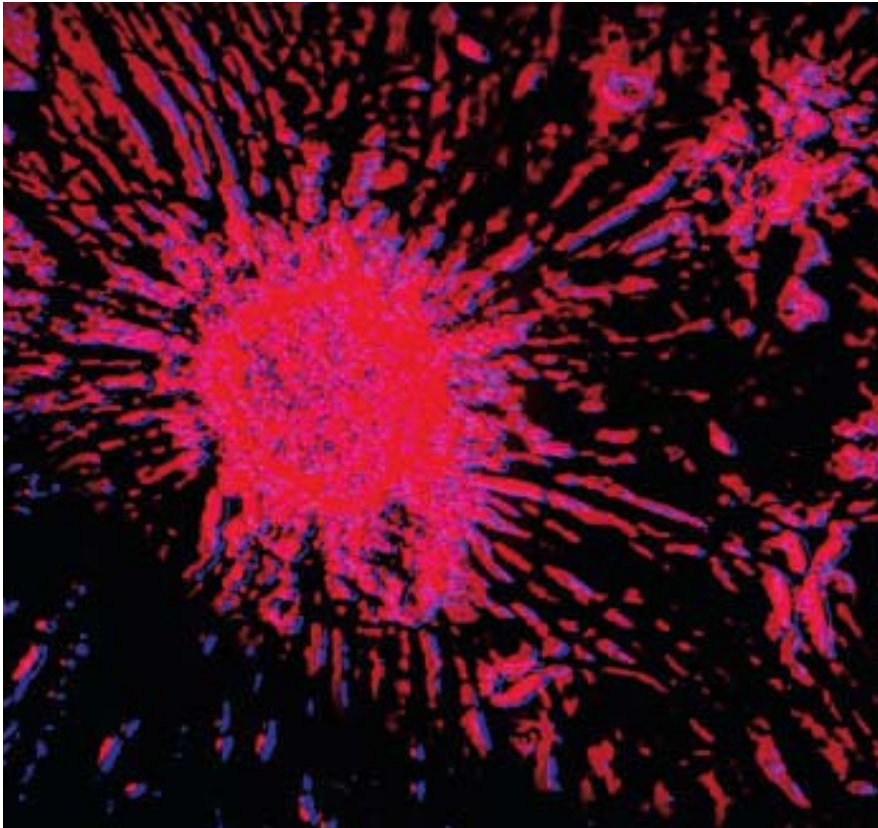


Search for the Magic Bullet against Cancer



Most people are familiar with the often cited statistic that more than one in three of us will develop cancer at some point in our lives.^a

Scientists have been trying for many years to find better and more effective treatments – even a cure – for cancer. The biochemical industry is currently at the leading edge of these attempts.

Biochemical therapies were first developed as long ago as the 1970s. Only recently, however, with the mapping of the human genome and the increasing understanding and technical sophistication this has given us, have oncologists become really excited about their potential.

A number of recently published studies suggest we may at last be on the verge of significant breakthroughs against cancer.

There are many different types of biochemical therapies currently being developed. These include cancer growth blockers, cancer vaccines and Interferon, to name just a few. The following article, however, concentrates on the group called Monoclonal Antibodies (MAbs).

What are Monoclonal Antibodies (MAbs) and how are they made?

The idea behind MAbs is that they work like magic bullets, specifically targeting and destroying cancer cells.

MAbs are identical, mass-produced laboratory cells. They are created by a type of cell called a hybridoma, which is produced by fusing two different types of mouse cells.

The mainstay is a type of mouse bone marrow cancer cell, to which a mouse white blood cell (B lymphocyte) is fused. The cancer part of this cell gives the hybridoma the ability to live indefinitely.

The "B cell" part is designed to produce a particular type of antibody in the presence of a particular antigen. The antigen is a specific type of cancer cell. In other words it is designed to identify certain types of cancer cells and create antibodies. All the antibodies produced by the hybridoma are of the exact same type and are identical clones of one another. Hence they are monoclonal antibodies.

