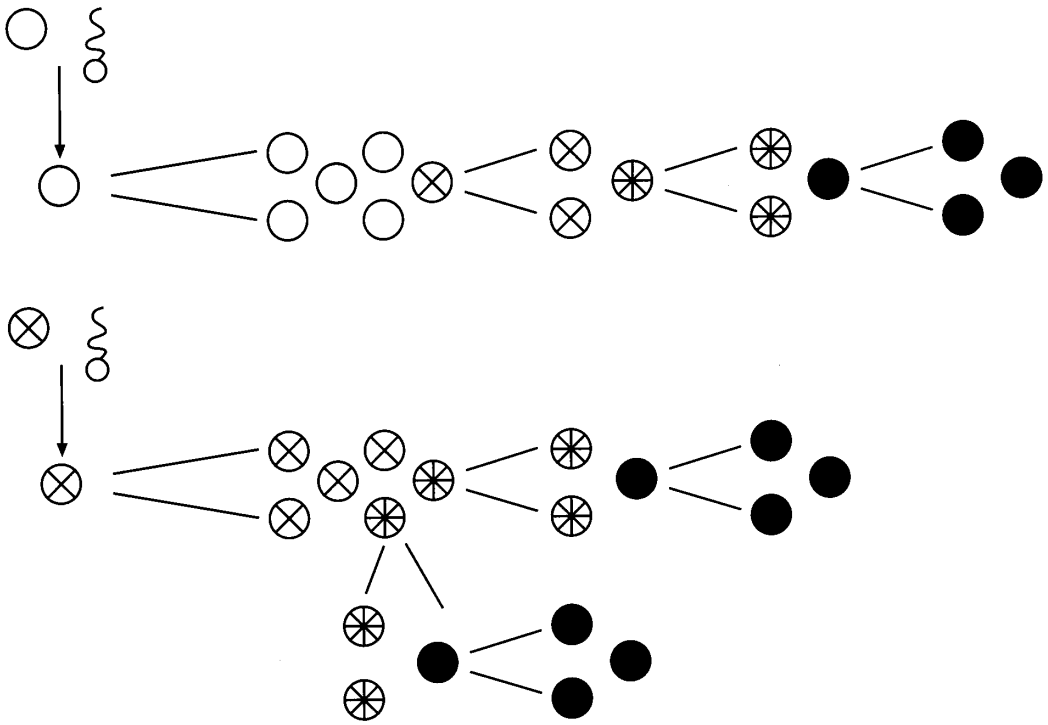
King's Fund

CANCER GENETICS



Report of a conference held on 9 December 1994, organised by Cancer Relief Macmillan Fund, Cancer Research Campaign, the King's Fund, and the Pharmaceutical Alliance in Cancer Care, with support from the Department of Health.

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Introduction

Sir Cecil Clothier chaired the conference and introduced the programme.

This is a very important gathering because of all the scientific and technological advances in medicine in recent years. The ability to manipulate genes is probably the most far reaching in it's implications. All major inventions have conferred enormous benefits on the human race. They also open an equal number of avenues for wickedness. It's hard to think of a human invention which has not been abused in some way or another, and, of course, the excitement and therefore the anxiety of genetics is that this particular science comes closer to the secret of life - makes us what we are and how we look and how we feel and how we behave than any discovery heretofore. We have all seen characteristics, both physical and intellectual, passing from generation to generation, so we have all been conscious that there was somehow an influence which was passed on from one human being to another without knowing very much about it; and the manipulation, of course, of that inheritance is by no means a novelty. It is merely the technology which has increased. After all, the great landed families of the past not only selected their horses and cattle, they also selected their wives on the same principle. They moved around the country looking for what they thought would be good stock. So this is not a novelty, it is simply an astonishing scientific development. So we have travelled a very great deal and the possibility of identifying the genetic cause of some diseases of course is so compelling in it's potential to relieve suffering that all right minded people want to press forward with research and gene therapy and associated sciences, but we have learned in recent years of the disasters that can be wrought by scientific progress if it presses ahead too fast or incautiously. The pharmaceutical field, for example, which I know as a lawyer, is littered with drugs that had enormous potential to relieve suffering and yet in the end had disastrous consequences for some. So the lesson obviously is that one has to proceed with great caution.

One of the most baffling problems of ethical import will arise as soon as we know exactly how to rectify with accuracy, a particular genetic defect which possibly leads to some fatal or horribly unpleasant disease and the question will arise very soon "Well, when do we treat it?". At present we all seem to be agreed that as soon as there are recognisable signs of a particular genetically mediated disease, it is proper and desirable to begin treatment, to arrest or reverse it's progress. But there are very good reasons in favour of, and not really very many against, correcting a genetic defect before the disease it causes takes any kind of grip on it's victim. Why wait? If the genetic defect can be detected and rectified with certainty at an early stage, why should we not do it? But the logic of this approach leads inexorably back to the germ line cell and the temptation to breed a disease free, handsome, and more alarming, psychiatrically well balanced, human race. Who shall be the judges of these attributes?

Perhaps it is too soon to worry about such a problem, since there is a long way yet to go. There are many things to be considered, and in the meantime a more pressing problem as well as the safety of any techniques that are developed, is, of course, the confidentiality of the information which may now be obtained about the temperament, the talents, the likely behaviour of human beings derived from knowledge of their genetic make-up. This information has, obviously, enormous implications for employment, for licensing to do all manner of things. Could one be fit to drive a car, fly a big jet, get married, and so forth? There are almost limitless possibilities to this information, both for good and, as I said earlier, for evil. So that somebody, somewhere is going to have to control the use to which this sort of information is put once it becomes generally available. As a lawyer I am particularly interested in regulation of new human advances because, of course, if you regulate too soon and too closely you are liable to stultify progress and deprive people of some tremendous advance which they ought to have enjoyed as soon as possible. On the other hand, if you don't regulate it, as I have already remarked, somebody, somewhere will manage to misuse the information. So regulation, I think, is bound to come in the end. We have a very good example with in-vitro fertilisation where we started off with the very few highly expert and highly reputable persons involved in that particular technology setting up their own voluntary, self regulating body, the Voluntary Licensing Authority. But in due course, as the information spread and more and more people were able to achieve this technology it became necessary to create a statutory regulating body to see that it was not abused. Gene therapy and maybe some other techniques, genetic screening, may have to follow the same path. I would urge those that govern us not to proceed too hastily lest we bar the way to progress.

Genetic Research

Professor Robin Weiss, Director of Research, Institute of Cancer Research, London

Although the title of todays meeting is The New Genetics, The King's Fund with the Cancer Research Campaign [CRC] and Cancer Relief Macmillan Fund have focussed the programme mainly on cancer and genetics, so although other aspects of genetic disease will come in we shall be focussing on cancer. The point of this talk is to introduce cancer as a genetic disease.

Cancer is an uncontrolled growth in the body; but if that was all, there would be no need for any other kind of doctors beside surgeons to cut it out. The other problem with cancer is that it spreads and that is why it is called cancer. It may spread to distant sites as well as being locally invasive, and that is the problem of controlling it from a medical point of view. Simply cutting out the lump doesn't always solve the problem.

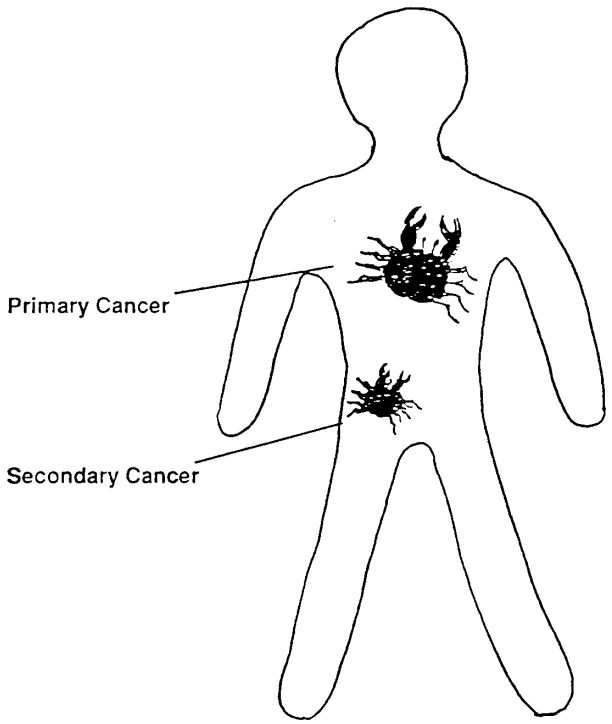
But what is actually growing in our own bodies when we have cancer? The body is built of billions of tiny building blocks called cells, and cells are made from thousands of different proteins. The nucleus inside the cell contains, DNA, the genetic material.

As far as genetics is concerned we must distinguish between the germ line and somatic cells. The egg and sperm create a fertilised egg and from that an embryo develops and eventually, the human body, which constitutes the somatic cells. But we contain future eggs and sperm which represent the germ line. A classical geneticist is really interested in germ cells which pass on inheritance; they are the vehicle for passing genes onto the next generation. On the other hand the phenotype, the expression of the genes that we inherit, is made manifest in our body tissues, the somatic cells.

How does cancer fit into this scheme? Genetic change affects the individual cells in our bodies. Some mutations occurring in a somatic cell may lead to an increased propensity for that cell to grow. Then a small population of that altered cells grows. There may be a further mutation which leads to a further sub-population and a further one until you get a fully malignant cell, or set of cells, which is in fact cancer. This means cancer is a clonal disease, that is, all the malignant cells within the cancerous tissues have come from a single cell in our bodies which has gone wrong genetically. This single cell has grown into a population of cells which is now destroying our normal tissues. It grows like a parasite in our body, growing at the expense of our body and as it goes along, it accumulates more mutations, becomes more malignant and becomes genetically destabilised, so that it easily develops resistance to drugs. This cancer is a disease of somatic cells derived from a single cell.

If all the cancer cells in the cancer come from a single origin, how many are there? I reckon there are about 10^{14} normal cells in an adult human body. How many cells would there be in the tumour, before you feel there's something wrong with you, and take yourself off to the GP? I would say at least 10^{10}, and if it was in a soft part of the body where the tumour didn't cause too much difficulty it could easily be 10^{11}. By the time you die it might be 10^{12}; that is 1% of the human mass, though it might be more. So if you are lucky you'll get diagnosed at 10^{10} and if you are not successfully treated it might grow up to 10^{12}. Now, the total human population on this planet is about five and a half billion. That is about five times 10^{9}. So, by the time a cancer becomes diagnosed there are as many cells in that one cancer as the total number of human beings, and as it is clonal, it has come from just one cell that has gone wrong. In genetic and biological terms, cancer has come a long way down the line before we get ill.

Figure 1.



Human Cancer does not cause symptoms until some thousands of millions of cancer cells have grown from a single aberrant clone. Secondary growths [metastases] spread from the same clone.

What causes cancer? Radiation causes mutations; carcinogenic chemicals cause mutations. The kinds of mutations may be single point mutations within a particular gene, or they might destroy larger fragments of the gene, or take out the whole gene or segments of the DNA surrounding the gene altogether. In some cancers one chromosome gets hitched up onto another in an abnormal way. There are also some viruses that cause cancer and they can be mutagenic too, by inserting their DNA into cellular DNA. But they may activate cancer in other

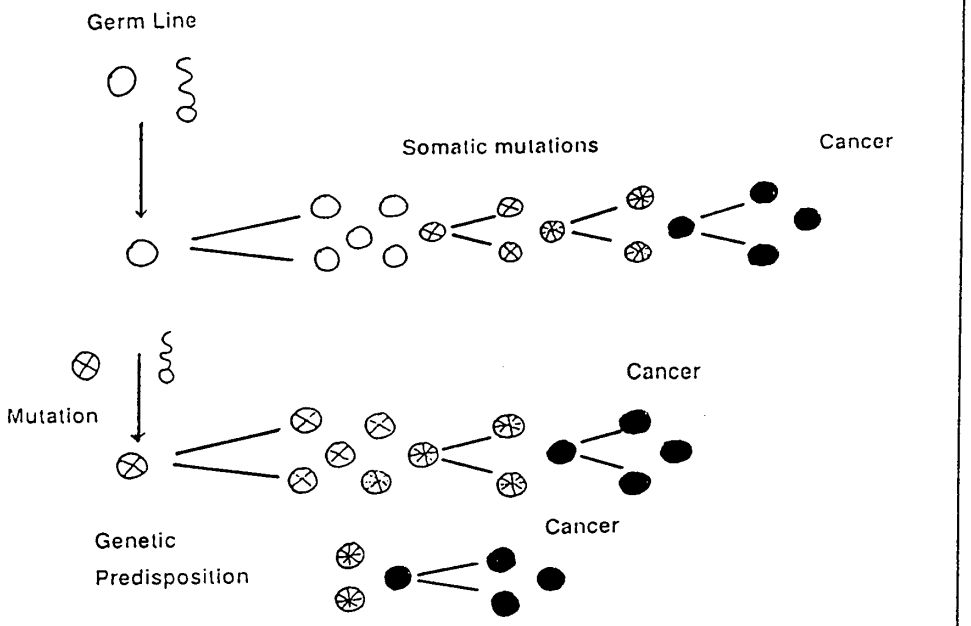
ways, or they may sequester proteins that are otherwise mutated. Thus, there is a common pathway for many different carcinogens.

Incidentally, it is my belief that the greatest opportunity for cancer prevention is vaccination against oncogenic viruses. About 20% of human cancer is caused by viruses and other microbes and if we could vaccinate against primary infection of those viruses we could eliminate a lot of human cancer. For instance, practically all cervical cancer, which is more prevalent than breast cancer, has a viral aetiology.

If we go back to cancer as a clonal disease, certain mutations,ie genetic alteration in cells cause cancer. This is exemplified in terms of somatic cells. If a cell mutates in the body, and permits some extra growth, there are further mutations and cancer may ensue.

If a similar mutation occurs in the germ line then you can inherit, not the cancer, but the predisposition to cancer. That's important in counselling. So there is a familial predisposition to cancer, but one is not born with the cancer itself because cancer is a multigenic disease. It is not caused by just one single mutation but all the cells in our body already have this first step, so that the probability of more mutations occurring is much greater. To go back to Mendel's Law, it is not exactly the new genetics, elucidated in 1866! We know that these mutations can be dominant or recessive. For dominant you only need a change a gene from one of your parents, mother or father, and it will be expressed in you. If it is recessive, you need a defect or mutation in both the genes you inherit from your mother and father. In the case of cancer this becomes a little bit blurred. Take retinoblastoma, for example. At the cellular level, we know that the defect is recessive. One good copy of the gene is sufficient to keep the cells normal. But if you only have one good copy all your body cells are at risk and the chances of one cell getting a deleterious mutation in the remaining good gene are very high because you have billions of cells and only one needs to mutate for the cancer to develop.

Figure 2.



