is a 1 in 2 risk of a son being affected but no risk to a daughter.

A Few Examples of Dominant Conditions

Achondroplasia
Dystrophia myotonica
Ehlers-Danlos Syndrome (skin elastic and fragile, joints hypermobile)
Huntington's Chorea
Marfan's Syndrome (arachnodactyly, ectopia lentis)
Multiple exostoses
Multiple Neurofibromatosis
Multiple polyposis of colon
Multiple telangiectasia
Myotonia congenita
Osteogensis imperfecta
Peutz's Syndrome (multiple polyposis of intestine, circumoral melanin spots)
Tuberous sclerosis

A Few Examples of Recessive Conditions

Amaurotic family idiocy
Congenital adrenal hyperplasia—all types
Congenital microcytosis (thalassaemia)
Cystic fibrosis of the pancreas
Epidermolysis bullosa dystrophica—severe form
Galactosaemia
Glycogen storage disease—all types
Infantile progressive muscular atrophy (Werdnig-Hoffmann)
Juvenile progressive muscular atrophy (Kugelberg-Welander)
Metachromatic leucodystrophy
Morquio's Disease (mucopolysaccharidosis type IV)
Phenylketonuria
Sickle cell anaemia

A Few Examples of X-Linked Conditions

Christmas Disease (factor IX deficiency)
Duchenne muscular dystrophy (severe X-linked muscular dystrophy in boys)
Glucose-6-phosphate dehydrogenase deficiency
Haemophilia
Nephrogenic diabetes insipidus

A Few Examples of Conditions which may have more than one type of genetic determination

Congenital deafness —most types recessive, but X-linked and dominant occur.

Gargoylism —Hurler type is recessive, Hunter type is X-linked

Muscular dystrophy —severe Duchenne type is X-linked, rather milder limb-girdle form recessive, facio-scapulo-humeral form dominant.

Retinitis pigmentosa—dominant, recessive and X-linked forms occur.

A Few Examples of Common Conditions with Partial and Complex Inheritance

Congenital pyloric stenosis
Spina bifida cystica
Anencephaly
Hare lip with or without cleft palate
Congenital dislocation of the hip
Congenital heart malformations
Diabetes
Schizophrenia
Manic depressive psychosis
Ankylosing spondylitis

Some Approximate Empirical Recurrence Risks for Common Conditions

Infantile Pyloric Stenosis—1 in 20 risk for brothers or sons and 1 in 40 risk for sisters or daughters of affected males.
1 in 5 risk for brothers or sons and 1 in 10 risk for sisters or daughters of affected females.

Spina Bifida Cystica; Anencephaly—1 in 20 risk for sibs of affected persons.

Cleft Lip (±Cleft Palate)—1 in 30 risk for sibs or sons and daughters of affected persons.

Congenital Dislocation of the Hip (neonatal diagnosis)—1 in 40 risk for brothers and sons, and 1 in 10 for sisters and daughters of affected females. There is a somewhat higher risk for relatives of affected males.

Talipes Equinovarus—1 in 50 risk for sibs of affected persons.

Down's Syndrome—In regular trisomy 21 about 1 in 100 risk for sibs of affected persons independent of maternal age. The risk may be higher if a translocation is present.

Congenital Malformation of Heart—About 1 in 30 risk, in all types of heart malformation taken together, for sibs of affected persons. Subdivision of risk according to type of malformation will be possible as more information from family studies becomes available.

Hirchsprung's Disease—Short segment—1 in 20 risk for brothers, and 1 in 100 risk for sisters of affected persons.

—long segment—1 in 10 risk for sibs of affected persons.

Diabetes—Onset under 30 Years—1 in 20 risk of early onset diabetes for sibs of affected persons.

With multifactorially determined conditions the recurrence risk is raised if there is already more than one affected person in the family. For example: if parents have already had two children with spina bifida cystica or anencephaly the recurrence risk rises to about 1 in 8; where a parent affected with cleft lip (± cleft palate) has already had one affected child the risk for further children rises to about 1 in 10.

