GENETICS IN MEDICINE

THOMPSON AND THOMPSON

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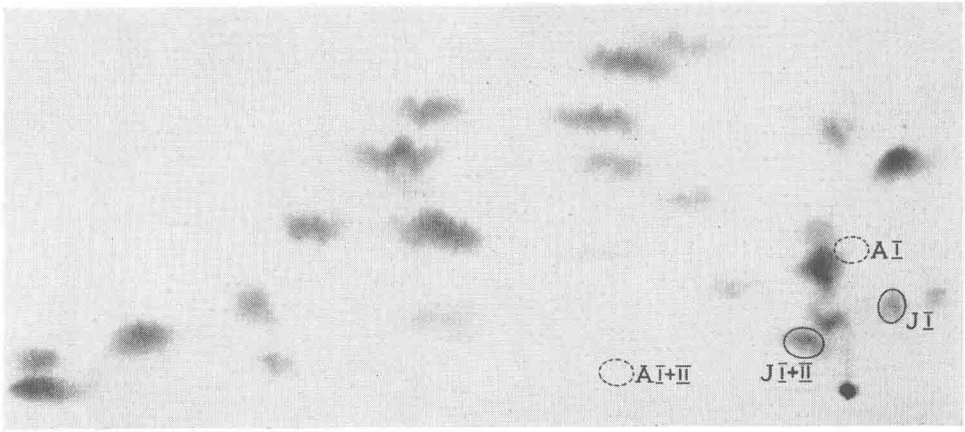
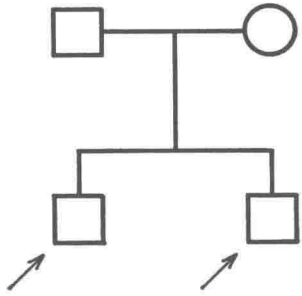


Fingerprint of Hemoglobin Jα Toronto, a New Abnormal Hemoglobin

To prepare a hemoglobin "fingerprint," the polypeptide chains of globin are first split into smaller peptide fragments by digestion with the proteolytic enzyme trypsin, which cleaves the chain wherever there is a lysine or an arginine residue. The small tryptic peptides (Tp) are then separated in two dimensions: horizontally by electrophoresis and vertically by chromatography. After staining with ninhydrin, each peptide appears as a dark spot in a characteristic position in the fingerprint.

Comparison of the fingerprint of Hb Jα Toronto with that of normal Hb A shows that two peptide spots have altered their positions, namely Tp I (known to contain the first seven amino acids of the alpha chain) and Tp I + II (containing the first eleven amino acids). In the illustration above, the positions of these two peptides in Hb A are labeled A I and A I + II, and their positions in Hb Jα Toronto are labeled J I and J I + II. Analysis of these peptides has revealed that the two hemoglobins differ by only a single amino acid: the alanine residue at the fifth posiiton in Hb A has been replaced by aspartic acid in Hb Jα Toronto (Crookston et al., 1965). Thus the precise formula of Hb Jα Toronto is $\alpha_2{}^{5asp}\beta_2$.



To our own F1

PREFACE

Genetics is fundamental to the basic sciences of preclinical medical education, and has important applications to clinical medicine, public health and medical research. With recognition of the role of genetics in medicine has come the problem of providing a place for it in the undergraduate curriculum, a problem which is as yet only partly solved in most medical schools. This book has been written to introduce the medical student to the principles of genetics as they apply to medicine, and to give him a background for his own reading of the extensive and rapidly growing literature in the field. If his senior colleagues also find it useful we shall be doubly satisfied.

We have attempted to make this discussion of genetic principles as clear and elementary as possible, and to focus it sharply upon medical aspects, rather than upon the mathematical aspects which are important in the methodology of genetical research but of less concern to the non-specialist. To reinforce the information contained in the text, we have added problems (with answers) which illustrate the kinds of genetical questions a physician may be called upon to answer. Most of them are quite simple, but even the simplest will require the student to spend a little time practicing the special terminology of genetics and thus make its special language his own.

