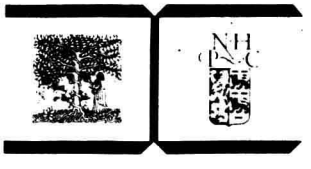
GENETIC METABOLIC DISEASES
Early diagnosis and prenatal analysis

Hans Galjaard, M.D., Ph D.
Professor of Cell Biology, Erasmus University, and
Head of the Department of Clinical Genetics,
University Hospital, Rotterdam, The Netherlands



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The illustration on the cover is a photograph made during fetoscopy in the second trimester of gestation, and is kindly provided by Dr. R. Rauskolb, Universitatsfrauenklinik, Giessen, West-Germany.

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Preface

Each time I look around in a scientific bookshop I think "why do people still write more books?"

The reason why I have nevertheless written the present book are, apart from vanity, the following.

- During the last decade there have been impressive advances in the area of early diagnosis and prenatal analysis and I thought it might be useful to put together the available data for all genetic metabolic diseases that can now be detected in early pregnancy.
- For several years our department has had the pleasure of receiving a large number of visiting scientists from many different countries who wanted to become acquainted with the techniques of (micro)biochemical analysis of cultured (hybrid) cells; I thought it might be useful for many others if details of these procedures were written down.
- In the practice of clinical genetics and as secretary of an advisory committee to the government on the organisation of early diagnosis, genetic counseling and prenatal diagnosis, I learned that most clinicians knew too little about biochemistry, that most biochemists had little idea about clinical heterogeneity and that both categories could know more about cell genetics.

I have therefore tried to write a book on the clinical features, pathological manifestations, biochemistry and (cell) genetic background of those metabolic diseases that can be diagnosed by analysis of cultured (amniotic fluid) cells. In the Appendices detailed information is given on methods allowing biochemical assays to be performed on small numbers of or single cultured cells.

This book is not meant to be read as a whole. Instead, each chapter and often each section is written in such a way that information can be derived more or less independently from the rest. Those few heroes who will read the whole book might therefore be annoyed by some duplication. I apologize to them, to my family and to my colleagues in the lab, and I promise to go to bookshops again.

Hans Galjaard

Acknowledgements

It will be no surprise to anybody when I say that a book like this could only be written with the help of many others. First of all I wish to thank the colleagues in our own department of Cell Biology and Genetics for their support, either directly by providing data or illustrations of their work, or indirectly by making me believe that writing this book was useful and even important.

In addition I have had great help from colleagues who are experts in various subjects which are dealt with in this book; their criticism and suggestions have significantly improved the quality of the particular chapters or sections. During the writing of the sections on carbohydrate metabolism I have had the support of Prof. J. Fernandes (Dept. of Pediatrics, Univ. of Groningen) and Dr. J.F. Koster (Dept. of Biochemistry, Erasmus Univ. Rotterdam); Prof. H. Kresse (Dept. of Physiological Chemistry, Univ. of Münster) helped with the section on mucopolysaccharidoses and Drs. F. van Sprang and S. Wadman (Dept. of Pediatrics, Univ. of Utrecht) and Dr. M. Mahoney (Dept. of Human Genetics, Yale University, New Haven) gave advice on the section on amino-acidopathies. Prof. D. Bootsma not only criticized the section on DNA repair but also gave me support at the moments I needed it most. I am grateful to Dr. J. Veltkamp (Dept. of Hematology, Univ. of Leiden) and to Dr. H. Busch (Dept. of Neurology, Univ. Hospital Rotterdam) for their contributions to the section on X-linked disease.

Dr. N. Horn (J.F. Kennedy Inst., Glostrup) and Dr. D.J.H. Brock (Dept. of Human Genetics, Univ. of Edinburgh) kindly provided unpublished data and I also thank all other colleagues, mentioned in the text of the book, who allowed me to use their data and illustrations. The collection of data on the practical experience with prenatal diagnosis of metabolic diseases has only been possible thanks to the cooperation of all colleagues mentioned in the list below.

