Breakthroughs in children’s medicine

Cancer
Cover: Astrid was treated for a type of cancer called lymphoblastic lymphoma. Thankfully she’s now doing well and has started primary school. She’s a delightful little girl who adores princesses and Dorothy from *The Wizard of Oz*. 
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Nurses on the hospital wards in the 1950s.
Cancer: an insurmountable challenge?

On 18 April 1895, a young boy from Islington was admitted to the Hospital for Sick Children – now Great Ormond Street Hospital. Percy was only 17 months old and the hospital notes show a diagnosis of leucocythaemia – an early description for leukaemia. His case did not have an unusual outcome, so unsurprisingly, the doctors could do nothing for little Percy and within 12 days he had died. He was just one of many thousands of children who came to the hospital during these early years with life-threatening or life-limiting diseases.

For decades to come, death was sadly the tragic outcome for most children with cancer. The disease was the largest cause of child deaths after accidents. There wasn’t even a specialist cancer ward at the hospital. Some localised solid tumours such as those of the kidney – Wilms’ tumour – might be cured by surgery alone, but the majority could not be controlled. Leukaemia was simply thought to be incurable – a medical text from 1914 suggested arsenic as having “undoubted but temporary value”. Chemotherapy was still relatively new and was only really able to prolong life, not save it. Cancer almost always returned and invariably proved fatal.

Right: The original hospital premises at 48-49 Great Ormond Street, 1870s.
1852 The Hospital for Sick Children (now Great Ormond Street Hospital) opens.
Majority of cancers and leukaemia still widely felt to be incurable.
A vision to change the future of children with cancer

From the 1950s, with the help of pioneers such as Roger Hardisty (left), startling breakthroughs began to move things dramatically forward.

Still only in his thirties, Dr Hardisty, later to become Professor Hardisty, joined Great Ormond Street Hospital in 1958 as a specialist trained in investigating diseases of the blood in adults. He stayed until his retirement 30 years later. In his three decades at the hospital he was pivotal in making changes that would see a 100 per cent death rate for children with leukaemia turn into an amazing 70 per cent survival rate.

Dr Hardisty started out in the hospital’s blood laboratories working on diseases such as haemophilia. Despite having no formal training as a paediatrician, no patients directly under his care, and no specialist cancer ward, he was able to make remarkable steps in understanding and treating leukaemia, as well as identifying various forms of the disease for the first time. Key to all Dr Hardisty’s work was the belief that a cure for many children suffering with leukaemia was possible and, to this end, he was a major driving force behind the remarkable changes that were about to take place.

Left: Dr Roger Hardisty.
With passionate clinicians such as Dr Hardisty now working hard to improve the prognosis for children with leukaemia, the 1960s saw some major developments in the battle against this frightening disease. But progress wasn’t all about amazing doctors making startling discoveries – the brave patients and their families, as always, played a major role.

In 1960, six-year-old Susan Eastwood (below) died within two months of being diagnosed with leukaemia. This terrible loss was the incentive for her family to launch what, for the hospital, became a highly influential fundraising appeal. “If we can achieve something, then we shall know our daughter died for a reason,” Susan’s parents said at the time. Their appeal made the headlines by raising £3,000 in little over a year (about £50,000 in today’s money), and it was the first donation to the hospital from the Leukaemia Research Fund (now Leukaemia and Lymphoma Research [LLR]).
When posed with the question “Are we prepared to have a go at tackling leukaemia?” Dr Hardisty gave an emphatic “Yes!”, despite Gordon Piller, LLR’s founder, likening the problem to climbing Everest with little equipment or knowledge of how to get to the top. Out of this came the country’s first leukaemia research unit, based at Great Ormond Street Hospital, and its partner the UCL Institute of Child Health, and led by Dr Hardisty.

And so this new unit began looking for the origins of the disease, testing new treatments against a background of near total fatality.

