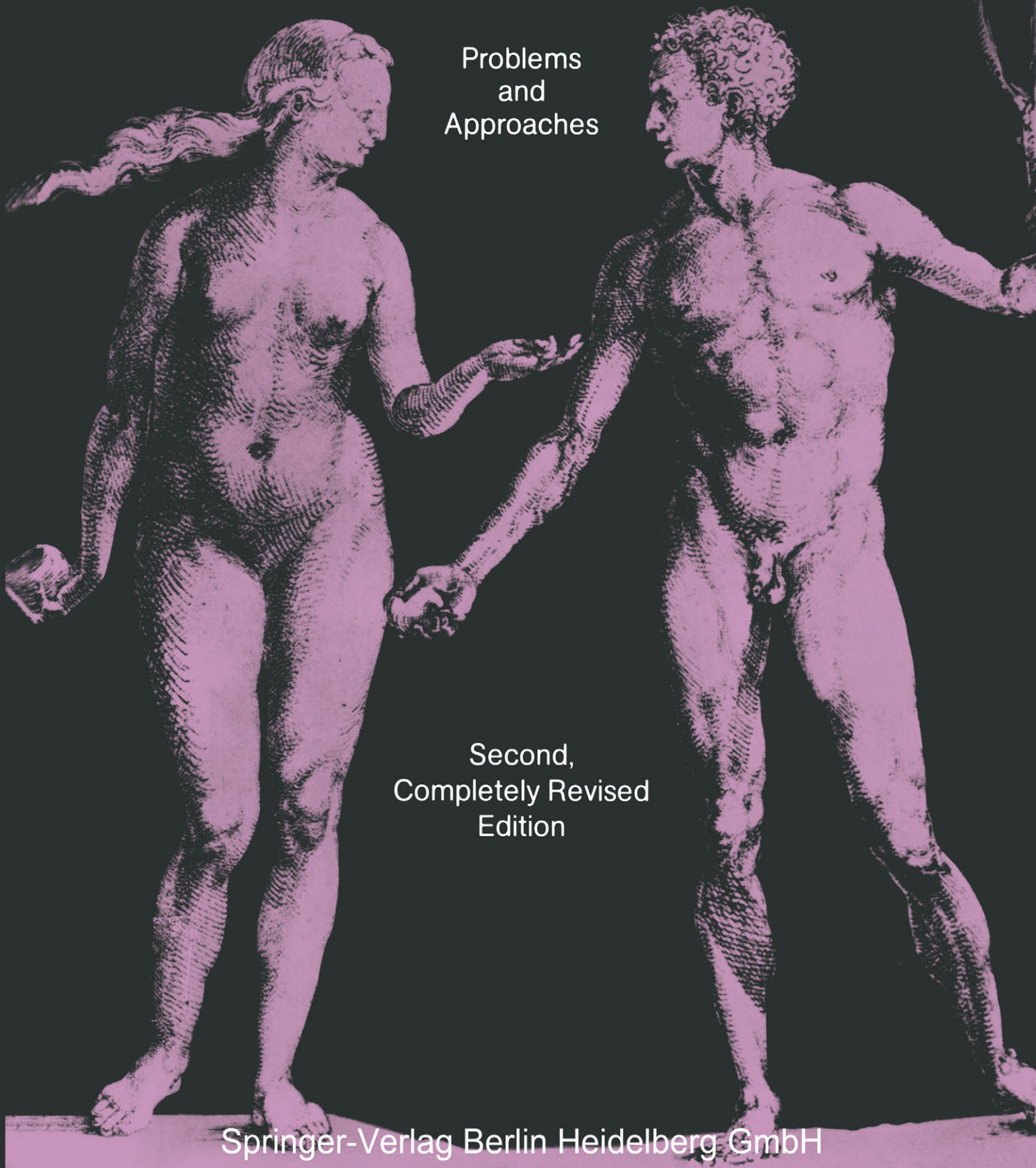
Vogel Motulsky

Human Genetics

Problems and Approaches



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F. Vogel A. G. Motulsky

Human Genetics

Problems and Approaches

Second, Completely Revised Edition

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To our wives and children

Preface to the Second Edition

The first edition of this book, published in 1979, was found useful by many students and was well received by the scientific community. Since the book was first written, human genetics has undergone dramatic developments, mainly due to the introduction of new concepts and techniques from molecular biology. Concomitantly, "basic" scientists have become increasingly interested in problems of human genetics. More than 700 human genes have been mapped, genes of previously unsuspected complexity - such as the gene for factor VIII - have become known, and the structure of noncoding DNA sequences is being analyzed with the aim of understanding gene regulation. DNA diagnosis is being rapidly introduced into medical genetics. All this, as well as the extensive progress in most other fields of human and medical genetics, had to be considered in the preparation of this second edition.

The book has been extensively revised and rewritten. A substantial new section dealing with gene and chromosomal structure at the molecular level has been added. The newer knowledge of molecular genetics has been incorporated, and the conceptual and practical contribution of DNA methods (for example in the hemoglobinopathies and in some other diseases) is discussed. Many new figures and tables have been added, and some illustrative material has been replaced.

