RECENT ADVANCES IN PAEDIATRIC SURGERY

Edited by

A. W. WILKINS

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PREFACE

DURING the last ten years interest in paediatric surgery, and especially in the care of the newly-born child, has steadily increased throughout the world. The ensuing accumulation of new information about many conditions has led to more accurate and earlier diagnosis and to large reductions in the morbidity and mortality rates associated with a number of rare conditions. As infantile mortality rates fall, with the control of infection and improvements in nutrition, the proportion of deaths in the first years of life due to congenital abnormalities rises, and surgical treatment becomes more important.

Although several large textbooks on paediatric surgery have recently been published there seems to be good reason for collecting periodically in one volume some of the newer knowledge and more recent changes or trends in practice. While such a book will probably contain material which subsequently may become accepted, at least for a time, as part of orthodox surgical practice, it will almost certainly also contain many things which are soon abandoned and some which are never widely accepted. If these are defects they are part of the price which must be paid for the stimulation of interest and ideas.

The scope of this book should help post-graduates working in the field of paediatrics and general surgeons who have to deal with children, as well as specialist paediatric surgeons, to appreciate the trends of recent developments in a broader fashion than is possible from the most detailed review of current practice in a single hospital. Advances in clinical practice and surgical techniques are uneven and spasmodic but an attempt has been made here to cover all the special interests in the care of children, with the exception of orthopaedics.

I am indebted to those who have so generously helped by writing for this present book. I should also like to thank Mr. Rivers and his staff of J. & A. Churchill Ltd. for the expeditious production of this latest addition to their well-known series.

A. W. WILKINSON

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Chapter 1

CLINICAL GENETICS

C. O. CARTER

CLINICAL genetics has three main contributions to make to paediatric surgery: to clarify the classification of certain diseases and malformations; to provide data on the probability that a particular pregnancy will result in a child with a specific malformation requiring surgical treatment; to make explicit the concept that the treatment of genetically or part-genetically determined disease usually has to be radical or prolonged.

Knowledge of family risks is helpful in early diagnosis and treatment. For example: neonatal intestinal obstruction in a child whose elder sib has long segment Hirschsprung's disease is probably due to Hirschsprung's disease; vomiting in the first 3 months of life in the son of a woman who herself had pyloric stenosis, should be assumed to be caused by pyloric stenosis until proved otherwise; the child of a man or woman with multiple polyposis needs regular sigmoidoscopy, since there is a 1 in 2 chance of the child developing polyps and requiring a total colectomy.

The concept that genetic or part-genetically determined disorders need radical or prolonged treatment is illustrated by the readiness with which certain environmentally determined conditions, for example severe genu recurvatum, respond to treatment, while other conditions, for example many instances of talipes equinovarus and congenital dislocation of the hip, are difficult to correct because of a genetically determined predisposition to an abnormal pattern of growth.

Nuclear and chromosomal sexing has clarified the distinction between inter-sex states which are essentially due to chromosomal mutations, such as Turner's and Klinefelter's syndromes, and those due to mutant genes, such as testicular femininization and adrenal hyperplasia. Genetic analysis, too, has sometimes made the distinction between two forms of a disease before this was recognized clinically, for example, the distinction between the autosomal and sex-linked recessive forms of gargoylism, the distinction between the sex-linked and autosomal forms of Duchenne type muscular dystrophy, and the distinction between the several types of cystinuria.

GENETIC PROGNOSIS

Single Gene Effects

Forecasting from the family history the probability that a particular child will be affected by a genetically or part-genetically determined condition is most accurate when a single gene locus is involved.

When those affected are heterozygous* for a dominant mutant gene, the main principle in giving a genetic prognosis is that the children of affected individuals have a 1 in 2 chance of being affected. Provided that those heterozygous for the gene are always clinically affected, then the later sibs of sporadic cases of the disorder are rarely affected, since most of these sporadic cases are due to fresh mutations, and the children of unaffected individuals in the family are not at risk. Some examples of conditions determined in this way which are of interest to paediatric surgeons are: achondroplasia, diaphyseal aclasis, multiple epiphyseal dysplasia, Marfan's syndrome, osteogenesis imperfecta, multiple polyposis of the colon, Peutz-Jegher's syndrome, multiple neurofibromatosis, acholuric jaundice (hereditary spherocytosis), von Willebrand's disease, the "adult" variety of polycystic kidneys.

