RECENT ADVANCES IN 7

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Edited by Roy Meadow

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Preface

There are several areas of paediatrics which have been involved in great advances in recent years. There has been a revolution in radio-diagnostic techniques, a boom in new genetics and, to a lesser extent, the direction of carriers of disease.

However, perusal of any paediatric journal will show that for most areas of everyday paediatric practice there have been few sensational advances. Most papers report competent studies that in themselves do not excite, though when set in the context of their subject they do explain and help to define it more clearly. Most of us do not understand the relevance of most of the published papers; only those with sufficient background knowledge can do so. Therefore most of the sections in this book address themselves to a common or important topic, and by considering more recent findings help us to understand or manage better a common condition, whether it be the child with wheezing or seizures, or the one requiring antibiotic therapy.

As a clinician one feels most secure with the investigational techniques and also with the drugs that one used during paediatric training. The problem for us in the management of hypertension or diabetes may be that we do not treat enough patients to become familiar with the more modern drugs and more rational dietary methods. Similarly, we can be aware of the repertoire of gastrointestinal investigational techniques without being able to put them in the right context or use them appropriately. Several sections in this book aim to lead the clinician into the enhanced security of modern investigation and management. Other subjects, for instance screening for cystic fibrosis, have been chosen because of the need for an overview of the plethora of research papers presenting apparently conflicting findings; and yet another group of subjects were chosen because they are particularly topical—ethical issues, food allergy and factitious illness.

I invited authors who combined authority, expertise and flair. They were invited because I knew I would enjoy what they wrote and that if I could remember part of what they wrote I would be a better doctor. I hope others may find their own blend of enjoyment, profit and stimulation too.

Leeds 1984 R.M.

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1. Carrier detection in genetic disorders

Peter S. Harper

The ability to recognise those individuals whose individuals who are themselves healthy but are at significant risk of transmitting a genetic disorder to their offspring is one of the most important preventive measures in the field of medical genetics. Not only does it make genetic counselling more precise by separating those who are truly at risk from the larger number who merely might be, but it also allows many individuals to be reassured and to avoid potentially hazardous antenatal predictive tests that might otherwise have been necessary.

Before discussing the subject of carrier detection in detail, it is essential to define what we mean by the carrier state, since the term is used differently and often loosely, in different fields of medicine. A brief but useful definition of the carrier state in genetic disorders is as follows: 'A carrier is an individual who possesses in heterozygous state the gene determining an inherited disorder, and who is essentially healthy at the time of study.' (Harper, 1981.)

It can be seen from this definition that the term 'carrier' is used in a restricted sense, and is not applied to all individuals whose offspring are at risk of a genetic disorder. In particular, the use of the word heterozygote implies that one is dealing with Mendelian inheritance, not with the more frequent situations where the genetic basis is multifactorial or poorly understood. Thus we know that a woman over 40 years is at considerably increased risk of having a child with trisomic Down's syndrome, but such a mother cannot be considered a 'carrier' for Down's syndrome. Similarly, the parents of a child with a congenital heart defect such as atrial septal defect cannot be regarded as carriers, except in those rare instances where a Mendelian syndrome (e.g. Holt Oram syndrome) is responsible. By contrast, a woman whose child has Duchenne muscular dystrophy, and who has other affected male relatives, can be considered as a carrier, since there is a clearly defined genetic abnormality which follows Mendelian inheritance.

The second important implication of our definition of a carrier is that the individual is essentially healthy at the time of study. This is not synonomous with total absence of clinical features; indeed minor clinical signs are among the most valuable criteria of the carrier state in many disorders. Thus heterozygotes for sickle cell disease show morphological abnormalities of the red blood cell and may develop clinical features at extremes of altitude or low pressure, but they are nonetheless essentially healthy. Equally, it should be recognised that the situation may not be a static one, especially for dominantly inherited disorders. Thus the carrier of the myotonic dystrophy gene whose only abnormality is microscopic lens changes, may in ten years show overt cataract and muscle disease. In such situations it can be seen that the distinction between carrier detection and preclinical detection is an arbitrary one.

Obligatory carriers

While most of this chapter is concerned with methods of detecting individuals who *may* be carriers for genetic disorders, it is important to recognise that there are certain categories of relative who *must* be carriers for genetic reasons, regardless of what tests may or may not show. In general such individuals do not require carrier tests and there is a real danger of negative results leading to a false reassurance. These obligatory carriers are, however, useful indicators of the efficiency of any test of carrier detection, since an ideal test should show abnormalities in all such cases.

