PATTERNS OF HUMAN HEREDITY

AN INTRODUCTION TO HUMAN GENETICS

James R. Brennan

PATTERNS OF HUMAN HEREDITY

AN INTRODUCTION TO HUMAN GENETICS

Prentice-Hall, Inc.

Library of Congress Cataloging in Publication Data

BRENNAN, JAMES R., date
Patterns of human heredity.

Includes bibliographies and index.
1. Human genetics. I. Title.
QH431.B664 1985 573.2'1 84-6798
ISBN 0-13-654245-X

Editorial/production supervision: Virginia Huebner
Interior design: A Good Thing: Howard Petlack
Cover design: Christine Gehring-Wolf
Manufacturing buyer: John Hall

Cover Photographs (James R. Brennan):

Top: Two different stages of contraction of human chromosomes in mitosis—white blood cells.
Middle left: Normal red blood cells and two white blood cells. The larger white cell is a polymorphonuclear leukocyte with a "drumstick" (condensed X-chromosome).
Middle right: Blood smear from Rh positive blood showing hemolysis due to Rh antibodies.
Bottom left: Cancerous tissue from human bronchus.
Center bottom: Blood smear of sickle-cell anemic showing sickled red blood cells.
Bottom right: Human cheek epithelium cell from the lining of the mouth.

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

ISBN: 0-13-654245-X 01

Prentice-Hall International, Inc., *London*
Prentice-Hall Australia Pty. Limited, *Sydney*
Editora Prentice-Hall do Brasil, Ltda., *Rio de Janeiro*
Prentice-Hall Canada Inc., *Toronto*
Prentice-Hall of India Private Limited, *New Delhi*
Prentice-Hall of Japan, Inc., *Tokyo*
Prentice-Hall of Southeast Asia Pte. Ltd., *Singapore*
Whitehall Books Limited, *Wellington, New Zealand*

PREFACE

Patterns of Human Heredity has been written for those who want to learn about the genetic basis of human life. It is hoped that it will provide a useful understanding of the hereditary mechanism at work in humans. Inherent in such an understanding should be a view of commonly shared genes within families and populations. Unique individuality arising from a background of vast diversity is a concept that deserves scientific support on this tense and crowded planet. All who profess to be educated today must know about the fundamental basis of individual differences.

The science of biology has expanded so greatly that it has become a contentious matter to design a "general" approach for college students. Opinions vary among professionals about what can and should be included now that so much must be left out. A commonplace approach in recent times has been to teach a one-semester course in "principles" and then allow nonmajor students to opt for an introductory course in a specialized area. I hope that students with diverse interests will see the merit to an exploration of human genetics in this context. It is hard to imagine a more interesting and relevant subject for a plethora of endeavors. Where "value oriented" courses are called for, this topic is significant.

The text is deliberately didactic and organized along lines that provide the most logical learning sequence for a novice human geneticist. Because we often learn best by repeating the historical development of a subject, this aspect has been emphasized.

The organizational sequence of topics is not likely to satisfy all others teaching human genetics. While the historical sequence is important and could be the best way for a beginner to approach the subject, the mathematics of Mendel seems much more meaningful after the gene has been defined chemically and physically. A good understanding of the reproductive process also provides a much clearer perception of the basics of genetics. Thus, these topics are placed ahead of a detailed look at Mendel's principles and examples of human genes. Chapter 7 could be dealt with immediately after Chapter 1. In this way Mendel's story of basic genetics could be studied first, followed by a chemical explanation of the gene (Chapter 4) and then the story of chromosomes (Chapters 5 and 6). If some prefer to do chromosomes prior to the chemical basis, the text is flexible enough for that option.

I prefer to discuss that important tool of human genetics, the pedigree chart, after all the basic genetics has been done (including sex linkage), at least for nonmajors. Again, an instructor could deal with Chapter 9 along with Mendelian genetics, or even do the first part of Chapter 9 before Chapter 7.

Instructors should feel free to change se-

quences. I believe that the text will be adaptable to such changes when it is necessary to fit a course structure.

The book will serve a most important function if it leads the reader to explore further the vast amount of knowledge that has been accumulated by the legions of international workers. Humans are quickly becoming the most well-known organism genetically, due to widespread interest and elegant new techniques. Every day exciting and astounding facts are added to the existing catalog of information.

Science in general, and biology in particular, is often viewed by students as studies centered on words. Many times memorization and regurgitation of terms are substituted for an understanding of concepts and ideas. Unfortunately, if one is to develop concepts and discuss them with others, a reasonable vocabulary of precise scientific terms is essential. To remind students of this, boldface type is used to draw attention to words that will be helpful in dealing with the concepts presented.