One of the problems encountered in practice is that, over time, the human body's immune system may recognise the mouse cells as foreign and reject them. It seems one way around this can be to disguise the foreign cells by combining part of the mouse antibody gene with part of a human antibody gene.

How do MAbs work

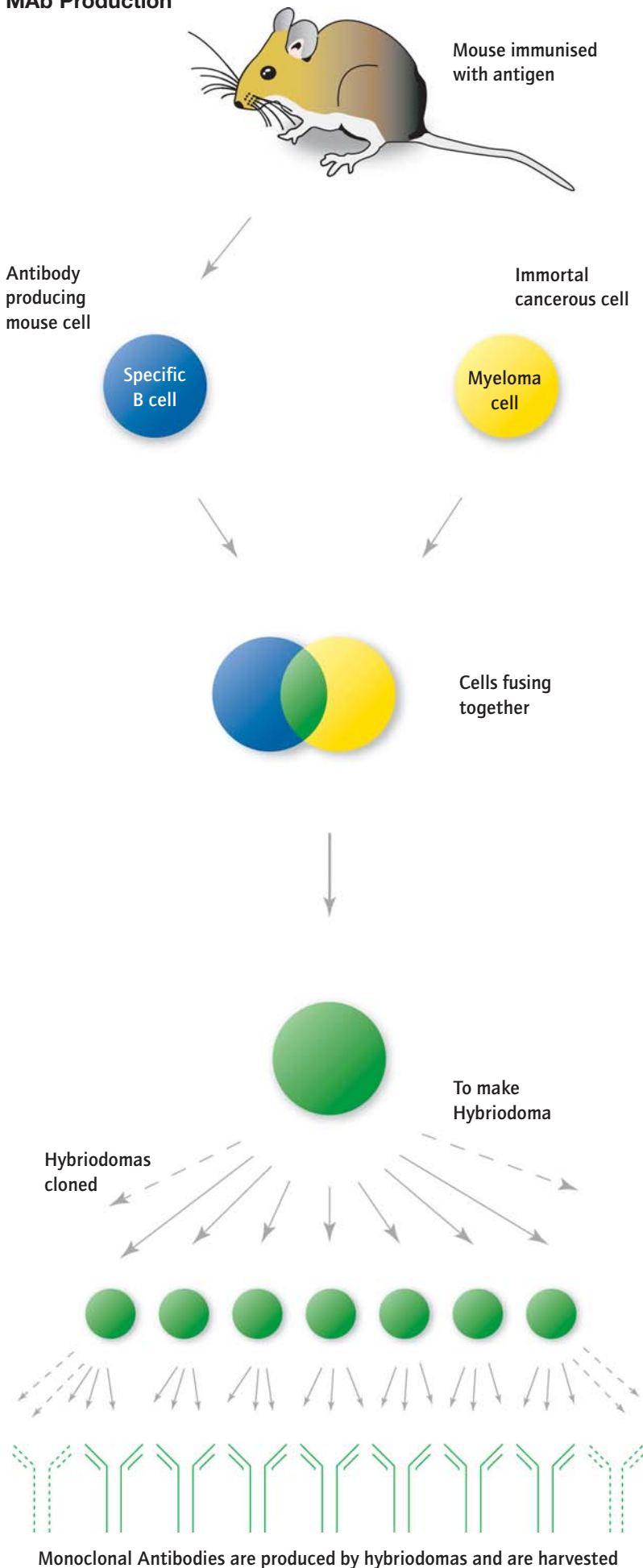
Scientists are getting better at identifying the particular antigens associated with cancer cells. New types of MAbs can be developed that will accurately target particular types of cancer cells.

There are two types of MAbs.

Naked and Conjugated MAbs

Naked MAbs work either by attaching themselves to particular sites where cancer cells grow – thereby blocking cancer cells from growing there – or by marking cancer cells so that the immune system can destroy them.

MAB Production



Conjugated MABs have substances attached to them that are deadly to cancer cells, such as drugs (chemolabeled), toxins (immunotoxins), or radioactive atoms (radioimmunotherapy). As the conjugated MABs circulate round the body, they locate and bond with cancer cells, which are then killed by the attached substances.