Figure 1.1 shows the main categories of obligatory carrier for the principal types of Mendelian inheritance. For an autosomal dominant disorder the occurrence of the

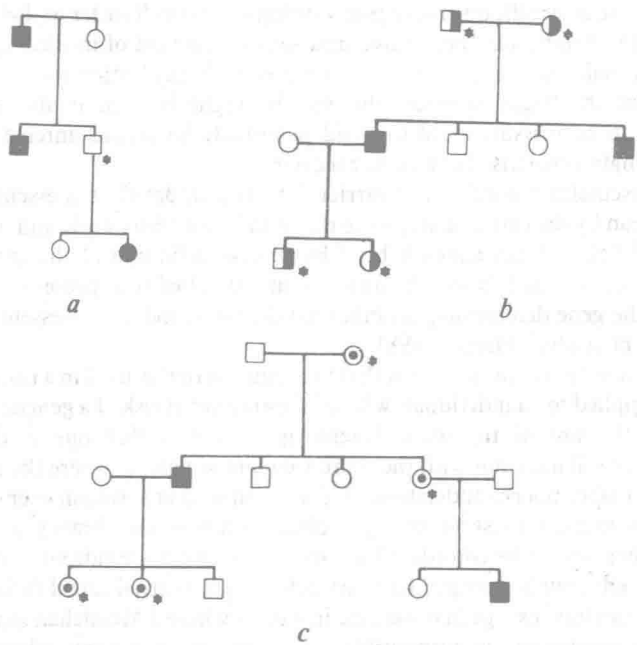

Fig. 1.1 Obligatory carriers in Mendelian inheritance. Obligatory carriers for the three major modes of inheritance are asterisked. By convention carriers for autosomal recessive disorder are half-shaded, those for X-linked disorders dotted. *a*, autosomal dominant inheritance. Any individual having both an affected parent and affected offspring must be a carrier. *b*, autosomal recessive inheritance. Both parents and all offspring of an affected individual are obligatory carriers. *c*, X-linked recessive inheritance. Obligatory carriers include all daughters of an affected male and all women who have an affected son and at least one other affected male relative.

disease in a child as well as in a parent can be taken as proof of the carrier state; such a situation is frequently seen in large kindreds with Huntington's chorea where the individual in question has died young, but has transmitted the disorder to offspring. For autosomal recessive inheritance both parents and children of an affected individual are obligatory carriers, while for X-linked disorders all the daughters of an affected male fall into this category. Table 1.1 gives the corresponding risks for offspring of definite carriers for the different types of Mendelian inheritance.

Table 1.1 Genetic risks for carriers of Mendelian disorders

Inheritance	Risk to offspring of carrier
Autosomal recessive	Very low unless: (a) disorder is extremely common, or (b) same disorder or consanguinity in spouse's family
Autosomal dominant	50% (risk of overt disease will vary with disorder)
X-linked recessive	50% of male offspring affected

APPROACHES TO CARRIER DETECTION

The methods available for the detection of carriers vary greatly according to our degree of understanding of the disorder, and range from the careful observation of specific clinical features to the direct identification of the genetic defect itself. Table 1.2 lists some of the available approaches and it is worth considering some of them in general at this point.

Table 1.2 Approaches to carrier detection

	Example
1. Direct gene analysis	
(a) Specific gene probe	Thalassaemias
(b) Related or linked restriction fragment length polymorphism	Sickle cell disease
2. Biochemical, primary defect known	
(a) Enzyme deficiency	Hexosaminidase A (Tay-Sachs disease)
(b) Non-enzymic protein defect	Factor VIII assays (haemophilia A)
3. Biochemical, primary defect	
(a) Unknown	Serum creatine kinase (Duchenne muscular dystrophy)
(b) Inaccessible	Phenylalanine load (phenylketonuria)
4. Physiological	
(a) Electroretinography	X-linked retinitis pigmentosa
(b) Electromyography	Muscular dystrophies (myotonic and Duchenne)
5. Microscopy	
(a) Blood	Sickle cell disease; thalassaemias
(b) Biopsy	Duchenne dystrophy
(c) Chromosomal studies	Balanced translocation carriers
(d) Ocular slit-lamp	X-linked ichthyosis, myotonic dystrophy
5. Radiology	Tuberous sclerosis (cerebral calcification)
6. Clinical	Skin (Fabry's disease) Eye (Choroideraemia) Muscle (Duchenne dystrophy)

