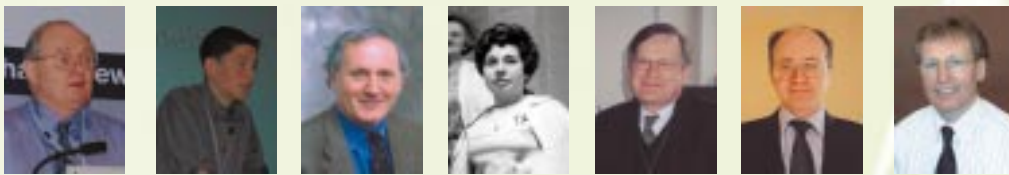




DNA

delivers

50 Years of
progress told
through the eyes
of patients and
their doctors.



The discovery 50 years ago of DNA was one of the greatest scientific breakthroughs of all time. Great things were expected to come of it. Ever since, further research has continuously brought new insight into the "blueprint" for human life.

The celebration of this golden anniversary of DNA prompts the question: "How has this discovery helped us to understand illnesses and treat and care for patients more effectively?"

The Genetic Interest Group has been talking to physicians and patients to find out their thoughts on how technology has benefited both patients and their carers - allowing us to reflect on their personal experiences as well as looking towards the future and further new developments on the horizon.

"With special thanks to Roche Diagnostics and GlaxoSmithKline for sponsoring this project. And above all a big thank you to everyone who participated in telling their story" - The Genetic Interest Group

Designer: Margaret Wall

Editor: Fran Broady

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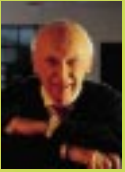
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The Genetic Interest Group (GIG) is a national alliance of organisations with a membership of over 120 charities that support children, families and individuals affected by genetic disorders. Our primary goal is to promote awareness and understanding of genetic disorders so that high quality services for people affected by these conditions are developed and made available to all who need them.



FOREWORD BY JAMES WATSON

Throughout history countless genetic diseases have blighted the lives of families, causing chronic ill health, progressive disability and often resulting in premature death. Fifty years ago we knew little or nothing about the biology of these conditions, and families could do little but watch them take their toll on those they affected.

DNA, and our rapidly increasing understanding of how it works has changed this dramatically. As the stories that follow show, the situation for families and for the doctors who support them is very different today. Research is advancing our knowledge so rapidly that, for more and more genetic diseases there is the prospect of effective prevention, treatment and a cure being developed.

In April 1953 when we wrote our letter to the scientific journal *Nature*, we had no idea that so much progress would result from understanding the messages in the double helix that is DNA in such a short time. Today, half a century on, we are on the brink of being able to lift the threat of genetic disease from millions of families. Progress is accelerating. The challenge for the next fifty years will be to use the knowledge that results from our endeavours for the benefit of all who need and hope for treatment and cure.

James D. Watson

COUNSELLING : HELPING PATIENTS TO MAKE INFORMED CHOICES

'One point we must always remember is that no matter with what ease we can do the DNA analysis today, the decisions that stem from the DNA analysis results are no easier to make.'

Professor Marcus Pembrey

The former Mothercare Professor of Clinical Genetics at the Institute of Child Health in London, Marcus Pembrey, trained as a clinical geneticist at Guy's Hospital combining research with counselling for families with genetic diseases in the 1970s. In 1979 he became head of the unit at Great Ormond Street and The Institute of Child Health.

When I came to Great Ormond Street there were no DNA tests to assist our genetic counselling. An X-linked disorder like Duchenne muscular dystrophy illustrates how difficult this was. Even now, this is a severe, untreatable condition. It is the commonest form of muscular dystrophy, affecting about 1 in 3000 – 4000 boys. They are in a wheelchair by 11 and usually dead by 25.

A woman who watched her brother grow up and die would ask herself whether she was a carrier of this mutated gene – and whether her own sons would suffer the same fate.

The most we could tell her was that, if another family member had been affected (say an uncle) her mother was a carrier. This would mean that she had a 50% chance of being a carrier and that any son she had would have a 25% chance of being affected. It was terribly difficult as we were unable to say which 50% she came under.

By the late 1970s we could identify some carriers of Duchenne muscular dystrophy. The patient would have to come back to the hospital three times to have blood samples taken. From these samples we could measure the enzymes that had leaked out from the muscles. If we found significantly higher levels of leaked enzymes we could say that it was highly likely that the patient was a carrier.

However, this test didn't work in pregnancies. If a patient was carrying a son, there was no test that we could offer to find out if the son was going to develop muscular dystrophy until after birth.

An alternative to this was to sex the pregnancy and terminate all male foetuses. When I first came to Great Ormond Street in 1979 we could only offer sexing of the baby at 16 weeks and the results would not be known until 18 weeks. Everything was delayed and it was very unsatisfactory for everyone involved.

GENE TRACKING

In the early 1980s once the gene for muscular dystrophy was located to a region of the X chromosome, we could use a technique called "gene tracking" for carrier testing. In the initial gene mapping research you could use what we called "markers" on the chromosome to find out what region the disease gene was in. Once mapped the same markers could be used for 'gene tracking' tests for that disease in families.

This research was closely tied in to our work with patients. We would approach families we had seen for counselling and ask them if they would be willing to participate in research. They were extremely good at co-operating in research, and by being able to study big extended families with a history of, for example, haemophilia, we were able to locate the gene and develop the test.

GENE MARKERS

In 1985 the Department of Health agreed to fund special developments in three centres: London, Cardiff and Manchester. We were to develop, assess and evaluate the use of these DNA markers in genetic counselling. The tests we had available at that time were carrier detection, carrier exclusion and pre-natal diagnosis.

There were many different varieties of markers – and these varied from one family to the next, which meant that we had to involve a lot of other family members to identify the markers specific to that family.

There were two drawbacks with the gene marker approach. One was that the marker was not always accurate, and there was a small percentage of mistakes (1 – 2%). Perhaps more important were 'uninformative' families. If for example the boy with Duchenne Muscular Dystrophy was the first in the family and the father was no longer around, you were left with only the child to do the test on. To help the sister find out if she was a carrier you needed to take blood from other members of the family to work out which chromosome the gene was tracking with to define the appropriate marker. Involving other members of the family was sometimes very difficult or impossible.

IDENTIFYING THE GENES FOR DISORDERS

When we moved from knowing roughly where the gene was on a chromosome to finding the gene sequence itself, we were in a much better position. We could compare the normal gene sequence with somebody who is affected and discover the abnormality.

At this point DNA enabled us to say if someone was a carrier – and also to say that they were not carriers, in a more confident way. For the first time, we could really exclude people from having or carrying the condition. DNA also enabled us to develop tests that could be carried out 10-11 weeks into a pregnancy instead of at 18 – 20 weeks of gestation.

Once we were able to detect the mutation itself, particularly the common one for cystic fibrosis, for example, we could offer screening, particularly to someone who was marrying into a family who had a history of a disorder. We could also then test just one person and not the whole family. The test was definitely more accurate than the gene tracking.

DIFFICULT DECISIONS

Even when you have been given very clear-cut information, there are some very difficult and worrying decisions to make. But much of the medical uncertainty has been removed.

This brought great poignancy for people who had been told in the 1970s that they had a high chance of being a carrier for an X-linked disorder and chose to terminate male pregnancies. Then new tests came along and they found out they weren't a carrier, after all.

One point we must always remember is that no matter with what ease we can do the DNA analysis today, the decisions that stem from the DNA analysis results are no easier to make. I think we have been able to help families who have gone from having no option other than to take a gamble with each pregnancy or terminate them, through to more precise advice. The matter of weighing up for them what is the right decision is still just as difficult.

EARLIER TESTING

DNA testing has made a terrific impact on families - and on the people counselling them, too. At times in the past it was sad as well as frustrating for us. I remember when we had to rely on a liver biopsy taken at 20 weeks gestation for a metabolic disorder. A patient who was an X-linked carrier had already lost two male babies. She came in for this test for a third time and had to wait until 21 weeks of pregnancy - having found out at about 18 weeks that this baby was a boy, too. When I went up to the bio-chemistry lab to collect her results everybody was in tears. They were the same as before.

Although having a test earlier in pregnancy has its downsides as well, couples benefit from having the ability to make it a private decision, as the tests are available early enough for the pregnancy not to be obvious to everybody. This takes away the pressure from relatives or those who think differently and they can make a truly personal decision about what they want to do. These days the tests are normally carried out at 10 weeks and the results normally take 2 weeks. Occasionally, but only for very compelling reasons people can be offered pre implantation genetic diagnosis.

BURDEN LIFTED

The exclusion of carrier status has really made an enormous difference. In the past all family members would have this hanging over them for life. If females with a history of Duchenne Muscular Dystrophy in their families, for example, were ever going to consider having children they were going to have to bear in mind that they had a high chance of being a carrier. Now that we are able to show who is, and is not, a carrier, those who are not are basically able to kiss doctors goodbye! They no longer have to think about it, or worry about having children. For those types of disorders some people have really had the burden lifted.