Right: Article from The Times, 7 December 1961.
Fewer than one in 100 children with leukaemia survive longer than four years.
 Scaling the mountain

In the early years of his research, Dr Hardisty needed to find long-term leukaemia survivors – those children whose disease had not returned for over four years. But the fact that he could only find 100 patients, about one per cent of all cases, proved just how accurate the Mount Everest comparison had been.

In the cases where drugs had managed to kill the cancerous cells and the child had entered remission, there was still little hope of a full recovery. Once the drugs were stopped, the cancer would come back, with symptoms such as bone marrow failure, anaemia and bleeding. And even when there was success in killing the leukaemic cells, many children died of common infections because of the damage the drugs had done on their bodies.

The situation with other, less common, cancers was not much better. Surgery was only an option for certain ‘solid’ tumours. For example, children with a particularly aggressive form of cancer, neuroblastoma, had less than a seven per cent chance of surviving more than two years from the time of diagnosis.

In addition to this stark prognosis for patients, there was little culture for local doctors to refer cancer patients to specialists and many children simply missed out on the chance of receiving potentially life-saving new treatments.

Left: A researcher in the early haematology laboratories.

1970 Long-term leukaemia survival rates increase by three times that of the 1960s.
Collaboration: the key to success

By the 1970s some of the hospital’s early research efforts were starting to show real reward. Early chemotherapy, for example, was improving and a 1971 study highlighted how long-term survival for children with acute leukaemia had trebled since 1963. Simultaneously, as microscopic and genetic research techniques became more sophisticated, researchers could better identify the many different types of cancer, and begin to understand how each would respond to different treatments.

The problem was that no single hospital saw more than a handful of patients with any one type of cancer. The resulting variability in how different local and specialist hospitals treated their patients meant it was almost impossible to test new therapies rigorously.

Remaining as determined as ever to improve matters, Dr Hardisty led the first national cancer studies, funded by the Medical Research Council. The first of these trialled a new treatment for acute lymphoblastic leukaemia, the most common form of childhood cancer. By delivering radiotherapy early to the brain and spine, the trial showed it was possible to kill ‘hidden’ leukaemia cells in the cerebrospinal fluid, and stop the

Left: The hospital’s first cancer consultants, Dr Judith Chessells (middle) and Dr Jon Pritchard (right), with fellow haematologist and oncologist, Dr Ian Hann.
cancer from coming back in a significant number of patients.

In 1973 Great Ormond Street Hospital opened a specialist five-bed cancer unit, with Dr Judith Chessells as lead clinical consultant. Soon to be joined by Dr Jon Pritchard, she helped to set up the UK Children’s Cancer Study Group in 1977. Medical teams could now pool ideas and standardise the way patients across the country were given experimental treatments, such as Dr Pritchard’s international role in introducing new combinations of chemotherapy to treat tumours of the liver.

Dr Chessells recalls these times:

In those days it was a huge challenge for us to raise awareness of our work, which we hoped would transform the research culture surrounding childhood cancer care. I remember the very first Study Group day for paediatricians where Roger presented his vision that things had to be better. Many of them were reluctant to refer patients to specialist centres to investigate and treat what they thought were fatal diseases. But with enough effort, and the success we were able to show with the children treated on the early collaborative cancer trials, support for these new ways of working began to grow.

The UK Children’s Cancer Study Group meant we could be sure that even children with rare types of cancer received the latest and best treatments. Even more importantly, it meant we could learn from the cases where things didn’t go so well. It kept us focused on the need to listen to each other if we wanted to make real progress.
Debbie, a researcher working at the hospital’s dedicated research partner, the UCL Institute of Child Health.
Great Ormond Street Hospital sets the pace for vital breakthroughs

The huge strides taken in the 1960s and 70s to improve chemotherapy have brought curative therapies to the majority of young cancer patients. New drugs are constantly being tested, doses refined, and our knowledge of the disease keeps on growing.

The early trials led by Dr Jon Pritchard transformed the ways in which chemotherapy was used to treat liver tumours and neuroblastoma. Survival rates soared, with the hospital at the forefront of international collaborations to deliver ever-better treatments.