Clinical observation

Clinical observation should not be underestimated in the detection of carriers, especially with variable autosomal dominant and X-linked disorders. Thus for myotonic dystrophy, a notoriously variable condition, studies of the author and others (Bundey et al, 1970; Harper 1973, 1979) have shown that minor clinical abnormalities such as myotonia and mild facial weakness could be detected in the majority of

asymptomatic gene carriers; only a small proportion required the use of more sophisticated tests such as electromyography or slit lamp examination. Carriers of the haemophilia A or B genes frequently give a history of a minor bleeding or bruising tendency, which coagulation studies will usually confirm as the result of a specific reduction in the particular clotting factor.

Against this one must advise caution in interpreting minor and non-specific clinical features as proof of the carrier state; wherever possible such observations should be confirmed by a more specific test. The overidentification of carriers is a real possibility: claims that minor degrees of muscle weakness can be found in almost all mothers of boys with Duchenne muscular dystrophy (Roses et al, 1977) have not been substantiated by other tests, while in early studies of myotonic dystrophy minor 'degenerative stigmata' were claimed to be present in almost all the offspring of affected patients; most of these features were probably entirely irrelevant to the disorder.

When assessing the value of a minor clinical feature in relation to the carrier state it is worth checking the family as a whole; surprisingly often the feature in question will turn out to be a harmless minor trait, often genetic, but not related to the condition under consideration.

Clinical investigations

Clinical investigations of a number of types can help identify carriers who are normal clinically. Many of these are relatively simple and non-invasive, though the help of colleagues in the appropriate specialties is often needed. Examples of such approaches include the use of the u.v. Woods lamp for identifying the depigmented patches of tuberose sclerosis (Bundey & Evans, 1969) cerebral computerised tomography in the same disorder (Baraitser, 1982), and slit-lamp examination for such varied problems as lens opacities in myotonic dystrophy (Harper, 1973) and in carriers for X-linked congenital cataract, corneal opacities in X-linked ichthyosis carriers (Sever et al, 1968) and minimal lens dislocation in the Marfan syndrome (McKusick, 1972).

Physiological studies

These, while often rather more complex to undertake, are valuable in a number of situations. Electromyography is especially important in detecting myotonia and minor myopathic changes, while nerve conduction abnormalities may be the only or earliest feature of some of the hereditary neuropathies (Harding & Thomas, 1980). Electroretinography will detect most carriers for X-linked retinitis pigmentosa (Warburg and Simonsen, 1968).

Microscopic evidence

Microscopic evidence of the carrier state can be obtained by muscle biopsy in a number of disorders, in particular Duchenne muscular dystrophy and the rare but lethal X-linked centronuclear myopathy (Van Wijngaarden et al, 1969). Histochemical and electronmicroscopic changes may also help in other congenital myopathies, where the pattern of inheritance is often uncertain. Skin biopsy is useful in confirming that a lesion that looks suspicious but (at least to the non-dermatologist) uncertain, is really specific for the disorder; Fabry's disease, tuberose sclerosis and neurofibromatosis are examples. Blood provides a particularly easy sample for microscopic studies,

and can show, or at least provide preliminary evidence for the carrier state in such disorders as sickle cell disease, the thalassaemias, and hereditary spherocytosis.

All the tests discussed so far are only indirectly related to the primary defect, usually because this is still unknown. They are often extremely useful, but the same cautions regarding lack of specificity and misinterpretation of minor changes have to be applied as were mentioned for clinical abnormalities. Since most of the disorders for which carrier detection is sought involve a single major gene, which can be expected to have a specific primary gene product, the approach to carrier detection is increasingly a biochemical one, with direct measurement of the primary gene product the goal whenever possible, and indirect changes as close as possible to the primary defect being used when the primary change is either inaccessible or still unknown.

Indirect biochemical tests

Indirect biochemical tests are still important in carrier detection for many disorders. Perhaps the most widely used (and misused) is the evaluation of serum creatine kinase in Duchenne muscular dystrophy, discussed later in more detail. Phenylketonuria provides an example of a disorder where the primary enzyme involved (phenylalanine hydroxylase) is known but inaccessible, being confined to the liver. Indirect tests, such as the blood phenylalanine levels following a phenylalanine load, and the phenylalanine/tyrosine ratio in a standardised midday sample, provide a reasonable substitute (Paul et al, 1978).