APPENDIX III

Genetic Advisory Centres

Hospital Areas

NEWCASTLE

Regional Genetics Advisory Service
Laboratory of Human Genetics
University Department of Child Health
19 Claremont Place
Newcastle-upon-Tyne NE2 4AA

Genetic Clinic
The Children's Hospital
Durham Road
Stockton-on-Tees
Co Durham TS19 0EA

LEEDS

Genetic Clinic
The General Infirmary of Leeds
Great George Street
Leeds LS1 3EX

SHEFFIELD

Centre for Human Genetics
(Sub-Department of Medical Genetics)
Langhill
117 Manchester Road
Sheffield S10 5DN

METROPOLITAN

North West

Galton Laboratory
Department of Human Genetics
University College, London
Wolfson House
4 Stephenson Way
London NW1 2HE

Genetic Clinic Paediatric Department
University College Hospital
Huntley Street
London WC1E 6AU

Genetic Clinic for Skin Disorders
The Institute of Dermatology
St John's Hospital for Diseases of the Skin
Lisle Street
Leicester Square
London WC2H 7BJ

	Institute of Child Health The Hospital for Sick Children Great Ormond Street London WC1N 3JH
	Kennedy Galton Unit (Research Centre) Harperbury Hospital Harper Lane Shenley Radlett Herts WD7 9HQ
North East	Examination Centre Royal Eastern Counties Hospital Turner Road Mile End Colchester CO3 38T
	Genetic Clinic Moorfields Eye Hospital City Road London EC1V 2PD
South East	Paediatric Research Unit Guy's Hospital London SE1 9RT
	The Maudsley Hospital Denmark Hill London SE5 8AZ
South West	Queen Mary's Hospital for Children Queen's Drive Beeches Carshalton Surrey*
Wessex	Genetic Counselling Centre Children's Hospital 154 Winchester Road Shirley Southampton SO9 4WR
Oxford	Population Genetics Research Unit Old Road Headington Oxford OX3 7LF

SOUTH WESTERN	Department of Child Health Bristol Royal Hospital for Sick Children St Michael's Hill Bristol BS2 8BJ Paediatric Research Unit Royal Devon and Exeter Hospital Gladstone Road Exeter EX1 2ED
BIRMINGHAM	Infant Development Unit Birmingham Maternity Hospital Edgbaston Birmingham B15 2TG Quarterly clinics at:— Central Out-patients Department North Staffordshire Hospital Centre Hartshill Road Stoke-on-Trent Staffs ST4 7PA Royal Salop Infirmary Shrewsbury Salop SY1 1DY Warwick Hospital Lakin Road Warwick* Worcester Royal Infirmary (Castle Street Branch) Castle Street Worcester WR1 3AS Referral through Paediatric Department of these hospitals
MANCHESTER	Department of Medical Genetics Manchester Royal Infirmary Oxford Road Manchester M13 9WL Medical Genetics Clinic County Medical Officer Health Department Pepper House Pepper Row Chester WD1 8SB

	Royal Manchester Children's Hospital Pendlebury Manchester M27 1HA
LIVERPOOL	Genetic Counselling Clinic Department of Child Health Alder Hey Children's Hospital Liverpool L12 2AP
	The Endocrine Clinic David Lewis Northern Hospital Leeds Street Liverpool L3 6AU
WALES	The Department of Child Health University Hospital of Wales Heath Park Cardiff CF4 4XN
SCOTLAND	
Northern	Paediatric Unit Raigmore Hospital Inverness*
Northern Eastern	Department of Human Genetics University Medical Buildings Foresterhill Aberdeen AB9 2ZD
Eastern	Dr V Marrian c/o Appointments Office Dundee Royal Infirmary Dundee DD1 9ND
South Eastern	Medical Genetics Clinic University Department of Human Genetics Western General Hospital Crewe Road Edinburgh EH4 2XU
Western	Department of Medical Genetics Royal Hospital for Sick Children Yorkhill, Glasgow G3 8SJ
NORTHERN IRELAND	Human Genetics Unit Department of Medical Statistics Institute of Clinical Science Grosvenor Road Belfast 12

