A giant step for genetics

Roger Highfield on a contentious bid by scientists worldwide to unravel the mysteries of human disease — and life itself

BIOLOGY

A GLOBAL initiative described as "the biological equivalent of the moon shot, only a lot more useful" will be launched next month. It will co-ordinate a £1 billion effort that biologists regard as the Holy Grail.

Sir Walter Bodmer, one of the first to recognise the importance of the Human Genome Project, believes it is the "most important application of modern biology; one that will give us what I call the handbook of man".

The launch of the initiative, to coincide with the first meeting of Hugo, the Human Genome Organisation, aims to co-ordinate worldwide research. The challenge is to unravel the blueprint to life itself, enlarging profoundly our understanding of all living things and providing the means to deal with a huge range of diseases.

Sir Walter, research director of the Imperial Cancer Research Fund, says the genome project will be a major step towards:

- **Finding** ways of treating the 4,000 known inherited diseases — from Cystic Fibrosis to mental retardation — of which only the genetic code of less than three per cent have been unravelled;
- **Understanding** what predisposes people to disorders such as high blood pressure, heart disease, cancer and diabetes;
- **Discovering** how the brain works;
- **Observing** human functions at the molecular level so scientists can understand the feedback systems which orchestrate the billions of cells in the body;
- **Gaining** an insight into the greatest mystery of all: how a single, fertilised egg evolves into a human being consisting of 100 million cells.

Research to crack the human body's full genetic blueprint (the genome) has been under way in a piecemeal fashion for a decade or more.

Now, Britain has established an Advisory Board for the Human Genome Project, chaired jointly by Sir Walter and Dr Dai Rees, secretary of the Medical Research Council.

This effort is likely to become part of a preliminary two-year, £10 million Human Genome Project, recently formally adopted by the European Commission.

With Hugo, European initiatives now will be co-ordinated with huge programmes under way in the United States, Japan and the Soviet Union, where the Academy of Sciences is considering a proposal to create an "Institute of Man".

The Human Genome Project will generate more data than any other single project in biology and require massive computing power to collect and interpret the life code. Computers will be more than just repositories of information: they will hunt for genes, compare them and find the genetic machinery that turns them on.

A new generation of computers, called neural nets, are already being trained to do this at Los Alamos National Laboratory in New Mexico. Neural net computers are modelled after the human brain and are especially good at pattern recognition.

Dr Peter Goodfellow, of the ICRF, says the Human Genome Project will also make way for research to unravel the genomes of farm animals and crops, leading to major improvements in agriculture.

Mice are high on the priority list because the mouse genome is the same size as that of man and its important genes are the same: fundamental genes vary little between species.

Sir Walter says mice will provide ways to test the function of genes identified in the Human Genome Project. "Humanised mice" containing human genes would develop analogous genetic diseases to those found in man, providing an invaluable animal model.

Comparisons of the genomes of various animals will also throw light on our ancestry. Dr Larry Deaven, of Los Alamos, says it will "solve enormous mysteries about human evolution".

This vast project, on the scale of the development of nuclear power, has caught the imagination of many scientists. However, like nuclear power, it is controversial. Many fear a crash programme will divert funding from more immediate biological research.

They also question how much can be learnt when only five per cent of the genome seems to represent genes. The function of the rest is at best unknown or at worst meaningless junk — the remains of useless genes discarded during evolution.

Commercial and legal issues surround the project. Should it be possible to copyright sequences from the human genome and, if so, by whom? Should a central agency own the patents and what are the implications for international collaboration?

The NRC says it believes "that human genome sequences should be a public trust and therefore should not be subject to copyright".

The most contentious area, the NRC says, is how the findings would be used. They must be given serious consideration, says a proposal for the project made to the European Commission.

Genetic information, it says, "will benefit individuals by informing them about health risks, but it could also be used to their detriment by third parties such as employers".

Doctors could be asked to perform genetic analysis to identify those who pose occupation or insurance risks, say, because they are more predisposed to having heart attacks.

Another issue is the degree of freedom that should be given to families to determine the traits of their children. This will pose many problems for doctors deciding what diseases merit prenatal diagnosis.

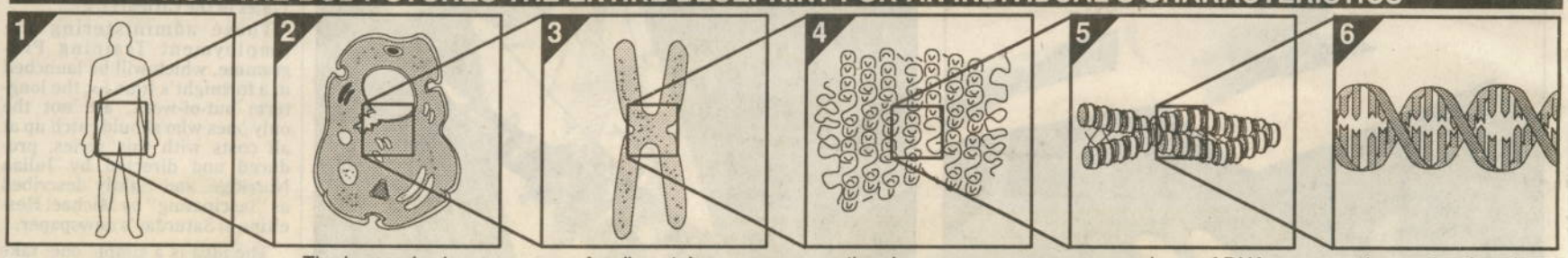
It could even lead to eugenics, says Jeremy Rifkin, America's leading "biofundamentalist", of the Foundation on Economic Trends.