Direct biochemical tests

Direct biochemical tests for the primary gene product are now available for a large and increasing number of disorders. Most of these are inborn errors of metabolism due to a specific enzyme defect. Depending on the disorder it may be preferable to use serum, red blood cells, white blood cells or cultured fibroblasts. One of the major advances in carrier detection has been the finding that the enzymatic changes are usually demonstrable in these readily available cell types even though the disorder itself may be confined to such inaccessible organs as the brain.

Most enzymatic defects follow autosomal recessive inheritance, and in general enzyme levels in carriers are around 50% of normal, though with considerable scatter. This generally means that the carrier state can be identified or excluded with confidence in most individuals, provided that the laboratory concerned has an adquate range of normals and obligatory carriers, and that such factors as age and sex have been taken into account.

For the small but important group of X-linked disorders where specific biochemical tests are available, a much greater variation in enzyme levels is to be expected, owing to the phenomenon of X-chromosome inactivation. This causes serious practical problems, as discussed later, and has led to the use of tissues with a specific clonal origin, such as hair bulbs, to circumvent some of the difficulties.

Direct study of the gene

Until very recently identification of the gene product was the goal of carrier detection tests, and study of the gene defect itself would have seemed impracticable. This situation has changed totally with the advent of recombinant DNA technology (Weatherall, 1982), which has allowed the isolation and identification of small DNA

fragments, and their labelling to provide diagnostic gene probes. So far the main applications of this approach have been in the haemoglobinopathies and in a few other disorders whose gene product is fully identified, allowing the production of a complementary DNA gene probe. It is probably true to say that such probes are currently more relevant to prenatal diagnosis than to carrier detection (Kan & Dozy, 1978; Weatherall & Clegg, 1981).

An even more exciting prospect is offered by the possibility of using these techniques to study genetic disorders whose gene products are largely or totally unknown. The existence of polymorphisms in DNA, revealed by different size of fragments when digested with restriction enzymes, provides an abundant supply of gene markers that can be used to map the genome and to predict the inheritance of neighbouring disease genes. Obviously the accuracy of prediction will depend on the closeness of linkage, but it is possible to envisage this type of prediction for all Mendelian disorders. DNA markers have already been identified on the X chromosome, close to the Duchenne and Becker muscular dystrophy locus (Murray et al, 1982; Davies et al, 1983; Kingston et al 1983); and the results can already be applied in selected families to carrier detection in this disorder (Harper et al, 1983). Work is in progress on markers for such disorders as myotonic dystrophy and Huntington's chorea.

DOMINANTLY INHERITED DISORDERS

Where the gene for an autosomal dominant disorder is regularly expressed from an early age, there is no such thing as a carrier and no need for carrier detection tests, since all heterozygotes show the disease. Thus all individuals with the achondroplasia gene have the disorder achondroplasia, and a healthy relative can be confidently reassured that there is no risk of transmitting it. Unfortunately, many dominantly inherited disorders are far from being so regular, with a corresponding need for tests that will identify the symptomless gene carrier.

Lack of penetrance

This is an uncommon but well recognised feature in certain dominantly inherited disorders (see Table 1.3). In retinoblastoma certain relatives may show no signs whatever of the disorder, yet may transmit it to their relatives. There is no test in this

Table 1.3 Some features of autosomal dominant disorders

A. Lack of penetrance
retinoblastoma
hereditary pancreatitis
von Hippel Lindau syndrome
ectrodactyly
B. Late onset of clinical symptoms
Huntington's chorea
myotonic dystrophy
polycystic kidney disease (adult type)
polyposis coli
multiple endocrine neoplasia (types 1 and 2)
hereditary ataxias (various types)
hereditary spastic paraplegia

condition, nor in the others listed, that will conclusively confirm or exclude the presence of the gene, though if the case is one of the minority associated with a small deletion on chromosome 13, the absence of any such defect in a relative makes it unlikely that individual will transmit the disorder.

