The Cancer Revolution

Every week, it kills more than 3,000 people in Britain. But the news is encouraging: Britain's two largest cancer charities are about to merge, and Sir Paul Nurse and Tim Hunt are about to receive the Nobel Prize.

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The story of Gregor Mendel is one of the most romantic that science has to offer. In 1854, an ambitious abbot at a cold monastery in Brno, Czechoslovakia, started devoting his spare time to the study of pea-breeding. He was interested in inheritance - why some peas came out yellow and some green, why some pods grew longer than others - and his work on hybrids established several important principles of heredity. Though he was largely dismissed at the time as a harebrained obsessive, his work gained him the posthumous reputation as the father of genetics.

His monastery was built in 1322, and is currently something of a tourist attraction. It is also crumbling, and needs large sums to repair it. To this end, Sir Paul Nurse, the director general of the Imperial Cancer Research Fund (ICRF), has been attending meetings to raise funds and awareness of its plight. He's on a distinguished committee: another member is Jim Watson, the American who won a Nobel Prize for his co- discovery of the molecular structure of DNA.

Two months ago, on Monday 8 October, one of these fundraising meetings at an architect's office in London's Warren Street was interrupted by a receptionist with a request for Nurse to switch on his mobile phone. He left the room and heard a distorted piece of voicemail with a Swedish accent. 'I thought it was telling me I'd won the Nobel Prize,' he remembers, 'but the message was so broken up that I had to play it back three times. At first, I thought it might possibly be a Swedish journalist asking me to comment on the prize. After three plays I'd pieced together enough to think I probably had won, but I couldn't make out the name of the other winners. So I went back to the meeting and said, "I think I've won the Nobel Prize," - which sounds like a stupid thing to say. People, of course, were very pleased, but there was still an element of doubt.'

Nurse left the meeting and went back to his own office overlooking Lincoln's Inn Fields. He phoned his colleague Tim Hunt, who had already left a message saying that he thought they may have won it together. 'But when I called him back he was incredibly sceptical, and said he wouldn't believe it until he saw it written somewhere. And then someone from my office came in to say it was on the Nobel site on the internet.'

This is how good news is spread these days - on cellphones, on websites. Modern technology has made the dissemination of knowledge a smoother and more confusing thing; messages get through, but they can take a little while to

understand. Paul Nurse's important work on the mechanics of human cell division - the work that won him the biggest prize in science and a call from the producer of Desert Island Discs - was initially conducted in the 1980s, but it has taken the Nobel people this long to acknowledge it.

This is not unusual. 'I did think there was a chance sometime in my life,' Nurse says. 'But it could just as easily have been when I was 72.' At present he is 52, has his silvery-grey hair done in an ageing-popstar way and rides a big motorbike - a well-cultivated non-labcoat persona that has turned him into what the Americans like to call a poster boy of the British cancer world. Spending time with him in the sofa area of his office, it is possible to forget that he is among the most brilliant research scientists of his generation.

Nurse says that he was first alerted to the possibility of winning the Nobel Prize for Medicine when he was awarded two other prizes that often serve as precursors, the Gairdner from Canada and the Lasker from the United States. 'If you win any of these other things, nobody could give a monkey's,' he observes of the wider world. 'But if you win the Nobel, you move up from the basement to the 25th floor overnight.'

The prize, which has been given jointly to Nurse, Tim Hunt and Leland Hartwell of the Fred Hutchinson Cancer Research Center in Seattle, will officially be awarded tomorrow in Stockholm after a week of Swedish dinners and receptions. Each will receive a little over £200,000, some of which Nurse will spend on a new bike. After this, he hopes his life may return to normal and the relatively quiet task of increasing our understanding of a group of diseases that continues to kill 3,000 people in the UK each week.

Despite its huge complexities, cancer research is not a theoretical problem to those who work on it. Nurse's father-in-law died of bladder cancer almost 10 years ago, his first personal experience of the disease. Then a good friend of his called Keith Palmer was diagnosed with leukaemia. 'I was at university with him. He fell ill at an age when the outcome wasn't that rosy, and I spent a lot of time with him because it wasn't clear whether he'd pull through or not. But he did, which was fantastic, and he's been clear now for five years or so. Seeing it right in your face does make a difference, and it does change you. My work is right at the front end so I'm not dealing with patients, but you do realise that what you contribute does help eventually.'

