Genetic Counselling

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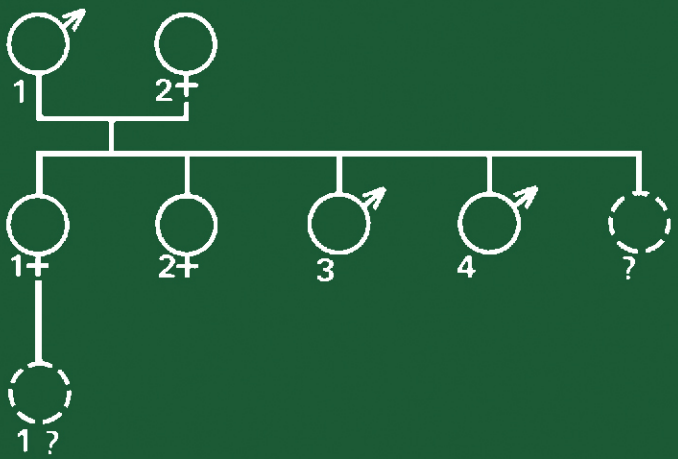
Second Edition



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Contents

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Preface to First Edition

It is hoped that this book will be found helpful by those who are consulted by patients about the implications of hereditary and congenital disorders. Everyone in clinical practice is asked about these problems from time to time but those most frequently involved are probably general practitioners, paediatricians, and obstetricians. When considering defects and disorders an attempt has been made to indicate where risk estimates should present no problems to the practising physician, and where, by reason of genetical, statistical, or diagnostic complexities, it may be advisable to seek some specialist opinion.

It is impossible for anyone to have more than a superficial knowledge of all the medical specialties. The authors have, therefore, had to have discussions with, and to seek advice from, many of their colleagues. We have drawn extensively on their opinions and have had the privilege of their criticisms of the drafts of several of the chapters. The text has been greatly improved as a result and many mistakes avoided, but we must accept full responsibility for the final version.

In addition to thanking present and past colleagues in the unit we wish particularly to acknowledge the interest and advice of Professor R. B. Duthie, Professor M. G. Gelder, Mr. B. S. Jay, Dr. Patricia Morton, Mr. W. G. Pearce, Dr. E. W. Poole, Dr. R. T. C. Pratt, Dr. J. M. K. Spalding, Dr. R. Smith and Dr. R. S. Wells.

We are also greatly indebted to Mrs. Anne Naylor, who typed most of the text, for her constant interest and care. We also had substantial secretarial assistance from Mrs. Gene Harris and Mrs. Glenys Lee. We are indebted to our colleagues Dr. P. Pearson and Mr. G. Clarke for several of the photographs.

We are grateful to the Editor of the *Journal of Medical Genetics* for permission to reproduce Plate 1 in Chapter XIV and to the Editor of the *Journal of Obstetrics and Gynaecology of the British Commonwealth*, and Dr. D. J. Bartlett for their permission to reproduce Plate 2(b) in Chapter XVI. We should like to thank Professor J. Chassar Moir, Dr. D. H. Garrow, Mr. T. J. S. Patterson, Mr. W. G. Pearce, Dr. R. S. Wells and Dr. R. Wigglesworth for allowing us to use photographs of their patients.

A.C.S.
B.C.C.D.

1970

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Preface to Second Edition

As pointed out in the preface to the first edition, this book is intended mainly as a guide to clinicians and possibly as an aide-memoire to medical geneticists. The advent of differential staining of chromosomes and the extensive use of amniocentesis and other techniques in pre-natal diagnosis necessitated additions and some rewriting of sections. The only other alterations in the book consist of corrections of textual mistakes and a few additions of relevant new information. The temptation to increase the detail of clinical descriptions of conditions has been resisted and so the size of the book is substantially unchanged. We are indebted to Mrs. Dorothy Hardick for her secretarial help in revising this book.

A.C.S.
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April, 1976

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Chapter 1

INTRODUCTION

Genetic counselling is concerned mainly with advising people about the risk that a member of a family will suffer from a congenital or hereditary disorder. Advice may be sought by parents before they decide to have a child, when the mother is already pregnant, or after a child has been born. However, patients also consult their medical advisors about a variety of miscellaneous problems, which are individually uncommon; for example, as to drug and radiation hazards, or when children with an adverse family history are being considered for adoption, and in connection with justification for sterilization and termination of pregnancy.