Likewise, a fairly short glossary (by biological standards) appears at the end of the text. Some of the more frequently used and significant terms that are printed in boldface type have been included. Terms that are likely to be encountered only once or twice in the text, or that do not carry broad significance, have not been included. Specific disease names or detailed structures and chemicals are also not in the Glossary. The definitions provided are brief and simple, limited in their utility to the context of this subject. More thorough and technical definitions can be found in dictionaries or more detailed texts.

By no means is an exhaustive list of genetic traits included here. It would not serve the intended purpose of this fundamental approach, nor would it be possible. Once the basic ideas have been mastered and a vocabulary developed, students can find information about the genetics of many other human traits simply by involving themselves in some detailed research.

At the end of each chapter a short list of additional readings is provided. Some are general, some very specific; some are easy to read, some fairly rigorous. The list only samples some topics; as always, they will lead on to even more sources of information.

The Review Questions at the end of each chapter are there for the purpose of getting students involved directly. They are not easy and sometimes a direct, undebatable answer cannot be found. The questions may require a student to delve into additional sources of information and to spend some time thinking about responses. This thinking will often lead participants to a topic covered later in the text. Whether assigned or not, the questions are integral parts of the text that should expand each student's understanding considerably.

Each chapter ends with a summary. When all work on a chapter is finished, including any additional reading and problem solutions, students can profit from using the summary to review the material. If an attempt is made to expand and embellish he concise summary with as many details as can be remembered, a student is likely to view the material as a unit and not as a series of disjunct facts and ideas.

I am indebted to Bridgewater State College and The Open University in Milton Keynes, England, for providing good colleagues and a quiet, intellectual atmosphere where thinking is stimulated. Mostly my thanks are due to people who shared their thoughts and time. Cathy Lauwers, Diane Peabody, and Walter Morin have read manuscript and made valuable comments. Claire Devincentis has turned my unreadable scratchings into neatly typed pages. The sketches of historical personalities by Christine Polivogianis added greatly to the descriptions. Thanks to all who have helped, directly or indirectly!

JAMES R. BRENNAN
Bridgewater, Massachusetts

CONTENTS

8

9

10

CHAPTER

1

THE ORIGIN OF A SCIENCE

Who wer as lyke as one pease is to another.
John Lyly, *Euphues* (1578).

As long as humans have been able to make thoughtful observations of themselves and their characteristics, there have surely been questions about inheritance of various traits. It is embarrassing sometimes to a child to stand up to comparisons made by relatives and friends in regard to real or imagined similarities and differences between parents and offspring or among siblings. This comparative process must have taken place in early periods of human history, with no adequate explanations for the mechanism of heredity and variation in offspring.

However, some basic, sophisticated knowledge of hereditary patterns was possessed by certain cultural groups of humans early in history. A familial association of red-green colorblindness was known to the ancient Greeks, while the Hebrews in the second century A.D. showed a rudimentary understanding of the association of hemophilia to sex determination. However, such isolated bits of knowledge did not constitute a body of concepts that could be distinguished as a science.

The development of a valid explanation for the patterns of **heredity** and **variation** was impeded because early observers tried to fathom simultaneously the mechanism determining inheritance for many characteristics in a single individual. An adequate explanation could only be obtained easily by considering one trait at a time. Science is sometimes a deceptive field of endeavor: The simplest explanation, disdained by great thinkers, is often the only valid route to true understanding. Genetics thus eluded the powers of human understanding until one man carefully considered the patterns he found in one of his favorite living things. Using the powers of mathematical logic in his train of thought, he was able to analyze in a fashion that brought forth an explanation.

THE BEGINNING

For many years prior to 1865, biologists attempted without success to understand the principles of inheritance. Many prominent scientists observed and studied various characteristics of living organisms in an effort to interpret the mechanism involved in the passage of traits from one generation to the next. However, no satisfactory explanations were proposed until 1865 when an Austrian monk named Gregor Mendel (Fig. 1.1) offered a well-documented theory at a meeting of the Brunn Society for the Study of Natural Science. His work, compiled after eight years of careful research, was clearly organized and logically designed to explain the process of inheritance, but Mendel was years ahead of the scientific world. Little was understood concerning reproduction and cellular structure, and the significance of his work was not clear to his fellow scientists. Mendel's research made little impression on those present at the meeting, and only slight recognition was given to the carefully assembled data. The paper that Mendel presented in two successive readings in February and March of 1865 was published in the Proceedings of the Brunn Society and appeared in print

Figure 1.1. Gregor Mendel (1822–1884), whose careful research with pea plants revealed the basic mechanism of heredity.

in 1866, but it was overlooked by Mendel's contemporaries. Other scientists saw the publication in later years, but they also missed its significance.