THE CONTRIBUTION OF DNA TECHNOLOGY TO GENETIC COUNSELLING

by Professor Shirley Hodgson

DNA technology has revolutionised our ability to diagnose genetic conditions and to offer genetic counselling to relatives of an individual with an inherited disorder.

For many genetic disorders we can now obtain an accurate diagnosis by doing a genetic test identifying the fault in the gene which causes the condition.

This enables the patients and their close relatives to be advised accurately about the nature of the disorder, how it is likely to develop, how it should be treated, and how likely it is to occur again in the family.

Tests then can be arranged for relatives of that patient to see whether they carry the gene themselves and could transmit it to their offspring.

Often the determination of the underlying genetic cause of a disorder gives new insight into the way the disorder develops and improvements in treatment. Gene therapy is beginning to come a reality for the treatment of some genetic conditions.

Pre-implantation diagnosis of some genetic disorders is becoming available to couples unwilling to consider prenatal diagnosis - which is now available for many genetic conditions.

Our understanding of the genetics of cancer has enabled us to identify people with a strong family history of cancer who may have inherited a genetic predisposition to a specific cancer. Genetic tests may be possible in a minority of families, allowing us to identify people at high risk of cancer who can be screened and offered preventative surgery as appropriate.

Our knowledge of the role of inherited factors in many common diseases will help us to understand how to prevent and treat these conditions. In addition, our knowledge of the genetic factors controlling how we respond to drugs will have a major impact on our ability to tailor drug treatment.

Certain genetic changes are more common in people from a specific region of the world. Screening for specific genetic mutations in such populations can identify carriers of these mutations - who can then be offered genetic counselling regarding the risk to them and their children.



POLYMERASE CHAIN REACTION – A DIAGNOSTIC BREAKTHROUGH

'I remember a very famous meeting on a Thursday in November 1986. A small group had met to discuss pre-implantation genetic diagnosis. Bob Edwards, who had developed IVF, was saying that we just can't do it because we would need too many cells from the early embryos to do the DNA analysis. I told him about the new polymerase chain reaction technique, and I remember Bob jumping round the room saying "we did it, we did it!!" The technique is now used all the time in DNA analysis.'

Marcus Pembrey

Early pre-natal tests and IVF have developed at the same time as advances in DNA testing, and at times the two areas have converged. Polymerase Chain Reaction opened up a way for scientists to take just a few strands from one or two single cells and amplify up the relevant bit of DNA to millions of copies.

This meant that, for the first time, it was possible to develop tests for pre-implantation genetic diagnosis that could be used within an IVF treatment programme before a pregnancy was established. A single cell is taken from embryos created through IVF, and a 24-hour test used to see if it is affected or not. Embryos that are not affected are then put back.

"Many couples who were carriers of genetic disorders had been asking for this type of test," commented Marcus Pembrey. "It is a good illustration of how the needs of families drive research. You learn from your patients and families and then you help them."

Dr. Sybil Simon explains how the test works : "Polymerase Chain Reaction (PCR) was first used in the mid-1980s and now plays a regular part in many diagnostic tests and medical research. If scientists know the gene sequence of a particular gene likely to cause a medical problem, this test can be used to identify that gene in patients and their unborn children – at the very earliest stages of pregnancy."

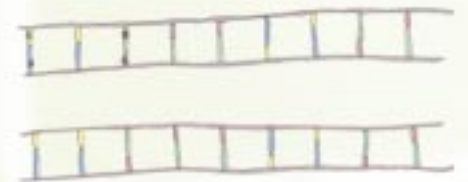
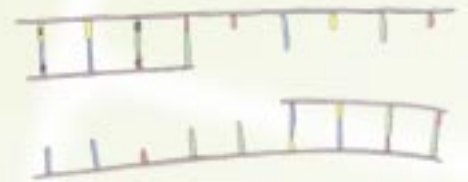
The technique is used to make multiple copies of – or "amplify" - part of the DNA of genes. There are three main steps to follow :

- A A double strand of DNA is separated into two single strands by heat
- B Next, two rows of nucleotides are masked or "primed" by two short strands (oligonucleotides) designed to bind on a section of interest in the gene
- C Thirdly a polymerase enzyme synthesises a copy of the nucleotide sequence, between the primer, a new double strand.

This process is repeated. At each stage, the number of copies is doubled. These reactions are controlled by changing the temperature, each cycle taking only a few minutes. Millions of copies of DNA can be generated in a matter of hours.

Before using this method to detect whether a gene with a particular sequence is present, you need to know some of the sequence of the gene. Tiny amounts of foetal tissue, obtained in early (10 week) pregnancy by chorionic villus biopsy, can be probed for the presence of abnormal genes. If the parents carry a known mutation, this can be sought using PCR in specialised DNA laboratories.

"Results are available within 2 – 3 days, enabling parents to make the toughest decisions knowing that they are based on accurate information," Dr Simon added.





TAY SACHS DISORDER (TSD)

by Dr. Sybil Simon

Like Gaucher's Disease, the rare, fatal Tay Sachs Disorder is a recessive genetic disorder. Genetic tests can now identify carriers as well as accurately diagnosing whether TSD is present in early pregnancy.

HISTORY

Tay-Sachs is a fatal genetic disorder that affects the brain of infants, causing blindness, deafness, and often seizures. Even with the best care it causes muscle weakness, an inability to move or cough and a vulnerability to chest infections, causing death by the age of 4 or 5.

The first description of the changes in the optic nerve-head caused by the disorder was published by the British ophthalmologist Dr. Warren Tay in 1881. Shortly after this, in New York in 1887, Bernard Sachs studied families with affected children and applied his special interest in pathology to describe the build-up of fatty substances in the brain caused by TSD.

GENETIC STUDIES

In 1970, the vital enzyme Hexosaminidase A (Hex. A) was recognised and identified as being absent in affected infants. Without Hex. A, a fatty layer around nerve cells was not removed when its useful life declined. New fatty layers were added to the old and eventually a build-up of pressure reduced the effective activities of the cells.

TSD is an autonomic recessive disorder. Both parents must be carriers of the inactive gene to be at risk, (25% risk for each pregnancy). Being a carrier does not affect mother or father in any way, adult carriers have no indication that they carry an inactive gene. When both parents are carriers, there is a 50/50 chance in each pregnancy of producing a child who is a carrier, like the parents, boy or girl, and a 25% chance of a non-carrier.

Recessive genetic disorders like Tay-Sachs often occur in defined groups. TSD was first found in patients of Eastern European (Ashkenazi) Jewish descent, then in non-Jewish French Canadians. It has since been discovered in people of every ethnic origin.

COUNSELLING FOR PREVENTION

The TSD-mutated gene can be carried through many generations. Before carrier testing was introduced, people only discovered their carrier status when they became parents of a Tay-Sachs baby.

In 1968, a successful test to measure the level of Hex-A in serum, lower than normal in parents of Tay-Sachs infants, was reported from the University of California. In 1970, amniocentesis, (taking fluid from the sac around the baby, in utero), was first used to diagnose TSD in Brooklyn, New York. During the past 10 years, this has been replaced by Chorionic Villus sampling (from the foetal side of the placenta) at 10 – 11 weeks of pregnancy. It often takes just 24 – 36 hours to get the results from this test – enabling parents to take informed decisions at a very early stage.

SCIENTIFIC DEVELOPMENTS

The results from early enzyme studies were not always satisfactory because they were measuring serum levels - without any white cells - and the enzyme was subsequently found to be stored in packets in white cells. Studying the enzyme levels in white cells gave more consistent and accurate results – and white-cell enzymes were subsequently studied in many disorders.

In 1953, Watson and Crick realised that genetic information in the nuclei of cells was carried on the chromosomes, which had the shape of a double helix. Essentially, the normal single strand of DNA follows a recognisable sequence, such as CAT-CAT-CAT. If a very small mistake occurs such as deleting a T and a C, the sequence of CA/ATC-ATC, would not make sense. This deletion would be copied every time the chromosome (on which it was carried) replicated. The mutated gene would not enable the protein to be produced for which it normally, actively codes. The mutant gene is often called an "inactive" gene.

The Hex.A gene was isolated and characterised in 1987. It is 35,000 bases long.

FINDING THE MUTATIONS

In Tay-Sachs Disorder, the search for mutations originally concentrated on the Ashkenazi Jewish and French-Canadian populations, both of which showed higher carrier rates and levels of infantile TSD. It had long been suspected that a mutation had persisted in Eastern Europe because the families concerned were only able to marry within a very limited number of towns or village populations. Unknowingly, they may have married distant relatives, allowing recessive genes to persist. This was called a founder effect.

When the analysis of DNA was undertaken to detect the first known mutation in 1988, the founder effect theory was not proven. Unexpectedly, it accounted for only 20 – 30% of the cases of infantile TSD among the Ashkenazi families studied. In later studies, only 18% had this mutation.

Within the same year, a second major mutation was reported which accounted for about 70% of the families studied over the past 10 years. A third mutation associated with the less severe adult-onset form of TSD has also since been found.

