THE GENETIC JIGSAW

The story of the new genetics

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Foreword

by SIR WALTER BODMER

Apart from identical twins, we are all different in a multitude of ways. Identical twins are the only pairs of human individuals who are exactly the same genetically. All the rest of us differ in what we have inherited, and it is mainly those inherited differences that make each of us the unique individual that we are.

Among those differences are many diseases. Indeed most diseases, other than infections, have a substantial inherited component, or, in other words, are determined to a considerable extent by our genetic make-up. That genetic make-up, the individual blue-print that determines the features of all the cells in the body and how they work together to make up the whole human being, is determined by DNA, the key chemical of life.

Over the past ten years, there as been a revolution in our ability to analyse, handle, and interpret the language of the DNA molecule, which is the true language of life. Once obscure afflictions like colour blindness, or troublesome diseases like duchenne muscular dystrophy, can now be understood at the detailed molecular level. That understanding provides enormous power for new approaches to preventing and curing the major chronic diseases of our age: cancer, heart disease, mental disease, and the destructive auto-immune diseases such as rheumatoid arthritis.

Robin McKie has produced, for the non-specialist, a most readable and exciting account of this revolution in our ability to read and understand the genetic language. From his text you can experience some of the excitement that underlies the greatest adventure yet undertaken in understanding the human organism. Of course there are problems raised by this new understanding. They must be faced and discussed and explained. All new knowledge has the potential for good and evil uses and it is the responsibility of an informed society to ensure that the good prevails. Ignorance is incomparably more wicked than knowledge. This book makes a valuable contribution to the public understanding of the scientific issues underlying the modern revolution in genetics, an understanding which is needed if the benefits of this revolution are to realize their full potential.

Acknowledgements

The purpose of this book is to relate the remarkable story of the new genetics, a science which will soon have a profound impact on all our lives. It has been written for the general reader who has no particular knowledge of scientific matters but who is anxious to learn about this exciting and important new topic. As a result, I have endeavoured to make genetics as accessible as possible and have tried to avoid using the many complex terms that form the language of genetics and which can bedevil people's attempts to understand the subject.

To this end, many scientists, doctors, and health workers gave invaluable assistance and time in explaining their work. I am particularly indebted to Sir Walter Bodmer, of the Imperial Cancer Research Fund, and to Dr Bernadette Modell, of University College Hospital, London. They not only provided information, read the manuscript and offered expert advice, but gave support for the book when it was most needed. In addition, Professor Bob Williamson of St. Mary's Hospital, London, provided much advice and help.

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Introduction

Inside our bodies, tiny biological time-bombs are ticking away In the cells that make up our muscles, bones, and organs are genes that have gone wrong Each of us has about a hundred thousand genes which determine our physical characteristics and attributes—but every person also has at least five or six that have become altered in a dangerous way. These are genes for genetic diseases.

Usually people are unaware they are carriers of such hereditary disorders—because their health is unaffected. But sometimes a carrier meets and marries another carrier—unaware of their mutual condition –and they produce a child that has a genetic disease. When that happens, one of these biological bombs 'explodes' Parents can face the harrowing experience of watching a child slowly die or undergo painful treatment and surgery

Fortunately, although we all carry defective genes, these differ greatly from person to person Only unlucky carriers produce offspring with spouses who are carrying exactly the same defective genes As a result, birth rates for most inherited diseases are low For instance, Tay Sachs disease, which causes blindness and mental retardation, affects only one child in 200,000; thalassaemia, one in 20,000; and haemophilia, one in 10,000

Other genetic diseases are more common, however Cystic fibrosis, a fatal, wasting affliction of the metabolism occurs in one in 2,000 births in the West, while muscular dystrophy, a progressive weakening of the muscles, affects one in 5,000

In all, about 5 per cent of children admitted to hospitals have genetic disorders And each, no matter how rare is their condition, is a source of anguish to parents who feel helplessness and guilt Many families break apart as they struggle to cope with a

crippled or dying child. 'If only we'd known' is the frequent, understandable cry of parents.

But now signs of hope are emerging. Some parents are already being given tests that can provide crucial early warnings. In American and British hospitals it is now standard practice to test all newborn children for the recessive disorder phenylketonuria (PKU), which can cause childhood mental retardation. A sample of the baby's blood is spotted on to filter paper and given a simple chemical test. Children found to be positive can then be fed on a special diet that prevents mental retardation occurring in later life.