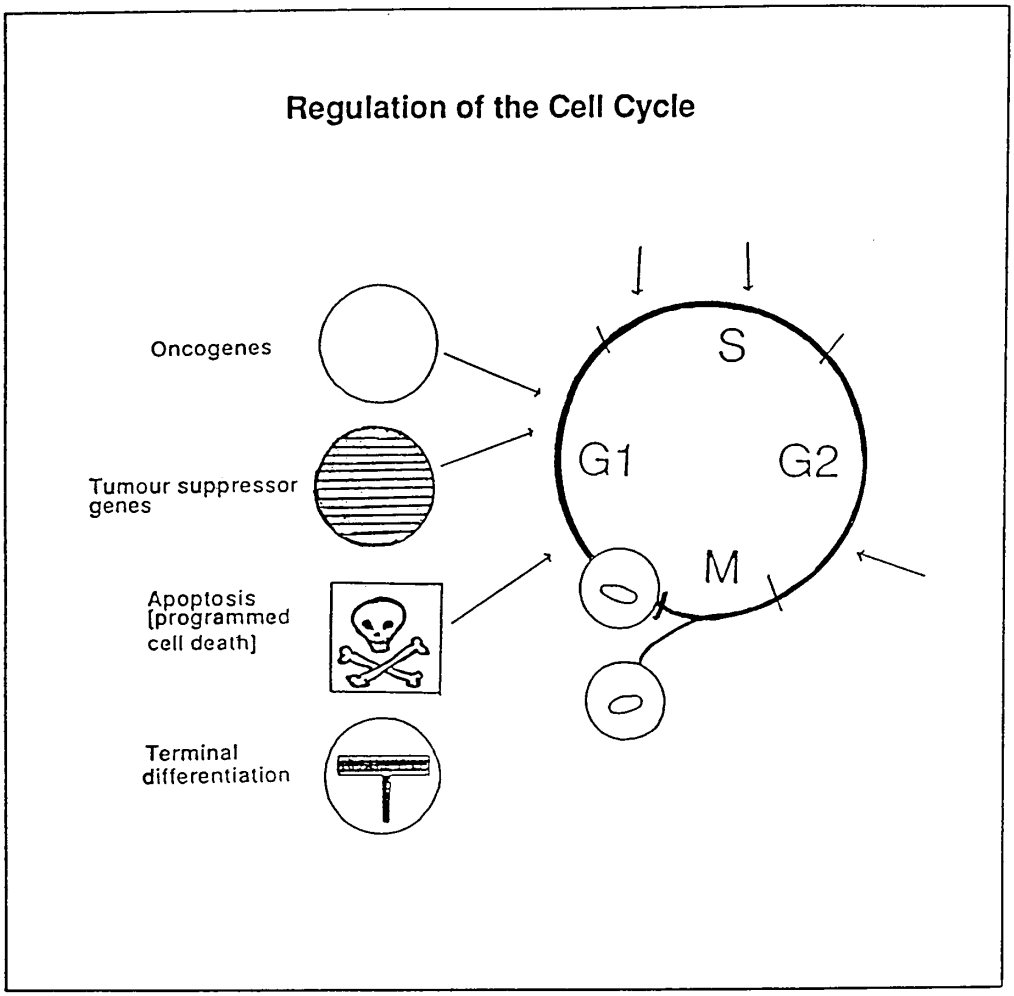
Heritable mutations underlie the development of cancer

Thus the inheritance of retinoblastoma in families appears to be dominant because almost every child with one defective gene, will develop the cancer. If you succeed in curing the tumour by taking a whole eye out, as often happens, then the child may get a second cancer, maybe in the bone, or indeed in the other eye. So the genetic predisposition in that situation is very strong, practically 100%. The newly identified breast cancer genes, the BRCA1, the BRCA2, also have a very high predisposition to cancer, though we don't know yet exactly what proportion of people carrying these defective genes are going to develop breast cancer.

We should also bear in mind that our genetic inheritance for cancer is played out against our lifestyle, the environmental insults we receive, and carcinogens we are exposed to. For example, fifty years ago, breast cancer was an extraordinarily rare disease in Japan. Very few Japanese women developed breast cancer, but very many of them had stomach cancer. Among the Japanese women who migrated to California, breast cancer incidence went up and stomach cancer went down. Yet they still had a far lower incidence of breast cancer than their Caucasian and black neighbours in California. What about the next generation of Japanese? Most of the first generation married Japanese men so they carried their genes from Japan to California - they weren't exchanging genes with any other ethnic groups. Yet their daughters got breast cancer at a higher incidence and by the time the grand daughters become elderly, they are getting breast cancer at a similar incidence as their Caucasian neighbours. Their genes haven't changed but their environment has, their body weight has, their intake of fat and sugar has increased, but it is not possible yet to pin down what the culprit is. Obviously it is very important that we don't become completely infatuated with the genetic side of cancer. It is a very powerful tool but it is played out against the lives we live and there are enormous opportunities for prevention if we could find out how to change life styles.

To move onto the cell division cycle, which means the cell multiplication cycle. The cell is geared up to produce more cells. There is a lot of turnover in our bodies and we have to keep on producing more cells, not only as embryos and infants but as adults as well. Cell division is highly regulated by a series of go signals, stop signals and cul-de-sacs.

Figure 3.

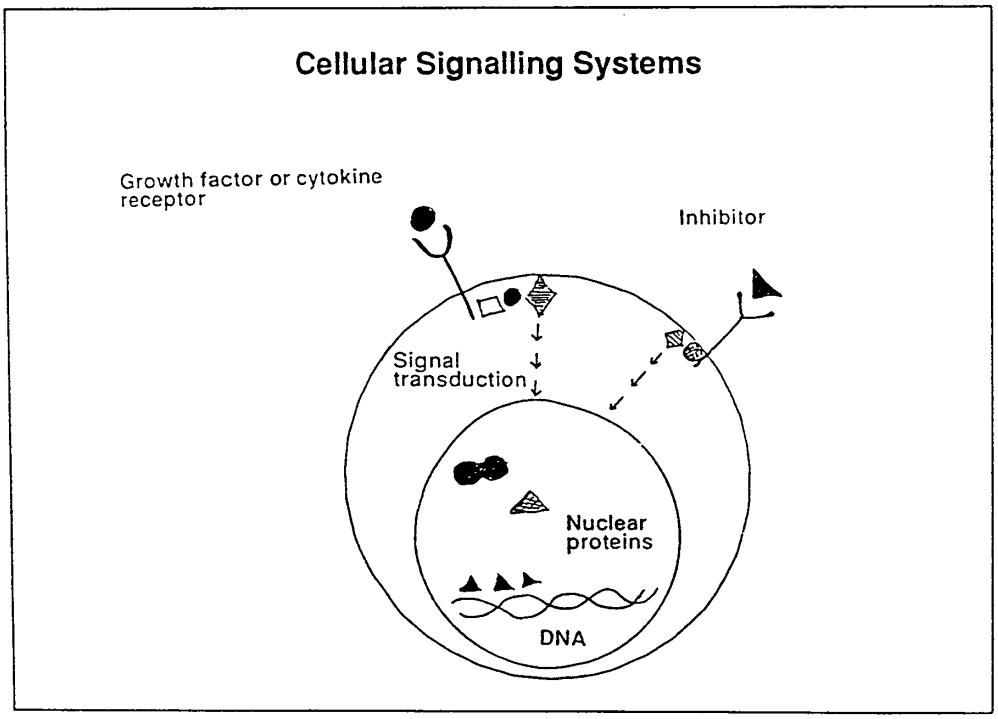


Many of the cells undergo what we call terminal differentiation. For example, the cells in our skin are continuously producing new cells as the old cells slough off. The same occurs with our blood. The average white blood scavenger cell, the neutrophil, has a half life of about 48 hours. Red cells last about 90 days and we are continually producing more blood cells in our bone marrow. The particular genes that go wrong in cancer, in terms of growth, are ones that give go signals when they shouldn't, or stop giving stop signals, or stop giving signals that allow terminal differentiation of the cells. Evolution has built in some fail-safe signals. A lot of cells when they go wrong switch into a program of self destruction, of suicide which we call

the genes involving cancer are mutations that override the death wish.

What do the proteins encoded by these genes actually do? If we look at a single cell (Figure 4) there is a very complicated network of signalling in the stop/go/pause/differentiate type of signals which are finely tuned. A lot of the signals are received from outside the cell such as growth factors, hormones and surfaces of other cells nestling up closely. There are receptors on the cell surface to receive these signals and interact with a whole set of proteins that send further signals down into the cytoplasm and eventually to the nucleus where the genes reside. These might be positive go signals saying "get a move on", "grow", or they may be stop signals, that say "let's put the brakes on". If there are mutations in the genes for these signalling proteins which don't allow the circuit to work properly, those mutations can lead to cancer. We call go signals oncogenes and stop signals tumour suppressor genes.

Figure 4.



How many genes are there in each human cell? About 100,000 different genes code for different proteins. Some of them may be functional in every cell, doing common household jobs, whereas others may be specific to particular cells. My guess, and it is a very rough guess, is that not more than about 1000 out of that 100,000 [ie 1% of all the genes] are involved in the various control mechanisms that, when they go wrong, can lead to cancer. So although we have known for 70 years now, that carcinogens cause mutations, it is only recently, in the last 15 years or so, that we have begun to identify that particular subset, that contribute to cancer, by switching on go signals when they shouldn't be on, or failing to switch off stop signals and suicide messages. It is our knowledge of those particular genes which appear repeatedly, in familial predisposition, in somatic mutation, and in viral cancers that we have begun to get a grip on cancer and to control it.

Our understanding of the genetics of cancer, of the particular genes involved, is actually helping us to think more precisely about cancer. One day it may help us to devise better therapy. Current therapy removes the tumour by surgery or kills it (and normal tissue) by radiotherapy and chemotherapy. This is a blunderbuss approach.

But we are beginning to get a little bit more intelligent. For instance, there is a rare form of leukemia, promyelocytic leukemia, in which we can now persuade all the cells to differentiate out so that they can no longer divide. We can do this with a form of all-trans retinoic acid. (A discovery made in the People's Republic of China without high-tech genetics). By understanding cancer genetics, if we know that there is a mutation in a signal acting at one point in a chain of command, it is no use designing a molecular therapy that's going to work up stream because it is still going to go on firing downstream. So we want a molecular therapy that intervenes with what's gone wrong. Thus it is important to know which particular genes have gone wrong and how the proteins they encode work in the cell.

Gene Therapy

Mary Collins, Senior Scientist, Institute of Cancer Research, London

This paper is about potential new gene therapy approaches to the treatment of cancer. It is interesting that in the Clothier Committee's report on the regulation of gene therapy and potential applications of gene therapy, attention was directed to potential gene therapy for inherited genetic disorders, such as cystic fibrosis, or quite rare immune deficiency syndromes where children had inherited genetic disorders. In fact, most of the gene therapy applications that have been proposed since the Clothier Committee have been for cancer trials. This is probably the main way that this new therapy is actually going to be introduced into the clinic. There are various reasons for this, including the fact that cancer physicians have a long and distinguished history of introducing new experimental therapy in a series of stages of trials, which perhaps makes it easier to apply gene therapy to cancer than it does to inherited genetic disorders.

Various approaches have been proposed for treatment of cancer by gene therapy and this paper summarises three approaches that are actually being attempted in clinical trials either in the United States or in this country. The first is to try to repair one genetic defect. A lot of cancer cells have specific mutations in either oncogenes, or tumour suppressor genes, and it might be possible to insert a correct copy of one of these genes into the tumour cell and thereby reverse the cell's behaviour. This approach, I think, is rather naive, and with our current technology it is probably not possible. It requires correction of all of those 10^{9} cells, or probably 10^{12} cells, if you are pessimistic, that the patient will have, and our gene delivery methods are really not efficient enough. So if a single cell is missed, that cell will carry on regardless and will grow to another 10^{12}. This has been tried, for example for lung cancer in a clinical trial in the US, but it is probably unwise and unlikely to work very well.

The second approach is to try for better drug delivery. The way to do this is to deliver an enzyme gene that can convert a non-toxic drug to a toxic drug in the cancer cell. This is really a different drug delivery system, similar to some other localised drug delivery systems that have been tried for cancer but slightly more sophisticated. It is more specific than delivering a

toxic drug everywhere in the body. It will probably deliver a higher level of the drug in the tumour cell and will also give a more persistent level of the drug. This is so far being tried mostly with brain tumours.

The third, and probably the most frequently tried approach, is to try to stimulate the host anti-tumour immunity. Tumour immunology has had an up and down life in public perception and popularity. What is clear now is that we know a lot about the molecules that are involved in stimulating the immune system. We know about molecules on the tumour itself, and we know about molecules produced by other cells that can actually direct attack on the tumour cell by the host immune system. This approach is described in some detail because it is probably the approach that is being used in the majority of cancer gene therapy trials.

Figure 1.

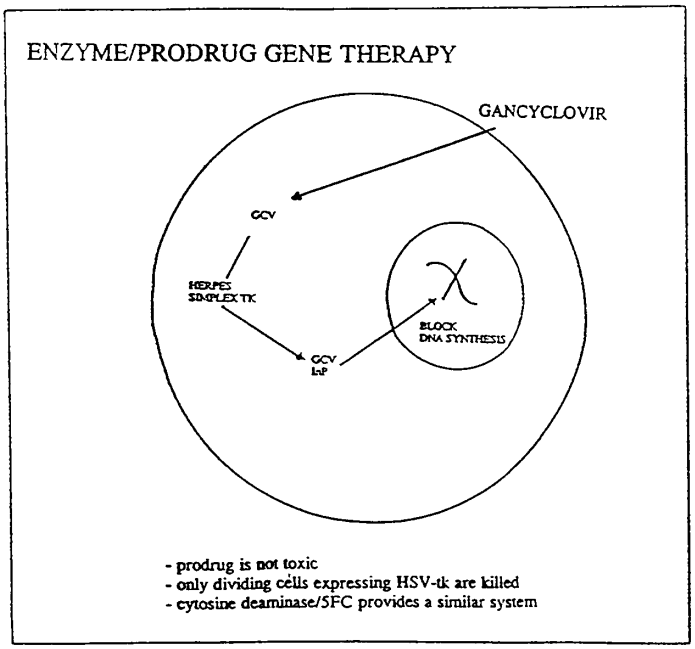


Figure 1 shows that if the enzyme, thymidine kinase from the herpes simplex virus is used, a prodrug gancyclovir can be delivered. This is a nucleotide analog, which then becomes phosphorolated by the enzyme, and inhibits DNA synthesis in the tumour cell. This has some advantages and some disadvantages. The prodrug is very non-toxic, indeed this is what is

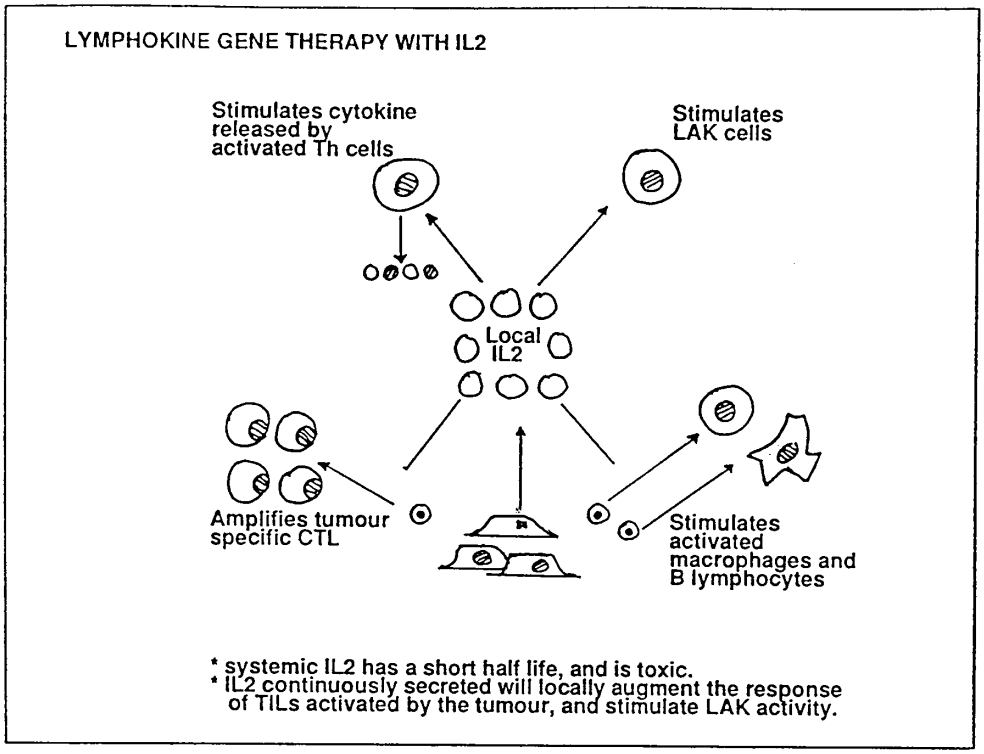
being used and advertised on television for treatment of cold sores. It is only dividing cells expressing this enzyme that it kills because it needs DNA synthesis to kill the cells. This could give some tumour selectivity. The disadvantage, perhaps, is that not all cells in human tumours are dividing very rapidly and , for example, the nitroreductase prodrug system that is being used at the Institute of Cancer Research gives a different angle because it makes an alkylating agent which kills cells when they are not dividing. In that case there may have to be a more tumour specific delivery system to give the enzyme to the tumour cells.