My most direct collaborators, A. Hoogeveen, H.A. de Wit-Verbeek and Dr. W.J. Kleijer, have not only contributed very much to the development of many of the (micro)biochemical techniques mentioned in this book, but they have also helped me with the collection of many procedures described in the Appendices; Prof. J.F. Jongkind, Ing. J.E. de Josselin de Jong and Mr. P. Hartwijk have made important contributions to the development and testing of the instrumentation.

I wish to express my gratitude to my friends and colleagues, Dr. M.F. Niermeijer, Dr. E. Sachs, Dr. M. Jahoda and Prof. H.K.A. Visser, all of the Erasmus University and University Hospital Rotterdam, for their continuous support and always pleasant collaboration in the field of clinical genetics.

Although an author might not say so, I am proud of the high quality of the illustrations (made by Mr. W.J. Visser) and the photographs (made by Mr. J. Fengler and Mr. T.M. van Os). In the initial stage of this book Dr. G. Galavazi kindly helped me with the translation and in the final stage Ms. T.L. Bak edited the manuscript; I thank both for their patient and competent help.

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P. Aula, Dept. of Pediatrics, Helsinki, Finland
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E. Buhler, Universitätskinderklinik Genet. Institut. Basel, Switzerland
M. Cantz, Dept. of Physiological Chemistry, University of Münster, West Germany
N. Carson, Institute of Clinical Science, Queen's University of Belfast, Ireland
C.O. Carter, Institute of Child Health, London, U.K.
J.C. Dreyfus and L. Poenaru, Institut Pathologie Moleculaire, Paris, France
P. Durand, Div. Pediatrica, Istituto G. Gaslini, Genova, Italy
K. Dörner, Universitäts-Kinderklinik, Kiel, West-Germany
J. Farriaux, Laboratoire de Recherche de la Clinique Pediatrique, Lille, France
M. Fraccaro, Euratom Unit for Human Rad. and Cytogenetics, University of Pavia, Italy
W. Fuhrmann, Institut für Human Genetik, Giessen, West Germany
S. Girard, Laboratoire Cytogénétique, Hôpital St. Vincent-de Paul, Paris, France
B. Goldman, Institute of Human Genetics, Chaim Sheba Medical Center, Tel Aviv, Israel
R.A. Harkness and D. Gibbs, Clin. Res. Centre, Northwick Park Hospital, Harrow, U.K.
K. Harzer, Institut für Hirnforschung, Universität Tübingen, West Germany

N. Horn and M. Mikkelsen, Dept. of Human Genetics, J.F. Kennedy Institute, Glostrup, Denmark
W.J. Kleijer, M.F. Niermeijer and E.S. Sachs, Dept. of Cell Biology and Genetics, Rotterdam, The Netherlands
J. Leroy, Dept. of Human Genetics, University of Antwerpen, Belgium
M. Mathieu, Service de Biochemie, Hôpital Debrousse, Lyon, France
A. McDermott and J. Holton, S.W. Regional Cytogenetics Centre, Southmead Hosp. Bristol, U.K.
A. Milunsky, Genetics Lab., Eunice Kennedy Shriver Center, Boston, U.S.A.
J.D. Murken and S. Stengel-Rutkowski, Kinderpoliklinik, Universität München, West Germany
A.D. Patrick, Institute of Child Health, University of London, U.K.
W. Schmid, Kinderspital, Zürich, Switzerland
M. Stockenius, Zytogenet. Unters., St. Hamburg, West Germany
L. Svennerholm, Dept. of Neurochemistry, St. Jörgen Hospital, Göteborg, Sweden
E. Vamos, Groupe de Diagnostic Prénatal, Hôpital St. Pierre, Bruxelles, Belgium
M.T. Vanier, Hôpital Sainte-Eugenie, Lyon, France
U. Wiesmann, Dept. of Pediatrics, University of Bern, Switzerland

Contents

Chapter I

Congenital Disease and (Infant) Mortality and Morbidity

1. General introduction

Less than a hundred years ago infant mortality was in the order of 120–150‰ in most Western countries and as high as 200–300‰ in some poor rural areas and overpopulated cities. During the last century, however, there has been some general improvement but in developing countries in Africa, Latin-America and Asia with crude birth rates of 40–45/1,000, infant mortality is still 120–140‰ (McNamara's address to MIT, 1977). It is clear that in these countries improvement of economic, social, hygienic and nutritional conditions together with treatment and prevention of infectious diseases, has the highest priority.

