Mr Hodgkin's disease

Peter McIntyre

Volker Diehl cultured the cells that characterise Hodgkin's disease when everyone else had failed. He has high hopes that molecular medicine will throw light on many questions that remain unanswered. But he stresses that it is the disciplined clinical work on the wards that saves lives in this disease, where the line between cure and fatal damage can be very thin.

Hodgkin's lymphoma is responsible for less than 1% of cancers in Europe. The cure rate in early disease is 98% and in advanced disease tops 85%. End of story. Move on.

Or put it another way. Hodgkin's disease is an unsolved detective story with subplots of mustard gas, sex, fraud and religion; a paradigm for other cancers in research and treatment; a cancer where the cure can be more dangerous than the disease; a story where the final chapter remains to be written.

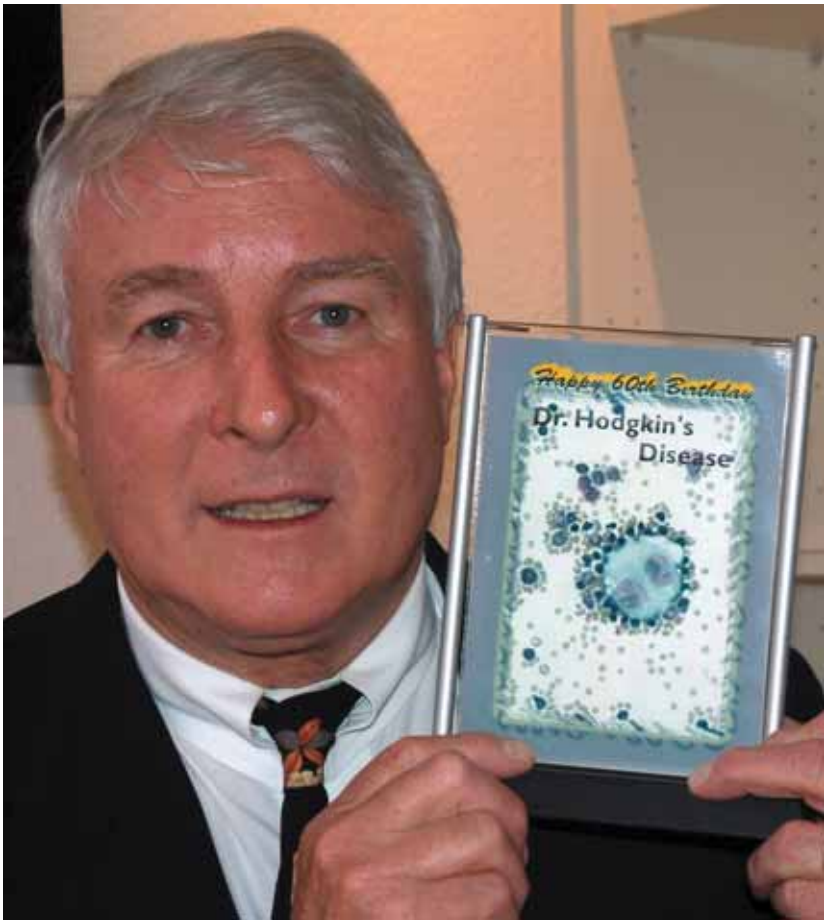
The search for understanding and treatment has inspired doctors and scientists in Europe and America over many decades. In recent years, the torch has been carried by Volker Diehl at the University of Köln, who developed the German Hodgkin Study Group and became known as "Mr Hodgkin's Disease".

As a researcher, Diehl made critical developments in understanding a virus associated with Hodgkin's; as a laboratory craftsman he succeeded in culturing the elusive Reed-Sternberg cell; as a clinician he has improved the treatment of advanced disease. Today, when it is possible to make a successful career studying a single characteristic of a single chromosome, the breadth of his work seems astounding. He is still looking to the future, to reduce the need for cocktails of poisons.