Late onset

This is a much commoner phenomenon, especially in neurological disorders, and presents particular problems for genetic counselling since symptoms may not develop until after an individual has reproduced. In some situations (e.g. adult polycystic kidney disease, myotonic dystrophy) (Harper, 1979) tests are available that will detect a high proportion of gene carriers by early adult life. It is important that relatives should be aware of the risks and be tested prior to having children. For disorders such as Huntington's chorea, where no such tests are currently reliable, the situation is more difficult. However, considerable help can be gained from knowledge of the distribution of age at onset, and the prior genetic risk must be interpreted in the framework of this and the patient's own age. Such information is available for Huntington's chorea (Newcombe et al, 1981), myotonic dystrophy (Harper, 1979), polycystic kidney disease (Milutinovic et al, 1980) and hereditary spastic paraplegia, among others.

Variable expression

Variable expression is characteristic of many autosomal dominant disorders, some of which are listed in Table 1.4. It is important to be aware of this variability, to examine patients at risk carefully, and not to accept a relative as truly affected unless appropriate studies have been done.

Table 1.4 Carrier detection in variable autosomal dominant disorders

Hereditary spherocytosis	Red cell morphology; osmotic fragility
Holt Oram syndrome	Minor digital abnormalities
Malignant hyperpyrexia	Elevated CK; muscle biopsy
Multiple epiphyseal dysplasia	Short stature; premature osteoarthritis
Muscular dystrophy (facioscapulohumeral)	Minimal weakness
Myotonic dystrophy	Minimal weakness; electromyography; lens opacities
Neurofibromatosis	Skin lesions
Osteogenesis imperfecta	Dental changes; deafness; blue sclerae
Tuberose sclerosis	Skin lesions (u.v. light) CT scan
Van der Woude syndrome	Lip pits
Von Hippel Lindau syndrome	Retinal lesions
Waardenburg syndrome	White forelock; hypertelorism

Carrier detection for dominantly inherited disorders raises some important general points. Firstly, for many conditions carrier detection is equivalent to presymptomatic detection, and gives important information, not only on the risk for children being affected (which is usually what is asked) but also on the future health of the individual tested (which may not be so welcome). Thus the development of a reliable test for the Huntington's chorea gene (likely in the near future) will cause serious difficulties in its wise application, and could in some cases do more harm than good.

By contrast, the detection of some other disorders in a symptomless form is of undoubted benefit for their health, as in those with the gene for malignant hyperpyrexia (Ellis & Halsall, 1980) or myotonic dystrophy, where there may be a serious anaesthetic risk, and for various inherited cancer syndromes, where early detection may allow successful treatment.

A second important general point is that it can rarely be guaranteed that an asymptomatic gene carrier for a variable autosomal dominant disease will be as mildly affected as the parent. It is more likely that the child will be closer to the mean severity for the disorder, which, by definition, is worse than the parental situation. Such disorders as tuberose sclerosis, myotonic dystrophy (especially when maternally transmitted) and osteogenesis imperfecta, provide frequent examples of severely affected children born to parents who are almost or completely asymptomatic, but who would in most cases be readily identified by the appropriate tests.

The number of autosomal dominant disorders where a primary biochemical defect can be shown is extremely limited, as shown by Table 1.5. It is thus in this type of inheritance that identification of the gene itself or of closely linked gene markers is likely to be of the greatest importance, with the added advantage of being age independent and applicable to readily accessible samples, such as blood.

Table 1.5 Biochemical prediction in some autosomal dominant disorders

Angioedema, hereditary	C_1 esterase inhibitor
Hypercholesterolaemia, familial	LDL cholesterol
Porphyria, acute intermittent	Uroporphyrinogen synthetase
Porphyria variegata	Protoporphyrinogen oxidase
Coproporphyria	Coproporphyrinogen oxidase

AUTOSOMAL RECESSIVE DISORDERS

Here we have a marked contrast with the previous group in that not only are both parents of an affected child obligatory carriers, but also that carriers are almost without exception entirely healthy. Since a carrier has to marry another carrier in order to have an affected child, the risk of this will be extremely small in all but the commonest disorders, again in complete contrast to dominantly inherited disorders.

Thus, in general, one can say to relatives of a patient with a recessively inherited disorder that being a carrier is of no significant relevance to their own health or to that of their children, and that carrier tests are not merely unnecessary but positively harmful in most instances. The author has seen a considerable amount of needless worry, guilt, and stigmatisation resulting from the thoughtless misapplication of carrier tests in rare recessive disorders, which has greatly outweighed any supposed benefits. It should be remembered that we are all carriers for at least one serious recessive disorder.