Success to date

There is a wide range of MAB drugs currently undergoing clinical trials. Whilst these can have serious side effects, results now coming through suggest that real progress is being made. Patients on these trials have often tried conventional treatments such as chemotherapy without success and have moved into the advanced metastasised stages of their cancers.

Not until years after a trial's conclusion do we have necessary data to determine the extent to which survival rates have improved. Even so, it is widely hoped that if these drugs can help patients with very advanced cases of cancer they could prove even more successful if given to patients at an earlier stage of the disease.

Herceptin (Trastuzumab)

The MAB currently grabbing the headlines is Trastuzumab (trade name Herceptin), which is used in the treatment of an aggressive form of HER2 positive breast cancer. With over 41,000 cases diagnosed each year in this country, breast cancer accounts for one in three cancer cases among women. As well as being the most common form of cancer in the UK, it is also the third most common cause of death from cancer, resulting in more than 12,000 deaths during 2003. In women aged 35 to 54 breast cancer accounts for more fatalities (17%)^a than any other cause of all death.

Trastuzumab is a MAB that targets the HER2 protein found on HER2 positive breast cancer cells. It is thought that up to one in four breast cancers are HER2 positive.

The results of an initial randomised clinical trial of Trastuzumab were reported in the *New England Journal of Medicine* in 2001 (see Graphs 1 and 2). The patients involved all had advanced metastasised breast cancer and were scheduled to undergo chemotherapy. The group given Trastuzumab in addition to chemotherapy showed a 20 per cent reduction in the risk of death, and a longer time to disease progression (a median of 7.4 vs 4.6 months).

Based on these encouraging results in treating advanced breast cancers – and the fact that Trastuzumab appears to have relatively minor side effects compared with traditional chemotherapy treatment – three large clinical studies were set up to study its effects on early stage breast cancer.

Two of these studies are based in North America. The third is a worldwide study known as HERA. Initiated in December 2001, HERA involves over 5000 patients at 480 sites in 39 countries including the UK. The women enrolled have tested positive for the HER2 and their cancers have spread to the lymph nodes, thereby giving them a much higher chance of recurrence. Patients received either chemotherapy alone or chemotherapy plus Trastuzumab.

The studies aim to follow the women for up to 15 years.

In an unprecedented step, the early results from all three trials were announced this May at the annual meeting of the American Society of Clinical Oncology. The headline figures were certainly impressive.^b

- 52 per cent reduction in the risk of cancer reoccurring (from one in three to one in six over a four-year period)
- And a 33 per cent reduction in the risk of death after two years.

The studies are still immature and more time will have to elapse before we know whether the results hold up. So great has been their impact, however, that many women with early stage HER2 positive breast cancer are already asking whether they should be taking the drug now.

Other MABs

Several other drugs are also showing very promising early results.

A small trial of Tositumomab for the treatment of a type of Non Hodgkin's Lymphoma has produced very encouraging results. The drug was given to patients suffering from advanced stage follicular B cell-lymphoma, which is currently considered incurable. In 75 per cent of participants, the cancer disappeared. As patients typically survive for between 7 and 10 years, we will have to wait to see the full results and – importantly – to find out whether the cancers return.

Bevacizumab is a MAB that has been licensed for use in late stage colorectal cancer. It works by interfering with blood supply to cancer tumours, and has been shown to cause tumour shrinkage and delayed progression. It is now being put through clinical trials for a variety of cancer types, in particular against advanced Non Small Cell Lung Cancer. Augmenting standard chemotherapy with Bevacizumab, increased overall the survival period from an average of 10.2 months to 12.5 months^c. Whilst this may seem a modest gain, it is nevertheless a significant improvement.

Different stage trials are now under way for most major types of cancer, with a variety of drugs being developed by the major players in the pharmaceutical industry.

