The identical twin on the right was given various treatments as a child for acute lymphoblastic leukaemia.

DRUG SAFETY

# Double jeopardy

*Leukaemia in children is highly curable, but many survivors suffer severe, even life-threatening, long-term effects. Scientists are seeking ways to deliver a safer cure.*

BY MARY CARMICHAEL

One of Jolene Hanson's earliest memories is of eating birthday cake in a wheelchair at the University of Minnesota Medical Center in Fairview. It was 13 March 1976, her fourth birthday, and just 16 days after she was diagnosed with acute lymphoblastic leukaemia (ALL). In those days, ALL killed around two-thirds of the children it struck.

Hanson remembers little about her treatment except that her mother crushed one of her drugs and put it in her ice-cream. But her medical records show she was taking methotrexate, vincristine, doxorubicin, asparaginase, prednisone, cyclophosphamide and cytarabine, and had 12 rounds of radiation to her developing brain.

This intense therapy cured her. But it came with a curse: its long-term side effects have dogged her for 37 years. She is just 4 feet 8 inches tall — the radiation left her with growth hormone deficiency — and permanently bald. Her medical diary runs to nine pages of travails: 15 October 1987, "Dr Ingvaldstat drained an ovarian cyst on my right side that was the size of an orange"; 20 July 1999, "I had a basal cell carcinoma spot removed from the posterior 3rd–4th lumbar vertebrae region"; and August 2004, "A few months of infertility drugs and seeing high risk doctors led to the conclusion of not being able to get pregnant."

She tries to stay upbeat despite all her medical problems. "Sometimes I just have to laugh about it," she says. "What else can I do?"

That question — what else can I do? — is also a pressing one for doctors seeking to treat leukaemia without leaving behind sequelae that echo for decades, such as heart damage, cognitive deficits, secondary cancers and stroke.

## LONG-TERM DAMAGE

These days, many cases of leukaemia are curable: more than 85% of children with ALL, the most common childhood leukaemia, survive. But more than a quarter of childhood cancer survivors report at least one severe, life-threatening or disabling health condition in the first 25 years after treatment.

The challenge for researchers is to find ways to lower the risk of these late effects without lowering the effectiveness of therapy. To minimize the risk, they introduce drugs that protect patients from some of the damage, replace harmful treatments, and seek biomarkers that indicate which patients are most vulnerable.

"There used to be this philosophy of 'Just be thankful you're alive and accept whatever problems come with treatment'," says K. Scott Baker, a paediatric oncologist at the Fred Hutchinson Cancer Research Center in Seattle, Washington. "But that mindset has changed."

The doctors who treated paediatric leukaemia with radiation to the brain in the 1970s and '80s were less concerned with secondary effects than they were with the prospect of relapse. Most chemotherapy drugs leave the brain vulnerable to invading leukaemia cells because the drugs generally do not cross the blood–brain barrier.

"They weren't really thinking about what was going to happen to their patients in 20 or 30 years because they didn't know if they could cure anyone," says Lisa Diller, a paediatric oncologist who leads a survivors' programme at the Dana-Farber Cancer Institute in Boston, Massachusetts. Only when children began to survive in significant numbers did the risks of radiation to the developing brain become clear (see 'Late effects'): it caused brain tumours, growth hormone deficiency, hypothyroidism and problems with learning and memory.

## REDUCING THE RISK

Today, many hospitals use radiation for children only where there is a high risk of relapse in the brain — if leukaemic cells have already taken hold there, for example, or if the disease is an unusually aggressive form that affects T cells.

They also administer less radiation these days — rarely more than 1,200 centigrays, half the cumulative dose Hanson received. Most children receive no radiation at all: doctors prefer to protect their young patients' brains from leukaemic invasion by injecting drugs such as methotrexate and cytarabine into their spinal fluid.