In parallel, changes in supportive technology, such as sterile air processing and antiviral/antifungal drugs, as well as the specialist attention of our teams of nurses, mean infection remains at a minimum. Our Late Effects team keeps a close eye on patients for many years after their treatment, to deal with any complications that might arise.

But for some children with aggressive cancer, this simply isn’t enough. Only with world-leading research can we hope to make a difference to their lives. For patients with immune disorders and recurrent leukaemia, the hospital’s bone marrow transplant programme, launched in 1979, has provided a series of remarkable breakthroughs.

Left: Great Ormond Street Hospital leads efforts to conduct clinical trials of new therapies in a safe environment appropriate for the needs of its young patients.
Jenny and Mark’s joint struggle against leukaemia

When Jenny (far right) was two-and-a-half years old, her doctor referred her to Great Ormond Street Hospital where she was diagnosed with acute myeloid leukaemia. The standard treatment was a very intense course of chemotherapy and Jenny spent seven months at the hospital.

A year after being sent home, she relapsed and returned to the hospital needing a bone marrow transplant. As no one in her family was compatible to donate, she had to have an autologous transplant – a treatment using her own stem cells. It cured the underlying leukaemia but Jenny developed a number of permanent side effects, including lung and heart problems.

When she was 13, and by a terrible coincidence, her brother Mark (right) was diagnosed with exactly the same leukaemia – an incredibly rare and unexpected event. He also came to Great Ormond Street Hospital, but in comparison to his big sister, his treatment was much gentler. His hair didn’t fall out and he had more energy for playing. As with Jenny, Mark needed a bone marrow transplant but he was given a newer form of treatment and didn’t experience the same side effects as his sister.

Sadly, when she was only 26, Jenny died from those side effects. But Mark is now 21 and doing well with no complications from the drugs. The family believe it was the advances in research in the years between Jenny’s and Mark’s treatments that made the difference.
Jenny and Mark’s joint struggle against leukaemia

Above and right: Mark and his sister Jenny.
Mini transplants with major outcomes

One of the most devastating side effects from having a bone marrow transplant comes from the treatment needed to stop the patient’s own immune system attacking and rejecting the donated tissue. The problem comes from the intensive chemotherapy used to kill the existing bone marrow cells and create a space for the transplant. It wipes out the patient’s own immune system, leaving children already weakened by diseases such as leukaemia unable to fight infection and at a severe risk of organ failure.

In the early days of the hospital’s bone marrow transplant programme, this meant many children simply weren’t able to undergo the treatment – their bodies just wouldn’t tolerate the chemotherapy. Not only this, but those who did receive a transplant and survive often faced irreversible infertility.

Since then, we’ve applied our knowledge of how children’s immune systems work to find better ways of ensuring a successful transplant. By using antibodies – a type of biological molecule that can target specific tissues in the body – our researchers have found ways of creating a space for the donated bone marrow tissue, without the high doses of chemotherapy – a ‘mini’ bone marrow transplant.

Because this doesn’t rely on killing off all the existing bone marrow cells in a child’s body, it means far fewer side effects such as hair loss, sore mouths and guts, and a greater chance of children growing up still able to have children of their own. The survival rates of children over the years speak for themselves – the transplant might be mini, but the difference to children is huge.
Graph showing long-term survival of children treated with a bone marrow transplant at Great Ormond Street Hospital since 1978.

Above: Data supplied by Ashley Waterman, Bone Marrow Transplant unit, Great Ormond Street Hospital.

1999 The hospital pioneers ‘mini’ transplants for children too weak for a standard transplant.
Oscar’s long road to recovery

When Oscar (left) was three weeks old, he suffered reflux and was constantly having to go to hospital. Diagnosed with Noonan’s syndrome, which is associated with heart problems, he was monitored at the Royal Brompton Hospital. But on his third birthday he was diagnosed with acute lymphoblastic leukaemia and transferred to Great Ormond Street Hospital.