The biological world at the time was preoccupied with a new theory by Charles Darwin and Alfred Wallace. Their work concerned **evolution** through **natural selection**, and it stimulated much scientific thought, debate, and controversy. So startling were the ideas of Darwin and Wallace concerning the common ancestry of living things, there is little wonder that the biological world overlooked the unimpressive experiments of an obscure monk. Darwin and Wallace were right in their basic theory that living things change and adapt with time and circumstances. Unfortunately, they had no idea what the mechanisms of inheritance were which permitted such a phenomenon. Ironically, Mendel's work contained an explanation for the way in which evolution is directed, but the relationship would not be recognized by biologists for many years.

In 1900 three biologists from different parts of the world independently rediscovered the principles Mendel had outlined and recognized the value of his work. Carl Correns in Germany, Hugo de Vries in Holland, and Erich von Tschermak-Seysenegg in Austria had conducted original studies concerning the mechanism of inheritance and noted the original work in their reports (Fig. 1.2). Technically, the science of **genetics** was born with Mendel's first report in 1865. In reality, its birth

Figure 1.2. Clockwise from upper left: Erich von Tschermak-Seysenegg (1871–1962), Hugo de Vries (1848–1935), and Carl Correns (1864–1933) who all independently rediscovered Mendel's principles of heredity in 1900.

occurred in the year 1900. In the decades that followed research into the study of heredity proceeded rapidly, leading to one important discovery after another. Seldom does such a clear-cut and well-documented origin exist for a field of study.

Science rarely proceeds smoothly, in effect, with a simple sequence of discoveries that logically lead to more complex ideas. Even though the seeds for an explanation of evolution through natural selection were present in Mendel's work, Darwin's theory was thoroughly debated and discussed without consideration for the mechanism of inheritance, often with rather weak arguments on both sides. So it was also with Mendel's ideas. Biologists of his time primarily observed and described what they saw and they were unable to apply mathematics to biological phenomena. Mendel himself knew practically nothing about cell structure and chromosomes. In his work even the process of reproduction was vague and basic descriptions of the process were almost nonexistent. No doubt Mendel would have been able to analyze more accurately and understand more thoroughly if he had known more about **cells, chromosomes, fertilization,** and formation of **reproductive cells.** Likewise, if Darwin and Wallace had known and understood the principles outlined by Mendel before proposing their evolutionary ideas, their theory of evolution through natural selection might have been more solidly based.

Genetics has had many contributors to the understanding of the simple, underlying processes, and it is somewhat unfair in a short discussion to select a small number of the most important workers in the field. However, the parade of biologists who followed Mendel is long and varied, and it is not difficult to name some who contributed significantly to the origin of the science.

The new science of biological inheritance came to be known as **genetics,** a name applied by William Bateson of England in 1906. He developed this name by using the word **gene,** a term that had been coined by Wilhelm Johannsen, a Danish botanist, in 1902. Mendel had referred to the units of inheritance simply as **factors.** He implied that some sort of particle was transmitted from generation to generation, but could not define it. He did not understand that cells were involved. Neither Johannsen nor Bateson knew what type of particle was involved, but this did not prevent genetic experiments or the naming of the unseen units.

William Sutton, an American graduate student, and Theodor Boveri, a German researcher (Fig. 1.3), knew something about the internal structure of cells and the process of reproduction. They were involved in studies in another new and rapidly developing science, **cytology,** the study of cells. They were familiar with the developments in genetics and recognized a similarity between genes and objects found in living cells called "chromosomes." Both suggested in 1902, from their own separate studies, that the genes are located on the chromosomes. (The evidence suggesting this theory is discussed in depth in Chapter 2).