After this firm caution it should be stated at once that there are certain situations where carrier detection for recessive disorders is of great importance. Foremost are those relatively common conditions where the gene (and thus the heterozygous carrier) is at high frequency in the population, and where the chance of a marriage between carriers is thus considerable. The thalassaemias and other haemoglobinopathies including sickle cell disease, are of extreme importance in many parts of the

world, and carrier detection is now feasible using a variety of techniques, such as the sickle cell test and haemoglobin electrophoresis in sickle cell disease, red cell morphology and other more detailed measurements in the thalassaemias, and now tests based on DNA; these may be the direct identification of a gene deletion (α^0-thalassaemia) or the use of polymorphisms within the gene (Sickle cell disease), or adjacent to it (β-thalassaemia). In general the simpler tests are more appropriate for large scale carrier detection, and the frequency of the problem in many countries has led to widespread programmes of screening for the carrier state for β-thalassaemia in the Mediterranean countries, and in Britain among such immigrants as Greek Cypriots and various Asian groups. The general approach to screening for carriers is discussed later, but it can be noted here that the success of this for the thalassaemias has been related to the parallel development of prentatal diagnostic techniques. (See Weatherall, 1982 and Weatherall and Clegg, 1981, for general reviews and further references.)

The commonest recessively inherited disorder in Britain, cystic fibrosis, currently has no reliable test for the carrier state, despite much work and many false hopes. Phenylketonuria, perhaps the next most common, is a less urgent problem since mass newborn screening for the disease and effective dietary treatment have greatly reduced the burden which it imposes. Certainly none of the other recessively inherited disorders in Britain are of general importance for carrier detection. Table 1.6 summarises the situation for some of the most important disorders.

Table 1.6 Carrier detection in some common or important autosomal recessive disorders

	Test
α-Antitrypsin deficiency	α-Antitrypsin electrophoretic typing
Combined immunodeficiency (one type)	Adenosine deaminase electrophoresis
Congenital adrenal hyperplasia	Not reliable at present (1983)
Cystic fibrosis	Not reliable at present (1983)
Galactosaemia	Galactose-1-phosphate uridyl transferase (red cells)
Mucopolysaccharidosis type 1 (Hurler)	α-Iduronidase (white cells)
Phenylketonuria	Phenylalanine load; phenylalanine/tyrosine serum ratio
Pseudocholinesterase deficiency	Pseudocholinesterase level; dibucaine number
Tay-Sachs disease	Hexosaminidase A (white cells)
Thalassaemias and other haemoglobinopathies	Red cell morphology, haemoglobin electrophoresis, direct gene analysis, DNA polymorphisms

The only situation in which carrier tests for rare recessive disorders is of importance is when consanguinity occurs. Thus the risks for a first cousin marriage will be considerably increased if a common relative has a recessively inherited disorder, and it is in this situation that enzymatic tests for various inherited metabolic diseases become important. Figure 1.2 illustrates the genetic risks in such a situation; it should be noted that the risk of the healthy sib of an affected individual being a carrier is $\frac{2}{3}$ (not $\frac{1}{2}$). Also, that each step more distant in the relationship between the individuals would halve the risk.

While consanguinity is not frequent in British-born people, it is extremely common in many middle and far-Eastern populations and in their corresponding immigrant groups in Britain. Even if deliberate consanguinity is absent, a high proportion of

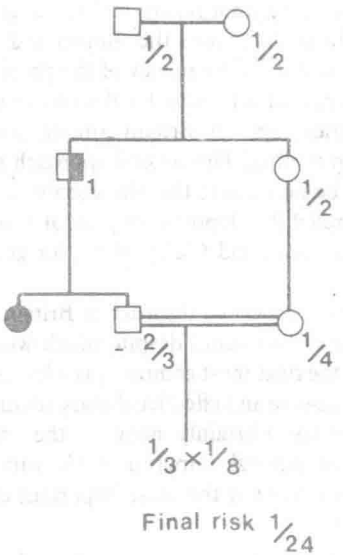

Fig. 1.2 Genetic risks in a first cousin marriage where a sib is affected by an autosomal recessive disorder. (Half-shaded = obligatory carrier.)

shared genes may be found in small and isolated populations, whether the isolation is the result of geographical factors (e.g. small islands), social factors (e.g. gypsies), or religious ones (e.g. the Amish of North America; McKusick, 1978).