Oscar was treated with chemotherapy, which initially worked well. But three years later he was diagnosed with a rarer and much more aggressive type of leukaemia – juvenile myelomonocytic leukaemia – and the only cure was a bone marrow transplant.

Nothing was ever straightforward for Oscar. After initially responding well to treatment, the situation would always seem to get more complicated – an operation to remove his spleen was followed by the return of the leukaemia. A second bone marrow transplant killed the leukaemia, but this then led to a battle with graft-versus-host disease, where the transplant attacks the rest of the body. Later an infection led to five brain haemorrhages and a stroke with partial paralysis needing intensive physiotherapy. Then the graft-versus-host disease returned.

Oscar eventually became the first child in the UK to receive a unique transplant of stem cells, never before trialled as a therapy. This successfully cured the graft-versus-host disease and Oscar went home in 2007. He’s now under the care of the hospital’s long-term follow-up clinic, and last year he was even guest editor of Great Ormond Street Hospital Children’s Charity’s *Lifeline* magazine.

Left: After a lengthy battle against leukaemia, Oscar was cured with a pioneering transplant.
Noah’s fight against neuroblastoma

When he was just six months old, Noah (right) was diagnosed with stage four neuroblastoma with bad biological features, an aggressive and rare form of cancer, and was given just a 30 per cent chance of survival.

A series of tumours – one 15cm long – had affected his shoulder, stomach and ankle, and had spread to his bones. But the medical team at Great Ormond Street Hospital decided to try an intensive and highly experimental new treatment combination.

For eight months, Noah was subjected to huge doses of chemotherapy and radiotherapy, followed by an intricate three-hour operation to remove any remaining cancerous cells. After this he was given very high dose chemotherapy, so high that he had to regrow his bone marrow from stem cells that were taken from him once he was in remission. He was very young to undergo a treatment of this intensity, but it was a success, and in November 2009 there was no evidence of cancer.

Everybody involved in Noah’s care is acutely aware that the cancer could return and, because he has already received the strongest possible treatment, it is likely that if it does, he won’t be able to fight it again. But without the Great Ormond Street Hospital team trying something new, his chances of survival would have been much lower.
Today
Noah's fight against neuroblastoma

Today 2009
Long-term survival rates for children with cancer are now over 70 per cent.
Support and symptom care

We’ve come a long way in finding cures for childhood cancer, but the sad truth is many children still face a limited chance of recovery. This is why, throughout our history, we’ve worked extremely hard to make sure we provide a supportive environment that’s appropriate for the very unique needs of our patients and families, and why Great Ormond Street Hospital has seen so many breakthroughs in symptom care.

This began with the formation in 1986 of a special symptom care team and the appointment of the country’s first consultant in palliative care. The vision of the team has always been to include the patient’s voice in the care they receive and help children and families through their treatment, no matter what stage it’s at.

Although families were unsure at first, they soon came to realise just how much this very specialist support could improve the situation for them and their child.

Today, we continue to lead efforts to ensure the physical, emotional, social and spiritual needs of the child and family are delivered seamlessly alongside disease-directed care. With the appointment of the UK’s first Chair in Children’s Palliative Care at the UCL Institute of Child Health (ICH) in 2010, we are now at a point where research and clinical efforts in this challenging field are set to expand significantly. The Louis Dundas Centre for Children’s Palliative Care at the hospital and ICH will provide world-leading expertise, ensuring all children – whatever the status of their disease – are given an opportunity to receive the supportive care they need.

Right: Play is one of the many important ways in which the hospital provides supportive care for children and their families.
The Louis Dundas Centre for Children's Palliative Care is launched at the hospital and ICH.

Great Grandad is the BEST.

By Parris Tiger-lily
age 8-11 months

Safa 5
Meet the team

None of the breakthroughs – or indeed the care – highlighted in this guide would be possible without the people who work in the hospital’s cancer unit. As one doctor says, “Working here is like working for the United Nations. People travel from all over the world to work here.”