The idea that genes are present on the chromosomes was proven through the efforts of T. H. Morgan and his coworkers starting in 1911. Most of their work was done using the common fruit fly *Drosophila* as experimental material. *Drosophila* proved to be an excellent organism for genetic studies. It has come to be the most completely studied and well-understood multicellular organism in regard to inheritance. These early studies in **cytogenetics** (cytology and genetics combined) con-

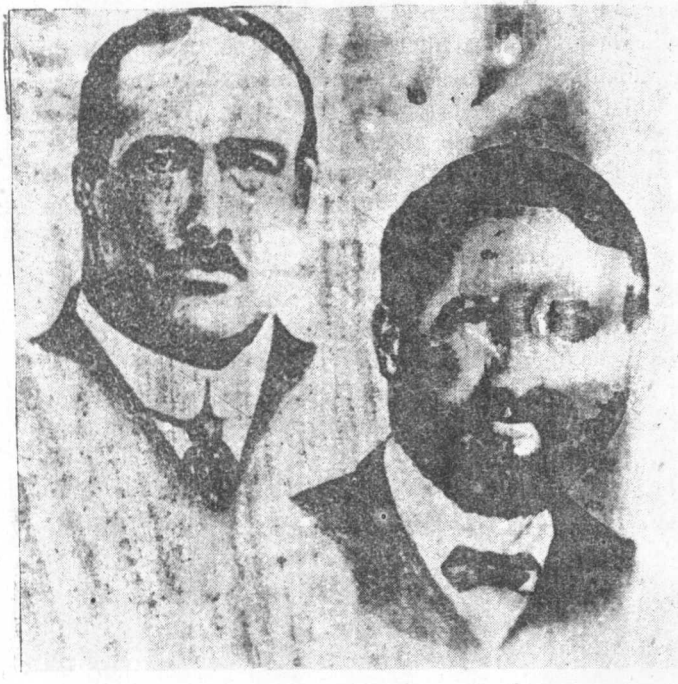

Figure 1.3 William Sutton (1877–1916) (left) and Theodor Boveri (1862–1915) (right) both independently recognized that chromosomes were the physical bases of Mendelian genetics.

firmed not only that genes are on chromosomes, but that there are many more than one gene per chromosome.

No description of the founding of the science of genetics would be complete without mentioning the work of William Bateson and R. C. Punnett. These early geneticists repeated and supplemented Mendel's work using sweet peas. They then studied poultry intensively in light of this new information concerning heredity. In all, they applied the principles discovered by Mendel to nine different genera of plants and four different genera of animals between the years of 1903 to 1913. Their work truly established genetics as an important and useful area of study.

INITIATION OF HUMAN HEREDITY STUDIES

It is difficult to determine when the early geneticists realized that their embryonic science had strong implications for the understanding of human patterns of inheritance. Possibly Mendel saw a parallel between his peas and humans. Certainly some of his followers did after the rediscovery of his work in the early 1900s. No matter what organism serves as experimental material for a biologist, no matter what phenomenon is being studied, sooner or later the comparisons to humans must develop.

Medical science is the area most concerned with an understanding of human biology. Therefore it is within the medical establishment that most of the advances

in understanding of human heredity have taken place. Because of the small number of offspring produced by individual human parents, as well as the cultural and moral restrictions imposed on the human mating process, humans are not suitable for the type of experimentation and analysis done on pea plants by Mendel. The most commonly analyzed human genetic traits are those associated with serious defects encountered in a medical context. Development of an understanding of human genetics in the past has therefore been slow and dependent on information obtained from other living organisms.

The painstaking process involved in understanding human genetics was illustrated in 1900 when Karl Landsteiner, a physician in Vienna, discovered the blood typing system and the **ABO** transfusion incompatibilities between **sera** and **red blood cells.** Although this discovery came to the biological world simultaneously with the rediscovery of Mendel's work, it was not until 1925 that Felix Bernstein, a German, was able to describe the correct hereditary mechanism controlling this basic human genetic trait.

The "father" of human genetics is usually considered to be Archibald E. Garrod, a British physician (Fig. 1.4). In 1901 he described 11 cases of **alkaptonuria,**

Figure 1.4. Archibald Garrod (1858–1936), recognized as the father of human genetics for work with his so-called "inborn errors of metabolism" such as alkaptonuria. He was the first to demonstrate genetic control of biochemical reactions in the body.

a **metabolic disorder** in which the compound alkapton accumulates and is excreted in large amounts in the urine. Garrod recognized that this condition resulted from a defective metabolic process and he classified the disease as an "inborn error of metabolism." Aware of Mendel's recently discovered work and noting similarities, he demonstrated that alkaptonuria was due to a single **recessive** gene which could then be associated with one enzyme.