We have read carefully the many friendly and sometimes flattering reviews of the first edition. A frequently voiced regret was that we did not deal more extensively with the practical aspects of clinical genetics. In response, we have added more material of clinical interest and have significantly expanded the chapter dealing with genetic counseling and prenatal diagnosis. However, the increasing body of knowledge of human genetics spanning both the basic and the clinical sciences makes it impossible to cover all hereditary diseases and their clinical implications. Furthermore, much of this material is dealt with in recent books and compendia which are listed in the enlarged general reference section. This book's aim remains the presentation of a cohesive and up-to-date exposition of the concepts, data, and problems underlying the theory and practice of human and medical genetics.

Many colleagues helped us in the preparation of this volume, including W. Buselmaier, T. Cremer, S. Gartler, E. Giblett, D. Götze, Vesna Najfeld, P. Propping, T. M. Schroeder-Kurth, K. Sperling, V. Sybert, and R. Stern. They should not be held responsible for any errors which may have crept in. Again, J. Krüger proved to be extremely helpful in all statistical matters. He advised us in replacing old-fashioned pencil-and-paper methods by the use of computers. Our secretaries, Adelheid Fengler in Heidelberg, Ingrid Rudolph in Berlin, and Sylvia Waggoner in Seattle, typed the new parts of the manuscript and succeeded in the formidable task of keeping everything in order. The new figures were again drawn by Edda Schalt.

Most of this edition was prepared in 1984, when we spent several months together at the Institute for Advanced Study *(Wissenschaftskolleg)* in Berlin (West), and in 1985. Partial support for A. G. M.'s stay in Berlin was provided by an Alexander v. Humboldt Award.

We hope that this second edition will, like the first, fulfill its purpose: to provide the necessary background of genetic concepts and their applications to those interested in and fascinated by the scientifically challenging and practically important field of human genetics.

