Scientists scent success in hunt for defective gene

Boost to cystic fibrosis research

By Roger Highfield
Technology Correspondent

FOUR hundred children are born with cystic fibrosis in Britain each year, many of whom will die prematurely when their lungs clog with mucus.

Tracking down the defective gene responsible for this, the most common hereditary disease, will mark the beginning of the end of the suffering.

Now four groups are engaged in the final stage of the gene hunt: one British, one Canadian and two American.

Prof. Bob Williamson, head of the cystic fibrosis group at St. Mary's Hospital Medical School in London, is confident the deadly gene and its role in the body will be identified by the end of the year "at the very latest". This will:

Carrier test

- Reveal the root cause of the disease and open up new research into ways to treat it effectively.
- Lead to a test to detect carriers in the community "almost immediately" and a 100 per cent accurate antenatal test.
- In the distant future, it may be possible to swop the defective gene for normal ones, using "gene therapy".

Gene hunts are the key to discovering the cause of all hereditary diseases like cystic fibrosis, but it is not easy when the root cause is unknown.

Genetic encyclopaedia

It is a task akin to leafing through the Encyclopaedia Britannica to find a single printing error.

In every cell is wound some two metres of DNA, a molecule on which is written the blueprint for life in a code consisting of a four letter alphabet. It is about three thousand million letters long.

This genetic encylopaedia, on which is written all the information to make Man, appears in cells in 23 different volumes, called chromosomes. The sections in each volume correspond to genes—the codes for, say, proteins, eye colour, and blood group.

Genetic diseases can be caused by minute errors in a gene—just one wrong letter. For instance, work by Dr Jerry Ware at the University of North Carolina, showed a mistake in one letter in a 35,000 letter gene, responsible for a clotting factor in blood, causes a form of haemophilia.

One in 20 carriers

In the case of cystic fibrosis, it is thought the defect lies in a gene responsible for proteins that help transport salts and mucus across cells. Because these proteins are either missing or defective in someone with the disease, it leads to pancreatic problems, salty sweat and sticky mucus in the lungs.

One in 20 people carries the defective gene. One in 400 marriages is between two carriers of the disease. Each child of those marriages stands a one in four chance of having an affected child.

Hunting down the volume or chromosome containing the error is the first step in gene hunting.

Linked gene

This is easy for a sex-linked disease like muscular dystrophy which is passed by mothers but only effects boys. The defective gene must sit on the 'x' chromosome, only one copy of which appears in boys.

Cystic fibrosis affects both sexes. Last year, the vital clue to the volume that contained the error was found by Prof. Hans Eiberg in Copenhagen, after several years work on gene genealogy.

Prof. Eiberg linked the unknown cystic fibrosis gene with another known gene as it was passed on through families. Because this "linked gene" was inherited with cystic fibrosis, he knew it was close to the cystic fibrosis gene and thus on the same chromosome.

The St Mary's, Salt Lake City and Toronto groups found the tracked gene, and thus the cystic fibrosis gene, lay in volume seven of the genetic encyclopaedia. "It was 'competitive collaboration'. We were phoning each other all the time, but trying to get there first," said Prof. Williamson.

Three methods

This part of the gene hunt has already helped fight the disease. A pre-natal test which can be performed nine weeks into pregnancy and tests to check for carriers of the gene in affected families were developed from the linked gene.

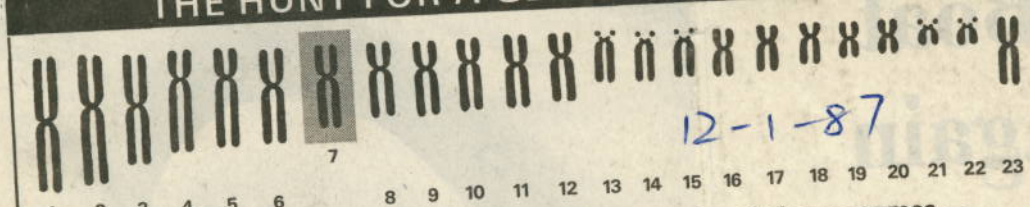
Similar work with another linked gene has narrowed the hunt to a stretch of code some two million letters of the genetic alphabet long.