Nurse's contribution did not begin with cancer in mind. His postgraduate work at the University of East Anglia was mostly concerned with what distinguishes living things from non-living. One basic property is the ability of a living object to reproduce itself, and the simplest example of that was the reproduction of a cell, the basic unit of life. His experiments were conducted on a form of yeast, which is the simplest example of cell reproduction in a big organism. He had known since school that uncontrolled cell division gave rise to cancer, but didn't think that his work on the molecule that produced bread and beer would yield any particularly useful clues regarding tumours.

He began to make significant advances in the 1970s, when he was still in his twenties. His main study was one of the simplest of all: what controls the division of a cell from one to two to four to eight. This wasn't a crowded field. 'Not a sexy area,' he says, 'because this was the time when people were doing their first

cloning, when molecular biology was still looking at RNA and protein and new, exciting things.' His work was largely abstract, and limited by what we would now regard as primitive technology.

All cancer researchers knew that cell division was crucial to their work, but they had no idea how to get a foot in the door. But by 1980, advances in gene cloning were showing practical applications, and Nurse's yeast samples were found to have valuable molecular structures. Not long before, the American researcher Lee Hartwell had also been working on yeast when he discovered that its cell division was dependent on one particular gene called cdc28. Nurse's type of yeast differed slightly, but he, too, located its key division gene - cdc2. His true breakthrough came after he had joined the ICRF in 1984, when he located the human version of cdc2, which creates the code for a protein called CDK1. 'The truth was that people weren't desperately interested in yeast per se,' Nurse says, 'but I think this took the world a bit by surprise - a real shock through the system.' It meant that the same gene controls everything in organisms from yeast to humans.

Subsequent research showed that cells employ a series of checkpoints that monitor progression through the cell cycle and delay the division process until any faulty DNA is repaired. If these checkpoints are themselves faulty, uncontrolled division may lead to tumours developing.

Although Nurse's new-found fame stems from old discoveries (a delay he attributes to the Nobel committee's need to ensure the work was correct and unravel its history), the recognition comes at an auspicious time for cancer research. Many pharmaceutical and biotech companies are engaged in a quest to find drugs that will interfere with some of the cell machinery identified by the trio, and there is an unmistakable sense of optimism in the cancer world in general, a mood less visible a decade ago. A great many small advances have been made in our understanding of the growth patterns of the major cancers (there are believed to be 200 or so in all, so a single 'cure for cancer' has long been regarded as folly). Recently, many of these individual advances have meshed together to produce inspiring results; they have even inspired some researchers to predict that 25 years from now most cancers will be treatable and non-fatal - just another chronic set of diseases. Even today, the first examples of smart drugs that work in an entirely new way from traditional chemo-therapy are having direct and exciting effects on leukaemia and breast cancer.

'Better biochemistry, better cell biology, better genetics,' Nurse says. 'We can now describe the disease and its causes in molecular terms in much greater detail. Instead of just seeing something as a lung cancer, we have enough reagents to be able to say that this is cancer type A1, this is B3 or whatever - and then that allows us to switch our attention to far more accurate and specific treatments aimed at particular changes.'

There are other improvements in established treatments which have been made possible by prolonged data. Best practice in breast-cancer screening and the use of the oestrogen-suppressing drug tamoxifen have significantly improved lives. Radiotherapy has also become more efficient, resulting in more lumpectomies as opposed to mastectomies.

'Over the past five years, we've seen absolutely clear evidence that if you do a, b and c, it doesn't cure, but it means about 3,000 more women survive each year,'

Nurse says. 'That's been wonderful.' Nurse is optimistic by nature and by profession: as the head of the ICRF, Britain's largest cancer research charity, it is good business to believe that big news is always around the corner so long as generous funding from the public is maintained. At the Cancer Research Campaign (CRC), which is not much smaller than the ICRF, the same may apply. But here, the mood of its director makes Nurse look like Scrooge.