There were some experiments in the early sixties, on tumour immunology, which found that animals that have grown a tumour were then protected against challenge by that tumour and this protection depends on the immune function in the animal and on a subset of lymphocytes known as T lymphocytes. T lymphocytes are white blood cells which have several functions. One of their main activities is to kill infected cells, or to kill foreign cells if you have a transplant, for example, and they also kill tumour cells. These sort of experiments suggested great promise for this approach in treating human cancer.

What we know now is that tumours can look foreign to the host immune system. They can express molecules that are not expressed by normal cells and we are beginning to understand a bit better what sort of molecules these may be. These molecules can either react with antibodies made by B lymphocytes or with the crucial T lymphocytes. The molecules they express which can trigger T lymphocyte function, tend to be small fragments of cellular protein that are put on the tumour cell surface and can include viral proteins. Quite a lot of human cancers are caused by viruses and there is excitement now in using vaccines against those viruses to stimulate immune responses. The fragments of protein could also be mutated cellular proteins, such as mutated oncogenes. There is less evidence for that. There can also be proteins that are highly expressed in tumour cells that do not seem to be expressed in very many normal cells; this has been shown to be the case for melanoma, one of the tumours most capable of stimulating the immune system. The melanoma cells express highly a series of antigens that are not really expressed by any normal cell.

So we get to the point that if tumours can look foreign to the immune system, can we think of a way of using this to actually treat the cancer. What the ICR and a lot of other groups did simultaneously was to think of making tumour cells produce molecules that could stimulate the immune system. One of the ones investigated initially was interlenken 2 (IL2) shown in figure 2.

Figure 2.



This is a small peptide growth factor that stimulates a number of different cells of the immune system. It is possible to show that if you make tumour cells themselves make this protein, immune activity is stimulated and host white blood cells are observed in the region of the tumour. The reason that this molecule was thought of was that trials in the United States by Steve Rosenberg had shown that administering systemic IL2, could actually give some reasonable cures, particularly for melanoma, but it tended to be toxic and it's effect tended to be rather erratic. It would work very well in some patients, not very well in others. The locally secreted approach was to get around the toxicity of administering it systemically so that it would actually hit the immune cells that were already at the site of the tumour, being activated. This was the theory.

Sure enough, in animal tumours it is possible to get nice results. Experiments were done with a mouse tumour model where unmodified tumour cells were injected into the animal and the animals rapidly grew tumours. If tumour cells that make this immuno-stimulatory IL2 are injected, it is possible to show that all those animals will reject those tumours. A certain number of those animals, if you then re-inject the parental tumour, will be protected against challenge with the unmodified tumour in tests. This approach certainly works. The only problem now is how to translate this from animal studies into what we might want to do for real tumour situations where there is a patient who already has a large tumour mass. Indeed, a huge number of different modifications of tumour cells will work in this type of assay. Tumours that express foreign proteins, that express more of the MHC molecules that actually put those proteins on the surface, that make a variety of different cytokines that will stimulate the immune system. What will work best in human tumours to stimulate the particular specific anti-tumour response is not clear and the current research is trying different approaches in human tumours.

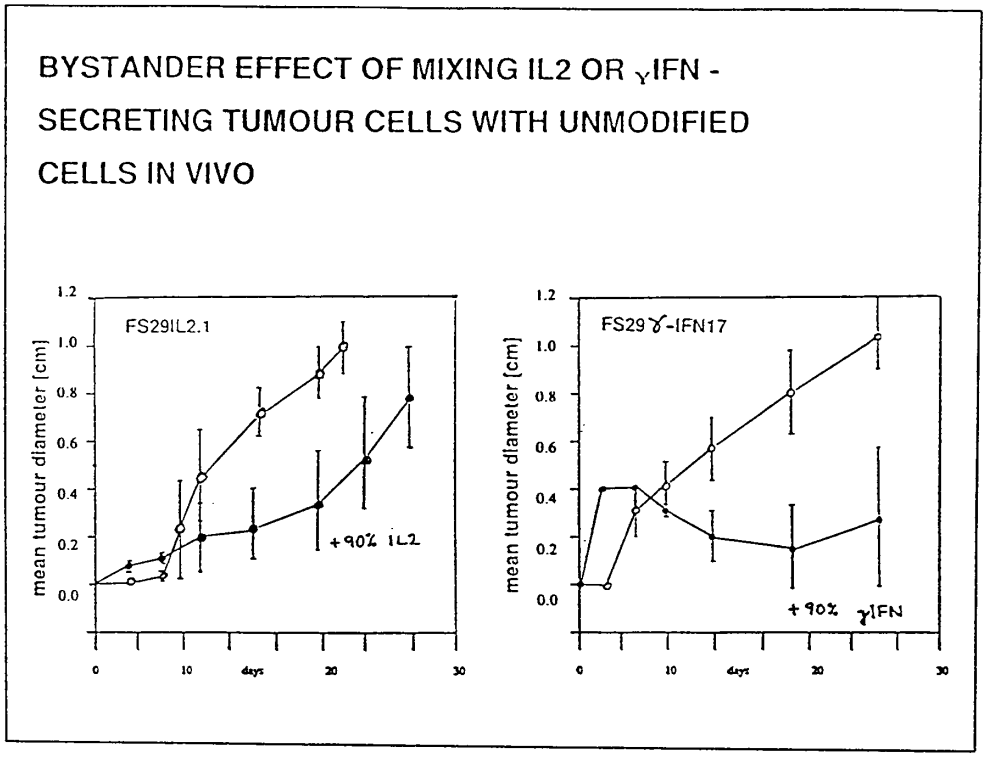
There are two ways to translate an animal experiment into actual therapy. Firstly, existing tumour masses could be treated by direct gene delivery into the tumour. Here, clearly, a very efficient method of gene delivery is needed, so that enough of the tumour cells are modified to be able to lead to the death of a large proportion of the tumour. If we think of the technicalities of this, there are various methods of gene delivery that may be more suitable for this sort of direct gene delivery in tumours. For example, physical methods, such as liposomes, where the DNA is coated with a lipid cover, or perhaps a virus that can be obtained with a very high viral particle number, such as adenovirus. Some type of targeting may be needed, either by infusing the whole delivery system into the tumour, by targeting to the tumour cell surface, or by targeting gene expression, so that it only works in the tumour. Clearly, if this approach is going to work, there will need to be modification of some cells leading to death of other cells, because the efficiency of gene delivery by any system is not that good. It will never be possible to hit every cell in a tumour, partly because of access, partly just because of the number of copies of a gene it is possible to inject near a tumour.

The other approach is a vaccine approach, where tumour cells are modified in a culture, outside the patient, and this modified cell vaccine preparation is injected to try to trigger an anti-tumour immune response, whereby the host immune cells will then circulate, find existing sites of unmodified tumour and kill them. This has a lot of advantages for many human cancers if it can be made to work, because most patients will have widespread metastatic disease. There are very few cancers where there will be a single incurable tumour because

approach probably, if one could get it to work, would give the option of treating more normal disease.

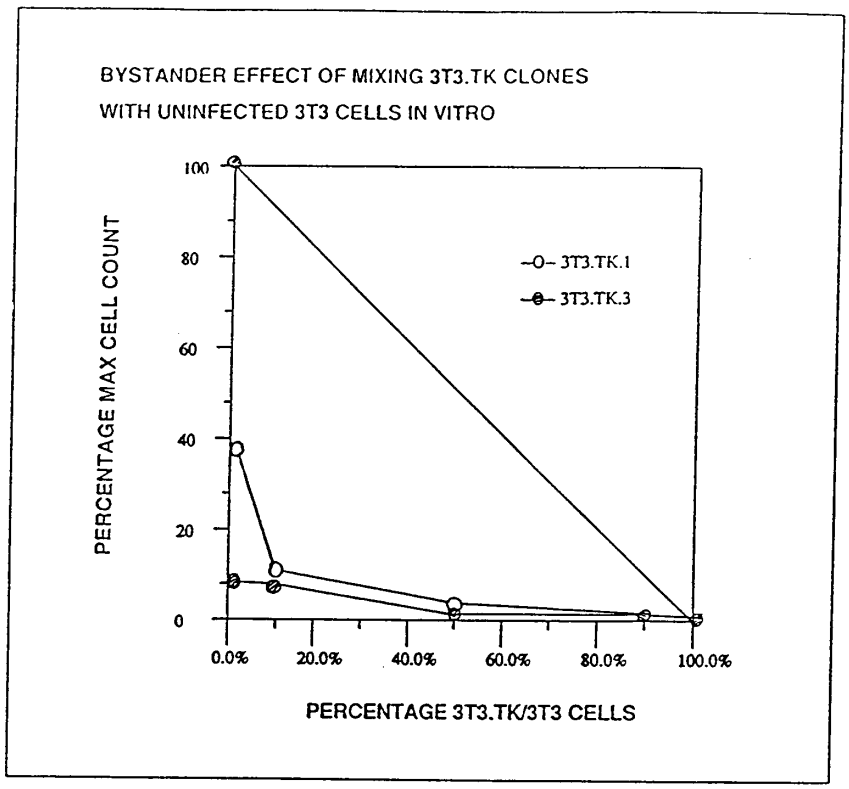
There are some experiments which tackle the problem of how much bystander killing occurs.

Figure 3



These are experiments where cells that secreted IL2 or cells that secreted another cytokine known as gamma interpheron were mixed with 10% unmodified cells. It was found that the unmodified cells in the case of the IL2 mixture rapidly outgrew, and so essentially, all the animals got tumours. In the gamma interpheron case there was a slightly better situation and in this experiment about 30% of the animals remained tumour free at the end. This illustrates the bystander effects with cytokines. They are not great. It would be necessary to modify 90% of the cells to have any significant effect and so we think that direct delivery of cytokines to tumours is probably not a good direction. What can clearly be seen is that there is a very good bystander killing when the enzyme thymidine kinase is used.

Figure 4



This is an experiment that was done in cell culture but it is possible to demonstrate the same sort of effect in tumours in animals. Other people have reported this. If a mixture of thymidine kinase expressing cells and unmodified cells are used, about 2% of the modified cells will kill a large excess of unmodified cells. This suggests that this sort of enzyme prodrug system may be more suitable for direct gene delivery to tumours in situ. It is possible to see some bystander killing effect with the nitro reductase enzyme prodrug system that we have been working with as well. This sort of approach may be better for direct gene delivery to tumours.

The way these results have been used and applied clinically is to try to proceed with the tumour vaccine approach. Results from an animal experiment suggested that interleuken 2 secreting cells can actually prevent the development of metastases in an animal. These are animals that at day 0 had a large primary tumour excised, the control group were either untreated or injected with irradiated parental tumour cells. All these animals came down with

liver and lung tumours. We found that if we repeatedly injected animals with interleuken 2 secreting tumour cells, twice weekly, for a four week period, at the beginning of this experiment, we could delay considerably the onset of metastases. In a patient with small metastatic deposits it might be possible to improve the situation by injecting immunogenic, modified tumour cells.

This is what we are trying to do in a clinical trial at the Royal Marsden, which has just started. What we have shown is that we can take melanoma biopsies, from patients at the Marsden and establish primary cell lines from these biopsies. Table 1 shows the initial results:

Table 1

Engineering Malignant Melanomas

Patients	Culture established	Interleukin-2 secretion
1	+	+ +
2	+	+ +
3	+	nd
4	-	
5	+	+
6	+	+
7	-	
8	+	+
9	+	in progress
10	+	in progress
11	+	in progress

We have about 40 or 50 tumour cell lines established now, and we can show that we can modify them to make interleuken 2. We do this by using a retro virus to transfer an expressed interleuken 2 gene because we don't need such a targeted gene delivery in this system where we are taking a cell out of the patient and modifying it.

The retrovirus gives pretty efficient and stable gene transfer and expression of the IL2 gene. We are using a bulk cell population, showing that they express the IL2 gene, that they are safe in the sense that they have not picked up any virus from the retroviral preparation used to

infect them and that they are sterile - they have not picked up infection in culture. We will then irradiate them and inject them back into the patient from whom we've established a cell line. Now, as with all phase one cancer trials, this is a small enterprise. We will start with probably 12 patients and what we are really monitoring is a biological endpoint, rather than a therapeutic endpoint because these patients will have quite a large tumour burden already. What we are measuring is those crucial cytotoxic T cells that we think are important for generating an anti-tumour immune response. So we are measuring the patient's cytotoxic T cell response against their tumour before and after injection to see if we are achieving anything by this procedure. The first patient will probably be injected in January.

The people involved in the work described are: Sue Eccles at the Institute of Cancer Research, who has done all the animal tumour work and her colleague Gary Box. Martin Gore who has been instrumental in setting up the melanoma trials at the Marsden, and Steve Russell, Poolam Patel, Claudia Fleming, Julian Harris, Dominique De Wit and John Bridgewater in my group.

Cancer Research

David Kerr, Professor of Clinical Oncology, Birmingham University

What advances have we, as clinicians, made during the last three decades? Many. There are tumours that are now curable. We can palliate, we can improve symptoms, we can improve the duration of the cancer patients life, but for the common solid cancers - lung, breast, bowel, common gynaecologic cancers, when they reach an advanced stage we cannot cure them. From my point of view there is a dual academic response to that - to do the very best we can with the drugs which are available to us, or to seek and search and strive to find new therapeutic strategies. Clinical need and scientific innovation somehow need to come together and with the prospect of genetic therapies that is going to be the case.

There is pivotal point when a new therapeutic strategy stretches from the laboratory bench to the patient's bedside. Every new drug, every new treatment has a journey, as has a patient. It requires a link and co-operation between scientists and clinicians. The purpose of a Phase I trial, as currently defined in cancer treatment, is not to improve the quality of the cancer patients life, not to cure them, not to improve their symptoms, not to prolong their life, but to define the maximum tolerated dose of that treatment. There are some absurdities in that premise - but it is one that has long been held. As the Americans would say 'there is no pain without gain', and therefore when we use our conventional anti-cancer treatments we use them at the very highest dose possible and the assumption that the more damage we are doing to the patient then we are producing, an order of magnitude more damage to the tumour. This is predicated upon an assumption, a pharmacologic one, that stepwise, if we increase the dose of a drug, not only will we increase its side effects but in parallel, statistically, we will improve the possibility of killing cancer cells. That is the assumption and it is one which is entirely challengable. As we grow older, wiser, more mature, we are actually seeing that that may not be the case for the common solid tumours. Clinicians should work hand in glove with scientists and try to be more thoughtful about the endpoints designed, not increasing the dose of drug until someone's nose turns black and falls off, but rather seeing if we can titrate, drug dose to therapeutic effects and so introduce a drug or therapeutic strategy at a dose that

works with a minimum of side effects.

How do we define the maximum tolerated dose? It is that dose of a drug or treatment which causes intolerable side effects. What happens is that in a Phase 1 trial whether it is viral particles, or a new drug, or a combination of the two, the trial starts at a dose that is very low and which we hope will be safe. The dose of the drug, or the number of viruses confusing the gene therapy is gradually increased in successive cohorts of three patients, until toxicity supervenes. When the side effects are intolerable we stop and define this as the maximum tolerated dose.

An important aspect of a Phase 1 Trial is concerned with ethical and moral dilemmas around the potential benefits to patients. We must be thoughtful and clever as how we go about changing the existing approach. I am proposing to do clinical trials in patients, in which I feel there is little potential benefit in terms of disease control but there are possibilities of side effects. The patients almost select themselves, in that patients whom we treat are patients who have cancer for whom there is no other therapeutic option, and for whom the very best that we can do, with conventional therapy, has been done. Therapeutic possibilities have been exhausted; the range of conventional treatments have been tried, there is nothing else to offer other than pain control, palliation, and the simple things we can do to improve the quality of life. There are many patients who cannot accept that, who say there must be some experimental treatment, and it is that self selecting group of patients who find their way to me. We meet in a marriage of convenience. I want to treat them because I need to learn if our new therapy will work and the patient wants to be treated.

We must be wary of how we explain things to these patients. We did some work where we taped interviews with patients and submitted them to an ethicist and to other members of our ethics committee, who agreed that we were being quite honest and deliberate in an attempt to gain a truly informed consent.