Since the original studies, families from many ethnic groups have been identified as having other mutations with varying levels of enzyme-activity and variable ages of onset.

GAUCHER'S DISEASE

Thirty years ago there was no cure for Gaucher's Disease. A splenectomy saved patients' lives but caused other health problems, such as early bone and joint disintegration.

In the 1990s, thanks to genetic research, enzyme replacement therapy was introduced. Removing the spleen is no longer necessary and patients can enjoy a good quality of life with regular infusions. But it will take years – and further genetic research – to find a cure.



HOW THINGS WERE: MELANIE'S STORY

A JOURNEY INTO THE PAST

When Melanie, now 44, was diagnosed in 1971 she was told she had a rare illness and there was no cure. She had her spleen removed (a splenectomy) at 26, only three months after her son's birth. She shared her story of 30 years of pain and hope with delegates at the Gaucher's Disease Association Conference on 11 November 2001.

In 1971, when I was fourteen, I returned home from school feeling poorly. Two weeks later I became ill again. Gaucher's disease was suspected and after a bone marrow test the dreaded diagnosis was confirmed.

No-one had ever heard of it. We were told: "Oh it's a very rare illness due to an enzyme deficiency and sorry but we don't have a cure at the moment so go away and don't worry too much and we'll just have to keep an eye on you."

My poor parents were frantic with this news. They were told that my spleen was enlarged but it would probably not have to be removed until I reached my mid-forties and I would just have to take it easy and not overdo things. During my teens my education was ruined by too many absences and my career suffered because of my ill health.

SPLEEN REMOVED

When I was pregnant with my first child, it was noted that my belly was somewhat larger than it should have been and a month after the birth I still looked about six months pregnant. I found out that my spleen had grown so large that it was protruding out of my left side. The next month I went to see a surgeon who advised me to have it removed as soon as possible. So in March 1984, three months after my son's birth, I had a splenectomy. My spleen was 9lbs when it was removed. I went into hospital not realising how horrific this operation would be, afterwards I was in agony but I remembered my three month old son and realised that I must fight for his sake.

PREGNANT AGAIN

Eight months later I fell pregnant again. This was not good news as my scar had not had much time to heal properly but after quite a healthy pregnancy I gave birth in June 1985 to a daughter by Caesarean section.

Two major operations within 16 months and two babies in the house was not easy. It took a couple of years for my health to become reasonable again as long as I took rest when needed - but I didn't realise that by removing my spleen, the illness was affecting my liver and my bones. When I needed an operation to remove the cartilage in my right knee an MRI scan showed that the bones in my legs were not normal. A few years later I needed to have my gall bladder removed.

NOT ALONE

Nearly ten years ago my mother saw an article in a newspaper written by someone from the Gaucher's Association. It was like coming home. At last here was someone who could empathise with my problems. Susan Lewis, founder of the Gaucher's Association, told me that there was to be a Conference held in Amsterdam in a few weeks where they would be discussing Gaucher's disease and a new breakthrough drug. I couldn't believe it. After visiting Amsterdam and seeing people from all over the world with the same problems, I realised that I was not alone and help was on the way. I discussed my case with a doctor there, who advised me to obtain a letter from my GP to visit Addenbrookes Hospital in Cambridge and meet Professor Cox to be assessed for this drug. Three months later this came to fruition.

INFUSIONS

I had my first infusion at Addenbrookes a few weeks later. I was a bit scared but very grateful that at last something was being done. After one year of visiting my local hospital in Manchester three times a week for infusions, I decided to be trained at home and after six months I began infusing myself.

Eight years on my condition has improved so much and I don't worry about infusions any more. I could probably do it blindfolded.

BACK TO THE FUTURE

So, back to the future. I am now 44, happy and healthy with two teenage kids, both well and successful. I attend college twice a week where I am learning computer skills and Spanish and I try to achieve everything I want.

I appreciate every healthy day. Without the Gaucher's Association and many others, none of this would have been possible. There are so many people I have met who have helped me and I thank them all.



HOW THINGS ARE: EMILY'S STORY

GROWING UP WITH GAUCHER'S DISEASE

Emily was diagnosed when she was 13. She started Cerezyme treatment soon after. She is now a beautiful 18-year-old. Her story, which she also told at the Gaucher's Disease Association Conference on 11 November 2001, describes how enzyme replacement therapy has enabled her to fulfil her potential - and contrasts with Melanie's account of her treatment after her diagnosis.

I was blissfully unaware that I had Gaucher's disease until just before my 14th birthday. Looking back there had been lots of little signs in my childhood, the nose bleeds, bruises on my legs, but these were all shrugged off, don't all children get these things?

It was Mother's Day and I had bought a flowering plant which we had not had at home before. A few days later swellings appeared on my legs and under my feet. Thinking it was an allergic reaction possibly to this plant, my mother took me to the doctor. Instead of looking at my legs he examined my stomach and to my horror announced that I had a tumour and must go to the hospital. After scooping my mother off the floor we somehow made it to the hospital where I was assigned to the chief paediatrician. After a brief examination he too announced that I had a tumour and I was whisked off for a scan.

This revealed no tumour but an enlarged spleen and liver. The next two days involved many tests and the result was that I might have something called Gaucher's disease which they had heard of but never seen. I was dispatched to Great Ormond Street Hospital for more tests including the dreaded bone marrow biopsy. The strange thing was that the swellings on my legs and feet never appeared again and have never been explained.

ENZYME REPLACEMENT THERAPY

At Great Ormond Street Hospital we met Dr. Ashok Vellodi who painstakingly explained Gaucher's disease to us. The realisation set in that I could not just take some pills and go home. I was shocked and overwhelmed.

The next few weeks were filled with anxiety of waiting to see if I could get funding for the treatment but Dr Vellodi had given us the Gaucher's Association telephone number and Susan Lewis became our guide. She told my mother that I would get the treatment I needed and that my spleen would go down and I would lead a normal life. We hardly dared believe her.

A whole new world opened up for me. Frequent trips to the hospital followed to receive the new enzyme infusions, with other visits to Great Ormond Street for consultations concerning my growth. Then gradually I learned with my mother to do the infusions ourselves at home - although there were many times when we did not succeed and we ended up back at the local hospital again! Four years later I have reached the point where I can administer the treatment myself.

LOOKING BACK

Once the initial shock was over there was a long and anxious wait to see if the treatment would have the desired effect. We hardly dared hope, but true to everything we were told, it worked.

I slowly saw all my symptoms disappear. I have now reached the point where the disease has almost no effect on my life and I hardly think about it between my fortnightly infusions.

Without the support and organisation of Genzyme, Healthcare at Home, Dr Vellodi and the Gaucher's Association I would not have been able to travel, go to university or lead a normal life. Indeed I am determined not to let Gaucher's stop me doing anything and since diagnosis I have been on a month's trip to Israel, spent 10 weeks in the USA and have received infusions away from home, fitting them in to university life.

PART OF EVERYDAY LIFE

Whilst in America I was assigned to Dr Greg Pastores at the New York University Hospital in Manhattan. Here for the first time I saw many Gaucher's patients having their infusions together. I was amazed! During the infusions their life carried on as normal and I even overheard someone speaking on the phone to their stockbrokers about stocks and share prices, in a typical New York style.

It made me realise that having Gaucher's disease is no big deal and infusions should be fitted into ordinary life as much as possible. The focus there seemed very much on practical problems like how early in a relationship to tell your partner about having the disease and choices that have to be faced when it comes to having children. I felt I was looking at the future right there and then. Everything about that Gaucher's clinic was positive and uplifting.

EXCITEMENT

In conclusion, not only have my recent experiences been positive, but I am excited to read about trials for alternative therapies. I was the third person in the UK to receive the synthetic form of glucocerebrosidase (Cerezyme) which has proved to be a total success. When I think that it was only in 1991 that enzyme replacement therapy was available at all, I feel very hopeful about the future.



GAUCHER'S DISEASE : THE MEDIC'S VIEW

Professor Timothy Cox

The condition

Gaucher's disease is an autosomal recessive genetic disease. Both parents must be carriers of this condition in order to have a one in four chance of passing it on to their children.

It is caused by a deficiency in one of the body's genes which produces an enzyme called glucocerebrosidase. This enzyme is involved in the breakdown and recycling of the fat cells in the membranes of cells. If the body cannot break these fatty molecules down and recycle them, this causes a build up of the partially digested molecules in the cells that break down - such as the spleen, or liver.

Gaucher's disease occurs in all ethnic groups but it is particularly common in the Ashkenazi Jewish population. (1 in 450, for type 1 Gauchers disease compared to 1 in 100,000 people in the general population.)

Diagnosis

Fatigue is an early sign of the condition, as well as easy bruising, bleeding after a tooth is removed, enlargement of the spleen and liver, and pain in the bones.

Early treatments

When I began working with this condition the only treatment was to remove the spleen. This was not a cure. It was very much a patch-up job. People suffered from early bone or joint disease through having their spleen removed and we would continue to patch them up, for example, when their hip joints disintegrated.