I have been treating children with cancer for nearly 30 years. During that time I have seen a real breakthrough in treatment outcomes for children with solid tumours. I never cease to be amazed at the courage of parents and families supporting their children through intensive treatment programmes. I love to work surrounded by amazing, dedicated and challenging nursing and medical colleagues. I need to know that if something can’t be done here then it probably can’t be done anywhere.

Dr Penelope Brock, Consultant Oncologist
No parent wants to hear the news that their child has cancer, but being treated at Great Ormond Street Hospital makes it easier to bear. One of the pleasures of my job as a childhood cancer specialist is to be able to reassure parents that we have treatments that can cure their child and that we are constantly striving through research to improve treatments and make them safer. Being able to offer virtually every type of therapy required under one roof makes working here extra-special for staff and less stressful for patients and their families.

Professor Kathy Pritchard-Jones, Professor of Paediatric Oncology

The massive improvement in survival seen in childhood leukaemia over the last 50 years is a testament to the power of the human spirit in times of great adversity. One only has to spend five minutes on our ward to see evidence of this and to understand the unique tradition of this hospital in leukaemia medicine. Our predecessors at Great Ormond Street Hospital were inspired by the determination of children and families not to be beaten by leukaemia. This continues to drive our team today. Our goal is simple: a cure for all children with minimal side effects.

Dr Nicholas Goulden, Consultant Haematologist
Advanced equipment such as the confocal microscope facility reveals the nature of disease at the smallest possible scale.
A brighter future

The differences between the early days, where children diagnosed with cancer were given little to no hope of a future, to now are startling. In what is a relatively short time we’ve reached a point where 99 per cent of children with acute lymphoblastic leukaemia, for example, now go into remission within a month and more than 90 per cent are cured.

Even in the case of rarer and more aggressive myeloid leukaemia – which accounts for 15 per cent of all leukaemia cases – two out of three patients survive. In fact, today, one in 1,000 adults is predicted to be a survivor of childhood cancer.

Despite this, one of the reasons we’re so much more successful at treating childhood cancer today is because research has shown that children can survive massive doses of chemotherapy. But chemotherapy is not without its own severe side effects. Ironically, this means that most patients are over-treated.

We’re continually driven on by the fact that there is still a long way to go. The urgency is now to reduce the side effects of treatment such as hair loss, sickness, organ damage and infertility and to reduce doses of chemotherapy and radiotherapy – where low risk children receive less harmful medicines – in other words, a tailored treatment directed to a patient’s individual needs.

Left: The hospital’s research partner, the UCL Institute of Child Health, viewed from Coram’s Fields.
Great Ormond Street Hospital’s track record of success in developing ever-better treatments means more and more children can now be confident of a real chance to beat cancer and leukaemia. But to ensure cancerous cells don’t return after a child’s treatment is stopped, standard practice, until recently, has been to set doses of chemotherapy to the maximum tolerated level. As children respond differently to their treatment, this means many receive more chemotherapy than they need and face unnecessarily severe side effects.

Great Ormond Street Hospital Children’s Charity is funding the next phase of research, led by Dr Nicholas Goulden, to detect tiny numbers of cancerous cells remaining in an acute leukaemia patient’s body after chemotherapy. By measuring the numbers of cancer cells left at various points along a child’s treatment, doctors can adjust chemotherapy to make sure patients with a low risk of relapse receive a lower dose.

Donations from our supporters mean we’ve been able to purchase a special counting machine, which can detect a single cancerous cell in 100,000. The machine lets us pick up the hidden traces of leukaemia and further refine our treatments at a fraction of the cost of current genetic testing techniques. This research means that we’re well on the way to becoming the UK’s leading centre for delivering minimal chemotherapy, while ensuring that we beat the underlying cancer. And, more importantly, it means we can reassure our patients they’re getting the smallest amount of potentially toxic treatment, with the highest chance of recovery and cure.
Cures with minimal side effects
Teaching the body to heal itself

Cancer causes such devastating illness because of its ability to evade the body’s inbuilt disease-fighting mechanisms. And, historically, there’s been little doctors could do to treat those types of cancer that don’t respond to chemotherapy or those in areas of the body inaccessible by surgery.