Tests for PKU and other similar conditions rely on the presence (or absence) of particular chemicals in the baby's body. But today scientists are perfecting a far more revolutionary technique. They have found ways to detect directly individual genes that are responsible for disorders such as cystic fibrosis and thalassaemia. Already, screening programmes to pinpoint carrier parents, and then to detect affected foetuses which can be terminated, have been launched successfully in several countries, including, intriguingly enough, several Catholic nations, such as Italy.

These families are the first beneficiaries of a genetic revolution which has started to sweep the medical world. This is the science of 'the new genetics'—the recent discoveries in molecular biology which now allow scientists to study and alter the fine structures of genes.

The revolution, which started in 1953 when Francis Crick and James Watson discovered the structure of DNA, the building blocks of life, is now in full motion. Subsequent discoveries showed molecular biologists how to cut DNA into small, precise fragments. These pieces can then be made to reproduce so scientists have ample copies on which to experiment. In addition, paediatricians have perfected new, simpler ways of taking samples of foetal tissue from pregnant women.

As doctors and scientists become increasingly successful in controlling environmental diseases—those caused by viruses, bacteria, or pollutants—then this newly acquired ability to tackle

disorders which are genetically determined will assume a greater and greater importance in modern health care.

But families at risk of gene disorders will not be the only ones to feel the dramatic impact of the new genetics. Very soon, it will permeate every aspect of our lives. In fact, scientists and doctors are now in the process of creating an entirely new type of medicine, one which acts at the level of our genes, those gossamer strands of DNA that lie coiled within the cells of our bodies, and which control our physical characteristics—our height, eye and hair colour, and other features

By tackling diseases at this level, doctors will be creating a very powerful new medical arsenal. 'I think it is impossible to overestimate the impact that this new medicine of molecular genetics will have', says one pioneer, Professor Bob Williamson, of St Mary's Hospital, London. 'We can now begin to tackle illnesses at a new deeper level—at the molecular level. It will revolutionize medicine in all sorts of ways '

But the new genetics will also raise many important moral questions about the type of people we wish to produce in future generations. As another of its pioneers, Oxford's Nuffield Professor of Clinical Medicine, Professor David Weatherall, acknowledges: 'The potential for serious social and psychological damage is immense.'

An example of possible danger is provided by the American attempt to set up a screening programme for the crippling blood disorder, sickle cell anaemia (which particularly affects black people). This ended in disaster. In some states, screening for carriers was made mandatory—without proper provision for education or counselling In addition, information about carriers was not kept confidential, and was used as an excuse to discriminate over jobs and insurance, though carriers posed no threat to anyone except their own unborn children.

In contrast, highly successful programmes for screening Jewish couples in America for Tay Sachs disease and Greek Cypriots in London for thalassaemia (diseases to which each group is prone) have been established, despite possible problems of provoking racial resentment.

Other worries concern tests that will pinpoint victims of fatal inherited disorders in an early, symptomless stage of their condition, and reveal if they will succumb in later life. One such disease is Huntington's chorea, a crippling muscular condition that leads to dementia and death in middle age. Many people, at present at risk of developing such ailments, are desperate to find out their true condition. Others are equally adamant that they would prefer not to know until symptoms do—or do not—appear. The widespread use of genetic screening tests, and their requirement by insurance firms and employers, would rob the latter group of people of their last psychological defence: ignorance. As Peter Rowley, professor of medicine, genetics, and microbiology at Rochester University, New York, puts it: 'Genetic screening is certainly not a panacea—nor is it an anathema.'

The use of genetic screening tests to detect Down's syndrome and other conditions that cause mental retardation in children is less contentious. Such disorders are related to a mother's age, to conditions in the womb, and to other factors. But some tend to run in families, and genetic tests may soon spot those at particular risks of producing affected babies—which will allow them to be selected for special screening.

But there are other, more general, health problems that are also destined to become the province of the new genetics. Most inherited diseases are disorders of single genes. However, combinations of several different interacting genes can also have unpleasant consequences. Heart disease, mental illnesses, autoimmune diseases (such as rheumatoid arthritis), and even cancer are all known to have complex genetic components.