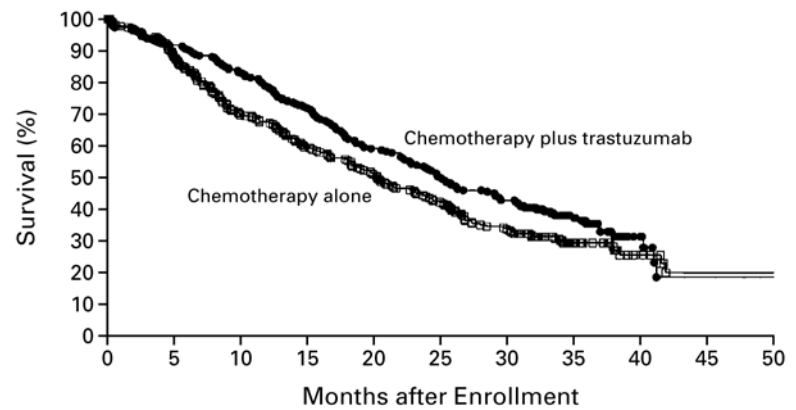
Cost

The research and development of these drugs costs the pharmaceutical industry an enormous amount of money. Some experts put a figure of \$800 million on the cost of developing a drug and bringing it to market. So it is hardly surprising that these highly engineered drugs are not cheap.

The key issue in the UK is who is going to pay for them.

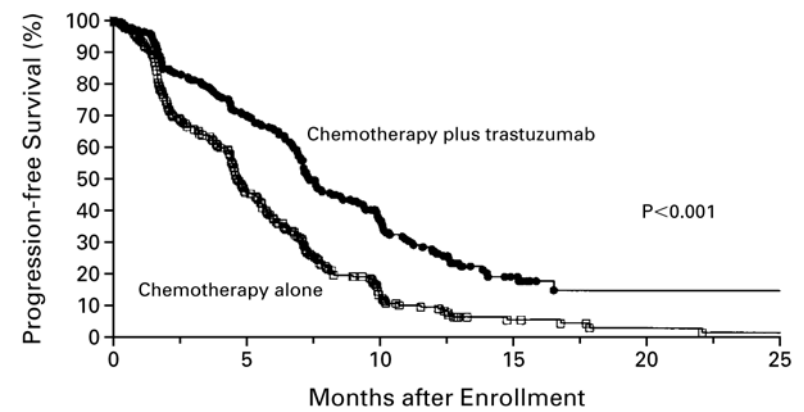
Herceptin (Trastuzumab) has been licensed for use in advanced cases of breast cancer in the UK since March 2002. The HERA trial remains ongoing, so it may be some time before Herceptin is licensed for use in early breast cancer here.

Graph 1 Randomised clinical trial of Trastuzumab



Source: Copyright© 2001 Massachusetts Medical Society. All rights reserved.

Graph 2 Randomised clinical trial of Trastuzumab



Source: Copyright© 2001 Massachusetts Medical Society. All rights reserved.

At a current cost of £27,000 to £30,000 a year, this is clearly a very expensive drug. Cancer experts predict that if Herceptin is licensed for the treatment of early case cancers the government would have to consider financing it as a special case. To do otherwise would put health authorities' existing budgets under significant pressure.

There has already been one case reported in the media of a young mother planning to sell her house to pay for the drug, having being quoted £27,000 for a year's private treatment. The case was raised in Parliament by her MP.

Implications for Insurance Products

Survival Rates

Cancer is responsible for more than one in five deaths among the over 65's. If survival rates were to increase, and people live longer, then a major breakthrough in the fight against cancer would have a significant impact on standard annuity experience.

Impaired Annuities

The pricing of impaired annuities relies on underwriters estimating the expected survival of the impaired life. In advanced cancer cases, MABs such as Bevacizumab and Tositumomab have pricing implications. Underwriters need to be aware of these potential treatments and factor in any anticipated improvements when estimating the survival times of severely impaired individuals.

Term Assurance

Cancer accounts for one in three deaths of adults under the age of 65. This is a substantial number of deaths. If it were to be reduced this would have pricing implications in the very competitive term assurance market.

Preliminary calculations now being reported suggest that Herceptin could save 2,800 women a year in the UK. If this turns out to be a fair estimate, then Herceptin alone could reduce mortality rates by several percent for females aged between 35 and 54.