Looking to the future, it would be helpful to be able to recognize early those who have inherited a dominant mutant gene which does not produce a clinical effect until later in childhood. For example, much sigmoidoscopy would be saved if a close linkage with one of the blood groups was established for the gene responsible for multiple polyposis of the colon, such that in many families the children of an affected individual, who had inherited the gene, could be distinguished by a sample of blood taken soon after birth.

Where those affected are homozygous for a recessive mutant gene, the main principle in genetic prognosis is that there is a 1 in 4 risk to their later brothers and sisters. There is little risk to the children of their unaffected sibs, unless these marry a close blood-relative. Some examples of conditions determined in this way are: meconium ileus (due to fibrocystic disease of the pancreas), rickets secondary to Fanconi's polyaminoaciduria syndrome, congenital adrenal hyperplasia, Morquio's disease, Ellis-van Creveld's syndrome, most forms of congenital deafness, the milder forms of Duchenne type muscular dystrophy, infantile progressive muscular atrophy (Werdnig-Hoffman), hypersensitivity to the muscle relaxant suxamethonium, and familial

* Heterozygotes for a particular gene are those who have the gene on only one member of the chromosome pair. Homozygotes are those who have the particular gene on both members of the chromosome pair.

mediterranean fever (a not uncommon cause of recurrent "abdominal crises" in North Africans and Sephardic Jews).

Where those affected are hemizygous for a sex-linked (i.e. X-borne) recessive mutant gene, the main principle is that if at least one other male relative is affected, later brothers of an index patient have a 1 in 2 chance of being affected and later sisters a 1 in 2 chance of being heterozygous carriers. With sporadic cases there is the possibility that the mutation may have occurred in the formation of the mother's ovum, and that sibs are not at risk; but it is at least as probable that the mother is a heterozygous carrier of the mutant gene as a result of a fresh mutation in a grandparental germ cell. The risk to later brothers and sisters of sporadic cases is therefore between 1 in 4 and 1 and 3, depending on the number of normal unaffected male relatives of the index patient. Some conditions determined in this way are: Vitamin D resistant rickets (renal phosphate loss type), classical haemophilia, Christmas disease and, probably, the severe form of Duchenne type muscular dystrophy and testicular feminization.*

Looking to the future, genetic prognosis for conditions due to autosomal or X-borne recessive genes will be improved when methods of detecting the heterozygous "carriers" become available. There are encouraging indications that the detection of heterozygous carriers of autosomal recessive genes will be possible in most instances, once the fundamental enzyme deficiencies which underlie most of these conditions have been discovered. Heterozygotes will be found to have a deficiency of the enzyme which is much less than the deficiency in the homozygote, but nevertheless detectable. This is not as yet possible for most of the recessively determined conditions of interest to paediatric surgeons. But with suxamethonium sensitivity the dibucaine number clearly distinguishes between homozygotes, heterozygotes and individuals who do not possess the gene. Similarly in acatalasia, the enzyme defect which may lead to dental sepsis and ulceration of the gums in childhood, first reported from Japan, heterozygotes can readily be detected since their blood shows about half the normal catalase activity.

Such methods not only make it possible to detect which of the unaffected sibs of an index patient are heterozygotes for the gene, but also make it possible to test their prospective marriage partners to see if they carry the same gene. This would obviously be useful in relation to such common conditions as fibrocystic disease of the pancreas,

* When the affected individuals never reproduce, it is difficult to distinguish the family pattern produced by X-borne recessive genes and sex-limited dominant autosomal genes producing an effect on male, but not female, heterozygotes. This distinction will in time be made by linkage studies.

where perhaps 1 in 20 of the population are heterozygotes, and so there is an appreciable chance of the sib of an affected child marrying another carrier. Such marriage prophylaxis is already being applied in the areas of Italy where Cooley's anaemia is a major cause of death in childhood. The numerous carriers are being ascertained, in the areas of high incidence, by haematological examination of all children in primary schools, and those discovered will be warned against marrying each other.