The current approach

Now, we don't remove the spleen. We have national centres where we give patients enzyme replacement therapy and they are able to lead a relatively normal life. The treatment is given by infusions, twice a week for a really ill patient, but usually either weekly or every two weeks. Patients can do this treatment at home after initial training at the hospital.

Cerezyme is one of the world's most expensive drugs and is only available in a very few countries. In the UK the drug bill for this enzyme replacement therapy is over 20 million pounds a year to treat about 190 patients. Alternative treatments are being developed because of the cost.

The future

I think that Gaucher's will definitely be a gene therapy target in the future, but the first trials have proved difficult so it will take time. I would like to see more competition in enzyme replacement therapy as well. It is very important to develop alternative mechanisms to understand the disease.

We don't yet have a full molecular understanding of this disease and unremitting, resolute studies will be needed if we are to understand the effects of the microphages (which are within cell compartments in the liposomes, that contain glucocerebrosidase) and why they do what they do.

The treatment, although extremely good at present, doesn't completely exclude the risk of having bone disease. It cannot repair established bone disease and it requires lifelong treatment.

The only way to know more is to get the molecular tools – and there is no question that this requires genetics.

EPIDERMOLYSIS BULLOSA (EB)

Epidermolysis Bullosa is a very wide-ranging condition with blistering of the skin as the shared symptom. In its most severe form, it is lethal. So far, DNA analysis has been important in enabling doctors to give a precise diagnosis. By defining which type of the disease a patient has, an accurate prognosis can be given for the future. It has also made early pre-natal diagnosis possible. But there is no cure. Research projects are currently looking for gene therapies to help alleviate some of the most debilitating symptoms.



EB : THE PATIENT'S VIEW

Murray Clifford has suffered from the dominant dystrophic form of EB for all of his 77 years. Disregarding advice to wrap himself up in cotton wool, his positive mental attitude has enabled him to lead a full and active life.

I was born in 1925. When I was six my parents realised that I had something wrong with my skin. I only ever had two fingernails on my hands, and no toe nails and my skin blistered at the slightest knock. They knew there was something wrong in the family, as far back as the early 19th century through my great grandfather, but nobody knew what it was.

Our local doctor didn't recognise my symptoms, so my parents took me to see one of England's leading skin specialists in Harley Street. His fees at that stage were five and half guineas for half a hour (which was two weeks' wages in 1931!) He had written a pioneering book on EB and was a world authority – and he told my parents that I was suffering from EB. All the correspondence between this doctor and my parents is held in the archives at St Thomas's Hospital in London.

DEPRESSING INFORMATION

The information that my parents were given at the time was very depressing. The treatment was really to wrap the patient in bandages and protect him or her from knocks and exposure. This meant that it was impossible to lead a normal life; for example at school I would not be allowed to play any rough games. This draconian treatment was due to the absence of any antibiotics to arrest infection. In those days infection was almost lethal, whereas today, thanks to antibiotics, treatment doesn't have to be so stringent. I disobeyed all the instructions and played all the games that I could! There was no treatment at the time so all we could do was to put dry dressings and bandages on my legs.

I joined the army after leaving school. In those days the army doctors didn't understand my disease, so I managed to bluff my way in. During the war in 1951 I remember popping my blisters by using a bayonet whilst in the jungle in Malaya! During my 14 years service, mainly through playing hockey when I got knocked, I continued to suffer from blisters. Septicaemia always lingered around the corner as well but the good Lord spared me!

I simply haven't let this condition affect me. I could have wrapped myself up as a child and set myself up as an invalid, but I didn't. On my medical files at the hospital it says PMA which stands for Positive Mental Attitude. This is very important with any illness.

RISK WITH CHILDREN

When my wife and I decided to have children it was a risk as we did not know if my skin condition would be passed on. Luckily my son does not appear to suffer from EB, and he has two daughters who do not have EB. My daughter has two sons, but they are not at risk as she is not affected by this condition or a carrier of it.

CHANGES OVER THE YEARS

Over the years I have noticed slight changes for the better; this is due to my age. The blobs on my legs have improved, my dressings are changed once a week. But my blood has thinned slightly in my veins, which means that I am more vulnerable to ulcers. I was in St Thomas's Hospital for a whole month in 1998 until eventually the ulcer healed. One of the main things that helped was a new type of dressing, a dry dressing which doesn't pull off the new skin. The healing was also enhanced by strong, firm, compression bandaging, which promotes the blood supply and which in turn helps the healing process.

I do still get blood and water blisters when I knock myself, particularly on the front of my legs where the skin is very thin. If I knocked myself, as a normal person I would just get a small scar forming but because of EB I get a blister. It wasn't until about ten years ago that the doctors were able to establish what type of EB I had – which was done through taking both a skin and blood biopsy.

EDUCATION AND SUPPORT

One problem I find is that it is still only the skin specialists who understand this condition and provide up-to-date information and treatment.

I go to St Thomas's where I am a guinea pig for new trainee doctors and nurses. Many of them have not seen a case before so it is very important that they learn to recognise it. When I was a child I did not know a single other person with this condition. There were no support groups when I was diagnosed in the 1930's I know that I am one of the oldest persons in England to suffer from this disease, I am nearly 78 now, I attend all the conferences that DEBRA holds.

My hope is that with the help of DNA research that is going on, an improvement in the effective treatment, leading to a cure of this condition will soon be possible.



EB : A MOTHER'S VIEW

Norah Simpson's son Ian suffered from Epidermolysis Bullosa. He died just four days before his 39th birthday on 4th June 2000. Ian suffered from the dystrophic recessive form of the condition - which is one of the most severe types.

Ian was diagnosed within the first month of being born, which I think was exceptionally good in 1961. I had never heard of EB before and there was no history of it in my family, so we didn't have a clue what to do. When Ian was born, he had no skin on his feet. It looked as if he had red ankle socks on. He also had one little blister on his nose.

During the next 24 hours he was sprouting blisters all over the place and nobody knew where they were coming from, or why they were developing. We were sent to the local isolation hospital because the nurses and doctors didn't know what to do. This was horrible for me, but it was the best thing for Ian. He was in hospital for just under 2 years. We got him home one week before his second birthday.

POOR INFORMATION

At the time of Ian's birth there was not really any information available to us. I was terribly upset, however when Ian was properly diagnosed, it was something that I had to accept.

Whilst Ian was in the Children's Hospital in Manchester they tried all sorts of weird and wonderful things to try and help his blistering. They worked terribly hard, but nothing made the slightest difference.

When we were able to take him home permanently his condition had not really improved at all - but I was able to go into the hospital to learn how to apply his dressings. He was wrapped in dressings around his legs and arms that needed to be changed every day. In the early days the treatment was really a matter of covering him up to protect him from injuring himself. The blisters were all over his body and the slightest touch would bring him out in a blister. It was terribly difficult when he was learning to walk. If he fell down, he would put his hands out to protect himself and then of course he had two blood blisters on either hand. When he was small and we used to bath him we couldn't use a towel so we had to dry him with a hairdryer.

DAILY LIFE

When he was older I used to have to put the things in the cupboard in a certain order and with gaps around the sides so that Ian could take them out without bumping his hands. Eating was always a big problem for Ian. He never ate a meal that hadn't gone through a food processor. If he ate anything that was a little bit sharp or lumpy it would cause a blister and there was nothing we could do about it. Sometimes if it was really bad he couldn't swallow at all - even saliva. This could go on for hours. Ian used to get very annoyed as he loved food!

There was no support network when Ian was a child at all. We were very much on our own. When he was about 14 - 15 years old, in 1978, I heard of Phyllis Hilton who is the founder of DEBRA. The charity is actually named after her daughter Debra who also had EB but died when she was about 17. Treatment for Ian did not change dramatically over the years but one of the great advantages of meeting with other families from DEBRA was that we could share information. We got to meet other people and you would hear about new creams or things that other people had tried.

PLASTIC SURGERY

Things began to change for Ian when his hands began to retract when he was about 12. The fingertips literally heeled down to the palm of the hand. He had plastic surgery to open his hands out so that he could use them. However this was not permanent and after about five years they would go back again. After doing this three times, he got so fed up that he just had his first finger and his thumb released so that he could hold a spoon or a pen.

Before this he drove a car with a loop adapting the hand brake so that he could put his whole arm through it rather than having to lift it up with his hand. He could also type!

In his 30s he also developed skin cancer on his knee. At first the cancerous areas were removed but they kept reappearing.

WORK AND CHARITY EVENTS

After Ian finished school he worked mostly in an administrative capacity. He was always involved in local events, plays or raising money for charity. He loved to meet people and had a wonderful talent for getting people to do anything! He organised a transport marathon where he did as many sporting events as possible in 24 hours, and he managed 72. He was in the Guinness book of records for quite some time! He didn't mention his disability to the organisers and by the end his arms were red raw, without any skin, from where people had been pulling him out of one thing and putting him into another. He never complained about it though and he raised over £13,000 for charity.

EB did not affect the other members of my family as my husband and I were both only children and our only living parent was my Dad, who didn't live locally. So really we had no immediate family.