Critical Illness

Whilst at first glance MABs would not appear to have any obvious implications for CI products, they could have a significant impact indirectly. Because MABs are highly sensitive and efficient in tracing cancer cells, they can be used as diagnostic tools for late stage cancers. It is not unreasonable to suppose that MABs could have applications in cancer screening tests. Any successful screening program would increase CI incidence rates through earlier initial diagnosis.

If major advances were to leave certain cancers looking less life-threatening than before, CI payouts would no longer serve the purpose for which they were originally intended. As the industry is well aware, this kind of risk will always exist if CI policies continue to pay out on current medical definitions rather than the underlying severity of the condition.

Private Medical Insurance

Along with heart operations and psychiatric cases, cancer claims are already one of the three main causes of very large PMI claims. The main issues around MABs like Trastuzumab from a PMI point of view are the cost of the drugs and the question of who pays for them.

PMI providers must be concerned about the prospect of paying for expensive drugs that will not be available, at least initially, on the NHS (in addition to the standard surgical and chemotherapy costs). For earlier stage cancers, where these drugs could bring about long-term remission, there is also the issue of whether the condition is no longer acute but has become chronic. The PMI market already suffers from rising premiums due to medical inflation. Policyholders are likely to request these expensive treatments more in the future, so providers need to formulate a coherent strategy.

Associated concerns include the fact that patients will continue to claim for the cost of these drugs for many years and will require constant monitoring and potentially further treatment for side effects and other conditions as they arise.

Income Protection

The implications for IP are potentially less significant. Cancer claims will be diluted amongst other conditions to a greater extent than for, say, term or critical illness. Whilst some claimants will no doubt survive longer than they would have done without biochemical therapies, others may potentially recover and return to work.

The Future

With drug companies concentrating their focus on developing novel and biologically targeted drug therapies, cancer therapy technology will only continue to improve. It is increasingly likely that we will see better and more successful drugs that significantly alter the prognosis for patients with cancer. The initial results for Stage III Trastuzumab trials around the world suggest this process could already be beginning.

Insurers should closely monitor the potential effects of cancer breakthroughs on protection products – not only in terms of raw mortality rates but also for impaired annuities, claims in PMI, IP experience, and the new technology's as a marker in diagnostic testing and how this could lead to a surge in early CI claims. There is also the possibility that new treatments could reduce the severity of certain cancers which, under current definitions, would still trigger a CI claim.

James Shattock

Assistant Manager – Actuarial Marketing

Cancer accounts for one in three deaths of adults under the age of 65.

Sources

- a Cancer Research, 2005
- b Clinical Care Options for Oncology – Trastuzumab Following Adjuvant Chemotherapy Prolongs Disease-Free Survival Patients With HER2-Positive Breast Cancer
- c Clinical Care Options for Oncology – Bevacizumab Added to First Line Paclitaxel/Carboplatin Improves Response and Survival in Patients With Advanced Nonsquamous NSCLC
- d Department of Health, 2005

Stop Press...

"I have decided that an early referral of Herceptin is necessary to allow NICE to begin preliminary work on the development of advice to the NHS on the clinical and cost effectiveness of these treatments and react as soon as possible after the drug is licensed."

"The manufacturer is analysing the trial results and if those are encouraging, we expect them to apply to the MHRA for an extended license for the drug. Once an application is made it could take as little as two to three months for an extended licence to be issued."

Patricia Hewitt

Secretary of State for Health. (20/07/05)^d

Diabetes

The following is a synopsis of a talk presented by Dr Bill Monday who is the Chief Medical Officer at Hannover Life Re South Africa. The talk was given at the International Underwriting Congress (IUC) which was held in Geneva in April of this year covering the latest on mortality and morbidity issues relating to metabolic syndrome and diabetes.

Diabetes has been around the block so to speak. The Egyptians alluded to it, Hippocrates discussed it, Hemingway had it. Never before though in Human history has diabetes been so prevalent in society.

It is now a pandemic of the 21st century along with its partner in crime, obesity. The topic of obesity has recently fallen under the spotlight so let us discuss diabetes against the framework of life insurance.