With X-borne recessive genes, there is even more reason to suppose from recent developments in genetics that it will be possible to detect heterozygous "carrier" females. It appears that only one X chromosome is active in a cell nucleus, and any other X chromosomes in a cell are resting and condensed. It is for this reason that the number of chromatin bodies present, the bodies which form the basis of "nuclear sexing" from buccal mucosal or other cells, is one less than the number of X chromosomes present. The normal male has one X chromosome and no chromatin bodies; the normal female has two X chromosomes and one chromatin body. But it may well be pure chance which X chromosome in a heterozygous woman is active in a particular cell, that carrying the mutant gene or that carrying the normal allele. The tissues in heterozygous females are therefore likely to be mosaics of cells with and without the abnormality caused by the mutant gene.

Such partial manifestation in heterozygous females is again best seen when the basic enzyme defect may be measured, for example in the case of the haemolytic anaemia due to glucose-6-phosphate dehydrogenase deficiency, which is important in the differential diagnosis of neonatal jaundice in areas such as Greece, Malaya and also probably parts of Africa. In the case of X-linked vitamin D resistant rickets, the enzyme deficiency is not known, but a proportion of the heterozygous females may show some skeletal disease, and many more will show hypophosphataemia. In most haemophilia families, the heterozygous females show normal antihaemophilic globulin titres, but in some families with paradoxically mild haemophilia, heterozygous females do show a reduced titre. An alternative method of detecting heterozygotes will come once some gene loci with several common alternative alleles are found with an X chromosome. The gene locus determining a blood group system on the X chromosome which has recently been discovered will be most valuable for this purpose, if further sources of the antiserum are found.

More Complicated Inheritance: Empirical Risks

Once the genetics of a condition become more complicated than complete determination by dominant, recessive autosomal or X-

linked genes, it naturally becomes more difficult to estimate genetic risks.

It is sometimes possible still to recognize the action of a single gene locus. Dominant mutant genes that do not always produce clinical disease may sometimes be detected by special tests or more careful examination. Both diaphyseal aclasis and multiple epiphyseal dysplasia are, to some extent, sex-limited, and women carrying the gene may show few abnormal clinical signs; but radiography will usually enable them to be detected. Similarly, with the common form of acholuric jaundice due to hereditary spherocytosis, the mutant gene concerned always causes spherocytosis with increased red cell fragility, though not all of those so affected develop haemolytic crises and jaundice.

Often, however, this is particularly the case with common disorders; the genetic predisposition to develop the disorder appears to be based on several genes, not just one. Twin and family studies show that most of the common congenital malformations, pyloric stenosis, harelip and cleft palate, congenital dislocation of the hip, talipes equinovarus, spina bifida cystica and hypospadias have a mixed genetic and environmental aetiology. The number of good twin studies is limited, the best are those for talipes equinovarus and congenital dislocation of the hip, carried out in Germany by Idelberger (1939, 1951). But such twin studies as there are indicate that the proportion also affected among the identical co-twins of index patients is lowest for congenital heart disease and spina bifida cystica, is about 25 per cent for talipes equinovarus, about 30 per cent for harelip (with or without cleft palate) and pyloric stenosis, about 40 per cent for congenital dislocation of the hip and 50 per cent for hypospadias. Family studies of patients with these malformations show that the proportion affected with the same disorder as the index patient tends to fall off sharply as one passes from first degree relatives (parents, sibs and children) to second degree relatives (for example, uncles and nephews), to third degree relatives (for example, first cousins). This sharp decrease in the proportion affected with decreasing degrees of relationship to the patient, suggests that more than one gene locus is concerned in the genetic predisposition to the disorder.