*Postal Codes not yet allocated by the Post Office

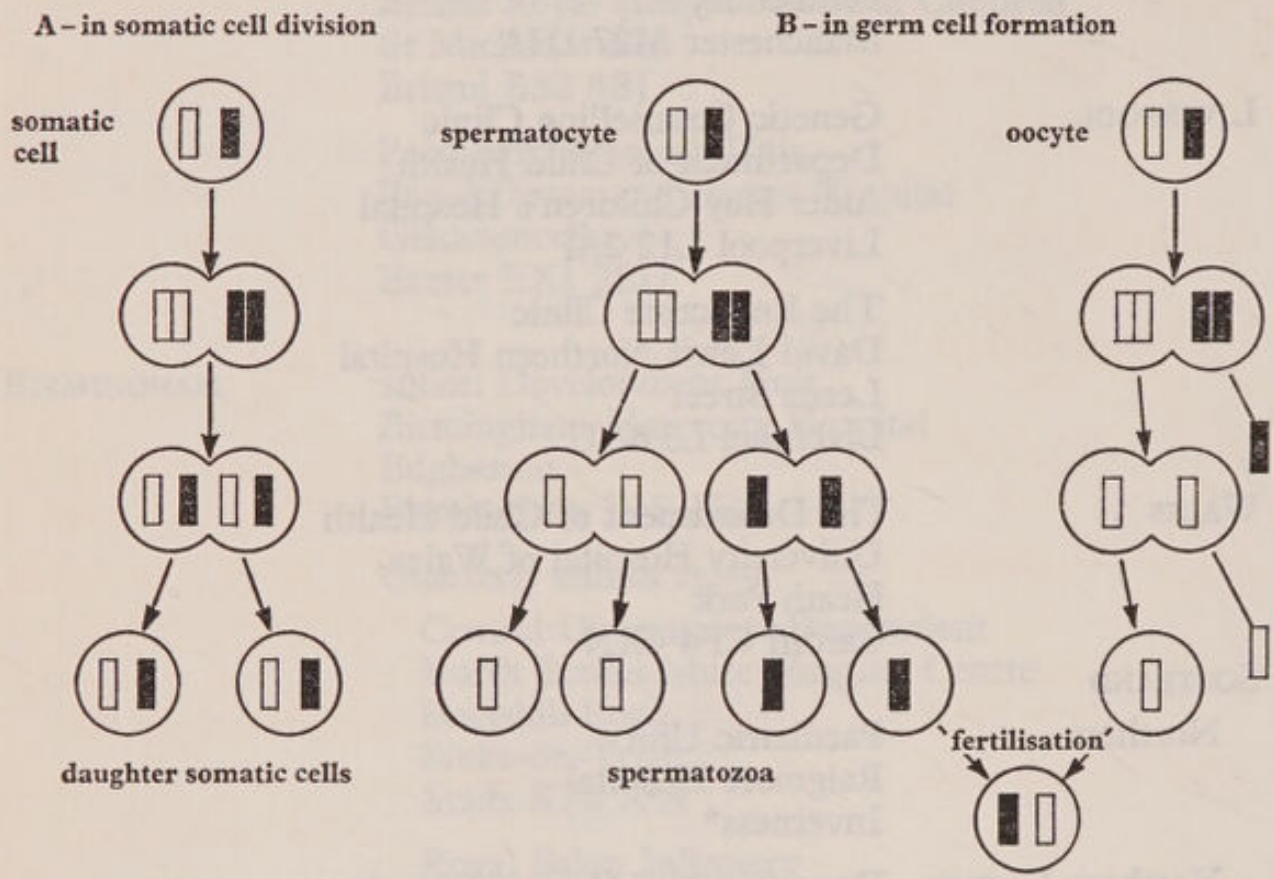

Fig. 1. Behaviour of one pair of chromosomes.