In the 19th century, Thomas Hodgkin carried out post-mortems at Guys Hospital, London, on children and adults who had died following swollen lymph nodes, fever and night sweats. He ruled out tuberculosis and syphilis, but in his 1832 paper, On Some Morbid Appearances of the Absorbent Glands and Spleen, said that on treatment, "I must confess that I have nothing to offer."

About 70 years later, Carl Sternberg and Dorothy Reed described the giant (Reed-Sternberg) cells responsible for Hodgkin's – a disease which, without treatment, has a 95%–98% mortality rate within five years.

Treatment progressed more or less by trial and error, with radiotherapy tried as early as 1902 and nitrogen mustard being tried after doctors noted the effects of mustard gas in World Wars I and II. (In 1943, 80 US sailors



PETER MCINTYRE

Diehl was the first to culture the fragile Reed-Sternberg cell. This certificate, which carries an image of the cell, was presented to him by a group of American pathologists

survived a German bombing attack on their convoy in Bari Harbour, but died later because one of their ships was secretly carrying mustard gas – a banned substance. Autopsies revealed how the gas attacked white cells and lymph tissues.)

By 1963, Easson and Russell of Christie Hospital, Manchester, England, summed up the hopes of a generation, in a *British Medical Journal* article entitled The Cure of Hodgkin's Disease.

In 1966, fresh from graduation at Freiberg Medical School, Diehl went to Pennsylvania to work with Werner and Gertrude Henle, alongside Harald zur Hausen, another young man destined to make his mark on the world of cancer (see Masterpiece, *Cancer World* issue 7). The Henles, Jews who had escaped from Hitler's Germany, were researching Epstein-Barr virus and recruited these two bright young researchers from Germany to help them. They knew that EB virus was a factor in Burkitt's lymphoma in Africa. Diehl's task was to find out what it did in the US. The Henles were tough bosses. Werner refused to talk to Diehl for six weeks until he learnt a few words of English. Gertrude worked her staff hard and hated it when anyone was off sick.

A METHODICAL SCIENTIST

When a young technician, Elaine Hutkin, failed to arrive one morning, Diehl called her at home and suggested that she drag herself into work. She arrived looking terrible, with a rash, huge lymph nodes, a sore throat, 40 degrees of fever and a yellow colour – the classic

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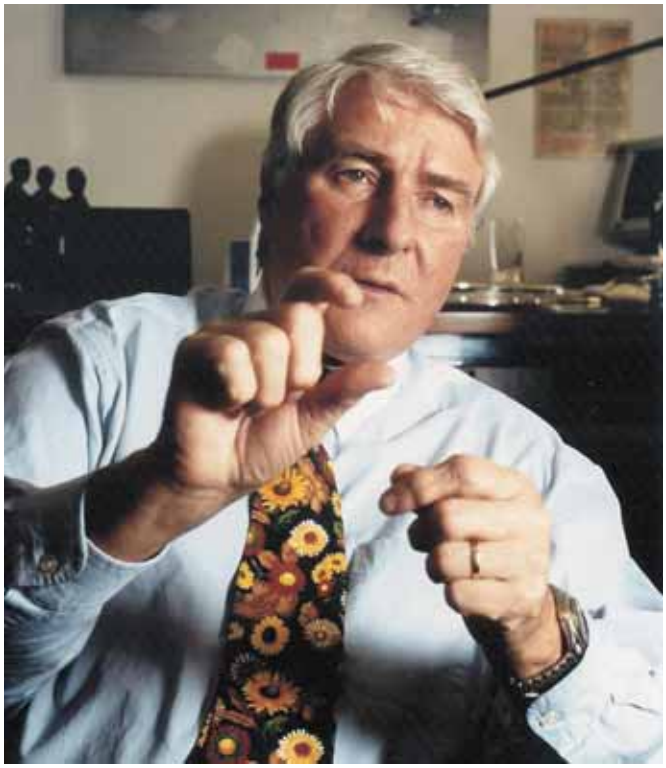

symptoms of infectious mononucleosis. Being a compassionate young man, Diehl gave her some medicine and sent her home. Being a methodical scientist, he took a blood sample before she left.