In trying to evaluate new forms of information as a scientist and a clinician we know that we can cure all mouse cancer. There are drugs which have been used in the laboratory which will act like a sort of 'domestos' to wipe out all mouse cancer in experimental animals. The problem is, when trying to translate laboratory findings into a package for patient or clinical good, they often do not work. The figures in Table 1 were collected from my experience of Phase 1 trials. We collected a number of very interesting novel drugs and therapeutic approaches. All of them wonderfully active and compelling on the laboratory side. We entered

260 patients, all with refractory end stage cancer, into these trials, and in all those years, and in all those patients, out of 260, only three benefited. That is the horn of my dilemma. Every time I establish or start a new phase one trial, needs must lead me to believe that there is some possibility for the patient benefiting. My harsh clinical experience and the reality of being in the front line mitigates against that.

Table 1.

1984 - 1992	
Response Rate =	3/260 PR
Treated Related Deaths =	3/260

CRC Clinical Oncology, Birmingham

Of the 260 patients entered in the trial, only three patients benefited. There are other ways that the patients do benefit in the sense that something is being done. Certain patient cannot rest, unless they feel that something active and directed against the cancer is being done. If they say to me, "what are the chances of me benefiting from this treatment?" I must say remote, almost invisible, the laboratory package is promising but we have no idea whatsoever as to whether that will translate into any form of clinical truth, and yet despite that, every patient that I ask to participate in a Phase I trial, and they are a very selected population, agrees. If there is even the tiniest prospect of hope, if there is the smallest beam of light at the end of the tunnel, patients will sign up to that, regardless of how bizarre the treatment sounds, or how unusual, or whatever the potential for toxicity. So it is an extraordinarily powerful interaction. I think that people like us have got to be aware of it and I hope that I convey that sense of it to you and the sense of there being the horns of a dilemma.

Counselling and Psychological Issues In Gene Therapy

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This paper deals with some of the general issues regarding the psychology and behaviour of cancer patients, or counsellees offered genetic consultations.

Superficially at least, gene therapy ought not to represent a major departure from established medical practice, or pose radical ethical challenges. In many respects it is like any new experimental cancer treatment and should be approached in the same way as other novel treatments from the point of view of clinical trials. However, with gene therapy there are added issues arising from the importance of lay perceptions of genetics, for example, the fact that people may not understand differences between somatic cell and germ line genetic processes. It is important, therefore, to take account of lay perceptions as they clearly could influence patients' participation in clinical trials of gene therapy and the need to obtain proper informed consent. Patients invited into clinical trials of gene therapy have a number of needs which should be addressed in the process of obtaining informed consent, their need to know of possible side effects, rights to withdraw, the need to have the purpose of the trial clearly explained, and the extent of commitment in terms of their time. Patients also need to know about the possible physical, emotional and psychological discomfort they may experience; and they need an opportunity to reflect prior to making a decision regarding participation in a trial. It is important that patients be clearly informed about the benefits or otherwise of their participation and that any misconceptions regarding genetics are thoroughly addressed. Failure to cover these issues adequately may have an impact upon the patients' mental health by causing undue worry, apprehension when unanticipated side-effects of treatment are experienced, and the possibility of non-compliance with treatment.

At present research regarding the possible psychological effects of participation in gene therapy trials is under-developed, although we assume these effects will be similar to those of patients entering other novel cancer therapies. It will, however, be necessary to find out how

much patients understand and what attitudes they have towards gene therapy and to look at their psychological well being and quality of life as well as the impact of lay perceptions of genetics upon patients' ability to cope with treatment. The role of the family in supporting patients in their decisions should also be considered. The recommendation, at present, would be to include a careful assessment of actors influencing the process of obtaining informed consent in new trials of gene therapy and an evaluation of the psychosocial impact of study participation. This is the very least owed to patients and the wider public who may need reassurances that the medical profession has a clear code of ethics for trials of gene therapy.

Familial Cancer Syndromes

Where patients seek genetic counselling or testing for risk of developing cancer because of a significant family history, the issues are somewhat different, although there are some parallels in terms of the ethical and psychosocial aspects. Department of Health guidelines [Figure 1] state that it is important to identify those who are at risk, facilitate their need to cope with those risks and ensure they are able to benefit from the advice they are given by clinical geneticists. Furthermore, it is important to be satisfied following a genetic consultation, that life is restored towards normal for those who are at risk of developing a specific genetic disorder. The latter may be a difficult goal for clinical geneticists given that educating people about their genetics risks must, on occasion, involve giving people information which, by its very nature, changes their lives. There is also a need to clarify whether the uncertainty which accompanies statistical estimates of risk is reduced as far as possible. Furthermore, recommendations indicate that genetic screening should always be accompanied by counselling and should be entirely voluntary. Refusal of screening should not jeopardise people's rights and information about genetic make-up should be treated as confidential and not freely available. Any breach of confidentiality would have to be fully justified.

Figure 1

Genetic Counselling

DOH guidelines on genetic services state that it will be important to:

1. Identify those who are at risk
2. Enable them to cope with their risk
3. Enable them to benefit from the advice given and the interventions available
4. Be satisfied that life is restored towards normal for those who are at risk of developing a specific genetic disorder
5. Clarify whether the uncertainty which accompanies statistical estimates of risk are reduced as far as possible

Recommendations suggested by the Department of Health will impact upon clinical service and genetic research. The Cancer Family Clinics are a relatively recent innovation within the UK and currently, 19 of these clinics exist nationwide. The primary aim is to educate people about their genetic risk and provide advice on how they might manage this risk. There is also a need to reassure those who over-estimate their risk and to monitor the psychological impact of genetic risk assessment.

There are a number of unresolved issues which have emerged as a result of advances in molecular genetics and the recent cloning of cancer predisposition genes and these will need to be the focus of future research.

Management of Risk

For many people seeking advice on genetic risk of cancer, their needs will revolve around the issue of how they will manage this risk. This is especially so, given that many of those

seeking a genetic consultation are well aware that cancer runs in their family. It is often the reason why they seek these consultations. There is some evidence to suggest that for many seeking genetic counselling, their worries will only be assuaged if they can be offered advice on how to manage their risk. This is nicely illustrated by one patient who stated that she did not want to know if she had 'a bad gene' but wanted to be told what she could do about it. Cancer prevention, therefore, is a focal issue to tackle and controversy surrounding secondary prevention [eg breast self-examination, mammography] needs to be resolved before we can begin to consider population-based screening for familial cancer syndromes. Primary prevention is limited, the main thrust being in terms of secondary prevention and the latter raises all sorts of quandaries and difficulties, especially in relation to familial breast cancer. These difficulties impact directly upon both how women cope psychologically, and how they behave as a result of attending a Cancer Family Clinic. Mammography is currently limited within the national breast screening programme to those aged 50 years or over and this is problematic in familial breast cancer where is an earlier than average age of onset. Clinical breast examinations can be offered, although this is perceived to be a less effective method of secondary prevention. Breast self examination as a secondary preventive method remains controversial and chemo-prevention is currently under investigation with results still many years away. The majority of breast lumps still tend to be found by women themselves although not through systematic breast self examination. Despite this, teaching of breast self examination is sometimes offered within the genetics clinic. Perhaps it is a false reassurance, we do not know, but this merits further investigation within the context of issues raised by the increases in cancer genetic counselling.

These controversies suggest that it would be important to integrate psychological counselling into plans to develop clinical genetic services and research will be needed on the psychosocial impact of genetic counselling and testing.

Behavioural and Psychological Issues

We need to evaluate the following areas before more widespread development of cancer genetic services can be advocated.

- do counsellees understand the complex genetic explanations which are likely to await them in their consultations with clinical geneticists?

- does the information they are given by clinical geneticists make any difference to their beliefs about the cancer risk?

- how does the information affect their cancer-related worry?

- are they reassured by this information?

- do they have clear ideas about how their risk may be managed?

- what are the barriers to uptake of risk management strategies?

- how is genetic risk information dealt with by families?

- will more widespread availability of genetic counselling and testing reduce cancer deaths?

All of these issues need to be addressed and resolved and until we have got to grips with these problems it would be extremely unwise to consider the introduction of population screening in cancer genetics.

Acknowledgements

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The Ethical Implications of the New Genetics

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We are living through a major advance in the life sciences. Much is being learnt about the genetic information encoded in each of us. Pathways have been traced between genetic variations and a number of rare diseases. Now pathways are being traced between genetic variations and more common diseases: breast, ovarian and colorectal cancers, for example. This new knowledge has not led, in most cases, to dramatic improvements in the prevention and treatment of these diseases. But scientific advance can be incremental and unpredictable and it would be unwise to rule anything out. On the other hand, one feature of the current advances seems to becoming clear. The pathways along which genetic information travels, seem to be relatively unobstructed only in the case of a small minority of rare diseases: monogenic conditions such as sickle cell anaemia, or Duchenne muscular dystrophy, for example, which add up to only 2% or 3% of the total number of diseases. When it comes to more common diseases, the beginning, middle, and end of the pathways all appear to be more complicated. Several genetic variations may be implicated and interacting at the beginning. Where they have been tracked down, and are associated with a high risk of breast, ovarian or colon cancer developing, this will occur in only a small minority (about 5%) of the people who eventually develop these diseases. A slightly larger proportion of people may develop cancers associated with some more common genes, but the presence of these commoner genes will be associated with a much lower risk of the disease developing.

This rapidly accumulating information about links between genes and disease clearly has exciting implications for bio-medical scientists. Their enthusiasm and expectations can be felt as one reads their papers. Let me just give one example, a quotation at random: "....*more recently, efforts have focussed on the genetic abnormalities responsible for hereditary, non-polyposis colorectal cancer which may possibly account for up to 15% of all colorectal malignancies. In the foreseeable future it is possible that significant population based genetic screening for this condition will be available. As the molecular basis of colorectal cancer is*

elucidated it will inevitably lead to radical changes in clinical management, particularly with the possible introduction of gene therapy and chemoprevention." [Steel. 1994]

Reading these scientific papers, it is tempting to undertake a linguistic analysis of their future conditionals, seeing where "may" shifts to "will", "possibly" to "inevitably", and perhaps examining what might be called the rhetorical art of being uneconomical with statistics. This temptation can be resisted by remembering the known individuals who have died from these forms of cancer and others who might. Even if only some people can be saved and some pains relieved, as a consequence of this typically scientific curiosity and enthusiasm, its efforts must be supported.

The ethics of that research, moreover, including clinical trials, do not seem essentially different to those involved in chemotherapy. The principles are agreed. The problem is their application to particular cases. Is it justifiable to ask that patient to submit to that procedure for the sake of that hypothesis?

That much is unquestionable. But we are still left with the problematic implications of this accumulating information, genetic information, for lay men and women whom it may concern in first person, rather than in third person terms. What do these varying percentage risks of one or more forms of cancers, or of other diseases, mean when you are told that you have them? Much will clearly depend on the degree of risk, on how you understand risk, on what you already know about the disease, perhaps from its effects on members of your own family, on how and where they were treated, how adequately, on the therapies or prophylactic measures available, on how radical these are, or what side effects they have.

The questions which this raises for individuals who may be affected are not entirely new: awareness of probably hereditary conditions has always existed in some families. But the margin of doubt, the possibility that it may not happen to you, was wider in the past. The knowledge was often, although not always, more private. It gave you a sense of greater control. Nowadays, the relevant knowledge has, or can much earlier, come into the control of someone else; someone who knows more about it, much more about it than you do. So there is a greater danger of fatalism. If the signals coming from your body tell you that you are, in your own terms, perfectly healthy, and you are then told that you may have a 'genetic disease or belong to a cancer family', what does that do for your self confidence? In people with monogenic conditions or at very high risk of some cancers, all the self confidence in the world may not affect the outcome. But how sure can we feel of that, particularly as the risks get

lower? The problem is complicated, moreover, by the fact that in the next few years, given human variety, we are likely to learn much more about genetic predispositions to a whole host of diseases other than cancers. How do you weigh an x risk of colorectal cancer at age 50 against a y risk of a heart attack at age 60, and a z risk of Alzeimer's at age 70? Thus what seems to be the present direction of research in medical genetics, seeking to identify one disease predisposition after another, could well induce a greater sense of fatalism and powerlessness - at least among those not robust enough to exercise their right not to know.

All this may be to make an equally fatalist assumption - namely that what seems to be the present direction of research, actually is, and will continue to be so. Certainly it is what the media, and some scientists who inform it, seem to want us to believe. Only last week, for example, The Independent carried a banner headline *"Genes, not greed, make you fat"*. The bit about the *"obesity gene"* not being the only factor and that *"it would take more than 10 years to produce a rational therapeutic"* was tucked away, as usual, at the very end of the article in small print.

But other scientists are saying something different. They are suggesting that this genetic business is rather more complicated. The complications seem to have to do with what happens on the pathways I mentioned earlier. Much of this is unknown, since most of the relevant medical research so far has been focussed on the beginning and the end, rather than the middle. Some geneticists [Strohman 1993; Sing, Zerba and Reilly 1994] are now arguing that the striking success of the single gene model for rare diseases may have misled medical researchers concerned with more common diseases. In most cases it is misguided to think of our genes providing the bio-musical score for, and also conducting, the opera (or perhaps soap opera) of our lives. Some notes may be struck in the beginning and reverberate to the end in a few instances. But mostly, the interactions between genes, their products and the environment in and of the growing organism, make it more like an orchestra with a mind of its own, improvising, as it were, by negotiation among its members (genes included) and with its audience.

That rather fanciful layman's interpretation of what is going on may suggest that, like a war artist finding himself in a minefield, I am whistling in the dark. To quote one of the recent scientific papers referred to. It says this... *"The etiology of an individual's functional phenotype at a particular time is a complex function of uncountable gene-gene and gene-environment interactions that influence physiological processes at all levels between the genome and the traits of interest. Neither genes nor environments alone cause the particular deviation of an individual's*

functional phenotype from the mean of the population. The phenotype is a derivative of physiological and biochemical functions that are themselves emergent properties of interactions among genes and environments. The dynamic expression of the genome type is orchestrated by the environments experienced over time by the individual." [Sing, Zerba, Reilly]

The critical point which these, and some other geneticists seem to be making, is that much of the current race to identify genes "predisposing" people to particular diseases is based on a greatly oversimplified view of genetic determinism. "What is going on", it is sometimes suggested, is a re-run of something like the old controversy between preformationists and epigeneticists. Preformation assumed a little person within each human egg, who just grew bigger. But the epigenetic theory sees development as the emergence of a series of non-preformed structures, with the organism itself being responsible for its own organisation.

If this epigenetic approach is correct, it has important ethical implications. The current race to identify genes predisposing us to this or that disease seems to be creating intellectual and practical problems. Intellectually, it is driven by the desire to seek out what the media call "bad" genes - it is easier to decide that a disease is bad than that some behavioural trait is good. But we know that some genetic traits which may be a burden in some situations can be an advantage in others; and the epigenetic approach encourages us to believe that a lot of other good things also may be happening in the encounters which take place along the criss-crossing pathways of life. If the epigenetic approach is correct, many of the present dilemmas about what should be told to whom, may be less acute than they seem. The genetic counsellor's duty may be more like that of the anaesthetist before surgery, who has to use his or her judgement regarding which risks the patient should hear about. The anaesthetist has to balance the requirements of informed consent, deriving from the principle of autonomy, against the requirement of not harming the patient by burdening him or her with knowledge of the more remote risks, while at the same time leaving an opportunity to tell more if the patient wishes it. Empowering the patient in this way is a matter of good communication skills, but it is also a matter of judgement, especially if the patient is not to be disempowered by information overload.

In the genetic area, of course, this task is currently complicated by the danger that as each new "predisposition" gene is identified, commercial tests (unaccompanied by counselling) will be offered; and this in turn will reinforce the financial incentive to focus on a "preformationist" approach to research in medical genetics. The epigenetic approach, again of course only if it is scientifically well founded, offers a way out of this vicious circle. It suggests that while all of

us are likely to be at some risk of developing several diseases as we age, the task of unravelling which are most likely to develop when, belongs to a future biology of the whole organism, vastly more complex than anything currently being researched. The `present research may be left to run its course, ending perhaps in a menu of disease "predispositions" so complicated that actuaries may give up and go into monasteries.

In the meantime, however, there will still be plenty for medicine and society to do. We need to seek more effective ways of treating and caring for the minority of the population with monogenic conditions or at very high risk of serious diseases. And we need to tackle all the identifiable and changeable factors in the environment, to which the generally well functioning human genome has serious difficulties in adapting.