THE FUTURE

First and foremost I would love a cure for this condition and if this is not possible I want people with EB to be able to lead a more comfortable life. It is a terribly painful condition that stops people from doing normal things.



EPIDERMOLYSIS BULLOSA : THE MEDIC'S VIEW

Professor Robin Eady. St. Thomas's Hospital London

Professor Eady is a leading expert in Epidermolysis Bullosa and has been working in the field for over 20 years.

THE CONDITION

Epidermolysis Bullosa (EB) is a very wide-ranging group of disorders ranging from simplex EB which is usually restricted to blistering on the feet and hands in warm weather, to the most severe junctional form where a baby will almost certainly die within the first 18 months of life. The disease is classified into 3 main types :

1. EB simplex is generally not a very severe form of the condition, with blisters arising in the most superficial part of the skin, in the epidermis.
2. Junctional EB's level of blistering is only a tiny bit deeper but it can sometimes be lethal. Some patients can have a normal life span, depending on the type of mutations they carry. An electron microscope is needed to show the level of blistering or splitting in the skin.
3. Dystrophic EB's blistering level is slightly deeper still. In its dominant form it is usually less severe but in its recessive form it is often much more severe. These are the forms which tend to generate public attention as the patients often live well into adult years but have very great difficulty with disability and may eventually develop cancer.

PRENATAL DIAGNOSIS

I first became interested in Epidermolysis Bullosa in 1979 when a colleague contacted me about a patient who already had a child with the most severe form of EB. She had become pregnant again and asked if we could test the unborn baby to see if the pregnancy was affected. My colleague wanted to try a new procedure - taking a skin biopsy from the foetus in the womb at about 18 weeks old - and asked me to use my expertise with an electron microscope to examine the biopsy and establish whether the foetus was affected. We gave it a try - and found that the foetus was affected - and the mother decided not to proceed with the pregnancy.

This was the first time we were able to offer pre-natal diagnosis for any form of EB. We have since used these techniques to look at a great number of pregnancies. In the early days we were looking at skin, but now we look for DNA defects - which means you can detect the disorder at a much earlier stage in the pregnancy.

RESEARCH

I then wanted to find out more about EB. I contacted DEBRA who were very interested in our work. We decided to develop a research project and that is how it all began.

It is only in the last 10 years that researchers have begun to identify the actual genetic cause of the disease. We now know that there are at least 10 distinct genes which underlie different forms of EB. I think more will be discovered and that some very similar conditions that haven't been grouped with EB will come under the same umbrella as we begin to understand the genetic basis for these disorders.

DNA ANALYSIS

DNA analysis has become invaluable for the precision with which we can inform the patient or the family of the nature of the condition. This is particularly important in the dystrophic forms of the disease which, when inherited as a recessive disorder, can be very mutilating and devastating, whereas in its dominantly inherited form, it is rarely that severe. So DNA analysis is not only very important in making a diagnosis but also in prognosis.

Another major application of DNA analysis is early prenatal diagnosis.

CHANGES IN DIAGNOSIS AND TREATMENT

In some ways the method used for diagnosing EB hasn't changed over the years. We still analyse skin biopsies using electron microscopy, - looking at things through a microscope using electrons rather than light as the first line of diagnosis. We also use immunofluorescence microscopy using fluorescent light to see if certain important sticky molecules are in the skin, as they should be to get a more accurate diagnosis from the biopsy.

For some of those with the milder form of the condition we don't need to take a biopsy. We can usually make a diagnosis confidently based on the medical and family history and the appearance of the lesions.

We have become more aware of using supportive treatment. EB is a very painful disorder and the treatment of the blisters and ulcers can make patients' lives much better. It is important to help patients avoid situations that predispose them to blisters. The most common form of EB is a form of EB simplex which affects the hands and feet in warm weather, so advice on how to keep cool, and how to get hold of the appropriate footwear, and so on, can all help.

Patients with the more severe form of recessive dystrophic EB have a very high risk of developing an aggressive skin cancer. We now have a regular cancer screening clinic where these patients are examined very thoroughly. We try to pick up any early changes which might suggest a cancer, so that these lesions can be biopsied and treated immediately.

ROLE OF DNA

So far, DNA research has brought more precise diagnosis and prenatal diagnosis.

We currently have collaborative international projects working on gene therapy for the severest forms of EB. That is probably going to be the most tangible development arising from the new discoveries from DNA technology and the next step should come within the next five years.

I would not wish people to interpret that by saying "oh there is going to be a cure" because if a cure means a total reversion to something which is normal, and I really don't think that is going to happen.

What I think is going to happen is that there will be better ways of treating certain problems with a specific therapy.

HAEMOCHROMATOSIS

Haemochromatosis is caused by the absorption of too much iron which damages body tissues. It is treated using a process called venesection, like giving blood.

The treatment has not changed – but the identification of the gene in 1996 led to the development of a genetic test. This gives an early diagnosis so that patients can now receive treatment before the condition has set in and caused irreparable damage to vital organs.

HAEMOCHROMATOSIS : THE PATIENT'S VIEW

Peter Thompson's life changed beyond recognition when he was diagnosed with haemochromatosis at 39. Being bled regularly keeps things in check – but cannot reverse the long-term problems already caused by the disease prior to instituting this treatment.

Until I was about 39 I was relatively fit. If I had anything wrong with me it was always something major, not the colds that people normally get. I found out when I was about 19 – 20 that I am allergic to alcohol. About 10 years ago I was told that I was diabetic. I have also had osteo-arthritis since I was about 30.

The doctors have since told me that this was due to haemochromatosis, but I didn't know it at the time. I was about 42 – 43 when I started to have real problems with arthritis. It kept flaring up all the time and I was having difficulty moving, my hands were really bad. Today my wrists get very sore, and my elbows get sore now and again as well. I now have arthritis in nearly every joint in my body apart from my shoulders and my hips.

LETHARGY

It had got to the stage where I felt very ill. I became lethargic. Everything was a struggle. This went on for a few years until a doctor I had been seeing about my cholesterol at Guys Hospital asked me what the matter was. I said "I don't know but I just don't feel well. I can't explain why. I feel tired all the time." He noticed that my hands were swollen, puffy and out of shape. He took a blood test which was analysed for haemochromatosis, and came back positive.

My serum ferritin levels were roughly 3900, compared to 50 for a normal male. After my diagnosis I was referred to the haematology unit as I had to be bled, once a week for the first 6 months, then once a fortnight, then once a month and now I am bled once every 6 months.

BREAKING THE NEWS

Once I was diagnosed I had to tell all my family to get tested. As it is a genetic condition they could also be at risk, or be carriers. My brother is a haematologist so he was extremely understanding! But my mother is one of these people who, if she doesn't know what something is, just sweeps it under the carpet. She didn't understand the need to be tested, felt that she was too old and had managed ok so far. After the results came through I found out that both my brother and my sister are carriers of the condition, but I am the only family member who actually suffers it.

It was a very difficult time for me. All I could see was the fact that I would have to be bled for the rest of my life. I became very depressed. I started to see less of my friends, as they were getting fed up with me always feeling ill and having to cancel arrangements. I had stopped working by this time as well as I found it very difficult to concentrate.

SUPPORT

The hospital had told me about the Haemochromatosis Society. They put me in touch with another person who had the condition. I think I must have been on the phone to him for about 6 hours! It was incredible. I was speaking to someone who had been through it all and had come out the other side. He knew exactly how I was feeling and he gave me tips on how to do things. It made such a difference.

LONG-TERM EFFECTS

I still have good days and bad days. Fortunately the bad days don't come as often. Taking the blood out doesn't cure the condition. Whatever damage has already been done, is done. It is not reversible. What it means is that it doesn't get any worse. So you become used to it, in that you know what is wrong with you.

It has cost me almost all my friends. I keep in touch with maybe three or four people from when I worked in the music industry as a record promoter. Some of them just didn't want to know which is hard to come to terms with. I used to be a workaholic, I would work 7 days a week for sometimes 18 – 20 hours a day. I have gone from that to not working at all, which is a real culture shock. I haven't worked for about 7 years now and I still can't get used to it.

HAEMOCHROMATOSIS : THE PATIENT'S VIEW

This patient, who would like to remain anonymous, discovered that she suffers from haemochromatosis after her brother became extremely ill with the condition. Because she had an early diagnosis she is hoping that she will not suffer any long-term damage.

I didn't know what haemochromatosis was until my brother was diagnosed a year ago. Before this there had been no history of it that we know of in my family.

My brother, who is 52, was extremely ill and was admitted to hospital with swollen joints. The doctors didn't know what was wrong with him. To be honest we thought he was not going to make it. After about six weeks the diagnosis was confirmed as haemochromatosis. Once he was diagnosed he began receiving treatment and he slowly began to get better, but he was very poorly. He had to literally teach himself how to walk again. His ferritin levels were around 4000 when he started his treatment (normal level is around 50 for men).