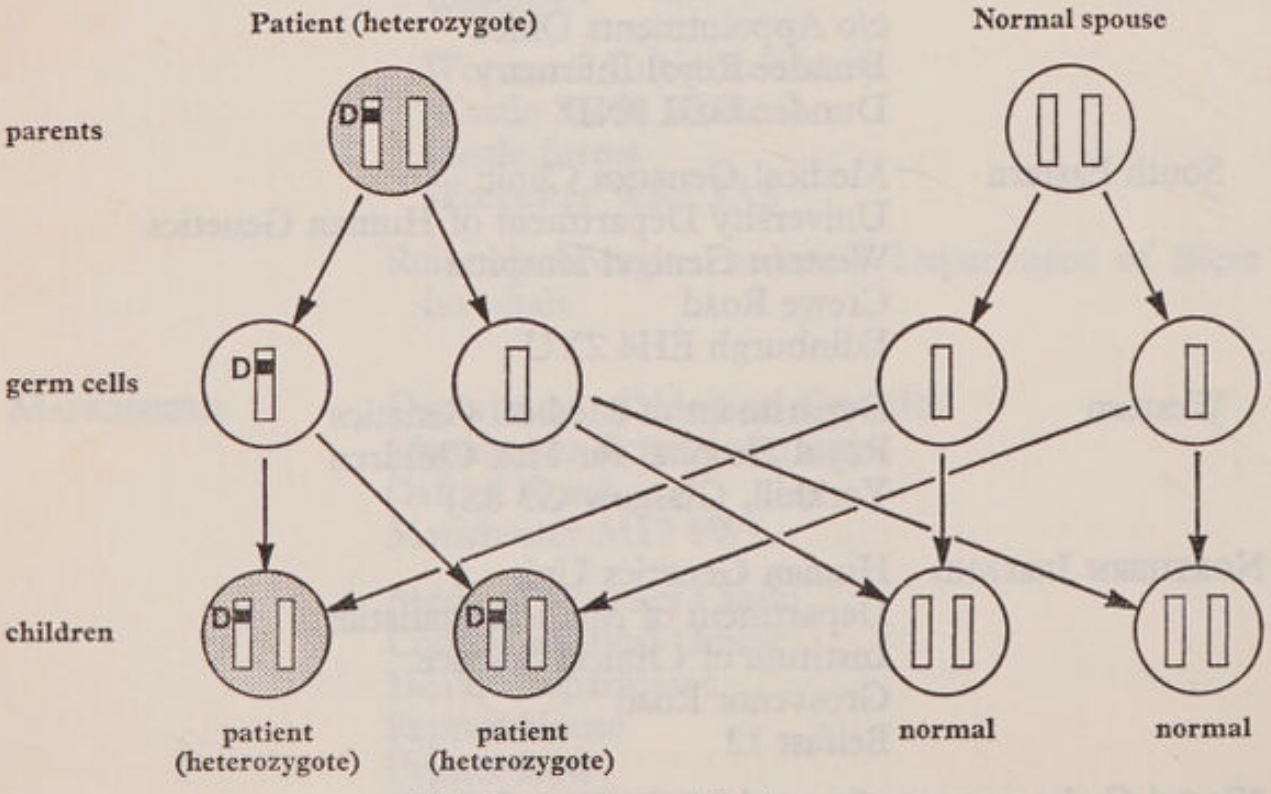

Fig. 2. Dominant inheritance.