Gordon McVie, an oncologist for almost 30 years, works in an office overlooking Regent's Park. He is a less flamboyant man than Nurse, but only in appearance. His talk is of 'revolution' in cancer treatments and of the technology 'stretching on as far as the eye can see', and of people 'not being able to move because of the excitement'. McVie has been at the CRC since 1989, first as its scientific director and, since 1996, in charge of the whole institution. He remembers the 1980s as a decade of gloom, 'the worst of both worlds' - no major improvements at the patient end and no apparent advances in the laboratories either. 'Nobody had been clever enough to turn oncogene (cancer gene) technology into diagnostics. Nobody could think of a good way of knocking out the oncogenes.'

There were, however, a few specific successes, the greatest of which was cisplatin, a drug that binds to DNA and uses platinum compounds to interfere with cell division. This had a spectacular impact on testicular cancer, transforming it from a disease that normally killed about 80 per cent of patients, to one which now effectively treats 90 per cent. Used in combination with other drugs, cisplatin can also have a marked effect on ovarian, bladder and bone cancers.

At the end of the 1980s, a new form of gene was described - a tumour-suppressor gene. Like many advances in cancer research, this knowledge was counter-intuitive to what had gone before: instead of having something extra in a cancerous cell, a mutated tumour suppressor led to something going missing. The proteins controlled by these genes serve as damage detectors, regulating healthy cell proliferation and blocking the action of other proteins required for normal function. We now know of many different actions: p53 controls DNA repair and natural cell death; RB regulates the cell cycle; APC enables cell-to-cell recognition. The mutations of these genes are now believed to play a key role in the creation of cancer.

In recent years, it was established that p53 exists in about 60 per cent of all common tumours, and antibody-detection tests were developed. 'This was riveting stuff,' says McVie. 'Suddenly you can pick up people with pre-malignant lesions. For instance, in oral cancer, you get this white leucoplakia thing before you get the cancer - you look in that and find the p53 is buggered, you know it's on the way to being a cancer cell. So now people began looking at mutated p53 as a target for new drug design and suddenly you're looking at about 300 new agents waiting to be tested in human trials. Just unbelievable. A revolution within a decade.'

The new treatments show one thing clearly: most of our early anti-cancer drugs were blunderbuss shots in the dark. Chemotherapy made patients feel awful, knocked out almost as many healthy cells as sick ones, and almost always killed them in the end. There were two important advances in chemotherapy in the 80s. The first concerned the use of drugs in more effective combinations. These

became so complex that clinicians referred to them by acronym: Chop, for example, stood for cyclophosphamide, H-doxorubicin, O-vinchristine and prednisolone, and was a treatment for non-Hodgkin's lymphoma. The other advance, if such it can be called, was that these cocktails often included increasingly powerful anti-emetics that ensured patients vomited out their new drugs less frequently. As is the case with any disease, many promising new drugs have arrived on a wave of hype in the past 30 years, and almost all have disappointed. Some have worked on cancers for a while, but then the tumours learnt how to beat them. Often it has been natural products derived from plants and fungi that have proved most effective against ovarian and bladder cancers - drugs like doxorubicin, vinchristine and Taxol - but they came with side effects that damaged bone marrow (laying a patient open to fatal infections) and clinicians had little real understanding of why they sometimes worked.

But recently, a new understanding of why they stopped working has proved even more rewarding. The discovery of P-glycoproteins - an array of pumps on the cell membrane that try to flick the drugs out of the cell as fast as they can be administered - has led to the development of new drugs that serve as pump blockers. The relatively new concept of apoptosis - programmed cell-death in normal tissue - has also led to a fundamental new comprehension of how treatments may work against tumours.

It's still a game of catch-up, but there is now a feeling that the winning post is attainable. 'People have only really begun to get clever because the technology is available,' McVie says. 'We can scan 6,000 genes from 200 breast cancer cells in two-and-a-half hours. We can then look at any mutated targets as possible diagnostic windows. You can tell from the range of mutations you've got in any particular tumour whether the thing will be able to escape treatment.'

But what McVie calls 'the ultimate glory' has been the ability to make highly specific drugs aimed at particular cell mutations. In the past two years, two new drugs have reached the market that are having a highly visible impact on certain forms of breast cancer and leukaemia. Herceptin is a drug designed to control the overexpression of the HER2 protein in a breast tumour, a protein whose growth runs out of control in 25 to 30 per cent of cases. The drug is administered alongside a more conventional chemo treatment, and has been found significantly to reduce the size of tumours in its limited trials.