In this layman's interpretation of "what is going on", I have probably already blundered into numerous mines and can only be thankful that they are only metaphorical. Let me hasten to my ethical conclusions by way of citing two authorities. The first is the French historian and philosopher of science, Georges Canguilhem. At the end of an interesting examination of Claude Bernard's use of 19th century liberal society as a model for biology, Canguilhem writes:

"The concept of the organism as a regulative totality controlling developments and functions has remained a permanent feature of biological thought since the time when Bernard was the first to demonstrate its experimental efficacy. Nevertheless, its fate is no longer bound up with that of the social model from which it originally drew support; an organism is not a society, although, like a society, it exhibits an organisational structure. In the most general sense, organisation is the solution to the problem of converting competition into compatibility. For an organism, organisation is a fact; for a society, organisation is a goal.

Society's goal: organisation as "the solution to the problem of converting competition into compatibility". Achieving that goal seems to be the real ethical challenge posed by the new cancer genetics. It is particularly important in relation to all the commercial concomitants - patenting the genome, marketing genetic tests, the implications for insurance, and so forth. These issues, together with the welfare and health care of the minority with monogenic or very high risk diseases, public education, and the direction of research -these are all ethical matters in which we have a common interest. This is not a party matter.

The second authority I want to quote is J S Mill, the great 19th century Liberal philosopher who was consciously following Coleridge, the great 19th century Conservative one, when he wrote that government should *"beneficially employ its powers, its means of information, and its pecuniary resources, (so far surpassing those of any other organisation, or any individual), in promoting the public welfare by a thousand means which individuals would never think of, would have no sufficient motives to attempt, or no sufficient power to accomplish.... a State ought to be considered as a great benefit society, or mutual insurance company, for helping (under the necessary regulations for preventing abuse) that large proportion of its members who can not help themselves."*

Today, as our knowledge of the genome grows, that large proportion potentially includes any or all of us.

These considerations may be sufficient for me to conclude simply by stating some practical implications of three generally accepted ethical principles. Since, for the time being, it seems likely that information about "susceptibility" genes for cancers and other diseases will continue to accumulate, and that pharmaceutical and insurance companies will continue to have legitimate commercial interest in this information:

1. The principle of informed consent requires not only full counselling before genetic screening, testing or therapy, but also public education in human genetics, to counteract media or commercial oversimplification of the issues, and to inform political as well as private decision-making.

2. The principle of justice requires that insurance to pay for the welfare and health care of those with disabling single-gene conditions, or at genetically identifiable higher risk of developing cancers or other serious diseases, should be met from funds raised by the state.

3. The principle of utility requires the research into the causes of cancers and other common diseases should focus not only on genetic factors, but also on their interaction with environmental influences. For some serious and otherwise untreatable conditions, gene therapy is desirable, and may be feasible . But in most cases, and for the long-term common good, it may be safer and simpler to try to modify the environment rather than the human genome.

The Legal Implications of the New Genetics

John Evans, Regional Legal Advisor, Trent RHA

So often, science seems to be ahead of the law and so often the answers to the questions people want answered are "well, maybe", or "well, perhaps", "on the one hand", "on the other hand"... we don't really know. In these situations it is better to offer some fairly constant basic principles and discuss them in such a way as to provide a legal framework to work with. There are a number of general issues: purchasing genetic services, risk (the cost of risk is huge and getting larger, and is something we have to take on), and lastly the issue of consent.

Purchasers of genetic services are the district health authorities who obtain their powers from the National Health Service Act. Their basic statutory duty is to purchase health care for local populations. There is no obligation to provide a uniform health service, or even a health service to meet all needs. Each District Health Authority has a duty to provide services, by purchasing, to such an extent as it considers necessary to meet all reasonable requirements.

Figure 1

NATIONAL HEALTH SERVICE ACT **1977 - SECTION 3** It is the [District Health Authority's] duty to provide..... to such extent as [it] considers necessary to meet all reasonable requirements hospital accommodation medical.....nursing.....services	such facilities for the prevention of illness, the care of persons suffering from illness, the aftercare of persons who have suffered from illness as [it] considers are appropriate as part of the health services;.... such other services as are required for the diagnosis and treatment of illness

The Act gives scope for a variety of "right" decisions in any given situation. Health Authorities (purchasers) can decide to provide a particular service, they can decide not to provide a particular service, they can decide to provide a particular service to a particular level, and then cut it off when the money runs out. All they need to do is to make a reasoned, rational go at making up their mind. In this case the District Health Authority would need to be persuaded, under those powers, to think that the genetic treatment of cancer is something that they are willing to pay for. To persuade them to invest large sums of capital in any scheme would involve the process of considering private finance, and considering where it might be available before the public purse is considered for that money. Subsequentally the new regional office must be approached and asked if they are willing to allow the hospital to borrow the private money or to borrow the public sector money. When all that is approved the District Health Authority may consider it but decide that it can not afford the revenue consequences year by year. Shall we actually purchase this? Thus, it is easy to see that that basic statutory power is one that in a very negative sense, provides rationing. In a positive sense it provides a diversity within the health service and allows things to be done at a different speed in different places, which may not be an entirely bad thing.

Risk

Risk comes from many sources. New drugs are a prime source. The NHS has already been through some huge actions - the HIV claims, the Opren claims, the Myodil claims, etc. Risk is something which is very much on the NHS agenda. The NHS Executive has said that the management of risk is something that every hospital has to be in to. We can no longer simply sit back and think "Well, we're insured, somebody else will pay. It is not a big enough financial issue." It is a huge financial issue now. Where does the liability come from? Two examples will illustrate the problems. The first, the liability for defective products and goods stems from the European Community [EC] law and has been on our statute books since 1987. It has not yet caused us a lot of problems, but only, I think, because it is young. Treatments since the 1987 Act came into force will more and more be caught by it. Many people think that the directive of this Act set up a no fault system, but it doesn't, exactly. A summary of what has be gone through to prove a claim under the 1987 Act is illustrated in Figure 2.

Figure 2

PRODUCT LIABILITY	THE PROFESSIONAL NEGLIGENCE TEST
STATE OF THE ART DEFENCE that the state of scientific and technical knowledge at the.....time was not such Consumer Protection Act 1987 that a producer of products of the same description as the produce in question might be expected to have discovered the defect..... Council Directive [85/374/EEC] as to enable the existence of the defect to be discovered	Has the Professional been proved guilty of such failure as no such professional of ordinary skills would be guilty of if acting with ordinary care OR Would a responsible body of opinion within the professional/speciality accept the judgement/action as proper

You need a defect in something that is purchased, used on a patient and that causes damage. The person who manufactures this, the person who makes the product, is then liable for the damage caused unless one of the answers to the claim set out in the Act can be proved. Now the Act is odd in that it defines a defect in a rather strange way. "There is a defect in a product if the safety of it is not such as persons are generally entitled to expect." The English Statute requires that the Producer might be expected to have discovered the defect. There is a subjective hole in the middle of this Act. What are persons generally entitled to expect, and what is a general entitlement? Is there a difference or not?

In deciding whether there is a defect in a product, in a drug, account has to be taken of all the circumstances that pertain at the time the product is administered, or purchased. It is possible to get different answers with different patients. One of the problems with the Act, and with this definition, is that it does stem from EC law and EC law is more concerned with consumers buying cars or washing machines, or fridges, and not with patients being treated with drugs. Amongst the things that have to be taken into account is the "get-up" of the product, in other words, the packaging, the way it is marketed, the information sheets that come with it. Where drugs are concerned, of course, the administering doctor is in the middle of that process, and

the Act does not consider how he relates to the case. Yet it is the doctor who knows the risks, and the doctor who decides the extent of the risk that is passed onto the patient. Talking about a defect in a product which is defined in circumstances like this is really rather difficult. It may be important to take account of the fact that when one is deciding to administer a particular drug, a particular method of dealing with a disease, the state of mind of the patient is important. There is a level of risk that a patient is willing to run, and highly material to the safety the persons are generally entitled to expect in those circumstances. Depending on the patient you might take a different level of risk. That Act and that particular part of it will cause us problems.

To return to one other issue: the defenses the manufacturer of the product can put up. One of the defenses is a simple denial. "Somebody else, something else did it." Of more importance, perhaps, in considering new problems and new methods of treatment, is the state of the art defense. The problem we have there is that English statute appears to say something different from the EC law. The English statute does set out that the product maker might be expected to have discovered the defect. Many people read that as importing an element of reasonableness to the process. If the information about the defect in the product is hidden in some rare bit of research that was published in, say, the People's Republic of China, or Tashkent, there is little reasonableness as to whether you would have found it or not and the English statute appears to allow you to miss some of these things.

The EC Directive is different. It refers to enabling the existence of the defect to be discovered. Many people think this means that if information is published anywhere, no matter how hidden it is, you have to know it. If you don't know it, you can't plead the state of the art defence.

The best advice one can give on this is that the EC Directive is the one that will count. The purpose of it is to protect the consumer, the patient. The purpose of it is not to protect the researcher. The view is that researchers can insure and therefore they do not carry the risks. It is the consumer that should have the benefit of the Act.

Turning now to negligence and the common law; this is the Bolam test, referring to the profession of ordinary skill acting with ordinary care. Referring to the responsible body within the specialty. It is that particular measure which is used when it comes to consent. Have you adequately consented a particular patient? The answer to that is yes or no depending on

whether a responsible body within the speciality would have accepted what you have done as proper. In that context, it is possible to move on to the concept of informed consent.

Nevertheless, what is the nature of the consent? We sit over lunch, we sit in rooms like this and we're rational, we're reasonable, we talk as though every patient is a rational, reasonable thinking person. The reality of it is that they are not. They are scared out of their minds half the time; they are incapable of comprehending what you are saying. On one level, there's the parent who comes in and flings the body of their young child down before you and says "save him", "save her", and that's all that's in their mind. Is that a consent to treat them? I suppose it is. But is it an informed consent to treat? I can't believe for one minute that people like that, behave as this reasonable occupant of the Clapham omnibus we used to talk about. Many people in dealing with their own conditions have a fear which takes away their reasoning. Yet we talk about informed consent, we talk about the overloads of the information that we give patients. The reality of consent, I think, is very far from what we talk about. In addition we do many procedures without any consent at all and it is accepted as good practice to do procedures, or some procedures without any consent at all. If you have a stroke victim, for example, well content to vegetate - you don't get their consent. You take them by the arm and you get them moving.

It is very difficult to find a logical thread in all this. It is difficult to define informed consent; impossible to define it, impossible to put it into words. Experience in handling claims indicates that consent problems are a very large part of the reason why people sue the NHS. On this basic principle the advice would invariably be to tell professionals that the best thing to do is to tell people as much as possible. But it does need to be recognised that for all sorts of reasons, people may not be able to take in all that they are being told. The legal structure around consent is unsatisfactory at the present time, and there are no signs indicating that it is going to get any better.

To talk about counselling patients; to talk about the issues that are material to the family, we meet even greater consent problems and the whole legal structure of the NHS is centred around "the patient". You owe your duties to "the patient", not to the patient's spouse, not to the patient's parents, but to "the patient". There are constant problems, because there isn't a satisfactory legal framework to allow lawyers to deal with the duties of confidence; to deal with the other issues within the concept of anything greater than "the single patient". There is

no answer to this situation and no indication of how it will be taken forward. It may be necessary to move as practice drives us, but the law may well be a long way behind.

Discussion

Question: "Is the law able to entertain only one concept? You said you couldn't make sense of the consent in ethical terms, we would try to triangulate, take respect, take non-harming, take interests of others, and try and get consent as those three pressures. Is that something the law can't do?"

Answer: Well, I would hope it could do it, but I don't think a legal process in my view, is very good at that.

Sir Cecil Clothier [Chairman]: Well, in the end, consent is a question of facts for the courts. The question is posed by the litigant. "I did not consent to this treatment" and the question will be "Well, how much was he told, what were the circumstances in which he came to be in contact with the doctor at all?". As Mr Evans said -you were brought in on a stretcher having had an accident - you hardly need any consent. The facts of the matter are, the circumstances are such that the fact of consent is assumed there without any further ado, by most courts, I should think, without any question. On the other hand, if you come to consult because you are not sure whether you want treatment or not, You are not even sure that there is anything very much the matter with you, but you would rather like to talk to a doctor about your problem, and then he proposes, well, perhaps something could be done about this, then you might expect something more. So that any case is a question of fact for the court - 'was there, or was there not, a free genuine consent?' and that, to my mind, means one that is sufficiently informed to be a free and genuine consent, because if you do not have any information, you can not really consider anything. The law has never involved a philosophical view of what consent is as an abstraction, which is what it is. Just takes them as they come, just like doctors do.

The Insurance Implications of the New Genetics

Roger Bowley, Executive Director/General Manager, Equitable Life Assurance Society. Chair, Association of British Insurers' Life Assurance and Medical Affairs Committee

The Association of British Insurers is a trade body covering 450 insurance companies, 120 of which are involved in Life Assurance The basic principles of life assurance are important to the context. These principles have been operated in this country for a long time, and are generally in most of the countries of Europe. The two prime objectives are:

1. to provide life cover for as many applicants as possible. They are the proposers.

2. to charge a premium to each proposer which is in line with the risk that the individual brings to the group in which he or she can be placed.

Under insurance arrangements in the UK, those premiums are pooled and invested, subject to deductions for costs. From that pool the policy holders' benefits on maturity or death if earlier are paid. In order to set a rate of premium that is fair both to the individual, and to the other members of the group, there needs to be proper assessment of risk, and obviously that is based on a number of factors including medical and financial information. The applicant provides a certain amount of medical information on the proposal form and then, depending on the underwriters assessment of that information, or the sum insured, a report may, with that individual's consent, be sought from his or her own doctor. Similarly, an independent medical examination may also be required.

Once this information has been gathered in, the underwriter, together with the medical adviser of the insurance company, can assess the rate of premium that is appropriate. Insurers have a duty of prudence which, while covering the obvious matters such as investment, also extends to the careful selection of lives, and the charging of the premium appropriate to the risk that each life brings to the pool. By that means all members of that pool are treated with equity, although not necessarily at the same rate of premium. My own company, which has been in existence for over 200 years, would not be so bold as to claim that we have got it exactly right but we've certainly used the same underlying basis of assessment, over that period, but of course introducing medical advances as they occur.

The second basic principle of insurance, and this is perhaps where our insurers approach is different from some of the approaches that you have to adopt, is that individuals are looked at as part of a group. Doctors will be looking at them individually from the health care aspect, and not as part of a group. We must be open about this. Insurers are in a commercial business of providing cover. They have no mandate from their policy holders to subsidise one group, or group of lives, at the expense of the rest. To provide cover for those who are uninsurable, for example, would mean charging others more - only governments can do that or pay subsidies for it through taxation.

The current position may, however, offer reassurance to you because 99% of all those who propose to life assurance companies in the UK are offered terms.

The Genetic Issue

Genetics and insurance first became the subject of media comment when Baroness Warnock stated that the ramifications of genetics were so important that legislation would be needed in connection with insurance. She made the statement at the 11th Human Gene Mapping Conference in London in August 1991. This was followed by the Nuffield Council which set up a working party on genetic screening - and I would stress that we understand that to be screening and not diagnosis -under the chairmanship of Dame June Lloyd. The Association of British Insurers gave evidence to her Working Party in July 1992, and our views were reported fairly, in our view, in that report, in the Nuffield Council Report published on 7 December 1993.

Nuffield Council Recommendations made in the context of genetic screening

1. That British insurance companies should adhere to their current policy of not requiring any genetic tests as prerequisite to obtaining insurance, and

2. that there should be early discussions between the Government and the British insurance industry about the future use of genetic data and, in the meantime, insurance companies should accept a temporary moratorium on requiring the disclosure of genetic data.

The first part deals with genetic tests - continue the current policy; the second one refers to genetic data, and a temporary moratorium was recommended.

There are, however, two exceptions under the recommendation proposed in 2. requiring full disclosure as follows:

a) for those individuals, where there is a known family history, which can be established by conventional questions about family history, then individuals may be asked to disclose results of a relevant genetic test, and

b) the moratorium should apply only to policies of moderate size, the level to be set between the government and the industry.

While I will cover our response in more detail further on, I should at this stage say that we welcome the Nuffield Council Report as an important contribution to genetic debate. It accepts the insurers' position in that the UK insurance industry has no intention within the foreseeable future of seeking genetic screening tests for insurance purposes.