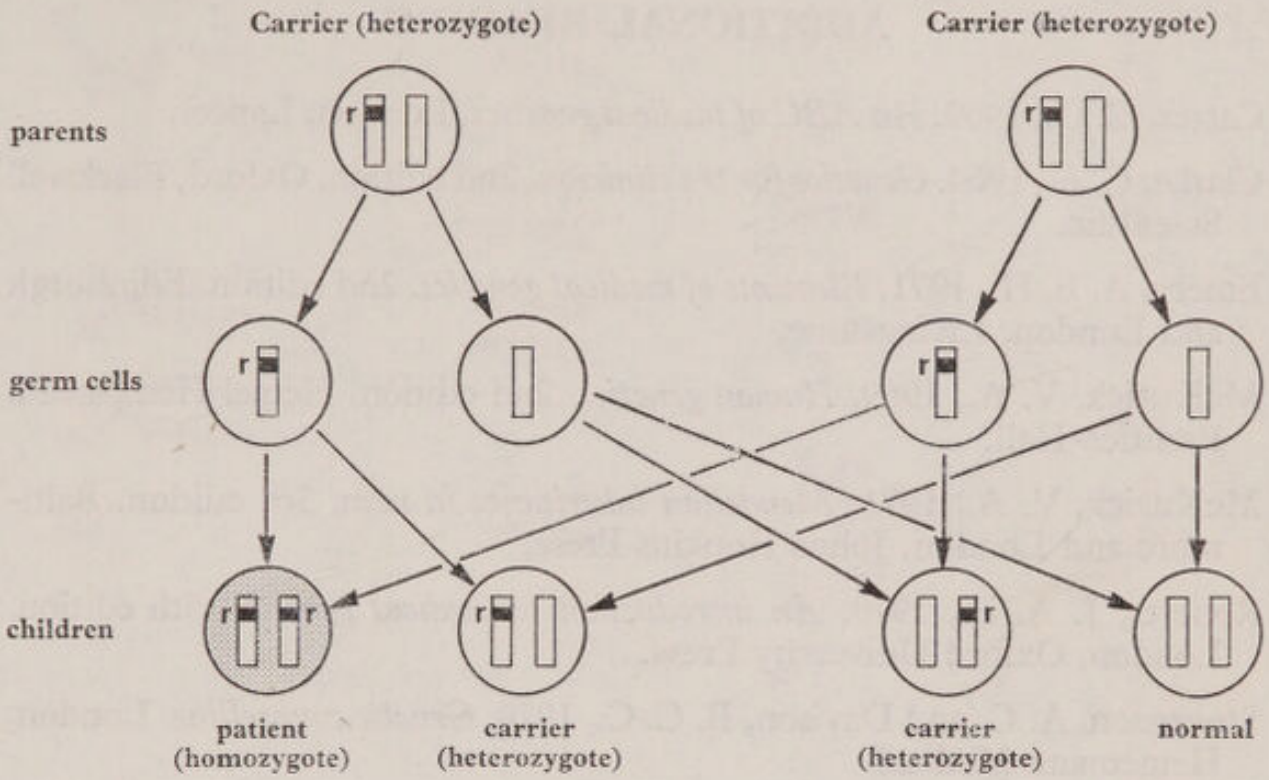

Fig. 3. Recessive inheritance.

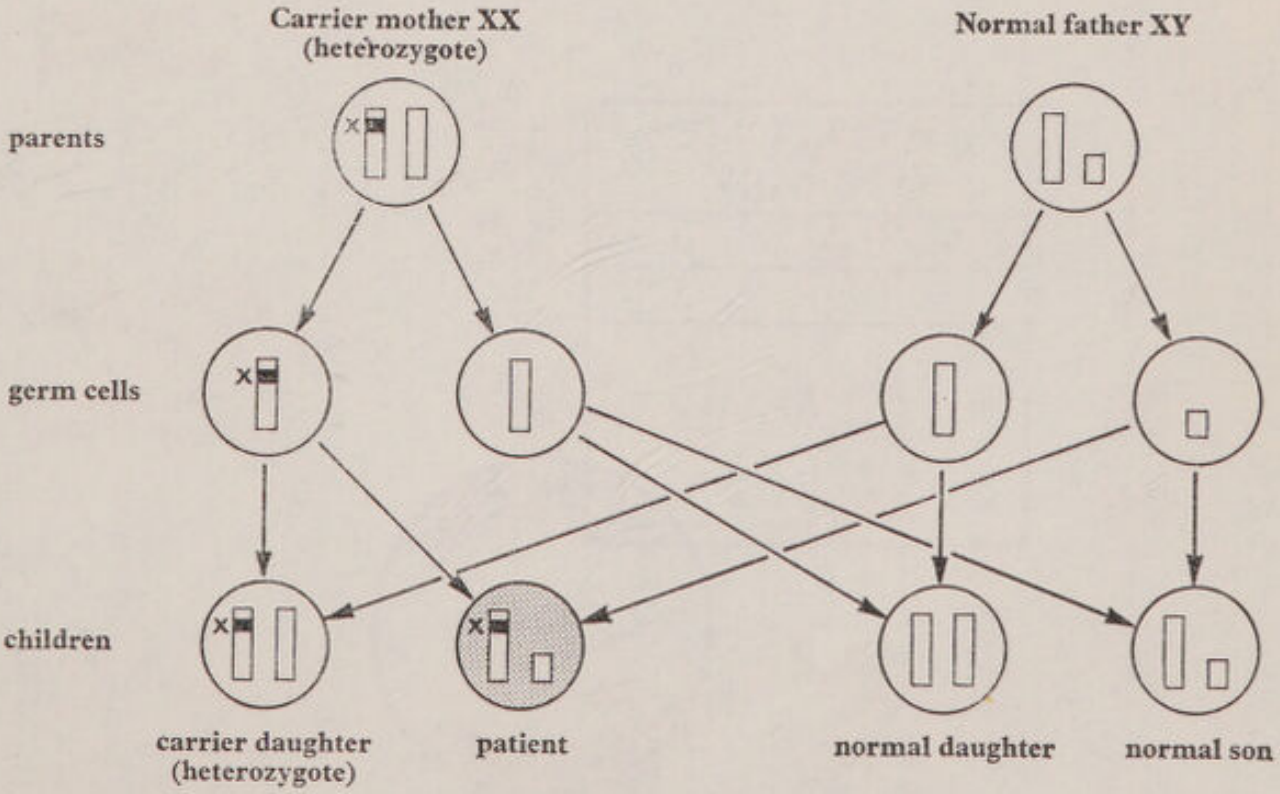

Fig. 4. X-Linked inheritance.

