MEDICAL GENETICS: Principles and Practice

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James J. Nora, M.D.
Professor and Chairman, Department of Pediatrics
State University of New York
Chief of Pediatrics, State University Hospital
and Kings County Hospital
Downstate Medical Center
Brooklyn, New York

F. Clarke Fraser, Ph.D., M.D.C.M., F.R.S.C., D.Sc. (Acadia)
Professor of Medical Genetics, Department of Biology
Associate Professor, Department of Paediatrics
McGill University, Montreal;
Director, Department of Medical Genetics
The Montreal Children's Hospital
Montreal, Canada

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PREFACE

The decision to write this book was reached in The Hague in September, 1969, at the Third International Conference on Congenital Malformations. The finished product will appear shortly after the Fourth International Conference in Vienna, in September, 1973.

The reason for undertaking this project was to provide within a single volume the basic genetic information and its application to the clinical problems that fall broadly within the sphere of medical genetics. Other texts vary widely in their emphasis on basic versus clinical material, depending on the authors' views of what is most suitable for the intended readers. Since pediatricians and obstetricians are more likely to become involved with genetic problems than other kinds of physicians, our examples are oriented in their direction. Nevertheless we hope that physicians from other disciplines and nonmedi-

cal genetic counselors will also find help in these pages. We are especially hopeful that this text is of appropriate breadth and depth to introduce medical students to the subject of medical genetics.

Our book does not attempt to be a catalogue of diseases with a more or less genetic basis—our choice of diseases has been limited by the dictates of practicality and by the bounds of our own knowledge and experience. We do not, moreover, presume it to be a general pediatric or medical text. Diagnostic criteria are discussed at a level that should warn physicians and counselors of diagnostic pitfalls, and methods of treatment are dealt with only in sufficient detail to give the physician/counselor an idea of what may be involved for the family.

For more sophisticated discussion of genetic theory and more authoritative information on diagnosis and treatment, the reader is referred to more extensive texts of genetics, pediatrics or medicine, to be kept in office, home or library. We hope this volume will find a place in hospital wards, clinics, counseling centers and medical school classrooms.

JAMES J. NORA
F. CLARKE FRASER

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Dr. Audrey Hart Nora wrote Chapters 21, 23 and 28. Ms. Marilyn Preus was largely responsible for writing Chapter 19. Ms. Joy Weishuhn,, Ms. Peggy Baldwin, and Mr. Ralph Jackson produced many of the illustrations and line drawings. Ms. Weishuhn and Ms. Marilyn Peterson helped with library research. Ms. Mildred Meek, Ms. Nan O'Keeffe, Ms. M. Forster, and Ms. Peterson typed the manuscript.

Previously unpublished photographs of patients and cytologic material have been provided by a number of colleagues: Dr. Anil Sinha, Dr. Dan McNamara, Dr. Ed-

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Finally we wish to acknowledge the many children and their parents who have cooperated in helping us to a better understanding of genetic diseases.

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Heredity and Disease

Chapter 1

HERITABILITY OF DISEASE

But this disease seems to me to be no more divine than others. . . . Its origin is hereditary like that of other diseases. . . . what is to hinder it from happening that where the father and mother were subject to this disease, certain of their offspring should be affected also? Hippocrates: On the Sacred Disease.

From the very beginning of the history of Western medicine, the heritability of physical traits and diseases has been recognized. Hippocrates not only observed that blue eyes and baldness ran in families, but that diseases such as epilepsy followed a similar pattern. Before the early twentieth century, inheritance was considered to be a blending, a continuous variation—and this is probably what Hippocrates had in mind. However, the emphasis shifted away from blended inheritance following the rediscovery of Mendel and unit inheritance and the locating of the hereditary particles, the genes, in chromosomes. Indeed, among the earliest published examples of mendelian inheritance was the disease alkaptonuria, described by Sir Archibald Garrod in 1902.[1] A large number of diseases attributed to single mutant genes followed this remarkable observation, until the current catalog of disorders considered to have a firm mendelian basis lists 866 conditions.[2] The terms "dominant" and "recessive" entered the medical vocabulary, and many diseases which have later been demonstrated to have no true basis in mendelian inheritance still carry such labels. If a disease was presumed to have a genetic basis, an effort at mendelian interpretation was made.

