



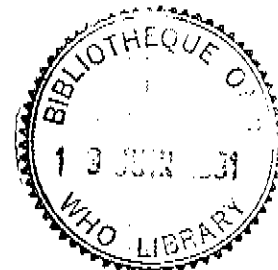
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What's new in gene therapy? Gene therapy and cystic fibrosis

by

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Ever since I started work on cystic fibrosis (CF) in 1979, trying to apply new techniques of gene analysis to the disease, I have looked forward to the possibility of better treatment for young (and not so young) people with the disease. Getting the gene was the first step - now we understand why CF occurs in the lungs and intestine, and can begin to work out the reasons why some cases are more mildly affected than others. Several large pharmaceutical firms are trying to find new medicines which can alter the shape of the "CFTR" protein (the one that is altered in the disease). And, of course, for those who are very ill, heart/lung transplantation remains an option which is often successful. Yet the biggest hope for the future is for "gene therapy", particularly if the more immediate attempts to make "designer drugs" do not give the hoped-for results.

Gene therapy is simple in concept. Most cells in the body (apart from the egg and the sperm cells) have two copies of the encyclopaedia of life (the "entries" are the genes, written in chemical language in the DNA). There are 23 volumes in this encyclopaedia (the chromosomes), and several hundred thousand entries. Lots of mistakes are found - but they rarely matter, since even if only one of the two entries is correct, this is usually enough to permit normal instructions to be carried out. We now know the CF entry (it is in volume 7 of the set, under "CFTR"), and we know the mistakes that cause CF (in most cases, one short "word" three letters long is missing, changing the meaning - as if the instruction "do not go home" were changed to "do go home"). We also know that there are two million carriers of CF who have one correct chromosome and one carrying the error, and that these people are completely healthy - there is only a chance of CF when two carriers each pass on the mistake-entry to a child, so it occurs in both volumes of the chemical instruction book. Gene therapy means trying to put the normal CFTR gene back into the cells of someone with CF, to turn him or her into the equivalent of a carrier, and therefore restore health.

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Gene therapy has not yet been done successfully for any disease. It is first necessary to isolate the gene that does not work properly, and to know why (now OK for CF). It is necessary to get the unaffected gene to the organ that is being damaged (possible for the lungs, perhaps, where one might "puff" an aerosol in, but what of the pancreas?). And even if the gene goes into the target cells (in the case of CF, the small cells at the base of each pocket of cells in the lung which secrete the mucus), will it work properly? Would it be possible to cause more harm than good to someone who may already be unwell?

Tests are now under way at the National Institutes of Health in Washington, D.C., to try gene therapy for another disease called severe immunodeficiency, where the children who are affected have no immunity and have to live in sterile tents to avoid infection. Here it is the white blood cells that do not work, because an enzyme ("ADA") is not made properly. Drs Anderson and Tolstoshev have isolated the gene coding for the enzyme, and can put it into bone marrow white cells from the patient, and replace these in the patient. These experiments have just been carried out, and it will be a few months before it is known whether they succeed.

However, the bone marrow is easier to get at than the lungs or digestive system, and (unlike the lung) can be treated in the test tube. Even for bone marrow, it is important to remember that transplantation (like heart/lung or kidney transplants) were not very successful at the start, and only have had a good chance of success for the past 10 years or so. There is also the problem of how and when to deliver the gene in CF. All procedures use some trick to get the gene into the cell, usually replacing the harmful and infectious part of a virus with the CFTR gene. The virus is genetically engineered so that, instead of delivering flu or a cold, it delivers the normal gene to the CF cell. But is this safe? We need exhaustive tests to make sure that it is, before trying anything on patients. (We have just isolated the related mouse CFTR gene, to help us understand which bits of the gene are essential and to permit a small number of essential safety experiments to be carried out in the laboratory before using the techniques on children).

The first "breakthrough" was the linkage to chromosome 7 (the volume), in 1985, then the isolation of the gene in 1989. Recently, two groups, those of Kathy Klinger, Alan Smith and Mike Welsh in Boston, USA, and Francis Collins and Ray Frizzell in Michigan, USA, announced that the normal gene corrects the CF defect in cells from the lung of a patient - in the test tube. This is really important, because it shows that IF the gene can be placed in the CF cell, the cell reverts to normal. (The most interesting thing is that it does not seem to be necessary to control precisely how much of the protein is made by the CFTR gene in the cell, which is great, since we do not yet know how to control this with accuracy).

One other problem remains - getting genes into cells in test tubes is not the same as getting them into the cells in the body. The lungs are accessible; the other tissues are harder to reach. Even the lungs have a powerful defence system against foreign bodies (as you all know from coughing in a dusty room). And how does one reach every cell - if one needs to? Will it be better to do the gene therapy very early in life, perhaps just after birth (when the immune system is less well developed), or wait until later childhood, or even adult life? Will treatment have to be lifelong, or will a single dose of the gene remain in the cells? These questions must be answered as quickly as possible.

Fortunately, there are several groups working in Britain (the largest are probably those at the MRC units in Edinburgh and Mill Hill in London, Pharmacology in Cambridge and Molecular Genetics at St. Mary's) looking at different aspects of these problems. Even if the big resources in North America mean that many advances are made there, we still want to be able to play our part, and to be sure that we can offer treatment to our patients as quickly as possible when the new and exciting developments happen.

This really is a message of hope. We want to provide the best set of choices for every family and every patient - the best methods of prevention, the best methods of treatment and care - side by side. It will not happen overnight, but let's hope that by the year 2000 we will see a new millennium for those with CF and their families.

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