CARRIERS IN THE FAMILY

At this time the family was also advised to be tested for this condition. I was the first to be tested, and lo and behold I also have it. I am not aware of any symptoms that I had prior to being tested, but I think this is because it was diagnosed very early. Some of the early signs can include fatigue and joint pains, and most of us at the time of diagnosis put these pains down to age! I am extremely lucky as my brother really saved my life.

Not all the family have been tested yet. I know that one of my sisters has been diagnosed with the condition and one of my other brothers is a carrier. My husband has been tested and he is not affected but both my children could be carriers. We have not had them tested yet as they are too young. My brother was so ill that I really don't want to scare them too much.

HAEMOCHROMATOSIS SOCIETY

I am now a member of the Haemochromatosis Society. The information they have sent me has been really helpful. Although I gathered a lot of information from the internet, the things I got from the Society seemed to make everything much clearer.

DIAGNOSIS

My GP tested me as soon as my brother had been diagnosed. When the results came back I was referred immediately to the specialist as my ferritin levels were so high, at 1288 for an average female it should be between 150 – 200.. I was diagnosed last July from the ferritin levels and I then saw the consultant in October with the results of my gene test. I began having venesections in January of this year and at present I have them every two weeks. As you can imagine having seen my brother so ill I am very impatient to have my ferritin levels returned to normal.

My biggest worry now is – have I got it in time? I am more concerned that I might already have some liver cirrhosis as it will be irreparable. I am due to have the liver biopsy in two weeks' time.

I have also had scans done on all my major organs, as if you have haemochromatosis you are more likely to suffer from liver cancer. I think I will now have 6 monthly scans.

FAMILY SHOCK

This has been a large shock for my family. I think that is part of the reason why not all my family members have been tested yet, they almost don't want to know, which I think is silly. If you've got it, you've got it, at the end of the day it is not going to go away by not having the test done and the condition is treatable.

IMPACT ON LIFESTYLE

I have really cut down my drinking now. I went out with my friends at the weekend and I was the driver. I used to like a glass of wine with my food, but since being diagnosed I have read that if you are going to drink it is better to do it without food as that makes the intake of iron higher. So now I have my meal with a glass of milk – which is much better for me!

THE FUTURE

I would like to see a lot more information made available to the general public about this condition. Nobody I have spoken to (other than those who have the condition) has heard of, or knows anything about it. There ought to be more information for medical professionals as well, and a standardised protocol for treatment. Haemochromatosis is not rare, that's what is so strange. It is so common and can be fatal if it is not treated.

HAEMOCHROMATOSIS : THE MEDIC'S VIEW

By Dr Adrian Bomford

Adrian Bomford is a liver physician working at Kings College Hospital and specialising in haemochromatosis research

THE CONDITION

Haemochromatosis is a medical term for iron in the tissues, which causes tissue damage. It is a late onset disease, occurring in adulthood and late adulthood. Patients build up excessive iron in the body because they absorb too much iron from their diet. Their dietary iron intake is normal.

Liver specialists are interested in haemochromatosis because the liver is one of the main sites damaged by this condition. Excess iron in the liver causes cirrhosis. Other organs that can be damaged are the pancreas, the pituitary gland, the joints and the heart – which means that patients with fully developed haemochromatosis can suffer from cirrhosis, diabetes, heart failure, pituitary failure, arthritis and sexual dysfunction.

TREATMENT

To cure this condition we have to remove the iron – which we can do by a process called venesection. This is like giving blood. The patient may have to have up to a pint of blood removed each week. The regular bleeding removes the iron over perhaps two or three years depending on how much iron there is in the body. After this they would have venesection about four times a year as the metabolic lesion does not go away. You treat the iron overload and then you prevent further build up.

Bleeding patients began in the 1950s and the treatment is very successful. Before that, the outlook was grim. The diabetes was treatable so that would get better but everything else was there to stay and people used to die of liver cancer or hepatoma. One of the most important factors in developing a hepatoma is the presence of cirrhosis which is what we now work tirelessly to avoid. Now that patients are bled their life expectancy is pretty normal, especially if they are diagnosed before cirrhosis has developed.

People can come to be bled after work, so in theory they should be able to lead a relatively normal life. We recommend less alcohol and to drink tea as the tannin makes the iron less easily absorbed.

FINDING THE GENE

It was hoped that the gene for haemochromatosis would be found far sooner than it was. In the 1970s a population geneticist described a linkage between haemochromatosis and the HLA3 gene. People felt that because we had this linkage we would soon have the gene. Unfortunately it took 25 years before the gene was finally identified..

The hereditary haemochromatosis gene has now been identified as being on chromosome 6 and the gene is called HFE. The cloning of the gene in 1996 allowed us to say with absolute certainty that haemochromatosis was present in a patient. Before this we make a diagnosis from the patient's symptoms, so we had a lot of information about the patient and the biochemistry but could not be sure about the genetic mutation.

A SURE DIAGNOSIS

The real value of genetics has been that, thanks to the genetic test we can start treating patients before any tissue damage, cirrhosis, or diabetes has occurred, which is extremely important. The treatment itself has not changed greatly.

In the past doctors could only look at iron biochemistry to test people for a pre-disposition to the condition. This is still the first step, but now we are able to do a DNA test to confirm whether people are carriers of a faulty gene, in which case we can monitor them more closely.

CURRENT RESEARCH

The discovery of the gene has also led to the identification of rarer forms of haemochromatosis that are not caused by a defect in the haemochromatosis gene. About 10% of cases are caused by defects in other genes, some of which we know and some of which we don't.

Also, even if you carry one of the genetic defects it is not 100% certain that you will have the symptoms. Some people have the genes but no expression of the disease and others have huge amounts of iron.

Scientists are now looking for other genes or genetic modifiers that could cause this variability in the condition. There are now four or five other sorts of mutations in other genes. We must also take into account environmental factors such as the amount of iron in peoples' diet.

NEW CONDITION

A condition known as juvenile haemochromatosis which has been recognised for some time is now known to be caused by a defect in a gene, on chromosome 1. Now we know the location of the gene, we are searching for the actual gene in chromosome 1. Discovering this gene will be very exciting as it may be that patients with a particularly severe form of adult haemochromatosis could have mutations on the juvenile gene that we have not yet identified. Once we have found the juvenile gene we will immediately start looking to see if this is the case.

Medical professionals have moved away from thinking that the haemochromatosis gene is the most important gene in iron balance. Very rapid progress in the identification of new genes has been possible because of the effort put into sequencing all the genes in humans, the mouse and many other varieties of animals and plants. In the field of iron metabolism many genes have been identified and their function discovered. Research workers at King's have recently identified two genes that reduce and transport dietary iron in the intestine.

More and more genetic information will enable us to understand the variation in peoples' conditions. We will be able to make a more accurate diagnosis and prepare people for treatment. Increased awareness and early diagnosis are extremely important.



MEN2A : the patient's view

HAVING YOUR ENGINE REMOVED!

Jean Ward felt well until she discovered that she had inherited the genetically transmitted cancer, MEN2A (multiple endocrine neoplasia type 2A) from her father. She had to have her thyroid removed and then her adrenal gland. The cancer is cured but the symptoms remain and her immune system is weak. Leading a normal family life is a struggle.

Men2a is a cancer that affects the endocrine, thyroid and the adrenal glands. The treatment for this is really to have the glands removed, which is rather like having your engine removed!

TWO INCIDENTS

My Dad was ill in the late 1950s with a tumour on his kidney. At the time that is all we thought it was. My aunt also had a similar thing and the doctors said that it was very unusual to have two incidents like that in one family, but that was the end of it. My father eventually collapsed in 1976 and at that point a lot of tests were done. They found that he had a tumour on his thyroid, which they thought he had probably had back in the 1950s and also one on his adrenal gland. Both were removed, but he was extremely ill, on a life support machine. Believe it or not he came through that.

TEST AND OPERATIONS

It was only at this point that I was tested as they realised that it was something hereditary. I had a nice glass of whiskey (as Prof Ponder has explained) to test if my thyroid was playing up, and we took it from there.

I was told that I needed my thyroid gland removed. Unlike my father I had not felt ill prior to this operation, so it was quite a shock. At the time I didn't know quite how involved it was, or what it was really going to mean for me. I had 3 children under the age of four at the time, one of whom was only 10 months old. After the operation I had to have 6 weeks of daily radiotherapy.

In 1985 when I was expecting my last daughter, I had a scan done on my adrenal glands and found that a tumour was beginning. This was different to my Dad, as he had had a full blown tumour when it had been removed, mine was only very tiny and it was caught a lot earlier. It was a bit more complicated as I was pregnant at the time with my fourth child and it meant that I wasn't able to give birth naturally. I had a caesarean and then they removed the adrenals straight afterwards. I was in hospital for quite some time, so my husband was at home looking after the three children as well as coming up to London to visit me.

Having the adrenal gland removed really did knock me for six. David, my husband has been off work since then to help look after us all. I wasn't able to take my youngest daughter Jeanne to school as I couldn't walk very far. Even today I can only walk to the end of the road and back and even that can sometimes be too much for me. It really changed the way I behaved towards Genine as I was unable to do so many of the things that I had done with the others, cello lessons, art lessons, pottery, I just didn't have the energy. So in some ways it was an entirely different childhood for her.