One such aggressive cancer, which affects about 30 children a year in the UK, is a rare type of brain tumour known as high grade glioma. Unlike other cancers, progress in creating new therapies for this condition has been slow.

With funding from Great Ormond Street Hospital Children’s Charity, Dr John Anderson has launched research to develop a special anti-tumour treatment to counteract this life-threatening disease.

The research project aims to extract a sample of a child’s disease-fighting immune cells, and expose them to fragments of the glioma removed from the patient. Once primed to recognise the glioma, these immune cells are then re-injected into the child, where researchers hope they will help the body to fight the remaining cancer cells.

The technique teaches the body’s own immune system to fight disease, a special type of anti-tumour vaccine – albeit one that’s tailor-made to suit each child individually. Under the lead of Dr Penelope Brock, the hospital is already leading international efforts to use similar immune-based therapies to treat neuroblastoma. If successful, it will be the first time that immune therapies will have really increased the chance of a cure in these advanced cancers.

Left: Dr John Anderson and his team are trialling vaccine techniques to treat childhood cancer.
Personalised medicine for unique illnesses

Though treatments have progressed immeasurably since the early days of chemotherapy at the hospital, in many cases there are still few answers to the question “Why do different types of cancer arise, and what triggers their growth?”

Detailed testing of samples of patients’ tissue plays a key part in revealing how severe the cancer is, and how much chemotherapy is needed to fight it. With support from Great Ormond Street Hospital Children’s Charity, Dr Thomas Jacques is carrying out research to find the precise biological markers that pinpoint the different types of tumour-causing cells. He’s hopeful that results will stimulate better clinical treatments.

My holy grail would be to be able to say precisely which children will respond to a particular treatment and which will not: a fundamental but pressing challenge. The project we’re now working on aims to accurately detect whether certain types of cells can trigger particularly severe forms of cancer. If successful, it means we will be a step closer to offering children personalised treatments based on the unique features of their disease. This is a very exciting time.

Dr Thomas Jacques, Clinician Scientist
Gene therapy – a new medical frontier

Our Bone Marrow Transplant unit has led the way in delivering cures to children born without an ability to fight disease and to those with severe recurrent leukaemia. Even though we’ve got much better at finding ways to deliver these transplants without using intensive, and life-limiting, chemotherapy, the treatment itself is still high risk. If we can remove the cause of disease at its source, or stop any damage associated with our treatments, then children might stand a far better chance of recovery.

Thankfully, with research at the leading-edge of biomedical science, we can now offer such treatments. Our researchers are one of the few groups in the world that have succeeded in curing an inherited disease. They achieved this by introducing functioning genes into children born with an error in the region of their DNA responsible for producing healthy disease-fighting cells.

This incredible technology, known as gene therapy, is now being rolled out to a number of disease areas where there was once little to no chance of a cure. Projects now in development include reprogramming children’s immune systems to fight severe leukaemia, as well as ways of stopping the body from rejecting life-saving bone marrow transplants. The research is at the very frontiers of modern healthcare – and its importance cannot be understated. Every new application of gene therapy technology has the potential to lead medicine in completely new directions.

Right: Genetic medicine is set to be the treatment of the future now that thousands of DNA tests can be performed on a slide no larger than a fingernail.
Find out more

Our website has more information about the specialists, patients and treatments you’ve read about in this guide, as well as the pioneering research the hospital carries out.

If you’d like to find out more, or you have your own stories that you’d like to share with us, please visit gosh.org/breakthroughs

To continue the legacy of breakthroughs at Great Ormond Street Hospital, we need to raise £50 million every year. This helps to rebuild and refurbish the hospital, buy vital equipment and fund pioneering research. As well as the developments in this guide, amazing things happen at Great Ormond Street Hospital every day. With your help we can keep the magic alive for our very ill children and their families.