Underwriting departments will be underwriting numerous diabetic applicants on a daily basis if the present prevalence of diabetes is considered. In 2004 there were 1.8 million or 3% of the UK population living with diabetes. By 2010 this figure is expected to reach 3 million. Britain is not alone. In the USA there are 17 million people living with diabetes. In 1960 2.6% of the American population over the age of 45 had diabetes. By 1990 this figure has risen to 7%.

There are two main reasons why the incidence and prevalence of diabetes is increasing.

The first is the ageing of the population in England. As an example in 1911 there were 102 Centenarians in the UK and in 2036 it is projected there will be 40 000! (That's enough to give Her Majesty writer's cramp signing all those congratulatory wishes) Ninety five percent of diabetics develop diabetes in middle and older age. Historically this type of diabetes has been known as Type 2 or Non Insulin Dependent Diabetes Mellitus (NIDDM for short). As more people survive to middle and old age it is expected that the incidence of diabetes will increase. The second cause for the dramatic increase in Diabetes is perhaps more alarming as it is, to some degree, preventable. It is obesity. Britain has the fastest growing rate of obesity in the developed world and the risk of



developing Type 2 diabetes increases by up to ten times in people with a body Mass index of more than 30. (If you are worried now and want to calculate your Body Mass Index or BMI, you take your weight in Kilograms and divide it by your height in metres, squared. As an example if you weighed 80kg (196lbs) and you were 1.8 metres tall your BMI would be $80/1.8 \times 1.8$ which gives a BMI of 24.7.

(Please refer to Issue 19 (March 2005) 'Epidemic Proportions?' for more information on Obesity).

From an individual and macro-economic perspective the above trends in the increase in diabetes are very worrying indeed.

Diabetes if not well controlled has the potential to cause considerable morbidity and unfortunately does have the potential to reduce life expectancy by up to 10 years.

From a macro-economic point of view the NHS spends approximately 5% of its budget or £10 million per day treating diabetes. It is projected that in 2040 the annual health care costs of diabetes alone will cost £2.2 billion pounds. No wonder the government is pushing fitness and Jamie Oliver is punting healthy school dinners! If left unchecked this rampant epidemic of obesity and diabetes is going to hit hard both medically and financially.

From an underwriting perspective diabetics who are individually underwritten for life insurance may attract a small additional loading to an outright decline. It really boils down to adequate management and control

of the disease as well as the presence of any complications relating to diabetes.

Diabetes affects the large and small vessels of the body. In Type 2 diabetes resistance to the effects of insulin leads to the pancreas producing higher and higher levels of insulin in an attempt to maintain glucose at a normal level. (This compensatory mechanism eventually exhausts the cells of the pancreas producing insulin and as insulin levels drop the diabetes becomes more overt.) Without going into detailed biochemistry, these high circulating levels of glucose and insulin provide the right milieu for cholesterol to be deposited in the arteries and for clotting to occur more readily within the arteries itself. The consequence of this is occlusion of the arteries and when it involves large arteries it causes heart attacks, strokes and peripheral vascular disease. When small vessels are involved in the eyes and kidneys it causes blindness and renal failure. These therefore are the dreaded consequences of diabetes namely heart attacks, strokes, peripheral vascular disease, blindness and kidney failure.

What you don't need as a diabetic are additional risk factors for any of the above events such as heart attacks and strokes. These additional risk factors include high blood pressure, raised cholesterol, smoking and any additional factors that cause increased clotting within the blood. It is however an unfortunate fact that individuals do indeed have multiple risk factors for heart disease and stroke. Take a middle aged man in a sedentary job. He puts on weight in middle age and develops diabetes. His excess weight also causes hypertension.

His unhealthy diet leads to elevated cholesterol. In this scenario you already have three major risk factors for a heart attack or stroke namely diabetes, hypertension and raised cholesterol. This triad of risks form part of a syndrome known as the 'metabolic syndrome' and these individuals are at high risk for heart attack and stroke. If you add smoking to this scenario it becomes a case of not 'if' they may have a heart attack in the future but 'when' they are going to have their heart attack.