On the second recommendation, about genetic data, the industry has been in discussion, not only with the Department of Health, but also with many other relevant bodies and researchers. Indeed, today is part of the ongoing discussion. Obviously the insurance industry is not alone in deciding what constitutes genetic data, but that is one of the crucial areas that we, and many others, are considering.

Current Scene: Four Main Points

1. Our view is that while genetics is a subject of central importance to all our lives, the issues it raises, such as relationships within families, appear to place the insurance aspects well behind some of the ethical and medical considerations. That is not to say that we are hanging back, but bearing in mind that no UK insurer is currently seeking genetic tests for the purpose of issuing insurance, it should remove virtually all the immediate concerns over insurance and let the debate focus on the important social and ethical issues.

While insurers are not seeking screening tests they are coming across cases where tests have been carried out for the purpose of diagnosis, and these concern the predictive tests for Cystic Fibrosis, Huntingdon's Chorea and a few other disorders. These tests, however, are undertaken on medical advice, not involving insurers, as part of health assessment, usually because of family risks and those cases are, from an insurers point of view, very few in number.

To give some encouragement insurers have been able to provide cover, albeit at an increased premium, for those at risk. The additional premiums will vary with the age of the individual being highest at 21+ years and reducing to a standard rate of premium at age 56. As might be expected, it is not possible to cover those who already have the disease.

2. Mortality rates on which insurance companies base their premium calculations will only be affected when therapies come into being and begin to change people's life expectancies, or possibly for sickness insurance, their illness patterns. In the meantime insurance companies continue to place lives in groups expected to experience broadly similar mortality on health grounds.

3. Much of the public debate has attributed to insurers the desire to seek genetic tests for the multifactorial disorders. We are following the developments and we are fully aware that where multifactorial issues are involved, environmental considerations, where there is still only limited knowledge, can play their part to modify the apparent risk. Consequently, until such time as the impact of each adverse genetic feature has been statistically and properly assessed by medical teams, insurers are unlikely to see benefits in using multifactorial genetic tests - always assuming that the tests exist. As I understand matters, we are years off any full assessment of a person's genetic makeup and its full meaning. If we were ever to get to a

known date of death for each individual, then there would be no need for life insurance. We are not within sight of such a detailed and concerning scenario.

The life assurance industry is a long term business, and should not reflect day to day research developments until their impact is certain and confirmed. In the meantime, insurers do not seek any form of genetic tests. They are used to dealing, via their medical officers, with multi medical problems, some of which include environmental impact. For example, insurance companies have broad markers for height/weight ratios, hypertension, etc. These are environmental as well, and because of expertise in these and other areas over 99% of proposers are able to obtain life insurance cover, with only about 4% being charged extra premiums because of health risks. Insurers have no ambition to reduce this 95% standard basis. The market is innovative, as well as being competitive, and it is likely that those who are "first class lives", ie within tight height/weight ratios and good family history considerations, may obtain discounts in the same way as no smoking discounts are offered at present. It is worth emphasising the market is competitive in all aspects, and this perhaps can be demonstrated by the fact that my own office has never offered a no smoking discount, but we are usually within the first three for the cost of the term of assurance.

4. As an industry we have devoted considerable time and effort to discussions on genetics because we do appreciate that in the future it will change the face of medicine. Our concerns cover individuals who may know something about themselves which increases their risk from an insurers point of view but do not declare that fact. Such action is unfair to other policy holders as experience shows in cases such as these the individual seeks higher then average sums assured.

General Points

It has been suggested that genetic information is different from other confidential medical information and that insurers should not be allowed access to it. We do not see it in that light and assume the reference arises from concerns that insurers will misinterpret or misuse that information. Aside from the matter of confidentiality to which insurance companies pay very careful attention, all life companies have medical consultants whose role is to advise their company and monitor all medical developments, including genetic developments. Similarly, the Association of British Insurers sees it as important to keep in touch with experts in different fields and ensure that alternative ways of offering cover are put forward wherever feasible: in situations where life cover cannot be offered in a standard form to a life.

I have spoken about genetic information and the fact that we consider it to be covered by the term medical information. As such, we consider that where individuals have had a genetic test, at present this is likely to be because of some perceived family risk, the test result forms part of their medical record, and with that individual's consent can be made available to insurers. On the question of consent and medical reports, I should mention that the Access to Medical Reports Act of 1988 imposes certain duties upon insurers in relation to medical information and gives certain rights to individuals, notably over the provision of consent, the right to see, amend, or withhold a medical report prepared for insurance or employment reasons.

Conclusion

In conclusion I would like to emphasise that insurers need the general population who are, after all their clients, either current or future, and are therefore not in the business of making it difficult for individuals to obtain insurance cover. That said, we are commercial organisations, as I think you will accept, and we look at some of the problems from a slightly different perspective. Our aim, however, is to do the best we can for our policy holders and deal with them in an equitable fashion.

Genetic developments are clearly going to continue and we in the insurance industry, and in particular our Chief Medical Officers, will be spending more time joining in the debate and reacting to developments.

Sir Cecil Clothier, **[Chairman]**: I am very grateful to have the chance of asking a question or two from someone as interested in the field as you are. I must say that this area has always puzzled me a little. It has always seemed to a lawyer that all contracts of insurance, have something in common with a gambling contract, in a sense that you are betting on the happening of a certain event which may or may not happen and chiefly the premature demise of the insured person, and no sensible person engages in such a contract without examining the form pretty carefully. To transfer it to a less emotional topic. If you are insuring a ship and its cargo, you inspect the ship very thoroughly indeed, through Lloyds or some agent of that sort, and if its an old rust bucket you just refuse flatly to insure it at all. There seems to be an assumption underlying some of what has been said about this topic that everyone is entitled to insurance and I don't think, from a lawyers point of view, that that can possibly be right. There must be some people so stricken by misfortune and providence, that really they are not insurable and before you even attempt to consider insuring them you really need to

know as much as you can about them just as you would about the ship going on a long voyage with a valuable cargo. What is the insurers attitude about this? I don't see that there is any absolute right to be insured. I think very desirable - you want to do business, you want to insure people and they want to be insured, but there is no positive obligation that these two should come together.

Roger Bowley: One of the great modern tendencies that consumerism is bringing is that there is a social right to have lots of things in this world and one of them is the social right to insurance, and I'm afraid, as insurance is organised in this country, that is not the case. There is no social right. As you say, the important element is to get the lives in the right categories so that you can apply the mortality tables. It the mortality tables are accurate, and they are based on a long history of measured mortality for those who have applied to insurance companies, then you can put them into the right bands. If the information is withheld, or you don't get a correct figure, then ultimately, if people insure for lots of high sum insurance, and lots of people do that, and insurance companies are taken advantage of, then ultimately all the other people will pay, and at the very end of the day the insurance company will become insolvent. I would say that insurance companies, as you probably know, are very highly regulated by the Department of Trade and Industry, and the Department is following this topic along with many others. You might be surprised that it isn't just the Department of Health, but involves the DTI, for the very reason that has been outlined. It is important that the information is provided on a level playing field. Clearly commercial considerations come into it. Insurance companies will not medically examine everybody. A certain amount has to be taken on trust, but if there is a skewed playing field then ultimately insurance companies will suffer materially and at the end of the day they may go under.

Question re: Insurance cover and HIV testing.

Answer: Yes, It has always been something of a mystery to me as to why there is the view that insurance companies would not offer normal terms if an HIV test proves negative. Now, insurance companies would offer normal terms in an HIV negative situation if there were no other risks and experience shows, in some instances, that not just the HIV negative element, obviously, but the other elements of a life, who presented with that history, may be such as to generate extra risks in the experience of the medical profession or the advisers to the insurance companies. I see nothing wrong, myself, in asking about that element, but it has now disappeared. There is another point too - it is important that the industry is sensitive to some of the elements that are around. That is to say that one moves fast enough with public

opinion, but within the realms of getting sufficient information. But I can take your point that most insurers, unless there were other risks, would have given normal terms to an HIV negative case.

Question re: Insurance rates following tests.

Answer: If the tests are medically proven or accepted then the information should be passed to the insurance company and the chief medical officer should consider it. One of the great things about genetic testing when it comes, is that everybody thinks of the down side but that's what is known as the one-sided coin. You have to average everybody who presents in a particular group, but nonetheless, when a risk is proved to be less than it was originally anticipated then, yes, you should encourage them to go back to the company to see if the rating can be reduced or withdrawn.

The Service Implications of the New Genetics in General Practice

Dr Hilary Harris, General Practitioner, Brooklands Medical Centre, Manchester

We are a two partner training practice with a trainee in post. We have a total list size of 4400, about the national average. In 1993 we carried out 15000 consultations in the practice, and about 2500 home visits, of which a third were out of hours. This means about 4 patient contacts per year.

Figure 1

SOUTH MANCHESTER 2 PARTNER TRAINING PRACTICE

LIST SIZE	4400
SURGERY CONSULTATIONS	14760
HOME VISITS	1783
OUT OF HOURS VISITS [INCLUDING NIGHT VISITS]	859

Figure 1 illustrates that with the current workload it is quite difficult to integrate genetic screening and counselling within a consultation that will last, only perhaps, 7 - 10 minutes. When I am talking to my trainee in the practice, I talk to them about the patients agenda and I say to them that metaphorically they come in and see us and they put their agenda on the desk. You can't see it but it is there, and until you've addressed that agenda then the patient is not going to be receptive to other health screening opportunities, be they genetic or anything else. It is really important to understand that.

So what is happening now to change patients awareness about genetic opportunities? The media are full of genetic information that doctors listen to, but so also do patients. Patients who have a family history of cancer have been worried for years. If you've lived in a family where your mother, or your sister, or both, or other family members have developed breast cancer, and inevitably, I'm afraid, died, often quite quickly, then you're going to be frightened and anxious. But of course media attention is now bringing patients into our practices to ask us about the opportunities that are going to be available, because they know that regular mammography, increased mammography, annual mammography, may be helpful. They have heard about trials for Tamoxofen. They have heard about prophylactic mastectomy and oophorectomy. They are aware of these things, so that the interest and opportunities to talk to patients has been increased.

Of course, patients often do not understand the basic population risk of developing breast cancer; that the risk in the general population, lifetime risk, is 1 in 12. They certainly don't know that if they have one family member, close family member, affected, that their risk is likely to be doubled, and if they have two close family members affected, particularly if these have developed breast cancer under the age of 50, that their risk may be increased 4 to 6-fold. Dr Evans, who runs the Family History Breast Cancer Clinic, in Manchester has done a survey in which he found that patients attending who already had a heightened awareness about their family risk,a quarter of them were underestimating their risk and a quarter of them were overestimating their risk. Unless family doctors know some of these figures then these Family History Clinics are simply going to be overwhelmed in the future. In fact, they are already overwhelmed. In Manchester the waiting list is 8 months.

In general practice we look after families, often for very many years. We may not know all the family relationships until one of the family members is stricken by serious disease. The population risk is that 1 in 12 women may develop breast cancer, and for every 20 who develop breast cancer one of them may have a genetic defect, may carry the BRCA1 gene, or another that is likely to be discovered in the near future. It is important that we know these figures.

In my own practice we have 27 patients with a known diagnosis of breast cancer and their age range at diagnosis is from 27 to 80. Attendance for mammography screening is on the practice computer and at the moment, this is 45%. In Manchester, as elsewhere in the country, patients are called from the age of 50. We also have a small cohort for research purposes who are being called from the age of 40. In my practice every women over the age

of 50 has a mammography heading on the current screen and when she comes into see me I can turn to this screen and if she hasn't attended the mammography, I can discuss this with her and the benefits of screening, so that I hope to be able to increase these update figures.

I have looked at three opportunities for family history taking in general practice. In 1991, we asked patients who were coming to book for their pregnancy, whether they had any problems in the family. We asked them a very general question and we got a 20% response from this. The answers they gave indicated that these patients gave us responses that related to anxieties that were current in the family at that particular time. We asked the wrong question and we got the inadequate answers.

We have been running a cystic fibrosis carrier testing project in eight North West practices with a population of about 50,000 patients and 27 general practitioners. We asked the GP's who were taking part in this study, if they would fill in the back of the laboratory card that accompanies the mouth wash specimens from their patients and we asked them to put down if two or more relatives of the patients they were screening, particularly if unusually young, were suffering from any of these diseases stroke, cancer, diabetes, or any other common disease such as asthma, epilepsy or hypertension, purely for research purposes, and again, to raise the awareness, in general practice, of the possibilities of genetic intervention in the future. Figure 2 shows the responses received: 773 questionnaires were completed and out of those 42 gave family history one or two relatives with either breast or bowel cancer.

Figure 2

FAMILY HISTORY DATA COLLECTED BY GPs DURING CF CARRIER SCREENING	
Questionnaire complete	773
Family history of 1 or 2 first degree relatives with breast/bowel cancer	42 [5.4%]

In my own practice, when patients come to register with the practice, or when they are sitting in the waiting room, waiting to be seen, they are asked to fill in a comprehensive medical questionnaire, and this is just a very small part of it. "Do you or your family have a history of the following conditions?" They are asked to give us as detailed information as possible. Obviously this is giving us very crude, rough figures, but it is a beginning.

Figure 3

FAMILY HISTORY DATA FROM QUESTIONNAIRES COMPLETED BY PATIENTS ATTENDING A SOUTH MANCHESTER GENERAL PRACTICE 1994	
FAMILY HISTORY	
Questionnaire Completed	1200
Breast Cancer	60
Gastrointestinal Cancer	11
Diabetes Mellitus	144
Ischaemic Heart Disease	154

Figure 3 shows the responses received - we have had 1200 questionnaires completed so far. Sixty patients gave a family history of breast cancer, this may well only be one family member affected, it may not have a genetic component, the member of the family may have developed breast cancer late on in life. Interestingly only 11 patients gave a history of gastro intestinal cancer, this diagnosis is much less precise for patients and their relatives.

The possibilities for the future of screening in general practice are enormous. About 70% of practices in Britain are now computerised. Some of them only use their computer for repeat prescriptions, some of them, like ours, use them for every patient encounter, for recording laboratory results, for recording health screenings, cervical cytology, mammography, a range of activities are placed on the computer. What is exciting is that the particular computer system that we use is shortly to be upgraded to allow us to write pedigrees, to integrate family histories, to integrate family illnesses, across the families that are registered with us. The issues of confidentiality must be addressed - the way forward is certainly with computers.

The role of the genetic associate is another important opportunity. What is a genetic associate? Traditionally, it was someone with a nursing background and an interest in genetics and perhaps qualifications in counselling. More recently it has changed to become someone with very good academic qualifications, often a degree in genetics, and perhaps a background in one of the caring professions. Their role in the future could be expanded and we will pilot this extended role in Manchester, with attachments to general practice. 'Attachment' staff include the District Nurse, Health Visitor, and Midwife. These are members of the primary health care team with whom we are in daily contact. I would envisage a genetic associate 'attached' to a number of practices. Their role would be in training of the primary health care team, support, in organising screening programmes, perhaps in writing protocols for the computer, obviously in counselling difficult genetic conditions, to co-operate and liaise with academic departments to organise research.

Figure 4 and 5 are about evaluation. New initiatives in primary care should be evaluated. Figure 4 is particularly pertinent to primary care, and this evaluation of the cystic fibrosis project was administered by two genetic associates who worked closely with me at St Mary's, but are independent of all the general practices. They administered a questionnaire, and an interview, with everybody who has received a cystic fibrosis carrier test. This was done in early pregnancy when the endpoint would be an offer of termination of pregnancy if the foetus was found to be affected. The end point in screening for breast cancer may well be bilateral

discuss the CF test that had been administered by their general practitioner - we were pleased to find that patients did feel that they had enough time, in primary care, even with all the pressures of the new contract.

We were also interested in whether patients remembered the information that they were given, because they were receiving information that is complex and difficult and it may have a profound effect on their life.