Many persons have contributed to the preparation of this book, and we wish to record our indebtedness to them. Those of our colleagues who have read sections of the manuscript dealing with areas of their own special competence include L. E. Butler, G. E. Connell, Marie Cutbush Crookston, John H. Crookston, Nathan Kaliss, D. J. McCallion, T. E. Reed, Nancy E. Simpson, I. Tallan, W. P. Thompson, and Norma Ford Walker. We have greatly appreciated their thoughtful criticisms, and have made every effort to incorporate their suggestions; nevertheless, we ourselves must take responsibility for any inaccuracies or deficiencies in the final version. Mrs. E. E. Furness has done many of the illustrations. Acknowledgment is made in the appropriate figure captions to the authors and publishers who have given us permission to use copyright material,

but we wish to thank them here for the prompt courtesy with which our requests for such material have been granted. We are grateful also for permission to use much unpublished material; this is individually acknowledged. In particular we wish to thank Murray L. Barr and David H. Carr, who have been most generous with material from their fine collection of published and unpublished material.

It has been said that books are begun in enthusiasm, continued in anxiety, and completed in exhaustion. Through all these stages we have been sustained by the cordial good will and encouragement of Mr. John Dusseau and his colleagues at the W. B. Saunders Company.

J. S. T.
M. W. T.

Toronto, September 1965.

CONTENTS

CHAPTER ONE

INTRODUCTION

"The dispersion of a Nobel award in the field of genetics symbolizes the convergent efforts of a world-wide community of investigators. That genetics should now be recognized is also timely—for its axial role in the conceptual structure of biology, and for its ripening yield for the theory and practice of medicine."

Joshua Lederberg

(From the Nobel prize lecture, "A View of Genetics," given at the Royal Caroline Medico-Surgical Institute, Stockholm, May 29, 1959. As reprinted in *Science* 131: 269-276, 1960.)

The place of genetics in medicine was not always as obvious as it is today. The discovery of the principles of heredity by Mendel, an Austrian monk, in 1865, received no recognition at all from medical scientists and virtually none from other biologists. In fact, Mendel's original paper lay unnoticed in the scientific literature, while Darwin, for whom it might have clarified many concepts, and Galton, one of the great figures of early medical genetics, remained quite unaware of its significance or even of its existence. Mendel himself, perhaps discouraged by the results of other, less favorably designed experiments, took the course followed by many successful scientists: he left research and became an administrator.

Mendel's laws, which form the cornerstone of the science of genetics, were derived from his experiments with garden peas, in which he crossed pure lines differing in one or more clearcut characteristics and followed the progeny of the crosses for at least two generations. The three laws he derived from the results of his experiments may be stated as follows:

1. **Unit inheritance.** Prior to Mendel's time, the characters of the parents were believed to blend in the offspring. Mendel clearly stated that blending did not occur, but the characters of the parents, though they might

not be expressed in the first-generation offspring, could reappear quite unchanged in a later generation. Modern genetics texts lay little stress upon this law and may not even mention it, but in Mendel's time it was an entirely new concept.

2. **Segregation.** The two members of a *single* pair of genes are never found in the same gamete, but always segregate and pass to different gametes.

3. **Independent assortment.** Members of *different* pairs of genes assort to the gametes independently of one another.

With the dawn of the new century, the rest of the scientific community was ready to catch up with Mendel. By a curious coincidence, three workers (de Vries in Holland, Correns in Germany and Tschermak in Austria) independently and simultaneously rediscovered Mendel's laws. The development of genetics as a science thus dates, not from Mendel's own paper, but from the papers that reported the rediscovery of his laws.

The universal nature of mendelian inheritance was soon recognized, and as early as 1902 Garrod, who ranks with Galton as a founder of medical genetics, could report the first example of mendelian inheritance in man, alcaptonuria. In this paper Garrod generously admitted his debt to the biologist Bateson, who had seen the significance of consanguineous marriage in the parents of recessively affected persons. This is the first clear evidence of the interaction of research by medical and non-medical geneticists.

In the early years of genetics its fundamental significance was not apparent, and genetics was regarded as concerned only with the inheritance of trivial and superficial characteristics. However, with increasing understanding of the universal nature of the biochemical structure and functioning of living organisms there developed an awareness of the controlling role of the gene in basic life processes, a concept which was clearly formulated by Beadle and Tatum in 1941 as the "one gene–one enzyme" hypothesis.

The surge of new genetic knowledge has had fruitful consequences for clinical medicine. These consequences are all the more important because there has been a striking reduction in the importance of pathogenic organisms as causes of disease, with a corresponding increase in the importance of genetic factors as pathogens. For one population, Northern Ireland, it has been estimated that one-quarter of all chronic hospital beds are now used by people with genetic diseases.