A further shift in emphasis began in 1959, when the first disorders were described that could be traced to abnormalities of chromosome number. During the next few years, several more syndromes associated with a chromosomal aberration were discovered. Then, in the minds of many students (and referring physicians), the erroneous idea took root that if a disease has a genetic basis, a chromosome karyotype must be ordered to establish the diagnosis. However, the consultant in genetics appreciates that a large percentage of the patients he is asked to see have dis-

orders that can be attributed to neither a single mutant gene nor a chromosomal anomaly (see Table 1–1). If there is a genetic basis for these diseases, then we must return through the full circle to Hippocrates and discuss the hereditary aspect of disease in its earliest sense, that is, predisposition or *diathesis*.

A useful classification of diseases having a genetic background would thus be:

1. Single mutant gene (mendelian) syndromes
2. Chromosomal aberration syndromes
3. Diseases determined by multifactorial inheritance – genetic predisposition with environmental interaction.

TABLE 1-1. Diagnosis for 495 Families Referred to a Genetics Clinic for Counseling

Autosomal Dominant	
Ullrich-Noonan syndrome	11
tuberous sclerosis	9
osteogenesis imperfecta	9
Huntington chorea	7
neurofibromatosis	6
Holt-Oram syndrome	5
Apert syndrome	4
retinoblastoma	4
ectodermal dystropy, hidrotic	3
Ehlers-Danlos syndrome	3
Crouzon disease	2
holoprosencephaly	2
Leber optic atrophy	2
lymphedema, hereditary	2
mandibulofacial dysostosis	2
Marfan syndrome	2
nerve deafness	2
Waardenburg syndrome	2
aniridia	3
polycystic kidneys	3
Other (1 each)	25
	108
X-Linked	
Duchenne muscular dystrophy	11
hemophilia	5
agammaglobulinemia	2
Other (1 each)	4
	22
Autosomal Recessive	
pancreatic cystic fibrosis	11
albinism	9
Friedreich ataxia	6
congenital deafness	5
Werdnig-Hoffman disease	4
cataracts	3
chondrodystrophia calcificans	3
cretinism	3
PKU	3
Tay-Sachs disease	3
thalassemia	3
ataxia telangiectasia	2
nerve deafness	2
Gaucher disease	2
Hurler syndrome	2
Larsen syndrome	2
Riley-Day syndrome	2
Other (1 each)	38
	103
Chromosomal	
Down syndrome	43
D/D translocation	2
XO Turner syndrome	2
Other (1 each)	6
	53
Multifactorial or Unclear	
congenital heart defects	44
neural tube defects	31
multiple congenital anomalies	21
mental retardation, nonspecific	19
convulsive disorders	16
limb malformations and mental retardation	5
microcephaly	5
de Lange syndrome	4
Goldenhar syndrome	4
leukemia, acute lymphoblastic	4
cerebral palsy	3
hemangioma	2
hydrocephalus	2
repeated abortion	3
omphalocoele	2
Robin syndrome	2
Rubinstein-Taybi syndrome	2
Other (1 each)	34
	203
Miscellaneous	
consanguinity	17
racial ancestry	2
exposure to mutagens or teratogens	4
Other (1 each)	3
	26

To these may be added a fourth category: maternal-fetal incompatibility, an example of which is erythroblastosis fetalis. This category is not considered separately but is discussed in the context of blood groups (Chapter 21).

The clinical geneticist is asked to see patients for several different reasons. Often an infant or child is born with a common malformation and the parents are concerned about the risk of recurrence. Is the malformation inherited? Is there something that the parents did to cause this problem? What is the chance that this may recur and what can be done to prevent it?