Now the intrepid hunters are frantically searching this last stretch where the gene is tucked away among some 30 other unknown genes. Three methods are at their disposal:

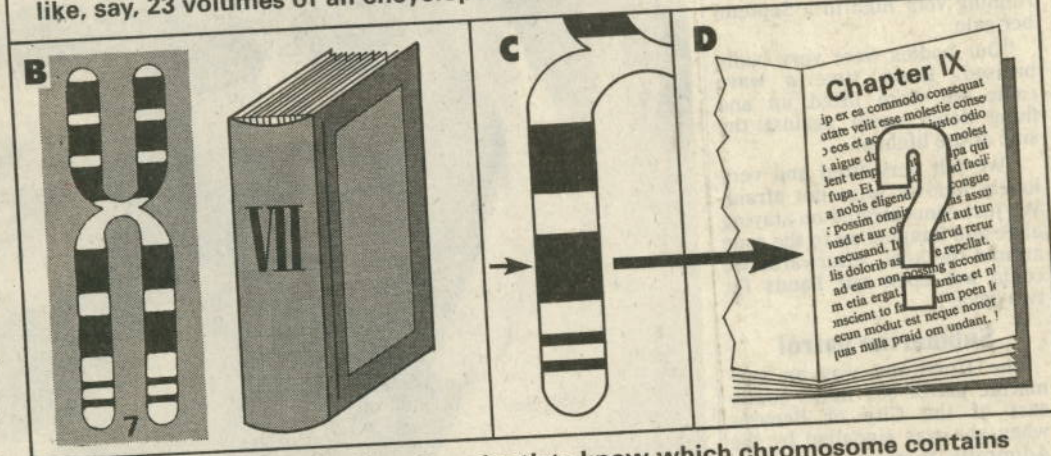
- A sledgehammer high technology method in which the unknown genetic code is read letter by letter. Here "molecular surgery" comes in handy in which a glass scalpel, so thin that it is invisible to the naked eye, is used to slice out the relevant secton of DNA. So far, Prof. Williamson's group has isolated half the region and has it under scrutiny.
- "Xerox copies" of the unknown section of chromosome 7, that contains the gene can reveal it: if these copies are isolated by scientists only from cells affected by the disease, such as the sweat glands, they must include the cystic fibrosis gene itself.
- Pages from the cystic fibrosis encylopaedia are swopped for those from a normal genetic encyclopaedia until the effects of cystic fibrosis are reversed in cells grown in culture. The gene is the section that eventually corrects the defect.

Once the cystic fibrosis gene is found, the process of unravelling its function in the body and understanding the disease at the molecular level can begin in earnest.

THE HUNT FOR A GENETIC 'MISPRINT'



A Every human cell has a package of 23 different pairs of chromosomes — like, say, 23 volumes of an encyclopedia.



B. In the case of cystic fibrosis, scientists know which chromosome contains the 'misprint' — they know it is 'volume 7'.
C. They have also tracked down the part of the chromosome which contains the 'misprint' — they know the 'chapter'.
D. But what exactly is the 'misprint' and on which 'page' and on which 'line' does it occur?

Funding cuts hamper work on genetic diseases

By Our Technology Correspondent

CUTS in funding, poor morale, and restrictive immigration rules are hampering Britain's search for the cause of common severe genetic diseases, such as cystic fibrosis.

Even prestige research projects, like that at St Mary's Hospital, London, have faced simultaneous cuts in university, health service, and Medical Research Council funds.

"When all three legs of a three legged stool are pulled away at once, it creates a very demoralising and difficult situation," said Prof. Williamson.

Funding of his 12-strong group is approximately one fifth of a similarly sized group in Canada. Of that money, two thirds comes from the Cystic Fibrosis Research Trust.

"If it wasn't for the extremely generous funding of the Trust we couldn't work at all. Even with that generosity, it is difficult to compete with groups in the US with ten times the funds," Prof. Williamson added.

Funding cuts had also meant that young scientists had found it increasingly difficult to get grants and had gone abroad.

International exchange of students was near impossible with current British immigration rules. "This is a field where you really want a lot of international interchange, now it is impossible to get work permits for our scientists coming to our lab from the States or Australia for a couple of years," said Prof. Williamson.