Figure 4

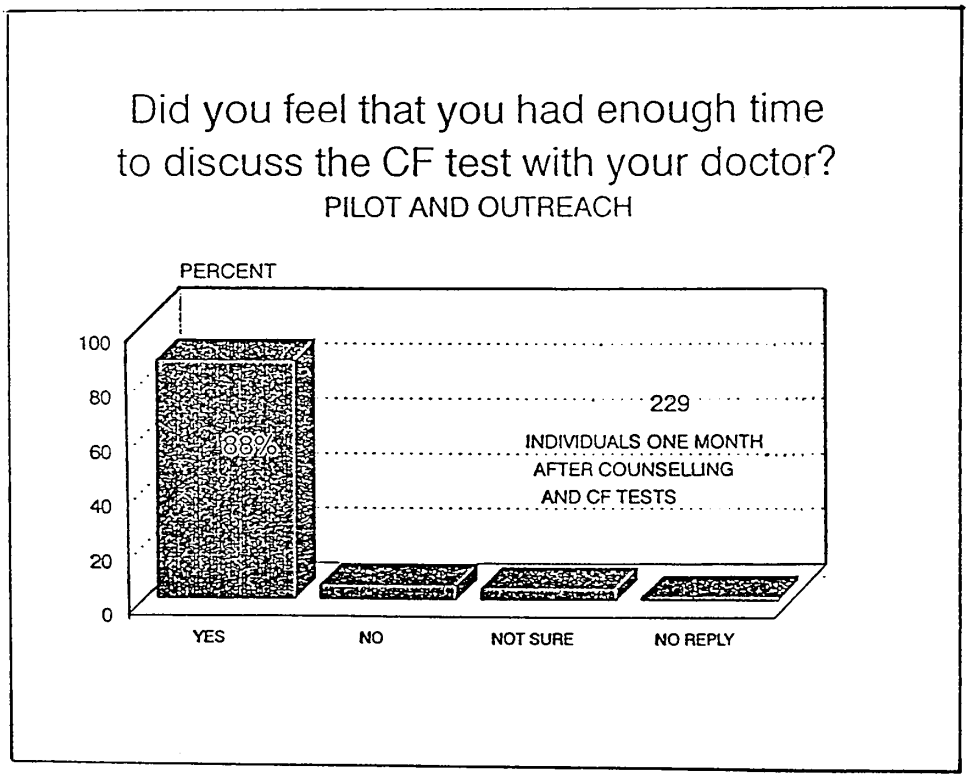
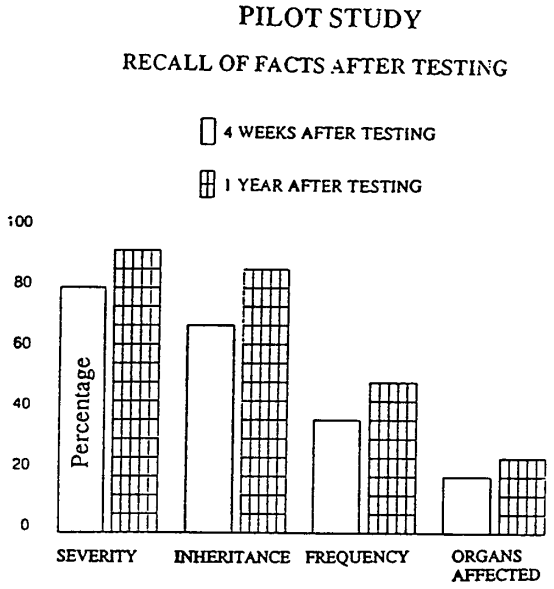


Figure 5



There are only about 200 trained clinical geneticists and co-workers in the whole of Britain. There are 33 000 general practitioners, and if you added in our attached staff, many of whom are very keen to take on other roles, our practice nurses, our midwifes, our health visitors, you could certainly treble that figure. We have a population of 57 000 000. The trained clinical geneticists are not going to be able to cope with this work load. We really have to address the problem of how we are going to go from mutation to consultation - how we are going to bridge that gap, in general practice.

This rather sobering statement by Steve Iliffe - *"the general practice workforce is not a homogeneous group in terms of skills, commitment to whole population perspectives, and attitudes to scientific medicine.*[1]" might be true of other groups of doctors other than general practitioners as well, but I think we have to address the problem because, in primary care, if we can't begin to deliver some of these scientific discoveries in a co-ordinated way, in an empathic way, an informed way, to our patients, first of all we are going to fail our patients,

and secondly I think we are going to completely prejudice all the spin-off effect of the human genome project.

"Bad advice and neglect are more to be feared than the defective gene we carry". There is no doubt that in primary care we have been overwhelmed with administration, with nonsense health promotion, with all sorts of activities which are totally unevaluated and useless. I am concerned to hear colleagues say "we're not going to have time for genetics in primary care". I believe we have to reappraise our workload and make time for this.

Reference:

Iliffe S, Munro J. General Practitioners and Incentives. BMJ editorial, November 6 1993. 307, p1156-7.

The Service Implications of the New Genetics for Hospital Services

Dr Mike Richards
Director of Cancer Services, Guy's and St Thomas' Hospitals

Can we define the aims of a clinical cancer genetics service? The goal of such a service is to reduce the morbidity and mortality associated with cancer through identification of individuals at high risk of developing cancer, thereby facilitating early detection of the disease when it develops in these individuals. Ideally, measures should be available to prevent the development of the disease in these high risk individuals. Another important aspect of the work of a cancer genetics service is to give appropriate reassurance to individuals who are not at high risk of developing cancer, thereby reducing their anxiety.

Components of the Service

The steps that need to be taken to achieve these aims are as follows:

1. Assessment of risk
2. Counselling
3. Screening/monitoring programmes for those at high risk
4. Preventive measures [when available]
5. Audit of outcome

Assessment of Risk

At present, the risk of developing cancer is largely assessed through careful analysis of an individual's family history. Individuals who are referred to a cancer genetics service [or cancer family clinic] may be sent a detailed questionnaire in advance of their attendance regarding the incidence of different types of cancer in their family and the ages at which cancer was diagnosed. This reduces the time required during the initial consultation. The information

derived from this questionnaire can be fed into a computer to generate a pedigree. However, the geneticist, or a deputy, will still need to check the information with the individual to ensure that the pedigree is accurate and complete. Other factors which may contribute to cancer risk will also need to be considered. For example, in women with a family history of breast cancer, their own reproductive history and use of oral contraceptives or hormone replacement therapy should be considered.

Additional information may need to be obtained from other hospitals to complete the pedigree. For example, a patient may know that her mother died with 'liver cancer' but not be certain whether this was due to metastases from a primary breast cancer. Through analysis of this information, it is possible to assess the risk to the individual in comparison with the standard risk in the population. If the risk to the person being assessed is in the region of four times that of the normal population, he or she may be deemed to be at 'high risk'.

Counselling

Once the degree of risk has been established, the implications need to be discussed with the patient. Those who have been shown to be at 'standard risk' will need to be appropriately advised and reassured. Those found to be at increased risk need to be carefully counselled as to what this means. In selected cases, additional investigations may need to be discussed [eg related to the BRCA1 gene in individuals with a strong family history of breast cancer]. The implications of undergoing genetic testing needs to be explained in much the same way as patients are counselled prior to HIV testing.

Monitoring and Screening

Patients found to be at increased risk of developing cancer should be offered a programme of screening investigations so that if a cancer develops it is detected at the earliest possible stage. This will involve a range of hospital services outwith the cancer genetics service. Depending on the nature of the family history, this may involve clinicians to examine the breasts, radiographers and radiologists for mammography and ultrasound and gastroenterologists to perform colonoscopy. The interval between investigations needs to be agreed in advance. Efficient organisation of these services is essential if the aim of decreasing morbidity and mortality from cancer is to be realised.

screening investigations or may hand this responsibility back to the patient and his/her GP. I believe that the programme is more likely to be successful if there is a centralised mechanism for making sure that the patient is recalled for appropriate investigations at the right time. This would be analogous to the mechanism developed for the National Breast Screening Programme with letters being sent to women, inviting them for mammography. A centralised mechanism would also facilitate audit to assess whether what is being done is effective. Guidelines should be agreed locally and nationally against which the services can be evaluated.

Preventive Measures

At present, the range of preventive measures is limited. Resection of the bowel may be indicated for patients with multiple colonic polyps and prophylactic mastectomy may be a reasonable approach for women identified as being at very high risk of breast cancer. Cancer genetics services will also have an important role in identifying suitable subjects for clinical trials of new preventive measures, such as the evaluation of Tamoxofen in women with a strong family history of breast cancer.

Organisation of Service

The number of referrals to cancer family clinics is increasing markedly. It is, however, difficult to assess the overall level of need for these services in the population. In the absence of reliable figures regarding future demand it is difficult to determine how many services should be established and what size of population each should serve. Clearly, a balance will need to be achieved between convenience for the patient in attending a service close to home and cost-effectiveness in terms of the resources and expertise required to deliver the service. I believe that at least one cancer genetics service will be needed for each of the 14 old health regions in England. As the number of referrals increases we should probably be aiming to have a cancer genetics service in each of the major Cancer Centres recommended by the Expert Advisory Group on Cancer. I hope that this issue will be discussed as part of the implementation process that will result from the Calman report on Cancer Services.

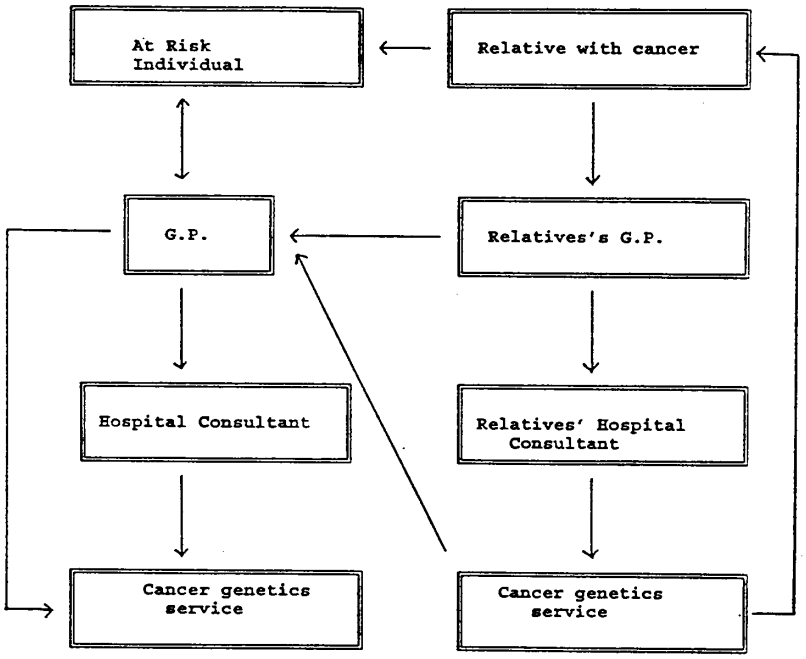
Manpower and Facilities

Each cancer genetics service will require core personnel including geneticists, counsellors, data managers and administrative staff. The number of core personnel will depend on the overall workload and on whether the staff are dedicated to cancer-related activity or have additional

duties related to other aspects of genetics. Alongside the core personnel, a range of other specialists will be required including cancer clinicians, radiologists, radiographers, ultrasonographers, colonoscopists and psychiatrists/pschologists.

Figure 1

ROUTES OF REFERRAL AND INFORMATION



Note: 'At risk individual' and 'relative with cancer' may live in different regions.

How should individuals be referred?

In the simplest scenario, individuals may recognise or think that they are at high risk of developing cancer. They may consult their GP who may either be able to reassure them directly or may feel that there is a need for further assessment and counselling. The GP can then refer the patient to a hospital clinician, such as a breast surgeon, who may arrange onward referral to the cancer genetics service or the GP may request direct referral to the service.

Some relatives of cancer patients may not have recognised that they are at high risk. The risk may be apparent either to the relative who has cancer or to the patients' GP or hospital consultant or to a cancer genetics service. These situations need to be sensitively handled. It would not be appropriate for the cancer genetics service to write directly to the 'at risk' individual who is not a patient. In some cases the individual may be approached by the relative who has cancer. If someone has cancer they can go to their own sister and say "would you mind going to a cancer genetics services and possibly having a blood test"? In other cases, it may be appropriate to involve the healthy relatives' GP. The situation becomes even more complex when relatives live at opposite ends of the country, served by separate cancer genetics services.

Audit of Services

Cancer genetics services should be audited at a number of different levels. First of all, are appropriate individuals being referred to the service? Not every individual who is referred will be found to be at high risk, if we define high risk as four times the population risk for that particular cancer. This may be entirely appropriate, because there will be some healthy people who are not at high risk, but who are extremely anxious and require expert assessment and counselling to be reassured. At present, over 80% of individuals referred to the cancer genetics service at Guy's Hospital are found to be at high risk. It is more difficult, however, to audit the number of people in the population who might benefit from referral, but are not being referred.

The impact of referral on anxiety levels should also be audited. The evidence so far is that referral to cancer genetics services decreases anxiety, but this will need to be checked over time.

The next level of audit will be to assess whether patients who are recommended to undergo screening adhere to these programmes. The most important questions for audit will be "*are the cancers that are subsequently detected being picked up earlier than would be expected in non-screening patients*"? and ultimately, "*is cancer related mortality actually reduced*"? The answer to the last question will not be available for some time, but highlights the need for adequate long term monitoring of these services.

Purchasing Genetics Services

Purchasers will need to be convinced of the need for and potential benefits from cancer genetics services. Increasingly, patients who perceive themselves as being at risk are requesting specialist advice. Hard-pressed front-line clinicians do not necessarily have the time or expertise to give this advice and are thus referring patients on to cancer genetics services. Existing cancer family clinics are heavily subsidised by charities such as Imperial Cancer Research Fund and the Cancer Research Campaign, with relatively little financial support from the NHS.

If the NHS is to take on the clinical [as opposed to the research] function of this work, contracting mechanisms will need to be developed. A debate with purchasers is therefore urgently required regarding both the priority to be given to these services and the contracting process. Ideally this should be undertaken nationally.

The service can be considered in two parts for contracting purposes: first the assessment and counselling service, and second the screening/monitoring function. The cost of the assessment and counselling service will include both staff costs [ie genetics, counsellors and administrative staff] and the laboratory costs associated with genetic testing. The total cost of this service can be dived by the number of referrals per annum to give a price per new patient.

As far as the costs of the subsequent screening services are concerned, it would be possible for the cancer genetics service to hold contracts with local health authorities to ensure that appropriate screening is undertaken. The cancer genetics service could then internally purchase the procedures/services required [eg mammography, ultrasound and colonoscopy].

Conclusion

A national network of cancer genetics services needs to be developed and funded by the NHS. The research that is associated with these services should, rightly, be funded either by charities or through NHS research and development initiatives. Initially, there should be at least one per 'old' health region [ie serving a population of 3-4 million], but in the future, each major Cancer Centre should almost certainly provide this type of service. Guidelines will need to be developed so that appropriate referrals can be made and so that the process and outcome of the care provided can be audited effectively. Development of a common contracting process would have major advantages.

The Service Implications of the New Genetics for Hospital Services

Neva Haites, Honorary Consultant in Clinical Genetics, Aberdeen Royal Infirmary

Clinical genetic services in Aberdeen deal with a population of about three quarters of a million. This paper considers the service implications, as experienced, from the referrals that we have had of individuals with a history of cancer, over about a four year period.

Patients and clinicians are increasingly becoming better informed about the both environmental influences on cancer predisposition, and the genetic influences. Patients are coming to us with an ever increasing amount of background information, be it from Time International, or from other sources. This source of information often refers to large families with strong family histories, and individuals are therefore looking into their background in a more informed, but perhaps also prejudiced way. It is not only the patient group that is becoming more informed. Clinical geneticists and oncologists with a special interests are also becoming more informed, and through research and clinical practice are daily learning more and more about how we should in fact be practicing our art and our profession.

In the UK there is a group called the Cancer Family Study Group which meets twice a year. The aim of this group is to exchange information, stimulate research, develop protocols and recommendations dealing with different groups of patients. Studies for and publications on better means of managing our patients are welcomed by that group. One recent publication is the Nuffield Council report on bio-ethics. This looked at genetic screening and referred to it as a search in a population which would identify individuals who may have, or be susceptible to have, a serious genetic disease; or may, although not be susceptible themselves, pass that on to their children.

The focus of this paper is not population screening, but rather targeted screening for families who have an extensive history of cancer or have a history of individuals with an unusual form of cancer, or set of cancers.