X-LINKAGE

Carrier detection for X-linked disorders is of particular importance, but also presents special problems. Its importance results from the fact that a woman heterozygous for an X-linked recessive disorder has a 50% chance of a son being affected, regardless of whom she marries. The risk is in no way diminished by a change of partner, in contrast to autosomal recessive inheritance, where a remarriage will normally greatly reduce the recurrence risk.

The problems associated with X-linked carrier detection stem largely from the variability of expression seen in the carrier females. Very few X-linked disorders are fully recessive; a proportion of carrier females usually show some clinical manifestation, which may in some instances be significant. Thus some carriers for haemophilia A and B have a mild bleeding tendency, while those for anhidrotic ectodermal dysplasia commonly show dental defects. A small number of Duchenne muscular dystrophy carriers show a late onset of weakness or wasting that may be mistaken for the autosomal recessive limb girdle form of muscular dystrophy (Moser & Emery, 1974).

These clinical manifestations may be extremely helpful in carrier detection, and contribute considerably to the list given in Table 1.7. Many of the changes are patchy or 'mosaic' in nature, notably the changes seen in retina and skin. This results from

Table 1.7 Carrier detection in X-linked disorders

Disorder	Abnormality in carrier
Adrenal leukodystrophy	Long-chain fatty acid synthesis (Moser et al, 1981)
Alport syndrome	Microscopic haematuria (O'Neill et al, 1978)
Amelogenesis imperfecta	Patchy enamel hypoplasia
Anhidrotic ectodermal dysplasia	Reduced sweat pores, dental defects (Kerr et al, 1966)
Becker muscular dystrophy	Serum creatine kinase (less effective than in Duchenne). Linked DNA markers (Skinner et al, 1975; Kingston et al, 1983)
Centronuclear myopathy (lethal type)	Muscle biopsy changes (Van Wijngaarden et al, 1969)
Choroideraemia	Pigmentary retinal changes (Harris and Miller, 1968)
Chronic granulomatous disease	Partial NAD Ph oxidase deficiency; discoid lupus-like skin lesions (Finlay and Kingston, 1982)
Duchenne muscular dystrophy	Serum creatine kinase; linked DNA markers (Harper, 1982; Harper et al, 1983)
Fabry's disease	Skin lesions; alphagalactosidase assay (Beaudet and Caskey, 1978)
Glucose-6-phosphate dehydrogenase deficiency	Quantitative enzyme assay and electrophoresis
Haemophilia A	Factor VIII assays (Graham, 1979)
Haemophilia B	Factor IX assay and gene probe (Gianelli et al, 1983)
Hunter's syndrome (MPS II)	Enzyme assay on hair bulbs and serum (Archer et al, 1983)
Hypogammaglobulinaemia (Bruton type)	Reduced IgG (some individuals only)
Lesch-Nyhan syndrome	HGPRT assay on hair bulbs (McKeran et al, 1975)
Lowe's syndrome	Amino aciduria, lens opacities (Johnson and Nevin, 1976)
Ocular albinism	Patchy fundal depigmentation
Retinoschisis	Cystic retinal changes
Vitamin D-resistant rickets	Serum phosphate (may be clinical features)
X-linked congenital cataract	Lens opacities
X-linked ichthyosis	Corneal opacities, reduced steroid sulphatase (Muller et al, 1980)
X-linked mental retardation	Visible fragile site on X-chromosome (Turner et al, 1980b)
X-linked retinitis pigmentosa	Pigmentary changes; abnormal electroretinogram (Warberg and Simonsen, 1968)

the inactivation of one of the two X chromosomes in the tissue derived from each stem cell; depending on whether the normal or the abnormal X is functioning, the patch of tissue will itself either be normal or abnormal. Unfortunately the same variation that provides overt disease in some females also causes other carriers to be almost or completely undetectable. It is thus much more difficult to say with confidence that a particular woman is *not* a carrier than that she is.

These difficulties have led to the use of cloned cultured cells and of hair bulbs. Since each hair bulb is usually derived mainly from a single line of cells, it will tend to show either normal or abnormal values for a particular enzymatic test; the presence of a double population is strong evidence for the carrier state. Figure 1.3 shows an example of this in Hunter's syndrome.

Two X-linked disorders, Duchenne muscular dystrophy and haemophilia A, require special mention, both because of their importance, and because of the danger