The term "genetic counselling" is not ideal, but it is difficult to think of any better. In particular "counselling" suggests that advice is given to patients as to what they should do, whereas the primary purpose is to answer the question that the patient asks in terms of the risk that the event which they fear will occur. There are some who feel that the term "genetic prognosis" would better describe the contents of a book such as this which concentrates on estimations of risk, a probability of a specified happening, usually that a child will have a particular disorder. It can be argued that the counsellor's job is simply to estimate this risk as well as possible and try to ensure that this is understood. This is, of course, true. It is entirely a matter for parents to decide whether to avoid having further children, or to seek sterilization or termination of a pregnancy.

The demand for advice continues to grow as the public becomes better informed from many sources, and referrals to genetic clinics certainly increase as the availability of specialist advice becomes known. At present about a thousand families are referred to the Genetics Unit in Oxford each year, and this is over twice as many as five years ago.

It is repeatedly emphasised in this book that the pre-requisites for adequate estimations of risks are as accurate a diagnosis as possible, and a knowledge either of the mechanisms of inheritance of the trait or availability of data on which to base empirical estimates, i.e. those derived from what is known to have happened to children born subsequently in parallel situations. There may be no dubiety about a diagnosis. For example, when an anencephalic child is born, where a

person has facio-scapulo-humeral muscular dystrophy, or classical complete albinism, no medical man should need to seek further advice. However, often a condition has to be specified in genetic as well as clinical terms before advice can be given. For example, what is clinically severe progressive childhood dystrophy is usually, but may not be, an X-linked gene trait, and a condition due to a chromosomal abnormality may or may not be inherited.

It is essential when investigating all cases of congenital and hereditary disorders to take as good a family history as possible. This, when adequately confirmed, may either serve definitely to identify the genetic make-up of the parents, or a parent, or in the case of traits where there is predisposition not determined by single genes, it may be important in determining the level of risk for a particular patient. For example, if a boy with progressive muscular dystrophy presents and it can be confirmed that a maternal uncle, or even his mother's maternal uncle, has muscular dystrophy, then his mother is at once identified as a carrier on pedigree evidence alone (Chapter 5). Again, if a man with myopia enquires about the risk that his children would also be severely short sighted, but there is no history of myopia in his family, the risk is lower than if one of his parents had myopia. If one parent and a sib of the other parent had myopia, then the risks would be further increased.

However, memories are fallible, "skeletons in the cupboard" may have been concealed, or knowledge of relatives may be minimal, and so the family histories have to be checked. This may be illustrated by two experiences. A man with syringomyelia said that his mother suffered from the same condition and had had radiating pains in her arm. She had died when aged about 40. However, hospital records showed that she had had a carcinoma of the breast for a number of years and that her arm pains were due to secondary deposits in cervical vertebrae. In another case a woman of average intelligence with adenoma sebaceum reported that a brother had died of a cerebral tumour. However, from the hospital autopsy report it was clear that he had had a mass of tuberous sclerosis in his brain; central necrosis and haemorrhage had caused the signs and symptoms of increased cranial pressure.

The family history should be recorded in diagrammatic pedigree form and should include live births, still births and miscarriages in the sibship of the index case, and in the preceding and succeeding generations. The extent of the pedigree will depend on the condition. The reliability of information as to whether or not relatives were affected will vary greatly.

Each individual on the pedigree should be identified by name (and maiden name) and dates and places of deaths should be noted. This will enable hospital records and death certificates to be traced.

In every case where the consultors are a man and his wife they

should be asked whether or not not only they but their own parents were related. Consanguinity is often considered something to be concealed or a question about it may be initially resented. It may even be construed as asking whether the man and woman are married! It must be left to the enquirer to phrase the question. However, "are you related in any way" followed by "not even 42nd cousins?" or other such remarks are appropriate. Certainly the question should be asked in various ways so that it is certain that it is understood.