MAN AS AN OBJECT OF GENETIC RESEARCH

A mouse can complete a generation within two months, a fruit fly within two weeks and a microorganism within 20 minutes, but man has a generation time of at least 20 years. In lower forms it is possible to make test matings to acquire desired information or to test hypotheses; but in humans nature makes the experiment and the investigator can only record the outcome. A mouse can produce scores of offspring in its lifetime, a fruit fly hundreds, and a microorganism millions; human families average

about three children each. Faced with these formidable obstacles, we must ask ourselves what compensations man has to offset his disadvantages as material for genetic research.

Whether or not it is true that, as Pope wrote, "the proper study of mankind is man," man's own fascination with himself facilitates research into his genetics. Since we consider man so important, we have expended more effort upon him than upon some of the more suitable research animals. Man is far more variable genetically than most other organisms, or at least his variations are better explored and documented; since most variations from the norm are deleterious, they come to the attention of the medical profession. Though the size of individual families is small, the population as a whole is very large; and though we cannot perform experimental matings, we are often fortunate enough to find that nature has performed the experiments for us. When population data can be fully extracted by computer analysis, there should be no lack of information on many aspects of human heredity. A brave beginning has already been made at exploring the genetics of human variation, and this has been successful to the point that some human diseases (notably the hemoglobinopathies) even provide the models upon which part of the conceptual structure of genetics has been erected. Some of the many areas in which genetics impinges upon medicine are described in the following chapters.

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CHAPTER TWO

THE PHYSICAL BASIS OF HEREDITY

When a cell divides, the nuclear material is seen to form a number of small, deeply staining bodies called **chromosomes.** The chromosomes replicate and the resulting chromosome pairs segregate in a very precise fashion so that each daughter cell receives a predictable complement of chromosomal material. Chromosomes are composed of **deoxyribonucleic acid** (DNA) on a framework of protein. The name chromosome refers to the property of staining deeply (*chromos* = color; *soma* = body). Segments of the DNA molecules comprise the **genes,** the units of heredity of which there are perhaps 100,000 per cell. Genes are arranged in a linear fashion along the chromosomes, each gene having a precise position known as a **locus**. Genes whose loci are in the same chromosomes are in linkage.

At any locus the actual biochemical composition of the individual gene may vary. All alternative forms of a gene found at one locus are called **alleles**, but any one chromosome bears only one allele for a given locus. The genes direct the synthesis of polypeptides, from which proteins are formed. Different alleles usually determine the production of different polypeptides.

The **genotype** of an individual is his full set of genes; the **phenotype** is the expression of those genes as physical, biochemical and physiological traits. (The same terms are frequently applied with a more limited meaning to signify specific genes and traits.)

The study of the relationship of the microscopic appearance of the chromosomes and their behavior during cell division to the genotype and phenotype of the individual forms the science of **cytogenetics.** Human cytogenetics made little headway until 1956, when Tjio and Levan developed especially effective techniques for the study of chromosomes in man. Since that time human cytogenetics has made rapid progress, and abnormalities of the chromosomes have been shown to have important scientific and clinical implications.

THE HUMAN CHROMOSOMES

Autosomes and Sex Chromosomes

There are 46 chromosomes in each human cell, each chromosome being one member of a homologous pair. There are therefore 23 pairs of chromosomes in each cell; one member of each pair has been received from the individual's father and one from his mother. Twenty-two pairs are alike in males and females and are called **autosomes**, but the remaining pair, the **sex chromosomes**, differ in the two sexes and are of major importance in sex determination. The two members of a pair of autosomes are usually microscopically indistinguishable. In the human female the sex chromosomes are also identical and are called **X chromosomes**. In the human male the two sex chromosomes are quite distinct, one being an X chromosome like the female X and the other being much smaller and known as a **Y chromosome.**

Chromosome Numbers

Since one member of each chromosome pair comes from the father and one from the mother, each parent contributes a total of 23 chromosomes, one of each kind. Each sex cell (**gamete**), whether **ovum** or **sperm**, is said to have the **haploid** (**n**) number of chromosomes (*haploos* = single); in man n = 23. The cell formed by the fusion of ovum and sperm (fertilization) is the **zygote**, and it has 23 *pairs* of chromosomes, or 46; this is the **diploid** (**2n**) number (*diploos* = double). Each normal human is composed almost entirely of diploid cells. (To avoid confusion note that we speak of "haploid" and "diploid" numbers although there is no such number as "ploid.")

MITOSIS

Mitosis is the type of cell division by which the body grows and replaces discarded cells. The cytoplasm at mitosis divides simply by cleaving in half, but the nucleus undergoes a very complicated series of activities which result in transmission to the two daughter cells of precisely the same chromosomal complement as that of the parent cell. Four stages of mitosis are distinguished: **prophase**, **metaphase**, **anaphase** and **telophase.** A cell which is not actively dividing is said to be in **interphase**. The stages of mitosis are shown diagrammatically in Fig. 2-1.