In most industrialized countries, improvement of the living conditions has already led to a decrease of infant mortality to 15–20‰ and differences between various socio-economic groups have diminished. Health statistics in several of the wealthier countries show that congenital disease has now become the major cause of infant mortality, accounting for 25–35% of all infant deaths.

During the last decade, in the Western countries there has been increasing interest for congenital disease and human genetics. This is not only true for experts in different disciplines of medicine and psychosocial care but also for ethicists, lawyers, certain managers of industry, administrators, politicians and the general public. This broad interest seems to be due to a combination of factors:

- Congenital disorders have not only become the major cause of infant mortality, but are also responsible for a considerable proportion of infant morbidity.
- More and more couples want to limit their family size and no longer consider the birth of a handicapped child as "something one has to accept". Instead, people want extensive information about the risks of pregnancy and confinement and about the various possibilities of preventing congenital handicaps.
- During the last decade there have been major developments in the methodology of early diagnosis of patients and of carriers of genetic disease. In combination with early treatment or with proper genetic counseling and prenatal monitoring followed by selective abortion this has given new perspectives to people at risk.
- The increasing costs of health care have directed the attention of many governments towards programs that aim at the prevention of disorders which are associated with long-term physical and/or mental handicaps.
- Advances in basic research in molecular genetics, biochemistry and cell biology have been quite impressive during the last decades. The result of this research has given a better insight into the molecular basis of heredity and has led to new ways of experimental manipulation of genetic material derived from different individuals and organisms.

Not all developments in molecular research and clinical genetics have met with general enthusiasm and during the last few years there has been much debate about the ethical aspects and the possible dangers of some new methods and approaches. Although early judgement of the (possible) practical and moral merits of important scientific and clinical developments is valuable and necessary, some public discussions on human genetics have also shown shortcomings. It often seemed that emotional debate arose as a result of publicity on different issues which are not related but which have been mixed up because they were not sufficiently understood. Within a relatively short period of time people could read in nearly every newspaper or magazine: "that fetal sex and genetic disease can be detected in utero"... "gene has been synthesized in the test-tube"..."mouse × human cell hybrids used for gene localization"..."human genes manipulated into bacteria"... and "first test-tube baby born". Who blames the layman if (s)he becomes concerned about the future when such different developments are brought into the same context? Another source of confusion is that some experts emphasize too much the potentialities of their new method without mentioning sufficiently its limitations.

In addition to new developments in basic research and clinical genetics we should also pay attention to the question whether the already existing methods of diagnosis and prevention of genetic disease are optimally used. There are still many children with a congenital disease due to a well-defined chromosomal aberration or single gene mutation, who die without proper diagnostic tests having been made. In institutes for the mentally retarded 35–65% of the patients are still undiagnosed (Moser and Wolf, 1971; Crome and Stern, 1972; Costeff et al., 1972; McDonald, 1973; Crocker, cited by Milunsky, 1975). Many patients with an adult variant of a genetic metabolic disease are not identified as such when clinicians do not think of "the unusual" or when they are not familiar with the modern methods of molecular diagnosis. In many instances lack of expertise or facilities and insufficient collaboration between people from various disciplines result in unnecessary delay in the diagnosis; this in turn has the danger that parents at risk will give birth to several affected children. Various studies indicate that even among parents of a child with a disease of recessive Mendelian inheritance 60–75% were not aware of their 1:4 recurrence risk (Taylor and Merrill, 1970; Sibinga and Friedman, 1971; McCrae et al., 1973; Hall et al., 1978). In most areas only 5–25% of the couples at risk for a genetic disease which is detectable in utero, are referred to a center for prenatal monitoring (see also Milunsky, 1976). Altogether, there are enough reasons to pay more attention to the application of available methods of early diagnosis and prevention of genetic disease. In the following section some information will be given on incidences and recurrence risks of the various categories of congenital disorders and the chapter will be completed with an introduction to early diagnosis and prevention.