We have followed the practice of giving a single figure for a risk in most of this book, although we have on occasion suggested a range. Risks are given in simple fractions in preference to percentages or decimals. It is not possible, except in a very few instances, to set statistical confidence limits to these single figure estimates and we have not done so. It will be clear that in all these situations, particularly where risks are derived empirically, the fraction given is a mean or average value for, although it is fully recognised that in differing circumstances the range may be wide, it is impossible to know, in a given family, whether the risks are high or low, and the best estimate is one derived as the average of many families. This is further discussed in Chapter 3.

It has been argued by many that it is not necessary to give a risk figure, but terms like "high", "not high" or "low" are sufficient. It is difficult for the writers to conceive that the patients they see would accept such general and relative terms. It has further been argued that, while there are many high risks, usually when single gene inheritance is involved, there are a few situations where they are intermediate between those which are high, and those which are of the order of $\frac{1}{50}$ or less, and so are "negligible" relative to the overall chance to any child of being stillborn, dying early, or having some severe congenital or hereditary defect. Although agreeing that overall risks have high and low peaks, we are of the opinion that a single figure estimate should be given and that many of these are in the intermediate range. In our opinion the single figure is not only the best way of expressing the true situation, but is most easily understood by those who are asking the question. It is not difficult to explain to those who can understand the concept of a best estimate which is a mean value while, for those who have difficulty in understanding, a single figure can at least be remembered and they can appreciate a simple chance or "odds", in terms of betting and football pools.

There are great differences in the extent to which genetic theory and cytogenetics are familiar to members of the medical profession. Even those who understand broad principles may need to refresh their memories on some point in order to understand a practical application used in this book. It was decided, therefore, that a short account should be given of these aspects of human genetics which are directly applied in the reasoning. This is considered in Chapter 2. The need for such an exposé is a recurring problem for human geneticists in writing for

medical colleagues. Chapter 2 reflects the difficulty as it has had to be very condensed. It may be found too short and to be difficult reading for some, and irritatingly elementary for others. Those who find it inadequate are advised to consult the books suggested in further reading at the end of this chapter.

It is essential in estimation of some risks to use the logic of elementary probability. The first few steps in such reasoning are always readily understood, but sustained argument in probability terms can be tedious and it is easy to make simple logical or arithmetical errors. In Chapters 4, 5 and 6 series of simple examples are given of the application of such probability methods.

The reader will find great variations in the amount of comment on clinical and genetic aspects of different conditions. At one extreme where a condition is unlikely to give rise to serious diagnostic problems and the mode of inheritance is straight forward, it may only appear as a name followed by the mode of inheritance of the single causal gene. In these circumstances risk estimates are to be derived as advised in the chapter dealing with the three simple modes of inheritance (Chapters 4 to 6).

Other conditions are considered in more detail for a variety of reasons; (i) they may be common and often the subject of enquiry by relatives as, for example, epilepsy and diabetes. (ii) They may raise particular problems in respect of risk estimates as, for example, Huntington's chorea and other pre-senile cerebral degenerations where the onset is so late. (iii) Where traits which are clinically similar, or at least difficult to distinguish clinically, may be inherited in different ways. In the latter circumstances a very precise diagnosis is essential, as exemplified by the chondrodystrophies and the severe early onset muscular dystrophies. (iv) The condition may appear as a single defect or may be part of a syndrome, and it is therefore important to be as certain as possible of the true diagnosis because the syndrome and the isolated defect may be inherited in different ways. This situation may be exemplified by hare lip and cleft palate, and the syndromes which include these anomalies.

References have not been given in respect of each of the hundreds of conditions mentioned in this book, and no attempt has been made to cite support from the literature for opinions offered. Empirical risk estimates in respect of many conditions represent value judgements after consideration of many sources of published data. Such sets of data often can be reconciled with each other only with difficulty, and some are clearly biased by the way in which they were collected. We have not given references to all such sources. Finally, there are many occasions on which it has been advisable to use some such phrase as "however, the condition has been reported in parent and child" and, again, we have not attempted to document the sources of this information.

Our compromise in referring to the literature has been to mention a number of key papers, or unique sources of data, and to indicate at the ends of chapters textbooks, good recent reviews, reports of symposia and conference proceedings, which are not only suitable for further reading and evaluation of the subject, but are sources of references. By adopting such a plan no doubt we shall annoy some readers whose interest is aroused by a statement which they would like immediately to have followed up. However, we have avoided having huge reference lists which, however appropriate to a review or a theoretical text book, are rather a daunting addendum to a book of practical advice.