Until more is discovered it is not possible to base genetic prognosis for such conditions on Mendelian laws. But it is possible and useful to work out empirical risks based on large family studies of carefully selected series of patients. The information, often incomplete, is available for some of the commoner conditions of interest to surgeons: clefts of the lip and palate, congenital pyloric stenosis, Hirschsprung's

disease, spina bifida cystica, congenital heart disease, congenital dislocation of the hip, talipes equinovarus and hypospadias. It must be recognized that in individual families the risk, for example to a later sib, may be better or worse than the average figure, and knowledge of the individual patient's family history will often make it possible to improve the estimate of the risk. For example, the risk to later sibs of a child with many of the common malformations increases substantially if one or other parent is also affected. With some conditions the risk increases if any other relative is affected.

Clefts of Lip and Palate

The first large scale family study of a common disorder was that of the Danish surgeon, P. Fogh-Andersen (1942), for clefts of the lip and palate. He established that harelip with or without lateral cleft palate was aetiologically distinct from midline cleft palate. The incidence of the first type of malformation was about 1·2 per thousand and the second about 0·4 per thousand, with a male to female sex ratio of about 2 for harelip (with or without cleft palate) and less than 1 for cleft palate alone. Instances where the malformations were associated with multiple other malformations constituted a third group. Harelip with or without a cleft palate appeared aetiologically homogeneous, and the different degrees of the malformation, from a small scar in the lip which needs no treatment to bilateral harelip and cleft palate, appeared to be due to the influence of the same genetic predisposition modified by unknown intra-uterine factors. The midline cleft palate group, however, did not appear aetiologically homogeneous: in some families genetic factors were important in causing the malformation but in others they were not.

Fogh-Andersen's results, together with the findings in a current survey from the Clinical Genetics Unit at The Hospital for Sick Children, London, are summarized for harelip ($\pm$ lateral cleft palate) in the table below. The latter survey was based on index patients treated at the Hospital a generation ago, and so is providing new information on the next generation, that is, children and nephews and nieces of index patients.

These figures may be used for advice to parents. Additional points in giving genetic risks are that if one or other parent is affected, the risk to later sibs of an index patient is increased from about 1 in 25 to about 1 in 8; the latter risk will also apply to further children once an index patient has already had one affected child. The risk to further children of parents who, though themselves unaffected, have already had two affected children, is not accurately known, but is perhaps of

the order of 1 in 10. But the presence of a second affected relative other than a parent or sib does not appear to alter the 4 per cent risk to later sibs. The risk to male relatives is always somewhat higher than to female relatives, as might be expected from the sex ratio of 2 males to 1 female. There are also indications that the risk to children of index patients is higher when the index patient is a mother rather than a father. For example, in the series from The Hospital for Sick Children, so far 6 in 128 children (5 per cent) of female index patients but only 6 in 307 of the children (2 per cent) of male index patients were also affected. Although the series is small, there is a strong indication

TABLE I. PROPORTION OF RELATIVES AFFECTED OF PATIENTS WITH HARELIP (± CLEFT PALATE) IN TWO LARGE SERIES

Category of relationship	*Denmark*		*London*		*Approximate comparison with general population*
	Total	*Affected (per cent)*	*Total*	*Affected (per cent)*	
Siblings	1,140	4·9	609	3·4	× 40
Children	—	—	435	2·8	× 30
Aunts and uncles	5,343	0·7	1,938	0·5	× 6
Nephews and nieces	—	—	874	0·6	
First cousins	7,703	0·3	2,669	0·2	× 2

that the risk to the children of female index patients may be appreciably higher than that to the children of male index patients.

In assessing risks to the unborn relatives of patients with midline cleft palate, more attention must be paid to the individual family history than with harelip, with or without lateral cleft palate. Thus in the Danish series the risk to a later sib of an index patient increases from about 1 or 2 per cent to 16 per cent (1 in 6) if a parent is affected, but also to about 12 per cent (1 in 8) if a relative other than a parent is affected.