Herceptin is what's known as a monoclonal antibody, a therapy engineered through biotechnology that has only been made possible by a greater understanding of molecular biology. Gleevec (sometimes spelt Glivec), a new treatment for chronic myelogenous leukeamia (CML), works in a similar way by attaching itself to a mutated protein on the outside of the cell, thus blocking the rapid and fatal cell growth. CML involves a massive overproduction of white blood cells that kills several thousand men and women in the UK each year. Gleevec was licensed in the United States in May, and is expected to receive approval for general prescription on the NHS next year.

These drugs are significant for a reason beyond their immediate use. They represent an entirely new approach to cancer, employing specialists from diverse fields of training. The result is often a novel line of attack: drugs known as angiogenesis inhibitors, for example, work on the blood vessels that feed tumours

rather than on the tumours themselves.
It is still early days for these new drugs, which do not work for everyone. And there is no doubt that the vast private fortunes to be amassed from an effective treatment combines with a desperation from doctors and patients to bring any new hope to the bedside at what may be over-hasty speed. But even the most battle-weary oncologists are aware that cancer treatment has entered a new dimension. Another example of a monoclonal antibody, Rituxan, designed to work against non-Hodgkin's lymphoma, is just one of many other new drugs from gene factories like Genentech and Novartis in production or undergoing early trials. The dream is that once one learns how to target two or three specific cancers, the rest are only a matter of time.
When I met Gordon McVie in mid-November, his desk was covered with papers outlining another important development in cancer research in this country, a proposed merger between the Cancer Research Campaign and the Imperial Cancer Research Fund. Together, the two charities fund about two-thirds of cancer research in the UK, with a joint spend last year of about £130m, and their merger will form the largest such charity outside the United States. Barring any last-minute legal hitches, the plans are due to be ratified by the charities' councils tomorrow, and a new name - Cancer Research UK - approved. At least 150 jobs are expected to go before the practical effects of the move become visible in February, a cut that will contribute to the proposed annual savings target of £3m.
There are several reasons for the development - more effective fundraising, the creation of a more powerful voice with government, less confusion among the public - and its timing is significant. The opportunities presented by the new tools of cellular biotechnology and genetics require a global view and increasingly complex research infrastructures, and a merger may lead to a more lucid scientific focus.
McVie's desk was also covered with several sheaths of slides for a lecture he was due to deliver in a few days' time to a gathering of cancer specialists in an ICRF office in London's Fulham Road. Essentially, it was a prognosis of how he saw things going in 25 years' time.
'What am I saying?' he asked as he held the slides up to the light to read his bullet-points. 'Therapeutics for early disease... targeting gene products and gene repair kits... intelligent, totally selective antibody- directed products...' This was a logical conclusion from the advances witnessed in the last year, but then he started to flex out.
'You won't need to "debulk" patients with big surgical operations in Western countries because people won't present with large cancers. We'll have a two-tier health system in the UK and, really, the only cancer problem will rest with the poor, who will continue having the same sorts of problems getting good cancer care as if they were in a Third World country. Early cancer will be the norm. Pre-malignancy correction clinics will replace hospices, but only in affluent areas. Primary care will be dominant and specialist hospitals for cancer will close. All patient documents will be on artificial neural networks controlled by the primary-care physician. Everything will start with your genetic signature, which will replace a pathologist looking down a microscope, and will show what's happening with your apoptopic genes, your metastatic genes, your angiogenesis genes...' He

admits that maybe he's 'pushing it a bit', but genuinely believes that this is how it will go. He is strangely proud of being singled out in The Lancet two years ago for his 'premature flagrant exaggeration'. He says that after almost 30 years in oncology, he can do this 'helicopter thing' with some conviction.
After his predictions, there were more improved realities. He remarked that, aside from the drugs, technological advances have helped cancer detection - X-rays that can 'bend' around a tumour to show (perhaps) its true oval shape; improved fibre-optics that aid colonoscopy - and brought about non-invasive treatments, that included blasting tumours with lasers. He has had one or two disappointments - chiefly the failure to come up with efficient delivery of gene therapy - but ultimately his rosy outlook is best tempered by sobering personal experience.
'I found my way into this because a favourite aunt of mine had ovarian cancer,' he says. 'I've had many people close to me diagnosed with cancer and gone through the mill, and you always feel especially impotent and especially pathetic when it's a member of your family. You realise that although you think you're doing quite well and have achieved a lot, you haven't actually achieved all that much yet.'