We have tried to make the index as complete as possible, and we have extensively cross-referred from one chapter to another. A glossary of genetic terms will be found in Appendix 5, although in most instances the explanation of the word used also appears on the first occasion it is mentioned in the text.

General reading in human genetics

Probably for medical men the best introduction is still Dr. J. A. Fraser-Roberts' *An Introduction to Medical Genetics*, 5th edition (Oxford University Press, 1970). Another excellent, rather more condensed but informative and clearly written book, is *Genetics in Medicine* by J. S. and Margaret W. Thompson (W. B. Saunders Co., 1966). A stage further on the theoretical side is represented by Curt Stern's *Principles of Human Genetics* (2nd edition, Freeman and Company, 1960) which is more technical but not so much orientated towards medical genetics.

As a quick source of reference on single gene traits, there is the magnificent *Mendelian Inheritance in Man. Catalogs of autosomal dominant, autosomal recessive, and X-linked phenotypes* by V. A. McKusick, The Johns Hopkins Press, Baltimore, 4th edition, 1975. This is a very remarkable production where traits which are considered to be, or suspected of being, monofactorial are listed with some comment and a few key references. It is excellent as a check list, a ready source of reference for uncommon conditions, and it has proved invaluable to the authors.

Books on special aspects of clinical genetics are considered at the end of appropriate chapters.

Chapter 2

ELEMENTARY GENETICS

The information necessary for continuity of a species, for orderly development and for physiological homeostasis of the individual is carried on the chromosomes in the nuclei of cells and transmitted in the male and female gametes. Probably there are some particles, as in plants, which are concerned with heredity and are transmitted in the cytoplasm of ova in man but the first generalization is generally valid. Chromosomes are thread-like or rod-like in form depending on the stage of the cell in the division cycle and in man, as in most mammals, they are paired, so that there is an even chromosome number in each cell in normal individuals the number being 46—the diploid number.

In the process of formation of spermatozoa and ova from the diploid germ cells only one of each pair of chromosomes passes into each gamete so that the chromosome number is 23—the haploid number. Finally, when an ovum is fertilized by a spermatozoon the haploid nuclei of the two gametes fuse to form the single diploid nucleus of the zygote—the first somatic cell of a new generation. Subsequent cell divisions of the zygote, termed mitoses, result in diploid daughter cells which by repeated divisions and differentiation form the new individual.

If all the genetic material on each of the chromosomes of the haploid set was identical then, as all individuals (apart from sex chromosomes) would receive exactly the same material from each parent, the only differences between individuals would be determined by environmental influences *in utero* and subsequently. In fact, apart from identical twins there are no two individuals who suggest such a situation and most of the differences reflect variation in the genetic material transmitted on the chromosomes received from both parents.

In this chapter only a short and oversimplified account of basic genetics will be given, ignoring anything which does not seem to have a direct application to the main purpose of the book. There are many excellent textbooks of general genetics, of cytology and of medical genetics available for further reading. In these will be found adequate accounts of molecular genetics concerned with the chemical nature of the heredity material, its relationship to coding and information storage, and concerning its role in initiating the synthesis of the innumerable and complex substances which the organism requires. For purposes of

counselling, however, with few exceptions which will be noted, the traditional genetic concepts and the terminology of chromosomes and genes are adequate.

Chromosomes

The backbones of chromosomes are long thread-like double stranded molecules of deoxyribose nucleic acid (DNA). The strands of the molecules are cross-connected and they are twisted round each other so that in general outline the appearance is that of a ladder repeatedly twisted on its long axis. The intensity of the spiralization varies with the stage of division in the cell division cycle and the length of the chromosome changes accordingly. At some point on the length of each chromosome there is a small non-staining region called the centromere, which is concerned with the mechanism of final splitting of chromosomes when they divide. The appearances of the chromosome vary greatly according to the position of the centromere.

Conventionally, twenty-two of the chromosome pairs are termed autosomes and are the same in the two sexes. The twenty-third pair in the female consists of two medium sized chromosomes, the so-called X chromosomes. In the male the pair consists of one such X chromosome and a small one called the Y chromosome. It follows that the female chromosome number is 44 + XX and that of the male is 44 + XY.