CHILDREN

In 1987, the year when the gene was found, my three girls were given the all-clear, but I had passed it on to my son. The doctors had already seen problems with him and had removed his thyroid gland (before the discovery of the gene) when Kieren was seven years old. For Kieren having the gene test really confirmed what we knew anyway. He had another operation when he was 16 to remove some more cancerous tissue in his throat. Then in 1998 he had one adrenal gland removed.

LONG-TERM IMPACT

I have been 17 years clear now, I am tested once a year. However I am still waiting to feel any better, the symptoms have remained the same over the 17 years. My immune system doesn't work very well anymore. If people are ill I don't allow them to come in the house, as I get so sick. I still have pills to take, the doses may have changed slightly over the years but the medication remains the same.

LACK OF INFORMATION

My husband and I are really finding things out as we go along. The condition is so rare that there are very few doctors who can supply us with information. Outside our family, we don't know anybody else who has this condition. There were only about 3 recognised families in the country when I had my first operation.

It's not just the condition that affects your family it is everything else that goes with the condition as well. There can be a lot of background pressure. Not knowing if the children were going to develop the condition was a big worry for me.

People can be quite ignorant and you spend a lot of time explaining everything. Because I don't look terribly ill, people think I am not, which is very hard. My family are very understanding but strangers generally are not.

We have been very lucky that our cancer has been caught in the early stages. I have a cousin in Canada who has lost her son to this condition, and he was only 20 years old. He went into hospital with pneumonia, and they found the tumour after he died.

THE FUTURE

We hope that genetics will help, and that a cure will be found. We have certainly seen some amazing progress since my father was ill. The tests now are so much better, a simple blood test, whereas my father had to have lots of hideous tests done. There is a lot of information out there, especially now we have the internet. We try to get as much information as possible, keep asking questions and pushing to get answers. THE FUTURE

MEN2

Identifying the gene for MEN2, the hereditary cancer of the thyroid, endocrine and adrenal glands, has led to more accurate testing for the condition. By identifying those affected early, many lives are being saved. Now the search is on for a better treatment than the current approach of surgical removal of the entire tissue for prevention of the tumours – and the long-term problems this brings for patients struggling to cope with lost hormones.



MULTIPLE ENDOCRINE NEOPLASIA TYPE 2 (MEN 2) : THE MEDIC'S VIEW

Professor Bruce Ponder

Bruce Ponder is a cancer specialist who became interested in MEN2 by chance...

THE CONDITION

MEN 2 is a rare inherited condition, first recognised in the 1960s. A faulty gene causes a particular type of cancer of the thyroid, and tumours of the adrenal glands. The thyroid cancers can be treated by surgical removal of the thyroid if they are picked up early enough, but once they have spread outside the thyroid, treatment is difficult. The adrenal tumours are not usually cancerous, but they make lots of adrenalin which, if it is suddenly squeezed out into the bloodstream – for example during childbirth – can cause sudden death from high blood pressure.

A child of someone with MEN2 has a 50:50 chance of inheriting the faulty gene, and may develop thyroid or adrenal tumours at any time from childhood to late adult life.

CHANCE INVOLVEMENT

In 1981, I was working at the Royal Marsden Hospital researching into bladder cancer. The bladder clinic was quiet one afternoon, so I went across to the thyroid clinic to help out. To my surprise, I came across two patients with thyroid cancer, who both had brothers, sisters and a parent affected with the same cancer.

The main concern was for the brothers and sisters and children who were still well, because they might have inherited the gene and be about to develop cancer. Several relatives of my clinic patients had already died, in their 20s and 30s, of thyroid cancer. Fortunately, the thyroid cancers could usually be detected at an early stage because their cells produce a hormone, calcitonin, which could be measured in a blood sample.

WHISKEY TEST

To make this test sensitive, a 'stimulus' was given to make the cells release their calcitonin: a double tot of whiskey, to be drunk within 30 seconds on an empty stomach, with blood samples immediately afterwards. The problem was that the test was not always reliable, and not surprisingly, children and even adults often did not fancy a double whiskey at 10am after no breakfast! Moreover, most doctors were not aware of the condition, so it often took two or even three cases of thyroid cancer, or sudden death from high blood pressure in the family before anyone realised what the problem was, and screening of family members was started. With better awareness, these deaths could be prevented.

NEW TECHNIQUES

In the early 1980s new techniques first made it possible to recognise subtle differences in the DNA between individuals. These differences could be used to build up genetic maps to find the faulty genes that ran in families to cause disease. I knew that the search had begun for the gene that caused Huntington's disease, and I thought perhaps we could make a similar search for the thyroid cancer gene. If we found the gene, we could predict quickly and accurately which family members would develop cancer and which would not; and if we knew how the gene worked, that might tell us how the cancer developed.

GENE SEARCH

So I started to collect families for the gene search. My wife Maggie would leave home before dawn to attend thyroid surgery at hospitals across the length of England. With the help of the Institute of Heraldic and Genealogical Studies in Canterbury, we linked small families with thyroid cancer to common ancestors in the 1800s; and our greatest piece of luck was to meet Dr. Margaretha Telenius-Berg, a Swedish doctor who had traced a single Swedish family back to 1617. By chance, we heard that a tiny piece of the then mostly empty gene map had been filled in by a researcher in eye diseases in Texas, and we were able to prove that the thyroid cancer gene was there too. After another six years of work by a lab team of up to 10 people (research which today with the human gene sequence and faster technology might take two people a matter of weeks), we had isolated the gene.

As soon as we saw the gene, we knew roughly how it worked. It belonged to a family of genes – the receptor tyrosine kinases – that was already well known although never before implicated in familial cancer. The gene, called *ret*, makes a protein which acts as a 'television aerial' to receive signals at the surface of the thyroid cell. When the signal is received, it is passed to the inside of the cell where it causes the cells to grow, and divide, and move about; but when there is no signal, the cells are quiet. The problem in the thyroid cancer families was an inherited mistake in the DNA instructions in the gene, which results in a faulty protein which makes a 'receiver' that is permanently switched on. As a result, the thyroid cells grow when they shouldn't, leading eventually to cancer.

IMPROVED TESTS

Finding the gene has, as we hoped, greatly improved the advice we can give to families. Children can be tested from a small blood sample soon after birth. If they have not inherited the faulty version of the gene the parents can be reassured. If they have inherited it, plans can be made for preventative treatment by surgery at a suitable age.

Older family members need no longer undergo yearly checks with the 'vodka test' (or its more recent equivalent in which vodka is replaced by a different stimulus given by injection), but can have the gene test and either be reassured or plan for thyroid surgery.

Previously, new families were not recognised until at least a second case had occurred, which was often not detected until after it was possible to treat the cancer successfully. Now, gene testing of every new case of the type of thyroid cancer that occurs in MEN2 has become standard practice. The relatives of cases that test positive are also offered screening.

The discovery of the MEN2 gene and informing of doctors about the possibilities of testing is probably saving up to 20 or so premature deaths each year in the UK - and sparing a much larger number of family members the discomfort, anxiety and uncertainty of the yearly screening tests that were previously used.

REMAINING PROBLEMS

Two main problems remain. The first is to find a better alternative for surgical removal of the entire tissue for prevention of the tumours. Adrenal surgery poses far greater difficulties in terms of replacing the lost hormones than thyroid removal.

The second is to translate knowledge of how the tumours develop into successful treatment. This is particularly important for the isolated - that is, non-hereditary - cases of the thyroid cancer. These are commoner than the inherited form, and difficult to treat; but they share the same fundamental problem of a faulty *ret* gene.

Recent research suggests that our knowledge of how the faulty *ret* gene sends misleading signals for the cell to grow is now sufficiently precise for the design of specific treatments to be possible soon.

Haemophilia

In the 1930s, 70% of haemophiliacs died before the age of 20. The introduction of factor concentrates treatment was a breakthrough - followed by devastation when many haemophiliacs became infected with the hepatitis and HIV viruses from those concentrates in the '70s and '80s. DNA engineering technology has brought factor treatments with no risk of infection, effective early diagnosis of sufferers and carriers - and a normal life expectancy. Hopes are high for further treatments emerging from genetic research in the future.



Haemophilia : the patient's view

"HAEMOPHILIA RARELY STOPS ME"

Dan Jolley is a teenager who has severe haemophilia A.

I was diagnosed when I was eight months old after my parents had struggled to find out why I kept bruising. I started my home treatment when I was eight years old and I was far from easy to inject. I have always had access to a high purity product. When I was between 9 and 10 I developed problems with my veins and eventually had to have a port-a-cath for one year. After my veins recovered, I progressed to self-infusion and now I am totally self-sufficient and can inject into both arms.