During **interphase** (Fig. 2-1a) the chromosomes are elongated and not individually distinguishable. The nuclear material thus appears granular. The chromosomes are metabolically active (with the exception of the sex chromatin body, a condensed and inactive piece of chromatin; see page 112). At this stage they do not stain differentially. As the cell prepares to divide, the chromosomes begin to condense by coiling up and so become visible as deeply staining bodies. As soon as the appearance of the nucleus changes and the chromosomes begin to be distinguishable, the cell has entered the first stage of cell division, prophase.

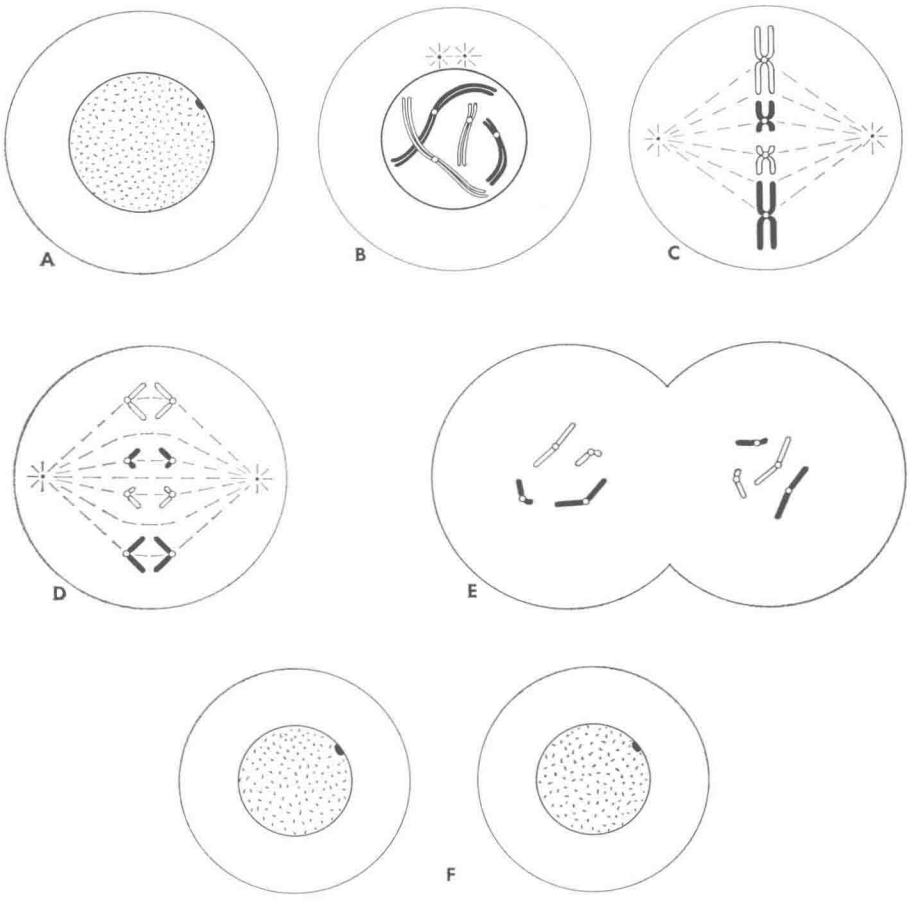

Figure 2-1. The stages of mitosis. Only two of the 23 chromosome pairs are shown. Chromosomes from one parent are shown in outline; chromosomes from the other parent in black. For detailed description, see text. (A) Interphase, (B) prophase, (C) metaphase, (D) anaphase, (E) telophase, (F) interphase.

1. **Prophase** (Fig. 2-1b). When the chromosomes have become visible, but before any pattern is discernible in their arrangement, the cell is in prophase. By this time the DNA content of the cell has doubled, and each chromosome can be seen to consist of two long, thin, parallel strands, the **chromatids**, held together at one spot, the **centromere** (**kinetochore**). (Homologous chromosomes are shown in black and white to signify that one member of each pair is derived from the father, the other from the mother.) The position of the centromere is constant for any one chromosome. Most of the chromosome material stains deeply and is said to be **euchromatic**, but certain areas stain differently, probably because of differential coiling, and these areas are called **heterochromatic**. (The types of chromatin associated with euchromatic and heterochromatic areas are **euchromatin** and **heterochromatin**.)