Everyone who worked at the lab had already routinely given blood for tests. Elaine's stood out because she was one of the few who did not have antibodies for Epstein-Barr virus, often a sign of a protected childhood. Five to ten days after her second sample was taken, EB virus cells started to grow. Mononucleosis is known as "kissing disease", and Diehl knew that Elaine had a new boyfriend. He felt certain that she had acquired the EB virus from her boyfriend, and that this had transformed her lymphocytes.

The Henle team contacted Yale – knowing that University doctors routinely took blood samples when students arrived, and asked for samples from all the students who developed mononucleosis, both pre- and post-illness. The results were a tribute to protective parents and to delayed passion. "These were often girls who had an academic mother or father, who were not allowed to go out and play with other children in their local area. Then they came to Yale and met other students and for the first time kissed with an intensive exchange of cells. We got about 40 pre- and post-illness sera, and in five days we knew that all these mononucleosis kids were EB negative beforehand and EB positive after the illness."

Diehl recalls the excitement of the results, showing EB virus as a causative agent in mononucleosis. In 1968, he got a scholarship to Kenya from the US National Cancer Institute (NCI) to see whether patients with Burkitt's lymphoma also showed signs of mononucleosis. This project turned to dust within days of arrival. The mission doctors had never heard of infectious mononucleosis. "I said it is a triad of very heavy tonsillitis, lymphadenopathy, fever and a big spleen and a big liver," and they laughed". At a 5 am clinic, he found hundreds of patients with malaria and hook worm, with enlarged lymph glands, tonsillitis, anaemia, fever and an enlarged spleen. As it turned out, none had mononucleosis, because they'd all been exposed to it at a very early age. The research was over before it began.

"I was very disappointed. I said I wanted to stay in this beautiful country. I told the flying doctor service that I would operate with them if they would help me in what I wanted to do."

He decided to collect sera to see whether people who developed Burkitt's showed a change in their EB virus status. This was a typical Diehl strategy: combining lateral thinking

Diehl's 3,000 serum samples became the basis of the current huge WHO database

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with painstaking (some might say, tedious) field-craft. Over the course of a year, he criss-crossed Uganda and Kenya, collecting 3,000 serum samples. This became the first WHO serum collection, the basis of the current huge WHO database, the original samples of which are still used for HIV studies.

The following year, Diehl went to Sweden, arriving for the second time in a country where he spoke not a word of the language. He trained in radiotherapy and chemotherapy (and learned Swedish) at Radiumhemmet and the Karolinska Institute.

Coming across Hodgkin's disease for the first time, he began, like many others, to try to culture the Reed-Sternberg cell, and with the same lack of success. "Once you can get the tumour cell out of the body and put it in a tissue culture, you can study it day or night. This Reed-Sternberg cell is very intelligent, but very fragile, and does not want to be examined; it will die in 20 minutes when you take it out of the body. In the body, it calls feeder cells, small lymphocytes, to protect it from the body's killer cells. But as soon as you put it in a little Petri dish, the culture dies."

In Hanover, he continued to try to culture the cell, focusing on those that looked right – like owl monkey cells, with many nuclei and very large nucleoli. They also had to be monoclonal and aneuploid. In 1978, at the 428th attempt, he succeeded.

"This could only have been a Japanese or Teutonic endeavour," Diehl says, with a hint of self-mockery. "A British or American scientist would never have done it. You needed someone who would do it again and again."

Even today, when there have been maybe a quarter of a million attempts to culture Reed-Sternberg cells, there are only 14 cell lines in the world. Five of these were cultured by Diehl.

Packing his cell line into a basket, Diehl went to show them in America, which greeted him with scepticism. Henry Kaplan at Stanford sent him to John Long at Harvard, who had also cultured the cells. Diehl was made welcome, but when he offered to exchange cell cultures, Long turned evasive. The laboratory was in a mess. He was very busy. Rebuffed, Diehl returned to Germany, just before Long was exposed by an assistant as a fraud. His Reed-Sternberg cells did not just look like owl monkeys; they actually were brown-footed owl monkey cells!