Any cell whose chromosome number is a simple multiple of the haploid number, 23, is termed "euploid". Per contra, any cell whose chromosome number is not a simple multiple of 23 is termed "aneuploid". Thus 23 chromosome gametes are euploid, as are the cells of normal individuals having 46 chromosomes, while those with 47 chromosomes, as in most cases of Down's syndrome, or 45 chromosomes, as in many cases of Turner's syndrome where there is only one sex chromosome (an X), are aneuploid. Cells with an extra chromosome of one pair as in 47 chromosome mongolism are termed "trisomic" whereas those missing one chromosome of a pair are termed "monosomic".

For completeness, where the chromosome number is euploid but where the chromosome number is more than 46 the cell is termed "polyploid", e.g. cells with 69 chromosomes are triploid, and those with 92 chromosomes tetraploid.

Mitosis—Behaviour of chromosomes in somatic cell divisions

Between divisions, cells are described as in "interphase". At this stage the chromosomes are very long and thread-like, cannot be detected with the optical microscope and the nucleus has a granular

amorphous appearance. The long chromosomes can only be accommodated in the nucleus by repeated folding or bending so that they are like many long threads forming a ball in the nucleus. During interphase the nucleus is very active metabolically and by the end of this stage almost all the DNA needed for two daughter chromosomes has been manufactured. The new DNA is transcribed or copied from existing molecules and the two strands are lying opposed to each other.

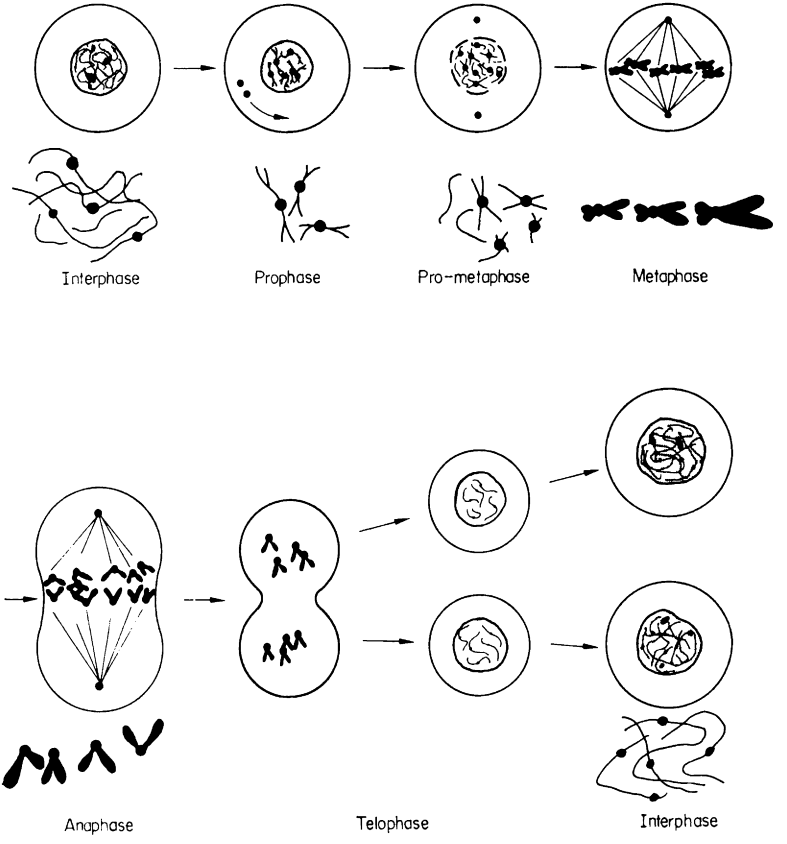

FIG. 1 Diagrammatic representation of mitosis
The appearances of chromosomes are shown beneath each cell diagram.
The black dots appearing in the cytoplasm in prophase are the centrosomes.

Fig. 1 shows in diagrammatic form the appearance of the cell nuclei and the chromosomes in this and subsequent stages of mitosis.

The start of the next conventional stage in the cell cycle, "prophase", is evident under the microscope when the amorphous or finely granular appearance of the interphase nucleus is replaced by coarser granules.