The majority of cancers that occur in the population as sporadic, and so although patients may come with a history, we have to attempt, from that history, and from the information obtained from notes and pathology reports, to determine if it is likely to be a sporadic case in the family or part of a genetic syndrome. Obviously there may be genetic influences even in sporadic cancers which interact with environmental influences, and all these issues have to be researched for each separate case.

In families with autosomal dominant predispositions to cancer there are now new possibilities with the identification of some of these predisposing genes. We know, in certain families identified and studied that there is a high risk to the individuals who carry a damaged copy of the gene, of developing cancer. While there may well be ascertainment bias, as we have been studying families with a high incidence of cancer, it is also possible that there are other mutations that may only be expressed in a small number of carriers, perhaps relating to specific environmental influences. By separating out and identifying these different groups, it is hoped that we will be able to identify environmental influences that can vary the expression of these disease causing mutations.

The Cancer Family Clinic in Scotland, exists as four separate centres, some of them quite recently established. It has been hypothesized by one of our colleagues, Professor Michael Steele, that we are likely to see around 1000 new patients per year in Scotland. This is reflected in our own referral pattern. (Who under the age of 50 are at least twice the population risk). Each of those individual women will have 1.35 or so close relatives. Over a 5 year period the service would accumulate a large number of ladies who are in this high risk category and research on the most appropriate ways of managing these women and modifying their risks is of great importance.

In the last three and a half years Grampian has had 900 referrals of individuals who have a history of cancer. If the focus is on the truly high risk group, and the group for whom mutation testing may be possible, the actual workload is revealed. Table 1 shows, based on the presence of a family history of ovarian cancers, and varying numbers of breast and other cancers, the identification of 17 families who may well have the breast ovarial cancer syndrome with another 20 who are possibly in that group.

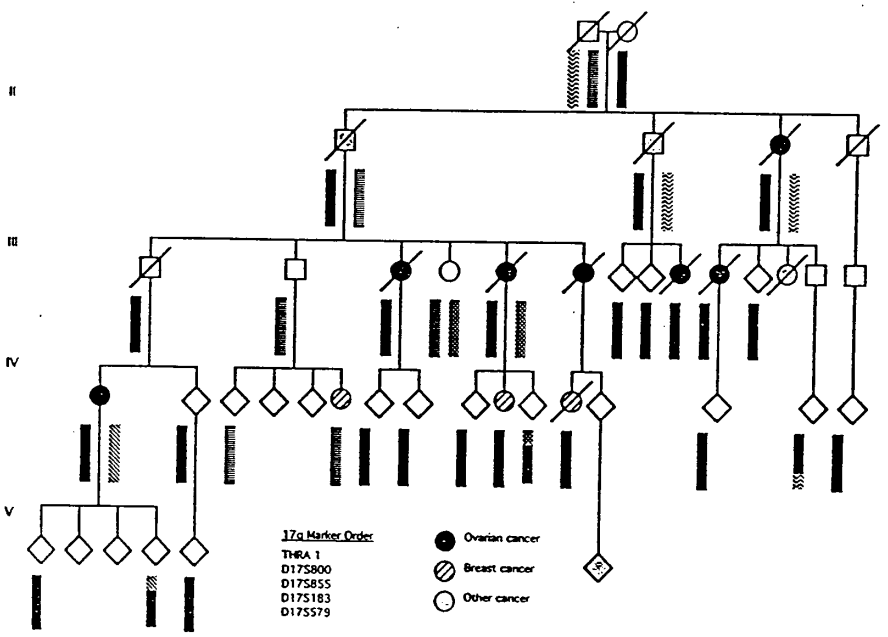
Table 1

Table 1								
NATURE OF CANCERS IN THE AUTOSOMAL DOMINANT FAMILIES								
CANCER FAMILY	NO. OF FAMILIES	CANCER TYPE						
		Ovarian	Breast	Bilat.breast	Testis	Colon	Stomach	Other
OVARIAN	1	6	0	0	0	0	0	0
BREAST/OVARIAN	10	15	21	2	0	0	0	0
OVARIAN & OTHER	6	10	7	1	4	5	2	1

We have studied one large family with the breast/ovarian syndrome for the last four or five years. In this family several women are at high risk of being carriers of a BRCA1 mutation which is likely to involve only about 2% of sporadic breast cancer. Other genes have also been implicated in predisposition to breast cancer in women. These are, again, quite rare genes. But include carriers of the ataxia telangectasia gene and the P53 gene (a syndrome called the Li Fraumeni syndrome). Such women, may be radiosensitive and may be an inappropriate group to be offering an increased rate of mammographic screening. It is thus important to be able to characterise these groups and to develop more appropriate kinds of investigations.

The original family that drew our interest to cancer genetics is represented in Figure 1, where there are five women in the third generation who have presented with ovarian cancer in their forties and one in the second generation who has presented with that condition, and in fact the great grandmother also had ovarian cancer, though in her 60's. Once we began to study the family, unfortunately another young individual presented with ovarian cancer and it looked as if this was an ovarian cancer family, until three young women presented with breast cancer in the fourth generation. Now there are 58 individuals in the fourth generation, and each of those have multiple progeny. It seemed to me that I could probably spend the rest of my clinical time simply looking after this family and others like it. In Figure 1, I have attempted to demonstrate that in fact, using DNA polymorphisms around the BRAC1 gene we have been able to sort out, who in fact in the family appear to be gene carriers.

Figure 1



These carriers in such families have a very high risk of developing breast cancer, up to 80% by the time they reached 70 years. The work of Doug Easton and Debbie Ford, is in fact a summary of all the families that they have studied to date, as part of an international collaboration. It is highly likely that specific mutations will, in fact, infer different risks for breast and ovarian cancers in different families.

The DNA studies carried out in Aberdeen in family 1 had a significant impact on the number of women who needed screening in that family. In Figure 2, it can be seen that there is a total of 29 women who are at 50%, 25% or 12.5% risk of being gene carriers, based on their position in the pedigree. Following DNA studies, there were 6 women, instead of 29, who were in fact, at high risk, and therefore, in fact, in our counselling, we were able to be very reassuring to the vast majority of women who had felt themselves to be at high risk. In addition in the fullness of time, we will be able to avoid any form of intervention or screening in these women as they have returned to the general population risk for these conditions.

Figure 2(a)

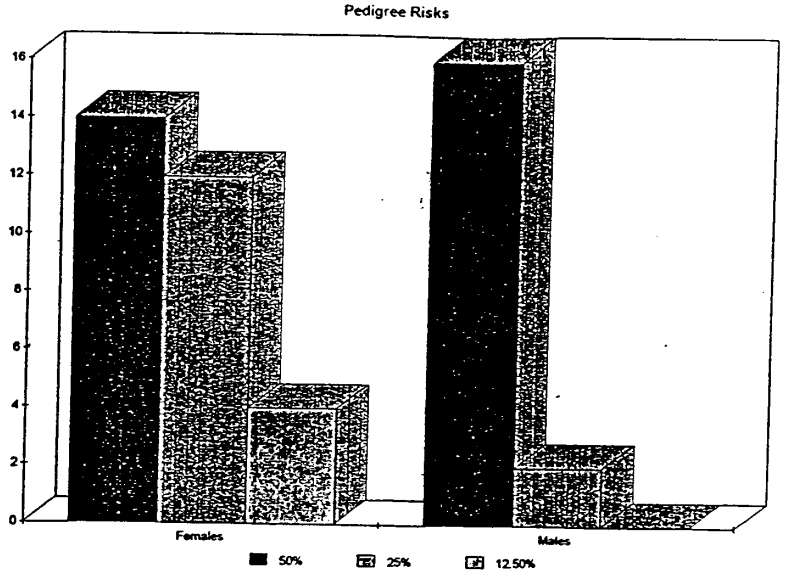
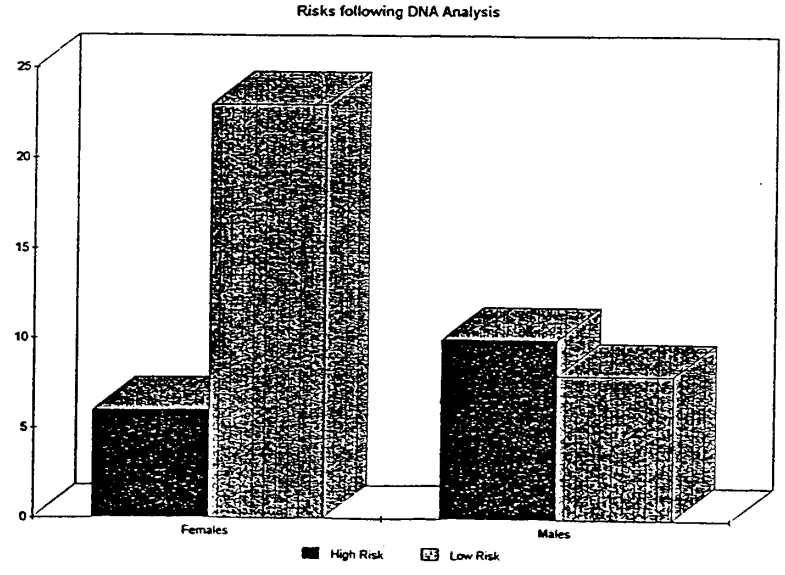


Figure 2(b)



Similarly, the current work load is looking at the men in the family who now have female offspring and are beginning to enquire about the risk to their daughters. In Figure 2, we can see that there are 16 men at high risk [50%] of being gene carriers, and once again we have been able to significantly reduce the number that are at high risk based on DNA studies. The number of girls (offspring) who are at risk, and are needing further investigation as a result is also reduced. This one family alone demonstrates one of the major advantages of this type of targeted screening within families, as by modifying the risk for individuals, appropriate management can be targeted to those at highest risk.

Families have also been described in which there is an inherited predisposition to colo-rectal cancer. Several of these genes have now been identified. Two separate genes appear to account for about 90% of the families with a condition in which there is a high incidence of colo-rectal cancer, endometrial cancer and other cancers. Once such families can be clearly identified targeted screening can be offered. By using colonoscopy to identify selectively, and remove polyps as they occur, it is possible to effectively prevent cancer in the majority of such individuals in these families.

Prostatic cancer is also beginning to be studied, and a group at the Royal Marsden is attempting to collect families in which there is a strong history of this condition. The vast majority of prostate cancers are sporadic, although about 10% appear to be due to a dominant predisposition. In the group who presented under 55 years, 40% of individuals appear to be in families with a dominant predisposition, which of course can be passed through unaffected women. Male carriers in these families, when studied, appeared to be at at least an 80% risk of developing prostate cancer by 85 years of age and that compares to non-carriers in the general population who have a 5% risk. So once again, it is likely that in the future we will be able to provide appropriate screening to individuals in these families, and thus offer management at an early stage.

In genetic screening we are attempting to provide information of an educational nature to our patients so that we can obtain as near to informed consent as possible to study the family and define risks. We attempt to discuss the results of screenings, be they DNA studies or family studies, and of course maintain confidentiality within families. Patients come to us at our genetic clinic, via our colleagues in the hospital and general practice. They come with a confused set of information that is often derived from their family -much of which might be historical information that is slightly inaccurate; from our colleagues who often are unsure about the facts on inherited conditions; and from the media, some of which is providing

excellent material. However, such information may mean that when they arrive at the clinic they are confused and often angry that they are at risk of something that has been passed through the family. They are terrified of their own risks, and feeling guilty for their children and the risks that they may have passed to them. In counselling we do our best to guide them through this minefield in the hope that they will come out able to make decisions regarding carrier testing and, perhaps, screening.

In this we attempt to provide non-directive counselling, but as we already know, by simply seeing the patient, in some ways we are already being directive. Patients feel they want to please their doctor and therefore they may well accept the tests that can be provided as a means of seeming to do what the doctor wants. As a result, it is important to spend sufficient time with these patients to ensure that it is they who make the decision regarding having tests and risk estimations.

In conclusion I will describe some of the problems we have encountered in a completely different area because although it is not a perfect model for cancer, it is a useful comparison. The Huntingtons disease protocols that have been establishing for estimating the risk to individuals of carrying this disease gene have been scrupulously designed to enable the patient to have plenty of time to make decisions, to have them seen by a psychiatrist to ensure that psychological ill effects can be avoided if possible: and still there are problems. The potential adverse effects are many and obviously depend upon the family situation of the individuals. Huntingtons -like many of the cancers is an adult onset disease. There is no curative therapy. There are implications for the rest of the family, as well as the individual being seen, and a reliable molecular test is now available to predict those carrying the gene.

In the 100 or so predictive tests done in Aberdeen to date, individuals have received 3-4 pre-test counselling sessions, including one with a psychiatrist. We have had nine cases of divorce, evidence of problems in determining family history because of adoption, illegitimacy, and individuals have described a wide variety of other problems in the counselling situation.

To concentrate on the divorced group; eight of the divorce/marital break-ups occurred in individuals who discovered that they did not have the gene. Not something that we had predicted, although perhaps, if we had given it enough thought we could have. One lady, when asked about this, said she'd only stayed with her husband because she knew he would

look after her once she got the disease, and once she knew she wasn't going to get she decided to leave him to go off and enjoy life.

The point that I am trying to make is that our aim as clinical geneticists and in medicine in general, is to prevent, or ameliorate, disease related suffering. We have to think extremely carefully about the pros and cons of everything we do. It is impossible to get it right all of the time but providing that we are aiming at that goal we are doing our best, and I think that as long as we continue to learn from the research and the work that our colleagues do, we will do better in the future.

Conclusions

Sir Cecil Clothier

The implications, as opened up by the various contributions, are really quite vast and challenging and there are obviously an enormous number of problems to be solved. I shall not attempt to summarise all the papers. The function of a chairman is not dissimilar to that of a judge, which is to sit there, look as wise as nature will permit, say as little as possible and instil some order into the proceedings. When I was at the bar it was always said that a judge should be brief, courteous and wrong because that enabled everyone to go to court with one and other. However that didn't entitle the Court of Appeals to be rude, long winded and right because that was reserved for the House of Lords. The need to keep this summary short is obvious.

What is important to note is the immensely positive feeling that I, as a layman, got from the whole proceedings. There are and were negative aspects, and to me the most distressing of those is our tendency to be litigeneous as a nation. I must say that I deplore it. It seems nowadays that every single mishap that occurs has to be laid at somebody's door, even when the person at whose door it is laid has been doing his or her best to assist the litigant. I find this a rather unhappy development, and it is, I am afraid, something to diminish the relationship between the caring profession and the people at large.

When I hear about strict liability and doctors or patients being entitled to monetary compensation whenever anything untoward happens to them in hospital, I wonder why there is so much compassion for people who suffer a misfortune because someone has been trying to help them, whereas the person stricken down by MS has just suffered a blow from providence and we don't want to seem to help them any more than is ordinary. Why this special compassion for those who have come to grief in the hands of those who have been doing their very best to help them. I find this inconsistent, illogical, a most unhappy development, and I hope that it gradually dies down.

But on the whole, I thought the upshot of the symposium was wonderfully positive and

progressive. We do make progress. One of the advantages of old age, which I now enjoy, is that one can look back over a tremendous vista and I remember being brought up in Everton and Liverpool in the 1930's when it was more common than not for children not to wear shoes and socks at any time of the year. Every winter there was a frightful outbreak of scarlet fever and diphtheria, a most horrible disease, and of course tuberculosis was rampant. There were children all over the place with limbs that had been attacked by rickets, and there was small pox occasionally, and measles was a very much more serious disease. Every summer we had the polio outbreak. Now all that has been swept away in my lifetime - has absolutely vanished, and the antibiotic revolution has changed the face of medicine, and even indeed of society. It may, incidentally, have, of course, brought us other problems in a rather elderly population who were previously carried away by the old man's friend at one time or another, but who now live on, not always, I think, to their own advantage. But there you are. One must make of it what one can.

On the whole that revolution has been a wonderful restorative of health to huge numbers of people. To me the fascinating thing about it all is that it didn't matter in the least degree which political party was in power at the time. Progress went on just the same; it struggled through, getting better and better, improving social conditions, improving our medical capacities, treating more people and treating them more cleverly, and that to me is the encouraging message of a symposium like this. That the good people engaged in this work will struggle on and make progress, no matter what happens and no matter who is supposed to be directing it. We will get there in the end. It gets more difficult from time to time, but nevertheless we struggle forward. This symposium has shown that the good work is going to go on.

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