Spring 1986

Friedrich Vogel, Heidelberg
Arno G. Motulsky, Seattle

Preface to the First Edition

Human genetics provides a theoretical framework for understanding the biology of the human species. It is a rapidly growing branch of science. New insights into the biochemical basis of heredity and the development of human cytogenetics in the 1950s heightened interest in this field. The number of research workers and clinicians who define themselves as full-time or part-time human and medical geneticists has increases sharply, and detailed wellfounded knowledge has augmented exponentially. Many scientists and physicians are confronted with genetic problems and use concepts and methodology of human genetics in research and diagnosis. Methods developed in many different fields of the biologic, chemical, medical, and statistical sciences are being utilized toward the solution of genetic problems. The increasing number and sophistication of well-defined and elegantly solved problems helps to refine an extensive framework of genetic theory. These new conceptual insights in their turn lead to solutions of new questions. To mention only one example, the structure of hemoglobin genes has been elucidated using methods derived from protein chemistry and DNA technology. It is an exciting experience to participate in these developments!
Moreover, scientific progress in genetics has practical implications for human well-being. Improved knowledge of the genetic cause of an increasing number of human diseases helps to refine diagnosis, to find new therapeutic approaches, and above all, to prevent genetic diseases. So far, human genetics has had less of an impact on the behavioral and social sciences. It is possible that genetic differences involved in shaping personality structure, cognitive faculties, and possibly human social behavior may be at least as important as genetic variation affecting health and disease. The data, however, are less clear and more controversial. These problems are discussed in detail in the text. The rapid progress of human genetics in recent decades has attracted - and is still attracting - an increasing number of students and scientists from other fields. Various elementary textbooks, more advanced monographs of various branches of the field, and the original journal literature are the usual sources of introduction to human genetics. What seems to be lacking, however, is a fairly thorough and up-to-date treatise on the conceptual basis of the entire field of human genetics and its practical applications. Often, the absence of a broadly based background in the field leads to misunderstanding of its scope, unclear goals for research, improper selection of methods, and imbalanced theoretical discussions. Human genetics is based on a powerful theory, but this implicit conceptual foundation should be made explicit. This goal is the purpose of this book. It certainly is a formidable and possibly even too audacious task for two sole authors. However, both of us have been active in the field for more than 25 years. We have worked on various problems and with a variety of methods. Since the early years of our careers, we have met occasionally, followed each other's writings, and were often surprised by the similarity of our opinions and judgments despite quite different early medical and scientific backgrounds. Moreover, our knowledge of the literature turned out to be in part overlapping and in part complementary. Since we are working in different continents, AGM had a better knowledge of concepts and results in the USA, while FV knew more of the continetal European literature. Moreover, both of us have extensive experience as editors of journals in human genetics

and one (FV) published a fairly comprehensive textbook in Germany some time ago (*Lehrbuch der allgemeinen Humangenetik,* Springer 1961), parts of which were still useful for the new book. We finally decided to take the risk, and, by writing an "advanced" text, to expose our deficiencies of knowledge, shortcomings of understanding, and biases of judgement.

A text endeavoring to expose the conceptual framework of human genetics cannot be dogmatic and has to be critical. Moreover, we could not confine ourselves to hard facts and well-proved statements. The cloud of conjectures and hypotheses surrounding a rapidly growing science had to be depicted. By doing so, we face the risk of being disproved by further results.

A number of colleagues helped by reading parts of the manuscript on which they had expert knowledge and by making useful suggestions: W. Buselmaier, U. Ehling, G. Flatz, W. Fuhrmann, S. Gartler, Eloise Giblett, P. Propping, Laureen Resnick, and Traute M. Schroeder. They should not be held responsible for possible errors. J. Krüger was of supreme help in the statistical parts. Our secretaries, Mrs. Adelheid Fengler and Mrs. Gabriele Bauer in Heidelberg, Mrs. Sylvia Waggoner in Seattle, and Mrs. Helena Smith in Stanford gave invaluable aid. The figures were drawn by Edda Schalt and Marianne Lebküchner. Miriam Gallaher and Susan Peters did an expert job of copy editing. The authors are especially grateful to Dr. Heinz Götze and Dr. Konrad F. Springer, of Springer Publishing Company, for the excellent production. The work could not have been achieved had the two authors not been invited to stay at the Center for Advanced Study in the Behavioral Sciences at Stanford (California) for the academic year of 1976/1977. The grant for AGM was kindly provided by the Kaiser Family Foundation, while the Spencer Foundation donated the grant for FV.

The cover of this book shows the mythical first human couple, Adam and Eve, as imagined by Albrecht Dürer (1504). They present themselves in the full beauty of their bodies, ennobled by the genius and skill of a great artist. The drawing should remind us of the uniqueness and dignity of the human individual. Human genetics can help us to understand humanity better and to make human life happier. This science is a cardinal example of Alexander Pope's statement. "The proper study of mankind is man."

Spring 1979

Friedrich Vogel, Heidelberg
Arno G. Motulsky, Seattle

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