By 1909 when Garrod's book, *Inborn Errors of Metabolism*, was published, he recognized that the features of alkaptonuria were caused by the accumulation of alkapton which resulted from a failure of the body to break it down. He was the first to identify a human gene according to the new Mendelian system and the first to recognize that genes can control biochemical processes which are mediated by **enzymes.**

Like Mendel, he was well ahead of his time, almost stating what has come to be known as the "one-gene, one-enzyme hypothesis." Not only did his work give rise to the field of human genetics, it also gave birth to **biochemical genetics.**

Because Garrod was a medical doctor, he was able to correlate a distinct, discontinuous medical trait with a familial inheritance pattern. The study of medically disabling genetic patterns was of great interest and significance in view of the predictability shown by Mendel for genes. Even today the most intensely studied human inherited traits are those that are disabling. Diseases are first recognized and most completely understood within a medical context. Thus, some of the most active efforts made in human genetics involved medical researchers and practitioners who were able to combine their work with genetic analyses.

The origin of human genetics studies occurred very close to the rediscovery of Mendel's work. In general, rapid and important advances took place in genetics, while human studies lagged somewhat. Landsteiner and Garrod had laid the groundwork for an understanding of human heredity at the cellular and molecular levels, but human traits were not obviously Mendelian in their inheritance patterns and humans were not easily studied in regard to genetics. A realistic understanding of human genetics evolved as the control of proteins by genes developed in the 1950s. An understanding of blood proteins and changes resulting from mutations opened up new vistas for study.

Blood proteins, enzymes, and finally the immune reaction based on proteins led to human applications of the rapidly expanding science of **molecular biology**. In the 1960s, new techniques of chromosome analysis provided the tools needed to associate specific genetic effects with chromosomal changes. An understanding of the molecular structure of the hereditary material in the 1950s and a detailed understanding of the means of controlling physical characteristics through the control of protein synthesis in the 1960s not only provided understanding but began to provide medical solutions to heretofore insoluble problems. Whereas bacterial cells provided a basic understanding of genetic mechanisms in the 1950s and 1960s, cultured human cells began to give answers specific to human chromosomes and genes in the 1970s. Infinitely more complex than bacteria and of considerably different structure, human chromosomes continue to be studied with exciting new results and astonishing prospects for manipulation and control.

Genetic mechanisms determining the characteristics of humans have been re-

vealed only after slow, painstaking studies of families showing distinctive patterns of inheritance. In the 1940s studies of ***erythroblastosis foetalis***, a serious blood disease in infants, went on simultaneously and independently from experimental studies of various *Rhesus* monkey blood types. Monkey blood types and *erythroblastosis* were found later to be due to the same phenomenon, resulting from similar blood chemicals. Thus, a genetic basis did not suddenly become apparent, but the divergent work of many investigators led to its discovery as an important feature of human genetics.

Research interest in human heredity is currently centered on many diseases and debilitating conditions which have been revealed to be hereditary during the last three or four decades. In well-known situations like **phenylketonuria**, a genetic metabolic disease that results in serious brain damage and retardation, and **erythroblastosis foetalis**, treatments have been devised which circumvent the genetic determination of characteristics. Thus, it has proved advantageous to identify such problems very early in an individual's life to allow medical remedies to be utilized.

There are inherited diseases for which no distinct treatment is available, and an important medico-genetic area of endeavor has centered around means of identifying individuals who may transmit genetic defects. As a result, counseling about options that may be available in such situations has become an important aspect of human genetics.

Because of the practical implications of such important areas of research, medical science has devoted much attention in recent years to the investigation of hereditary defects. A large amount of knowledge of human genetics has been assembled and a pattern for the understanding of other genetically controlled features has developed. As more genetic features are revealed, the search for cures for those that are detrimental goes on. In addition more efforts are being devoted to disseminating such knowledge to the public.

GREGOR MENDEL, THE FIRST SUCCESSFUL GENETICIST

One can only wonder whether Mendel really understood the importance of his unnoticed research report in 1865. The fact that his work looks simple and unspectacular in comparison to our current knowledge in the field does not lower its significance. Mendel, through his genius for painstaking study and careful assemblage of data, was able to determine the orderly operation of a process that seemed chaotic to others.

Gregor Mendel was uniquely well prepared for his discoveries. Because his father was a farmer, he had a basic understanding of agricultural practices. He knew about contrasting characteristics among pea plants and was familiar with methods of culturing them, as well as methods of making **viable crosses** between two chosen parents.

Mendel was also a mathematics teacher. He was able to analyze mathematically the numerous pea plants he grew in the monastery garden and visualize them as segments or proportions of a large family. Even though he had failed to graduate from