Diehl learnt an early lesson. "I always tell my students; listen to nature and our experiments will tell us whether our hypothesis is right or wrong, but never force nature. I always tried to devise subtle experiments that everyone could follow and repeat. I gave my cells away freely so that other people could repeat and correct what I had published, and in all my life I never had to revoke any findings."

At this stage in the late 1970s, radiotherapy in early (stage 1 & 2) Hodgkin's achieved a cure rate of 70%–80%, while chemotherapy cured 30%–40% of people with late-stage disease. Henry Kaplan's team introduced the first effective chemotherapy regimens and devised a classification system still used to stage Hodgkin's disease, according to the location and number of tumours.

A 14-day regimen of MOPP (mechlorethamine, vincristine (Oncovin), prednisone and procarbazine) was introduced in 1964 by Vince DeVita at the NCI. (Mechlorethamine, the "nitrogen mustard" was later replaced by cyclophosphamide, and MOPP became COPP.) In 1973, Gianni Bonadonna from the Italian National Tumour Institute at Milan introduced ABVD – doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine – as an alternative, and this became the gold standard treatment.

"Randomisation was unknown in Germany, and people said you are treating us like rabbits!"

Clinical trials

Diehl had been impressed by the way that Stanford conducted clinical trials, and when in 1978 the German government set aside money to improve research, Diehl and renowned radiotherapist Karl Musshoff started the first Hodgkin's study in Germany. In the first year, they had just five patients. "Randomisation was unknown in Germany, and people said you are treating us like rabbits! There was a 25% refusal rate by patients and doctors because of randomisation. A politician came from Berlin with her young son and she started to cry. She said she was a practising Catholic and didn't want to interfere with God's work. I said to her 'If you think that God really is sovereign, then he will know exactly into which arm of the trial he puts your son'. Others asked me 'What would you do?' I said that if I knew which of a, b, or c was better, it would be unethical to do the trial."

The arguments seemed to work. The German group is now the largest Hodgkin's study in the world, with 1,600 new patients a year, including 80% of German patients. The refusal rate is below 1%.

Amongst many developments, there have been two headline achievements.

The first, published in the *New England Journal of Medicine* in 1998, was a prognostic scoring system, which identified seven risk factors that make it less likely that a patient would remain free from progression of disease following treatment. With none of these factors, Diehl calculated that 84% of patients would remain disease free. With five or more factors, only 42% of patients would remain disease free.

Diehl and his colleagues also worked on improvements to chemotherapy. In the 1990s, the Köln team introduced a BEACOPP combination of drugs, combining drugs from COPP and ABVD, but replacing vinblastine and dacarbazine with etoposide. The timescale was concentrated, giving doxorubicin (Adriamycin) more frequently. Following publication in the NEJM in June 2003, escalated dosage BEACOPP is becoming the new gold standard to treat advanced disease. Diehl's team reported a 20% better tumour-free survival rate with escalated BEACOPP than with the alternatives. "This means that of 100 young patients 11 survive better with the BEACOPP escalated than with the COPP ABVD."

Although BEACOPP has gained ground, it is still not widely used in the US or in the UK, and an EORTC (European Organisation for Research and Treatment of Cancer) trial is currently comparing this regimen with ABVD in stage 3/4 patients. BEACOPP is not suitable in early-stage Hodgkin's, or in patients older than 60.

The high cure rate for Hodgkin's throws the spotlight onto the adverse effects of treatment – both radiation and chemotherapy. If, after treatment, a patient remains free of disease for 12–15 years, the risks from the after-effects of treatment start to outweigh the risk of death from Hodgkin's.

Extended field radiation used in the 1970s and 1980s raised a young woman's chance of later developing breast cancer by a factor of 90. The radiation dose has been reduced and organs are better shielded, but there are still many radiation-induced problems. Chemotherapy induces leukaemia, non-Hodgkin lymphoma, lung, breast, gastric and thyroid cancers, melanomas and sarcomas of bone and soft tissue. There is also an increased risk of cardiac and pulmonary disease.