ADDITIONAL READING

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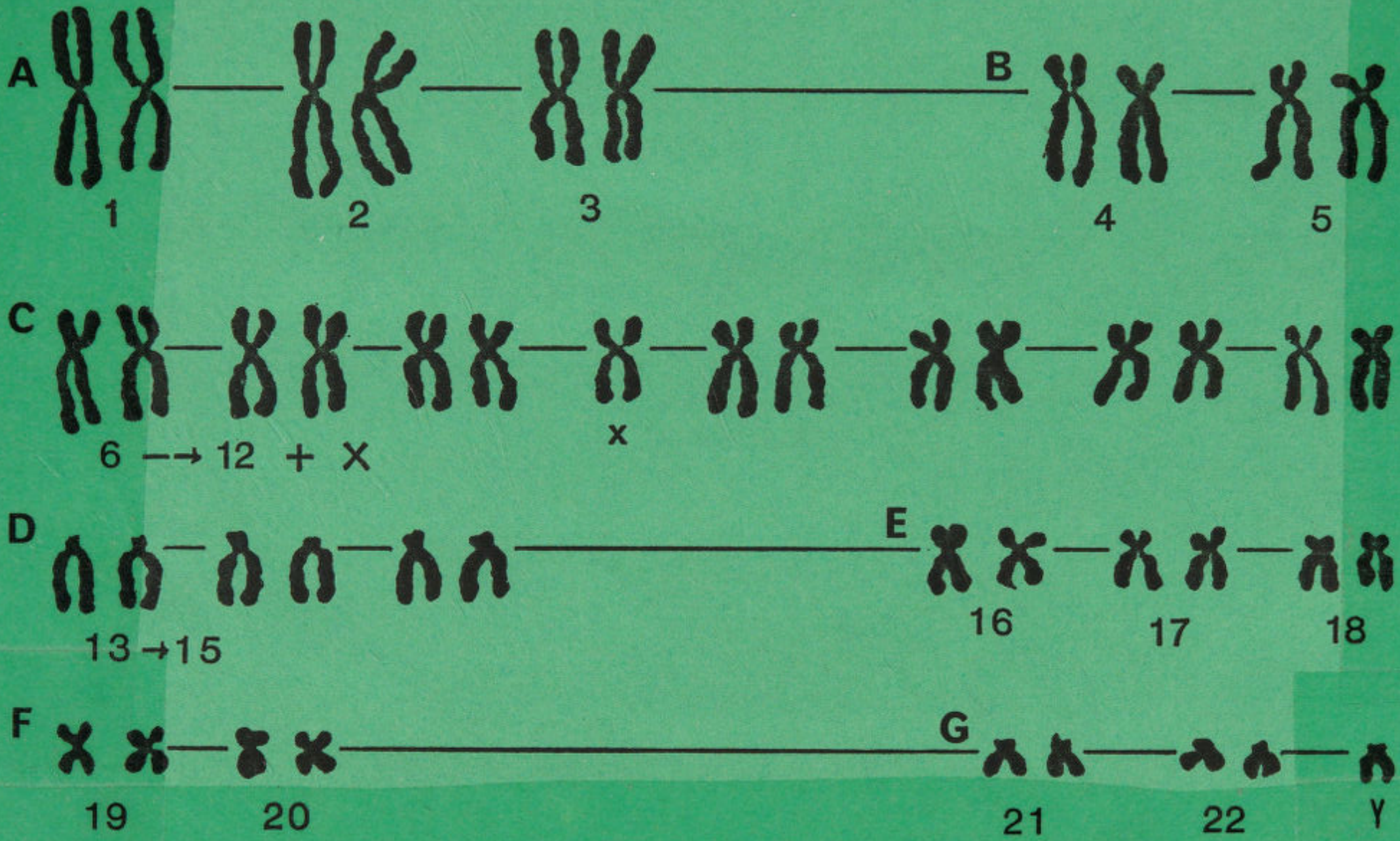

Chromosomes of the human male.