Another category of patients referred to the clinical genetics consultant is a patient with a pattern of anomalies in search of a diagnostic label. The hope here is that naming a disease will explain it. In some cases this is true. Determining that a patient has the Marfan syndrome provides a reasonable basis for medical management, prognosis and counseling. Very often, however, suggesting a label for a group of anomalies implies a greater understanding of the disease than actually exists. The cause of the condition is uppermost in the minds of the anxious parents. Invoking a difficult-to-pronounce eponym makes the geneticist appear to be a scholar, but he is deceiving both himself and his patients unless he acknowledges the limits of his diagnostic label. Does naming this disease answer the question of etiology? Does it provide a reasonably firm basis for discussing prognosis in the patient and risk of recurrence in the family? And how precise is the diagnosis of the Ballderdash syndrome, anyway? Could this be another condition entirely?

If the patient has a common malformation, the familial aspects of which have been well investigated (e.g., atrial septal defect), then meaningful genetic counseling may be offered. If the patient clearly has a specific syndrome about which there is usable etiologic and prognostic information (e.g., Hurler syndrome or 21 trisomy), it is possible for the geneticist to answer many urgent questions.

Knowledge in fundamental genetics has expanded explosively during the past decade to the point that it may be considered the central and unifying biologic science. The aim of this monograph is to explore the field of medical genetics following the map provided by investigation into the fundamental areas of genetics.

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2. McKusick, V. A.: Mendelian Inheritance in Man. Ed. 3. Baltimore, Johns Hopkins Press, 1971.

Chapter 2

CHROMOSOMAL BASIS OF HEREDITY

The general conceptions here advanced were evolved purely from cytological data, before the author had knowledge of the Mendelian principles. . . . As will appear hereafter they completely satisfy the conditions in typical Mendelian cases, and it seems that many of the known deviations from the Mendelian type may be explained by easily conceivable variations from the normal chromosomic processes. Walter S. Sutton: The chromosomes in heredity. Biological Bulletin, 4:231, 1903.

The word "chromosome" was introduced into the scientific vocabulary in 1888 by Waldeyer.[20] As is the case with so many important discoveries, the early recognition of the role of the chromosome as the carrier of the information of heredity must be credited to several investigators working in the late nineteenth and early twentieth centuries. Roux, Boveri, Wilson and Sutton, pursuing a course running parallel to that followed by genetic researchers, appreciated before the rediscovery of Mendel that the chromosomes could be the ultimate dividing units and carriers of heredity. However, it was the rediscovery of Mendel that provided the catalyst for the reaction that synthesized the discoveries of cytology and genetics into the discipline of cytogenetics. It became apparent to the cytologists that the behavior of the hereditary characters of Mendel was reflected by the behavior of the chromosomes in meiosis. Sutton[18] and Boveri[1] independently proposed the chromosomal hypothesis of inheritance (the "Sutton-Boveri hypothesis").

The remarkable contributions to the chromosomal basis of heredity that were made over the next decades were, of necessity, derived from studies in lower animals, the drosophila proving to be a most useful subject. As early as 1910, T. H. Morgan[11] was able to locate a specific gene locus on a specific chromosome of *Drosophila melanogaster*. The human, however, is in many ways an unsatisfactory subject for genetics research. This has been especially true in the area of cytogenetics. It was not until 1956 that the diploid number of human chromosomes was demonstrated to be 46 by Tjio and Levan.[19] For the 33 years prior

to this date, students of medicine and biology were taught that the human diploid complement was 48.[13] The reason for this discrepancy was not carelessness on the part of cytogeneticists. Rather, the determination of the correct diploid number had to await the development of techniques capable of accurately revealing the human chromosomes.

Recognizing that the hereditary material was carried by the chromosomes did not, of course, define the nature of the unit of inheritance, which Johannsen labeled the gene. The development of this line of investigation is undertaken in Chapter 5. It is sufficient for this discussion to state that the chromosome consists of the hereditary material, desoxyribonucleic acid (DNA), embedded in a protein matrix (histone in the human). The units of inheritance, the genes, are segments of DNA. The number of genes distributed throughout the 46 chromosomes of the human cell has been estimated to be of the order of 100,000.