Diehl says that balancing benefits and dangers requires not only the right treatment regimen, but also experience in treatment. "Effectiveness and lack of damage – this is always the balance. The therapeutic window is very small.

"With ABVD you get 40% regrowth of the tumour. With BEACOPP we get only 10% regrowth of the tumour. But BEACOPP creates infertility in boys in about 90% of cases and induces 1%–2% acute myelocytic leukaemia. Despite this, we still have an 11% higher cure rate after seven years follow-up, including these negative effects. This is the reason why I propose treating only advanced disease with BEACOPP. Early disease we treat with ABVD and radiotherapy.

"BEACOPP is a great poison. It is terrible. I would like to have something better! Sometimes I wake up in the night and ask what will happen to my young patients in 10 to 15 years. These are my nightmares. We propose that you should not treat advanced Hodgkin's disease if you do not have experience with leukaemia or a very aggressive oncology treatment, so you have platelet support and know what to do when you get septicaemia."

Because the cure rate is about 98% in early stages, in many countries Hodgkin's treatment is often in the hands of private doctors rather than cancer centres.

"Everybody wants to treat early disease because it is easy. A young, healthy, beautiful, rich patient says 'I have a lymph node here and I feel a little bit scratchy and I am itchy.' The doctor says 'You may have a virus.' After six weeks when the load has not gone away and the fever comes and goes, he says 'We should do a biopsy.' Then he finds that it is not just a virus, it is Hodgkin's disease. If you find it is stage 1, you give two courses of a very moderate ABVD chemotherapy and a little bit of radiation and you have a 98% cure rate. In an intermediate stage (two lymph nodes) you give four courses of

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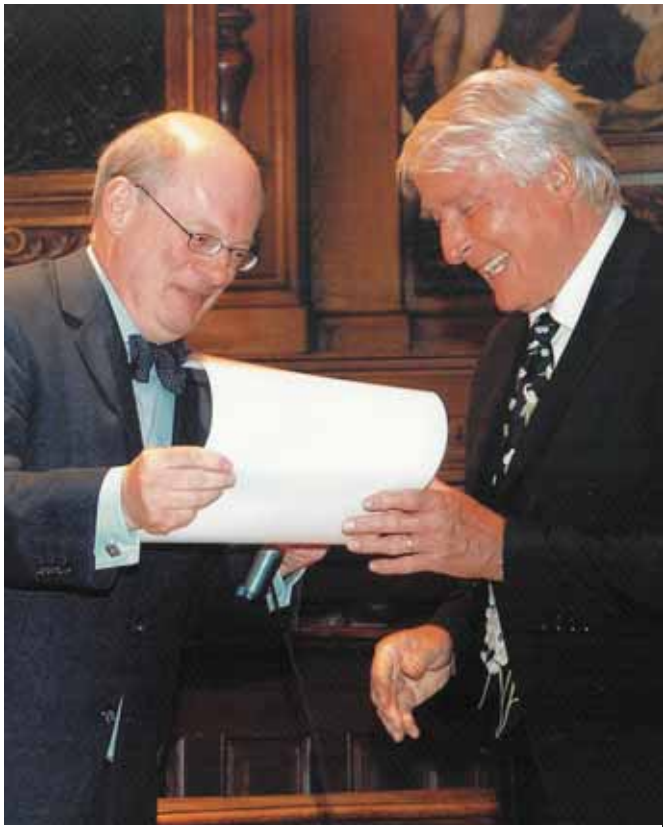

Receiving an honorary doctorate from the University of Heidelberg in July 2005 from geneticist, Klaus Bartram

ABVD and a little bit of radiation and you have about 89% to 95% cure.

"But if you get another patient who comes with Hodgkin's in the lymph nodes and in the spleen or the liver, he is very sick. If he has a stage 4 disease, he is very sick, has lost 10 kilos and has fever and night sweats. You had better take him to the ward and treat him with BEACOPP escalated, and you had better be very careful.