I keep mentioning heart attack and stroke in this discussion and there is good reason for this. Coronary artery disease accounts for 75% of all deaths in diabetics and stroke accounts for 15%. In the USA patients with diabetes account for 25% of the nearly 1.5 million coronary revascularizations performed each year in the USA. Unfortunately diabetics also experience worse outcomes from these procedures than non diabetics.

What can be done about these high risks in diabetics? Is there any light at the end of the tunnel? The answer is most positively yes! First and foremost is obviously preventative measures. Do not allow yourself to become obese! It is time to take out those trainers and hit the road!

For those with diabetes, the outlook has been improving since 1922 when insulin was first used as a treatment. Large trials in recent years have highlighted just how much impact good control of glucose levels and other risk factors may have on reducing future complications. Effectively controlled Type 2 diabetes can reduce the risk of:

- Heart disease by 44%
- Stroke by 46%
- Kidney by 33%
- Eye disease by 33%

What is good control in a diabetic? What other risk factors have to be addressed and what is optimal treatment in a diabetic with established cardiac disease?

First and foremost the blood glucose level should be maintained at a level as close to normal as possible. A blood test called an HBA1C gives an indication of the average blood concentration in the preceding weeks. This blood test should at least be below a level of 8 and optimally should be around the 5-6 mark. A diabetic should not smoke at all! Cholesterol should be treated if at all elevated and brought down to a level below 5.2. Blood pressure should be controlled and brought down to a level of 120/80. To be more specific certain classes of anti-hypertensive drugs should be used in diabetic patients especially diabetics with kidney involvement. These patients should be receiving ACE inhibitors as they have a protective effect on the kidney. Weight loss should occur if needed. All this will be taken into consideration at the underwriting stage when assessing future risk.

Long term studies are now available to show what is the best treatment for diabetics with coronary artery disease. This is obviously an important area given the extent of cardiovascular disease in diabetics. Coronary Artery Bypass Grafting appears to be more beneficial than using multiple stents in diabetics. If a stent is to be used in a diabetic the latest stents known as Drug Eluting Stents (DES) should be used. These new stents release an immunosuppressive drug that prevents reblockage or restenosis of the vessel which has plagued stents in the past. Diabetics should be considered for drugs known as beta-blockers after having a heart attack.

These are all important points when using evidence based medicine to assess future risk of morbidity and mortality.

What of the future?

In March this year the popular press in the UK reported on a certain Mr. Richard Lane who successfully underwent a new form of pancreatic transplant and was cured of his diabetes. In essence the cells that produce insulin were extracted from cadaver pancreases and injected into Mr. Lane's liver. The cells then started producing insulin in Mr. Lane and took over this function from his failed pancreas. This is a great step forward but it is prohibitively expensive, requires organ donation and requires ongoing use of immunosuppressive drugs which have their own risks. Mr. Lane was experiencing great difficulties controlling his diabetes prior to surgery and had failed all other treatment options. In other words this surgery at present is for the select few. What is promising in the future is stem cell research that will provide a source of insulin secreting cells without relying on cadaver organs and new ways to rejuvenate the failing pancreas cells within the body. Enhancements to insulin pumps that are placed within the body will occur and improvement in delivery of oral and nasal insulin. Diabetics will no longer have to prick themselves to test their glucose, they will have an instrument that will read the sugar level through the skin.

Underwriting diabetes, especially the diabetic with multiple risk factors is challenging to say the least. It behoves us to stay abreast of evidence based medicine to be in a position to best assess the future risk in such applicants. New treatment modalities and protocols will allow us to assess this risk more favourably. In turn the diabetic client must ensure that they do their best to reduce their risks for cardiovascular disease and renal disease by optimally controlling their diabetes and the other associated risk factors such as hypertension, elevated cholesterol, obesity and smoking. Woe betides the smoking diabetic who has a double cheeseburger and a pint and applies for insurance. It just isn't going to happen.

Dr Bill Monday
Chief Medical Officer
Hannover Life Re South Africa

We hope you enjoy **In Focus** and we welcome your feedback, please forward any comments to Kirsteen Grant. If you wish to be added to our mailing list contact Kirsteen on 01344 846833 or email uk.marketing@hannover-re.com.

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