Unfortunately, nothing is known in man of the intra-uterine environmental factors that must also play a part in the production of either harelip (± cleft palate) or cleft palate alone. If they were known, it might be possible to provide environmental prophylaxis for the embryos known to be genetically predisposed. Interesting work by Fraser and his colleagues (1957) in Montreal has illustrated the interaction of genetic and environmental factors causing midline cleft palate in mice. Some strains, but not others, developed cleft palate

when the pregnant female was injected with cortisone. In part the explanation is that the sensitive strains are characterized by a genetically determined tendency to late closure of the palatal processes. Reciprocal cross-breeding experiments between the sensitive and insensitive strains showed that the intra-uterine environment provided by the mother also played a part; the hybrid embryos showed a lower incidence of cleft palate when the mother, rather than the father, came from the resistant strain. At least one case of cleft palate in man has been plausibly attributed to the administration of large doses of cortisone at the critical period between the thirty-eighth and forty-fifth days of embryonic life.

A small group of patients with clefts of the lip and palate also have mucous pits of the lower lip. In these cases a single gene is responsible for which the patients are heterozygous. It is noteworthy, too, that clefts of the lip and palate appear to be a regular feature of the multiple malformations associated with trisomy 15,* and are not uncommon in trisomy 21 (Down's syndrome).

Congenital Hypertrophic Pyloric Stenosis

No large-scale twin studies are available for congenital pyloric stenosis; but probably at least 50 per cent of identical co-twins of index patients are unaffected, and therefore environmental factors are at least as important as genetic factors in causing the disease. The sex ratio is about 5 to 1 and the incidence in Britain about 1 in 200 male births and 1 in 1,000 female births.

The nature of the environmental factors concerned is not known. The excess of first-born children among index patients when the onset of symptoms is later than the first month of life, the later onset of symptoms in children born in hospital than at home and possibly in those fed 4-hourly than in those fed 3-hourly, all suggest that skill in handling the baby may play a part in postponing the onset of symptoms. Experience with premature babies indicates that it is the length of extra-uterine life rather than post-conceptional age which is important in determining the onset of symptoms.

Earlier family surveys have shown that the risk to sibs is raised some 12 times above the random risk; but because of the high case mortality of pyloric stenosis up till 1920 there has, until recently, been no information on the risks to the children of affected individuals. The findings

* No clear distinction can be made between the cytological appearances of the long acrocentric chromosomes 13, 14 and 15, so that it is somewhat arbitrary to talk of trisomy 15. In the same way it is now conventional to refer to the extra chromosome present in regular cases of Down's syndrome as number 21; but chromosomes 21 and 22 are not reliably distinguished, though the satellites are often more marked in pair 21.

in a current survey from the Clinical Genetics Research Unit at The Hospital for Sick Children, based on a series of index patients treated at the hospital a generation ago, are summarized below. Because of the sex ratio of 5 to 1, the findings in each sex are given separately. The relatives classed as affected all either had a pyloric tumour which

TABLE II. AFFECTED RELATIVES OF PATIENTS WITH PYLORIC STENOSIS

Category of relationship	*Male patients*			
	Total	*Affected*	*Proportion affected (per cent)*	*Comparison with general population*
Brothers	174	5	2·9	× 5
Sons	183	13	7·1	× 15
Sisters	186	5	2·7	× 25
Daughters	187	3	1·6	× 15
Nephews	176	2	1·1	× 2
Nieces	160	1	0·6	× 5
Boy cousins	707	4	0·6	× 1
Girl cousins	680	2	0·3	× 3
	Female patients			
Brothers	41	5	12·2	× 25
Sons	48	9	18·8	× 35
Sisters	43	1	2·1	× 20
Daughters	42	5	11·9	× 120
Nephews	38	1	2·6	× 5
Nieces	36	—	—	—
Boy cousins	185	2	1·1	× 2
Girl cousins	168	—	—	—

had been confirmed at Rammstedt's operation, or, if medically treated, the pyloric tumour had been felt by an experienced physician.

The high risk to the sons of affected women, which in the series so far is of the order of 1 in 5 or 6, is obviously of practical importance in diagnosis. One child at least in this group could not be scored as affected because although he had a typical history and died after a month of vomiting, he was never seen by a paediatrician and a diagnosis was never made. As with harelip and cleft palate, the sharp fall off in incidence as one moves from first to second degree relatives suggests that the genetic predisposition must be, in part at least, multifactorial.