"Without proper regulatory oversight, the mapping of the human genome could create a new and virulent form of discrimination based on the genetic make-up of individuals," he says.

Sir Walter disagrees. He says the genome information poses the same dilemma that has confronted man through history, from the day primitive man discovered fire: "You can use it to cook, you can use it to warm yourself and you can use it to kill your enemies. That is a matter for society to decide."

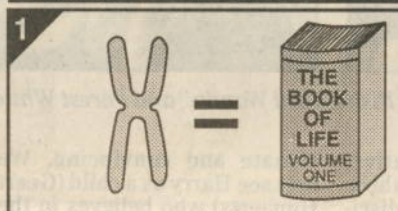
READING THE BOOK OF LIFE

HOW THE BODY STORES THE ENTIRE BLUEPRINT FOR AN INDIVIDUAL'S CHARACTERISTICS

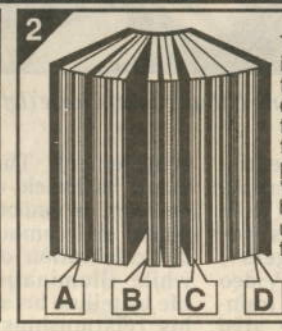


1. The human body contains around 10 trillion cells
2. A cell contains chromosomes in its nucleus...
3. ...the chromosome contains coiled fibres which are...
4. ...made up of DNA wrapped around proteins
5. A gene is a length of DNA, the so called blueprint of life

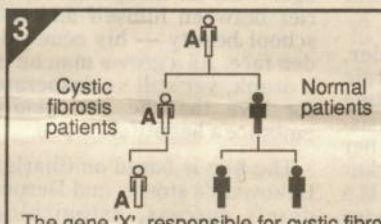
HOW TO FIND DEFECTIVE GENES RESPONSIBLE FOR A DISEASE



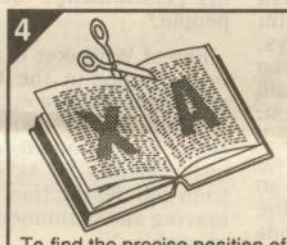
1. A chromosome can be thought of as a volume of 'The Book of Life' containing thousands of genes or 'pages'. But only a fraction of the book contains these relevant pages, the question is which part and what do they do?



2. The book is too huge to read in one go. Modern genetic techniques are used to hunt down each relevant page, say the defective gene responsible for cystic fibrosis. Known pages, genes 'A', 'B', 'C' and 'D', which represent distinct human characteristics, are used as aids to help locate the defective gene.



3. The gene 'X', responsible for cystic fibrosis is inherited by successive generations with other normal genes. By looking through family trees, scientists found that the cystic fibrosis gene 'X' was always inherited with gene 'A', and deduced that in the book pages 'X' and 'A' are close together.



4. To find the precise position of the cystic fibrosis gene the book is chopped into pieces. Chemical methods compare the pieces so the position of the cystic fibrosis page can be found with respect to page 'A'

5. Finally the cystic fibrosis page is read word by word, which gives valuable information on what the gene does in the body, the first step to finding a cure.

■ AS MANY AS 100 of the cells which make up our bodies could fit on this full stop. Each contains two metres of DNA — the coded details of our individual characteristics.

This is a classic example of the medium being the message: using a simple four-letter chemical alphabet, DNA spells out the body's life code in a message three billion letters long.

Regions containing between thousands and millions of letters spell out units of information called genes, most of which are responsible for protein molecules in the body.

The body's 50,000-100,000 genes serve as a biological construction manual which dictates the body's form (such as hair colour) and functions (such as digestion).

The entire complement of DNA (the genome) is divided into units called chromosomes. Found in each cell, they can be thought of as volumes in the construction manual.

Although we have been able to read the genetic alphabet for 30 years, mankind does not understand more than a fraction of this manual.

Finding and "reading" the genes has been possible on a large scale only recently.

The rough guide to the genome, called a map, is found through the way genes are inherited.

The diagram shows how this technique (called genetic mapping) is being used to find the Cystic Fibrosis gene and the actual distance, in letters, between genes (physical mapping).

These maps will provide the key to identifying genes responsible for all hereditary diseases, the starting point for finding their cause.

The US National Research Council has recommended that full-scale mapping "should begin immediately" and called for a $200 million-a-year initiative.

Mapping will take between 10 and 15 years, says Dr Anthony Carrano, of Lawrence Livermore National Laboratory's genetics group.

Eventually, scientists expect to read the life code, letter by letter, in a process known as sequencing. The trickiest step, it has been performed on only 0.1 per cent of the genome.

Sequencing first became practical in the Seventies when new methods enabled scientists to push their reading rate from 100 "letters" a year to about 5,000. Although it is now 10,000 a day, the NRC says robotics should be used to boost the rate another tenfold, a challenge being met by institutions worldwide.