If it is true that you should never trust a man with a tidy desk, then Sir Walter Bodmer may be the most reliable man in Oxford. Every surface in his principal's office at Hertford College is stacked with towers of paper - academic studies, scientific theories, clinical trial reports, funding applications, student essays, travel plans, printed emails - so that it resembles less a place of work than a storage facility. Perhaps this is apt; there can be few people in this country better suited to a wide-angled examination of the current state of progress.
Bodmer is in his late-sixties, and was Sir Paul Nurse's predecessor at the ICRF. He was responsible for hiring both Nurse and Hunt, and likes to bask in a little reflected glory from their recent triumphs. A geneticist by trade, he worked at Stanford University in California in the 1960s and as professor of genetics at Oxford the following decade, and he was responsible for the early location of genes on some chromosomes and became an initial promoter of the Human Genome Project. He joined the ICRF as director of research in 1979, taking over as director general in 1991; when he joined, it was already clear to him that cancer was essentially a genetic disease that arises partly from a defect in the genetic machinery regulating a cell.
Bodmer recently lost his wife to breast cancer, but even the dampest of winter afternoons finds him upbeat about the future. 'What bad things do you hear?' he asks. I mention the news from a week earlier that breast cancer has now overtaken lung cancer as the most common form in the UK (an estimated 39,500 cases diagnosed in 1998, compared with 29,743 10 years earlier; in 1989, there were 41,645 new cases of lung cancers in men and women, a figure that fell in 1998 to 38,900.) He says this is due largely to the reduction in lung disease caused by a reduction in smoking, and observes that the improved treatment for breast cancer has greatly extended lives (more than 70 per cent of women are now successfully treated). The higher rates of breast cancer are attributable to women having children later in life and greater levels of obesity.
'There is no news but good news,' he says. 'We keep going forward. The only bad

news is that we haven't answered it all yet.' He believes that laboratory researchers have always been relatively optimistic, but the despondency has traditionally come from the treatment end. 'There were all these amazing things being discovered that one could never imagine would be found out so quickly, but getting that into the clinic takes a long time. The fundamental discoveries that have led to Herceptin and Gleevec were actually made 17 years ago, and from the point of view of the patient that's a frustratingly long period to wait.'

Bodmer is still actively involved in research; at Oxford, his small lab maintains his studies into the genetic pathway leading to colorectal cancer. But he is also a highly regarded public educator, and he takes particular care to stress the continued role of prevention in the grand scheme. He is more than aware that even the most exciting developments in the lab have yet to make much impact on the oft-quoted statement that one in three people in the UK will get cancer at some point in their lives.

There is exasperation in his voice when he asks, 'How many of your friends like to go on holiday and come back with nice, brown skin?' The ICRF claims there are 40,000 new cases of skin cancer in the UK each year, the vast majority preventable, but Bodmer detects that education campaigns regarding the risks both of sunbathing and cigarette smoking have been primarily effective among higher-income groups. He sees a relatively low incidence of smoking among his students, but during the overseas summer courses 'They're smoking like crazy.'

Somewhere on a desk in his office, there is a reply to a letter he wrote to health secretary Alan Milburn in which he complained that the Labour government wasn't honouring its commitment to ban tobacco advertising and sponsorship. The reply described plans to reduce the incidence of smoking in the lower socio-economic groups from 32 to 26 per cent between now and 2010. 'That doesn't strike me as a huge advance,' he says. The response has confirmed in him the need for his annual delegation to the Chancellor, requesting a hike in tobacco tax.

His wife, the distinguished scientist Julia Bodmer, died of breast cancer in January. His brother has had prostate cancer. His sister-in-law has had two different cancers. His brother-in-law died of a breast cancer at the early age of 40.