By detecting such gene clusters, doctors will be able to warn patients about risks they face in later life. Already some American firms in the chemical and dye industries have announced plans to monitor workers for genetic susceptibilities to cancer. Those found to be specially prone would then be told to work elsewhere. Similar probes will also discover those at particular risk of heart disease, so they can be warned to avoid fatty foods that might otherwise cause blockage of arteries.

Such tests have obvious benefits. Doctors will be able to spot people who are prone to certain conditions, and then warn them about the dangers they face in particular environments or professions. Just as haemophiliacs know to avoid jobs in which there is danger of blood spilling (like butchery), so those prone to heart disease could be counselled about their diet from an early age.

It all sounds very rosy. But care will have to be taken with such tests. Inaccuracies would sentence some workers to unjustified redundancy. Researchers also argue that it is still more important for companies to clean up their industrial processes. Genetic screening programmes may simply give firms an excuse not to take such action. As one American union official put it: 'Never mind about weeding out the susceptibles, let's clean up the workplace.'

A more general, related problem is outlined by Professor Arno Motulsky, director of the Centre for Inherited Diseases at Washington University. 'Predictive medicine will become increasingly possible with the new developments in DNA and genetic marker technology', he says. 'And as public bodies assume a more direct role in health systems in many countries, confidentiality may become eroded, and genetic information may be used by social and health planners to assign individuals their niche in society.'

But the new genetics is likely to have an even more pervasive use—in the analysis, understanding, and exploitation of simple physical and intellectual skills. 'The most important aspect of all genetic variability is *that* affecting normal behaviour', says leading British geneticist, Sir Walter Bodmer. 'That variability determines differences in ability—physical, musical, or mathematical for instance. And these differences—which contribute so much to an individual's life-style—surely have major genetic components.'

'Genetic differences between individuals are very important factors in human society. The understanding of these factors may be a more fundamental contribution of genetic advances than their more obvious and direct applications to particular diseases.'

The new genetics will therefore take us from the relatively rare—from an understanding of specific single-gene disorders—to the very general—to an appreciation of everyday differences between humans. But what will we do with that understanding? It is a question that has produced lurid predictions about designer-made babies and cloned human beings. This is the more fanciful aspect of the new genetics to which most media attention has been devoted.

Nevertheless, scientists do acknowledge that one day they will be able to interfere directly with, and replace, human genes. In fact, they view screening programmes as mere stepping-stones to a better tomorrow. Selecting malformed babies for abortion is not their idea of good medicine. They want to put right malformations and save foetuses in the first place. Already tentative steps are being made towards that goal.

In America, scientists such as Dr Thomas Caskey, of Baylor College of Medicine, Houston, have been carrying out animal experiments in gene therapy. Target disorders are rare inherited diseases which prevent babies from fighting off infections. Sufferers have little hope of living beyond childhood. An attempt to use specially engineered 'vector' viruses to carry a crucial missing gene into a victim's body could provide the answer, says Caskey.

The technology is still crude, he admits, but it is developing rapidly. However, will it ultimately lead to the creation of genetically engineered humans worthy of a science fiction film? Most scientists are doubtful. At present, they are only considering inserting genes in cells that are not involved in reproduction and the passage of genes to a new generation. For the immediate future, gene therapy will affect only individuals, they say. Nevertheless, once that technology is perfected, it should become possible to affect reproduction cells as well. For the first time, scientists will be able to alter not just individuals but unborn generations. The entire gene pool of the human species will be open to the manipulations of scientists.

And where will it end? Could parents one day be offered the chance of adding or subtracting genes for attributes for their

children as they saw fit? The prospect horrifies some, but delights others. 'With human genetic engineering, we get something and we give up something', says Jeremy Rifkin, the American anti-biotechnology campaigner 'In return for securing our own physical well-being, we are forced to accept the idea of reducing the human species to a technology designed product.' But Oxford philosopher Jonathan Glover disagrees. 'To renounce genetic engineering would be to renounce any hope of fundamental improvement in what we are like', he states.

It remains to be seen just how far the new genetics will take us toward such a Brave New World With some care it may be possible to avoid the worst pitfalls.