The male preponderance cannot be attributed to sex linkage, since there are numerous examples of male index patients having affected sons. A somewhat crude interpretation of the findings is that the genetic predisposition must be stronger in females than in males to produce a clinical effect.

Looking to the future, a close study of particular children, such as the sons of affected females, who are known to have a high risk of developing pyloric stenosis, may well lead to knowledge of the environmental factors which are also concerned in the development of symptoms. There is scope here, too, for developing methods of detecting the condition early, and experimenting with antispasmodic drugs before vomiting starts.

Hirschsprung's Disease

The genetic analysis of patients with Hirschsprung's disease is still restricted by the fact that only one generation is available for study. Few patients cured by rectosigmoidectomy are yet old enough to have started their families, and so empirical risks to children are still not available. Estimations of the risks to earlier generations are unreliable because accurate histological diagnosis has only recently become available.

Findings in a survey from the Genetics Unit and the Department of Morbid Anatomy at The Hospital for Sick Children (Bodian and Carter, 1963) indicate that genetic factors, apart from sex, are more important in long segment than in short segment cases (In the latter the aganglionic segment is restricted to the rectum, or rectum and sigmoid colon). The overall sex ratio is 4 males to 1 female, but is about 8 to 1 where the rectum only is involved, and falls to near unity in the rare cases where all the colon and some small intestine is involved. The family risks in the survey hitherto are as follows: brothers of short segment patients, 9 affected in 173, sisters 1 in 145; brothers of long segment patients, 5 affected in 35, sisters 3 in 28. Although the numbers are small, they indicate that the risk to later sons of index patients with a short segment involved is of the order of 5 per cent, and the risk to sisters is low. The risk to the brothers of long segment cases is more than 1 in 10, and to sisters about 1 in 10. Further, it is found that in general the length of segment involved in the second affected child is usually similar to that in the first. The importance of careful observation in the neonatal period of the younger sibs of patients with long segment Hirschsprung's disease is self-evident.

Without a second generation it is not possible to speculate on the genetic mechanisms involved. There is a definite association with

Down's syndrome (trisomy 21), which is about ten-fold higher than one would expect by chance, and one case has already been reported in association with Klinefelter's syndrome. Relatives other than sibs are rarely affected, but examples are known where sisters or maternal aunts of index patients have had affected sons. In one family in The Hospital for Sick Children series, two sisters and a brother have each had an affected child, and a further sister was also probably affected.

Congenital Heart Disease

Twin family studies show that genetic factors are not important in the aetiology of most cases of congenital heart disease. The identical co-twins of affected children are rarely also affected. Family studies show that the risks to later brothers and sisters of affected children are of the order of only 1 in 50. With improved diagnosis and increasing use of surgical procedures, family studies are now being based on series of patients with individual types of heart malformations. However, all these also show low risks to sibs. There is a suggestion that the risks are somewhat higher than 1 in 50 for pulmonary valve stenosis and somewhat lower for intraventricular septal defect.

Occasionally families are encountered many of whose members have congenital malformations of the heart, and in these, estimates of family risks must be based on the pattern in the individual family.

Where the congenital heart disease is part of a syndrome, for example, Marfan's syndrome due to a dominant mutant gene, or Ellis-van Creveld syndrome or Marchesani's syndrome, both due to recessive mutant genes, the risks of recurrence are those of the main syndrome. It is noteworthy that congenital heart malformations are a regular feature of the syndromes due to extra autosomes whether trisomy 21 (Down's syndrome), 18 or 15. Congenital heart disease (coarctation of the aorta) is also commonly found in Turner's syndrome (genotype XO), but is not a feature of Klinefelter's syndrome (genotype XXY) or the XXX syndrome.

Spina Bifida

The incidence of spina bifida cystica in England is of the order of 2 to 3 per 1,000 births. Family studies indicate a link between all degrees of failure of closure of the neural tube, varying from anencephaly with an entirely open spinal column to small lumbar meningocoeles, and even to some cases of spina bifida occulta. Twin studies show that environmental as well as genetic factors are concerned in the aetiology of this group of malformations. The striking geographical