'I've had a certain amount of exposure to it,' he says. He was married to his wife for nearly 45 years and they worked closely together. When she fell ill, she was treated in Oxford by people they knew well. She was one of the 25 to 30 per cent of breast-cancer patients with the marker that allows treatment with Herceptin, and was one of the first to try it in this country. 'Unfortunately it didn't have the impact that one might have hoped because by the time she was first diagnosed it had already spread and the prognosis wasn't very good. It's hard to say on an individual case whether it gave some months of extra survival or not. There were two or three women she met as a patient who had this antibody treatment and had quite dramatic regressions of their cancers at quite a late stage.'

I asked him about the effect the Nobel awards may have on future research in the UK, and he said he hoped it would give it a boost. 'But it's unfortunate that even Nobel Prizes don't get quite the same prominence in this country as the news of whether or not David Beckham is playing football. I can tell you what I think is more important.'

Like Paul Nurse, Tim Hunt has gone from the basement to the 25th floor overnight. The strange thing is, he still works in an outpost near Potters Bar, Hertfordshire. Hunt's laboratories are known as Clare Hall, one of the ICRF's two main research facilities. The reception area has two things to read while you wait: there are newspaper clippings about Hunt's big prize, and there is a large sign that says: 'You Are Requested Not To Smoke', for to smoke here would be an insult to decades of discovery.

At 58, Hunt is more eccentric than Nurse, and more prone to maverick pronouncements. He says things like, 'I've lost lots of relatives and friends to cancer, and that's terrible, but personally I think the real reason why it's good to study cancer is because it's such an interesting problem.'

The work that won him this year's Nobel Prize occurred in 1982 in a more romantic spot, the Marine Biological Laboratory at Woods Hole, Massachusetts. The excitement of this cell-division work is best described in a letter Hunt sent back to his British friend, Richard Jackson, in August that year. 'The summer has been characterised mainly by its coldness, for which I am personally very grateful. We never got the dreadful enervating hot spell... The most amazing thing is what Tom and I have been working on. Translational control in the sea urchin Arabacia punctulata . As you know, it doesn't occur; but for reasons which I cannot now quite reconstruct, I wanted to see the patterns of protein synthesis right after fertilisation and, being lazy, used a continuous methionine label [a tagging method for proteins]. Judge to my surprise when one major band came up strongly very early, and then disappeared abruptly at about one hour. Subsequently it... reappears and disappears every time the cells divide.'

Hunt had located a key protein in cell division called a cyclin, another piece in the jigsaw of checkpoint regulation necessary for healthy growth. His discovery in his sea-urchin eggs that the levels of cyclin increase greatly as cells approach division, but then disappear, suggested that cell proliferation could eventually be artificially controlled by turning off or destroying these activating elements.

Tim Hunt's work has made a valuable contribution to the big picture, but has yet to make much of a dent on the big result - a reduction in deaths. He is not surprised by this; indeed, of all the scientists I talked to, he remains the most gloomy. 'I'm the hardened sceptic,' he says. He is also something of a traditionalist. He is excited by the potential of the new smart drugs, but has seen many excitements come and go. 'The key thing is, you don't want to just stop cancer cells growing - you want to kill them. They've got to go away. That's why shining beams of X-rays at them or cutting them out with a knife is actually still the best you can do in most cases, so long as they're confined and cuttable.'

He bases this judgement on two particular experiences. His mother died of colon cancer in 1977, being diagnosed at a stage when she only had a few months to live. 'She looked exactly like the mice I had given cancer to in the laboratory,' he says. 'Her belly was full of these swelling cells while her legs were withering away.' More recently, his mother-in-law was receiving anti-depressants because she felt unable to get out of bed. 'In fact, she had a tumour the size of a melon in her head, and immediately they discover that, they whip it out and she's better. Astonishing.'

He notes many failures in cancer treatments alongside the successes, and believes that often we still don't understand the reason for the difference. What is clear is that the more one can understand about the control of cell division in the body, the better off we'll be. Somebody somewhere is going to spot an angle that no one else has ever considered, and that will be another piece in the puzzle.
'People are always looking for this amazing great breakthrough because it's fun and newsworthy,' Hunt says. 'But I remember what motorcars were like when I was little. These cars would never start, especially on damp mornings, but now they always do. Was that a breakthrough? Probably not. It was a steady, methodical development over many years, using many technical refinements that work a little better than the ones used five years previously. And I think that's what's happening here.'

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