Nevertheless, there will certainly be problems, for the new genetics is developing at an astonishing rate. People must be informed now about its impact on their reproductive prospects. This will not be an easy process. Few have more than a basic inkling of the biology needed to make sense of the new genetics. Young people leave school today with little knowledge of biology and the laws of genetics—an inadequacy that reflects widespread ignorance about this most profound of topics. Francis Crick recalls a lady visitor to his Salk Institute in La Jolla, California, who, it transpired, thought that molecules were made of cells, and that worms were spontaneously generated in apples. In the face of such scientific backwardness, biologists might be excused more than a brief shudder. In addition, genetics, to some people, has unfortunate connotations due to past, extremely dubious, efforts to obtain political gain by exploiting alleged genetic differences between groups or races.

In the end, only careful explanations and meaningful descriptions of the issues that lie ahead will succeed in overcoming distrust and ignorance It is the aim of this book to tackle these problems, and to put the new genetics in an accessible form for readers.

The development of this exciting new field is an intriguing story. And like so many other tales of scientific breakthrough, it has taken place in a remarkably short time. Scientists did not even know of which chemicals our genes were made fifty years

ago. Today, they know all about their composition and their detailed behaviour in our cells. Now they are discovering how to alter their structure. The next fifty years will be even more exciting.

1 The Building Blocks of Life

There is nothing new about genetic manipulation. For several thousand years, mankind has been altering the genetic characteristics of other species, and, in the process, has domesticated wild animals and created thousands of different crop strains.

The power of this procedure is illustrated through the most far reaching of all breeding 'programmes'—that of the dog. Starting in Neolithic times with the wolf, humans have created a stunning variety of types in an extremely short time (judged by evolutionary standards, at least). Today, there are dogs of every shape and size—hunting dogs, herding dogs, guard dogs, pet dogs. And all—even the chihuahua and the poodle—are related to the wolf.

Such genetic 'experiments' were certainly not carried out in a carefully controlled way, however. They were matters of simple trial and error. Indeed, it is startling that such successful selection of characteristics was achieved despite general ignorance about the underlying processes of inheritance. People could plainly see family resemblances—red hair, blue eyes, and other traits—being passed on from generation to generation, just as they could see characteristics being passed between generations of livestock and cereal crops—such as colour of blossom, an animal's growth rate, or the number of grains in an ear of corn. But the process seemed haphazard. Sometimes characteristics missed a generation, sometimes they simply disappeared. So what were the rules governing inheritance, people wondered.

For his part, Aristotle thought that males and females made unequal contributions to their offspring. The female supplied the 'matter' as he called it, and the male the 'motion'. Similarly, the ancient Indian manuscript, 'The Institutes of Manu', maintained that the female acted in the role of a field, the male like a seed.

In the nineteenth century, there were many people who still

held views about inheritance which we now consider to be superstitions—such as telegony, the belief that a person's heredity is affected not only by his father but also by other males who had intercourse with the mother. (Belief in telegony was taken to extreme in the old British law which held that a man who seduced the wet nurse of the heir to the throne was guilty of polluting the royal family's 'blood'.) Others thought that what a pregnant woman saw and felt would profoundly affect the nature of her offspring—an idea that persists today.

More enlightened views, held by many nineteenth-century scientists, maintained that heredity was transmitted by blood. This belief gave rise to phrases like 'new blood' and 'blue blood'. However, the theory did not assert that red blood was the actual carrier of inheritance—it merely denoted a notion that a parent passed on all its characteristics to a child whose inherited traits were a blend acquired from both parents. The idea was popular, for it supported the notion of noble blood lines.

But the theory had persistent, nagging flaws that could not be explained away. Quite frequently, children could be seen with characteristics that were obviously not present in either their mother or father. How could two brown eyed parents produce a child with blue eyes, for instance? This idea of 'alloying' or blending of characteristics simply did not fit in with observations.

Then the French biologist Jean Lamarck proposed his theory that characteristics acquired during an individual's lifetime could be passed on to the next generation. A creature that developed strong muscles to dig for food would then be expected to pass on the trait for strong muscles to its offspring. It is an attractive, simple idea which helps to explain how animals adapt and evolve, and contains a sort of natural justice which suggests that an animal's endeavours can become part of its biological heritage.

For a while, Lamarckism held sway—particularly in revolutionary France, where its emphasis on an individual's power to impose his or her influence on future generations was popular. But the theory has its own faults. These were clearly exposed by scientists who amputated tails of generations of unfortunate mice and cats that, nevertheless, persistently produced offspring with