SPORT

During this time, I have always been very active and sporty. My parents' attitude throughout was not to wrap me in cotton wool. At the age of five, I was spotted by a local tennis coach and began to play "short" tennis. I played in a local club and won some tournaments and soon I progressed to tennis. Today I play doubles and singles for two clubs and I have won local and county tournaments in both. I have always played football and now at secondary school I also play basketball, and badminton cricket. I've recently started shooting and joined a club in order to give my ankle a rest!

I tried playing trumpet and got to grade 3 but breath control and the serving action of tennis gave me repeated stomach muscle bleeds which led to periods of inactivity and bed rest and lots of treatment and pain. This is not what I like so I gave up the trumpet and I'm very careful now with my serve!

TREATMENT

All of this activity is only possible with good treatment - prophylaxis is supposed to be three times a week.

When I was eight years old my ankle kept bleeding and wasn't getting any better - and they found I had inhibitors. This led to damage and arthritis. I received a high treatment regime and got rid of the inhibitors. Today I use a genetically manufactured factor treatment. I had an allergic reaction to the first one I tried but the one I use today is great.

My headmaster learned to inject me and he is my back-up for many school trips abroad. At school and with my family, I have visited ten countries and in July, I visited Malaysia with the school and my big bag of Factor VIII.

GREAT FUTURE

The future today looks great. My life is very full and active. I hope to do four A-levels and go on to do medicine. I have an active social life at church and school and recently passed my driving test.

Haemophilia rarely stops me. I fully appreciate the difference that regular high purity injections and the support of the centre and the doctors have made to the sort of life I can lead compared to what it would have been if I had been born 10 or 20 years earlier. So I'm going to make the most of my life, live it to the full and hopefully, if I become a doctor, be sympathetic to those who need lots of injections and suffer pain.



Haemophilia : the patient's view

TREATMENT IN A BOX

by Chris Hodgson, Chairman of the UK Haemophilia Society, who has lived with haemophilia for 62 years

If I reflect back on my life there have been enormous changes in treatment, many of which I would not have dreamed of when I was a young man. Life for someone with haemophilia in the 1940s and '50s was very little different to that experienced by Alexei, the son of the Russian Tsar or Queen Victoria's son Prince Leopold. To protect them most mothers tended almost to wrap them up in cotton wool.

The life expectancy when I was born in 1941 was about 16 years. Dr Charles Rizza used to counsel mothers of newly diagnosed people with haemophilia that they probably might not see their 12th birthday, but happily many of us did survive, mainly perhaps by luck or by the support of our families.

PAIN

What tends to be forgotten by a generation that has grown up with factor concentrates was the terrible fear of the pain caused by bleeding into joints and muscles. Nights without sleep, with no effective pain-killers, and doctors out of ignorance used to suggest aspirin. There were no small needles like we have today, with sometimes the need to cut into the veins of a baby to carry out a transfusion of blood then fresh frozen plasma. On top of this the hours in hospital. It took ages to receive any treatment and you would be very lucky to find a doctor who knew much about haemophilia.

Then there were so many days and hours lost at school. The need for bed rest and journeys to St Mary's Hospital, Paddington, for traction to straighten the joints and splints to stop knees becoming permanently bent. There was very little possibility of sport ; I managed some tennis but football was not considered, and when I asked to play cricket, my mother advised the school it would be far too dangerous. Many of us, of course, died of brain haemorrhages easily set off by a cricket ball.

HAEMOPHILIA SPECIALIST

When I obtained my first job in North Devon, I was looked after by the local hospital but had reviews by a centre director in Exeter. Dr Edgcumbe was the first doctor I ever met, apart from trips to Oxford, who specialised in haemophilia. For serious bleeds he worked out a system where a bag of fresh frozen plasma was placed in an insulated box then sent from his hospital in Exeter by train to Barnstaple where it was collected to be infused as quickly as possible. On reflection I can't imagine this happening today as the train takes twice as long to do the journey and only runs a few times each day! I can also remember one awful bleed in the forearm when, because of the pain and the threat of damage to the nerves, I was taken by ambulance to Exeter, then in the night to Oxford where Dr Rosemary Biggs contemplated amputating my right arm for the fear of gangrene. Thankfully, when she told me this was a possibility, I produced enough adrenaline to halt the bleeding.

OUTPATIENT TREATMENT

After North Devon I returned to our motor business in Petersfield and was advised by a surgeon friend of my father, Harry Haysom, that I could attend the Haemophilia Centre at Treloar College as an outpatient. This was the beginning of the treatment I experience today. We had our own ward, a dedicated haemophilia doctor and a haemophilia sister. At that time, Treloar was gaining tremendous expertise in haemophilia care because about 80% of the boys at the college suffered from severe haemophilia. They could enjoy a good education without the constant need to visit hospitals for their treatment. Now, of course, they can attend normal schools.

HEPATITIS AND HIV

In 1973 I received my first factor VIII concentrates and like the boys I was taught to carry out home treatment. For me it was a transformation. I had control over the bleeds but sadly, unknown to us, then came the devastation of the HIV and hepatitis viruses which has been described as one of the worst medical disasters of our generation.

It is painful for many of us to think back realising so many of those boys have now died from the infected concentrates which at that time transformed our lives.

PSYCHOLOGICAL ASPECTS

I can touch on the psychological aspects of living with haemophilia, which is something I am very interested in - particularly the difficulties experienced by the whole family, not just the sufferer. I feel a great need to keep positive, to lead as normal a life as possible, as well as the desire to test the limits of my disability; and from these feelings to try and be normal.

I have managed to lead a fairly active life. I have been able to run a business, to drive cars in rallies, to fly a glider and persuade my instructors I could, as I gained experience, teach others to do the same.

One strange coincidence was that one of my pupils turned out to have a son born with haemophilia. When I told him I had haemophilia he replied "I don't believe you, you must be pulling my leg!" His son has just got married and works in a law firm in the city having obtained a law degree at Oxford. His parents were told when he was born he could only lead a very protected life.

I still receive my treatment from the same comprehensive care centre now in Basingstoke, which was previously situated at Treloar College, Alton, Hampshire. My main concern now is national specification on haemophilia being produced by the Haemophilia Alliance. It has been a privilege to be involved with all the members of the Alliance in the production of this national document.



HAEMOPHILIA : THE MEDIC'S VIEW

Professor Paul Giangrande, Oxford Haemophilia Centre

Paul Giangrande worked as a doctor in general medicine before deciding to specialise in haematology in the 1980s.

THE CONDITION

Haemophilia is a bleeding disorder that you are born with. It is a sex-linked disorder on the X chromosome.

Females carry the faulty gene, as they have two X chromosomes (males have an X and a Y) the faulty chromosome is balanced out by the working one. As males have only one X chromosome if they receive the faulty one they have nothing with which to compensate, and that is when they suffer from the condition. A typical symptom is spontaneous bleeding to the joints. A patient will be able to tell you they have a bleed well before there are any external signs. They will typically complain of a slight pain or stiffness in their joint, and a sense of warmth. It can cause severe internal bleeding and in the absence of treatment it is unusual for children to survive into adolescence.

TREATMENTS

By the 1930s people realised that haemophilia was caused by a missing protein in the blood. It was then a case of finding that protein and naming it clotting factor VIII. The treatment was quite basic but pretty effective - to give fresh blood or better still to give fresh plasma. That might sound relatively easy but in those days there was no well-developed blood transfusion service. The other problem was that there is only a small amount of factor VIII in crude plasma so it took quite a large volume of plasma to treat a serious bleed.

In 1965 Dr. Judith Poole found that if you froze a bag of plasma at roughly minus 30 degrees and thawed it slowly up to about 4°C a substance called cryoprecipitate would appear that was very rich in factor VIII. This was a major advance as it meant you could concentrate factor VIII into relatively small volumes and store it in domestic refrigerators. This meant that for the first time patients could treat themselves at home, and it really did transform their lives.

Until this time we had usually treated people as and when they had bleeds, but this new treatment meant that we could give prophylactic treatment – treating patients two or three times a week to help prevent a bleed. This method also stops the development of disability. In the past you could treat the bleeds but there would still be blood in the joints and that would lead to joint destruction and arthritis.

INFECTION

It was a major setback when haemophilia patients began to be diagnosed with HIV and hepatitis C. This focused people on the source of the plasma. A way of screening donors was established very quickly and people worked very hard to find out how to treat the blood products patients received to make sure that all viruses had been inactivated.

People are now treated by recombinant factor VIII 1994 and factor IX 1997. Because these products have been genetically engineered, the risk of disease is no longer there. These products are very expensive and the UK government has only recently announced that all patients will be phased onto recombinant products over a three-year period.

ROLE OF DNA

DNA has helped us to understand the cause of haemophilia at a genetic level. This is important because we can now identify who in a family is at risk of having haemophilia. It has also enabled us to produce effective treatments such as the recombinant factor VIII and IX. The life expectancy of a patient without hepatitis C or HIV is now normal.

FUTURE RESEARCH

Our ultimate goal is to find a gene therapy to cure haemophilia but this is a long way off. Meanwhile, I would like to see genetic engineering applied to producing molecules with modified properties so that, instead of giving a patient an injection that will last for, say, 12 hours, it would last for days. I see this as the next step.



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