"When you treat him he really gets sick. BEACOPP is not a soft option. It is quite aggressive, with 2% early death rate due to the treatment if you do not do it right. You have to really know how to do it."

However, Diehl says that doctor-induced deaths have fallen to around 1% of patients, and that the cure rate in advanced disease has risen from 30% three decades ago to 85%–90% today with chemotherapy and radiotherapy.

Although he has high hopes for molecular medicine and targeted treatments, Diehl feels that funding neglects the painstaking clinical research that makes such a difference. "My molecular work was paid millions of euros from the Deutsche Forschungsgemeinschaft (German Research Foundation). We had a world-leading group of 40 people working on molecular research and Hodgkin's disease. I did not cure one patient with that. But we cured many, many patients by our disciplined clinical work with practitioners, the small hospitals and the doctors."

Expertise in the German Study Group is so high that it is bringing a reversal of policy by the German medical insurance companies. "Three years ago, the insurance companies and the government said that if a patient is in a clinical study, insurance money will not pay for it, because this is science, not medicine. This year an insurance company said we want every patient who comes down with Hodgkin's disease to be put into your study – otherwise we won't pay for them. The insurance company said this is a blueprint for all the big killing diseases for lung cancer, and so on."

Unanswered questions

But Hodgkin's still keeps its secrets. Diehl says, "My lifetime is Hodgkin's disease, and I am called Mr Hodgkin's disease, but I still don't know the answers to many questions."

Why, for example, is it the most common lymphoma in young adults in Sweden, but rare in China and Japan? There is clearly a genetic

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predisposition, as shown by a study on concordant twins in the US. But second- or third-generation Chinese in Vancouver or Hawaii have the same risk as the rest of the population, so there is also an environmental factor.

Then there is the strange age profile, with a small number of childhood cases, and then a cluster in the twenties and a second smaller peak between the ages of 50 and 60. Are these diseases the same disease or different? There is also the oddity that Hodgkin's has such a low proportion (1%–2%) of cancer cells in the 'tumour', with the rest made up of fibrous reactive tissue.

And still puzzling, after all these years, is the role of Epstein-Barr virus. Half of Hodgkin's patients have the EB genome in their tumour cells, and the other half don't. But a disproportionate number of patients had mononucleosis in childhood.

Diehl and his friend zur Hausen, the expert in viral links to cancer, discuss this endlessly. Diehl has a theory that the EB virus plays a "hit and run" role, introducing cancer cells which break free before the T-cells kill off the EB virus. "It makes the drop, and is so clever that it loses the virus and the genome has gone and there is no EB virus."

zur Hausen does not agree, saying that if the virus were the cause, it would be found. He and his wife, Ethel-Michele de Villiers, professor of virology at Heidelberg, have suggested a TT virus as a candidate for cases where EB virus is absent. Diehl is sure that molecular science will soon reveal the answers.

Hodgkin's has by no means been Diehl's only work. From 1982 to 2003, he was chair of internal medicine at Köln University, in charge of 120 beds, covering intensive care, nephrology, gastroenterology, rheumatology, immunology, haematology and oncology, as well as teaching 300–400 students. In 2003, he became the

Playing in a string quartet in 1955, during his time in Kenya. Diehl is on the *far left*

founding director of the Heidelberg Comprehensive Cancer Centre, aiming to boost transnational research and working with 15 university departments and several hospitals around the Deutsches Krebsforschungszentrum.

He was involved in the treatment of Russian politicians and the President of Hungary, President Antal. He now teaches for about a week each year in Russia.

He has experience both as a specialist and as a generalist, and when asked which is better, his daunting answer is "both". "I told my students to be a generalist in the phenomenology and the appearance of a disease. Know that when you have a pain in the back it could be a heart attack, it could be a pulmonary embolism or it could be kidney disease. But then when you dig down and get closer to the cause, you have to specialise. I told them never to be a clinician without having had some time in very good research, so that you know about the causes of disease and the pathways of the molecules. I tried to be a broad-minded doctor who knows the differential diagnosis of almost all the internal medicine diseases, but also a deep-rooted scientist who could be a world master in one field."

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