CHROMOSOMES

Chromosomes (*chromos* = color; *soma* = body) are not individually distinguishable except during cell division, at which time they may be seen under the light

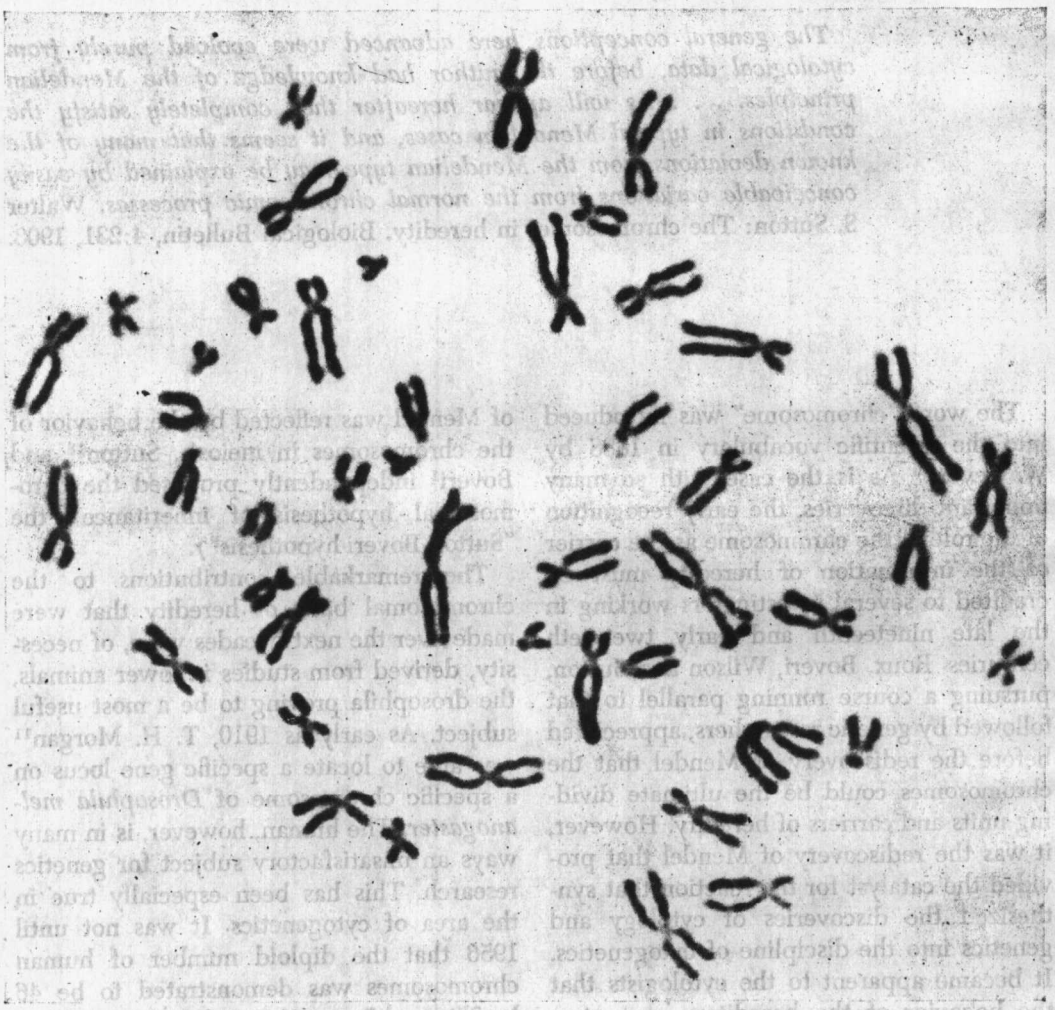

Figure 2-1. Human chromosomes in metaphase.