But these drugs can have long-term cognitive deficits and have other late effects of their own. Methotrexate, for example, may impair balance and the ability to walk normally. The drug is linked to so many problems, says Les Robison, an

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NEW ENGLAND JOURNAL OF MEDICINE, 2011

epidemiologist and cancer researcher at St Jude Children's Research Hospital in Memphis, Tennessee, that it may some day be viewed in the same way we now regard brain radiation — as a treatment with so many long-term side effects that it should be avoided whenever possible.

Another class of drugs, anthracyclines, which includes the widely used doxorubicin, is linked to a different, life-threatening late effect: heart damage. Doctors have known for decades that doxorubicin and a similar drug, daunorubicin, can leave the left ventricular wall thin and weak, leading to congestive heart failure in some patients.

Doctors can avoid some of these late effects simply by lowering the dose. High doses of doxorubicin, for instance, cause congestive heart failure in 30% of adults, but halving the dose can dramatically shrink that percentage. Children are not so fortunate, however, as even low doses raise the risk of heart problems. And lowering the dose may reduce the effectiveness.

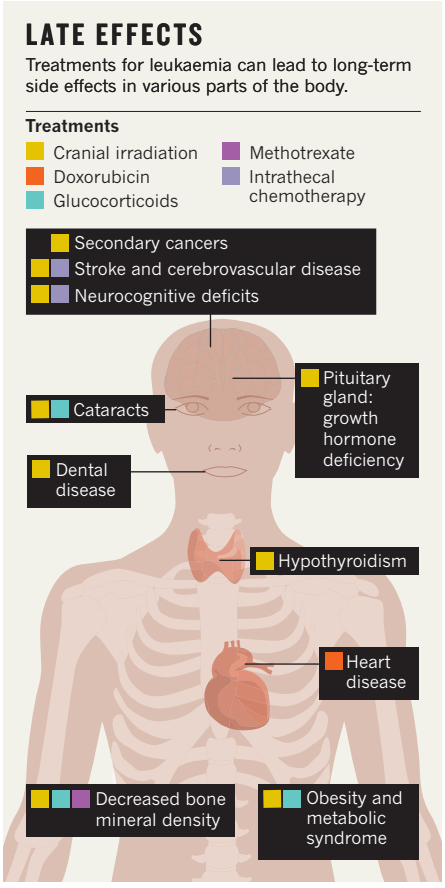
"If you take away some treatment to avoid toxicity, you're running the risk of taking away some efficacy," says Stephen Sallan, a paediatric oncologist at Dana-Farber. A better strategy may be to add a drug that can protect healthy cells against the damage caused by doxorubicin. But that is a tricky business, as research over the past three years makes clear.

No one really knows why doxorubicin is harmful to heart muscle. One possibility stems from the fact that the drug inhibits topoisomerase II, an enzyme that helps to relax DNA coils. Mice lacking this enzyme in their heart cells don't have cardiac injuries after doxorubicin treatment[1]. But many researchers, including Sallan, say that doxorubicin's toxicity may result from the free radicals it generates — in which case giving patients antioxidants could help.

One class of drugs with antioxidant properties — angiotensin-converting enzyme (ACE) inhibitors — has yielded tantalizing results in rats, including the discovery that two ACE inhibitors could "almost totally prevent" several types of cardiac damage[2]. There have also been some promising results in adult patients, but the drugs seem to be less effective in children. Sallan and his colleagues found that children who took ACE inhibitors after anthracycline therapy saw an initial strengthening of their left ventricular walls, but the effect did not last.

Sallan prefers to use a different cardioprotective drug, dexrazoxane, a free-radical scavenger used in women being treated for breast cancer. The drug seems to help, but the use of dexrazoxane is controversial. The European Medicines Agency barred doctors from prescribing it to children in 2011 after clinical trials showed that some children subsequently developed acute myeloid leukaemia and disorders that affect bone-marrow stem cells.

Sallan dismisses the agency's decision as "nuts" — and points out that those children were also receiving another drug linked to the same complications. But the US Food and Drug Administration took the European decision seriously enough to advise doctors of it, adding that dexrazoxane is not approved for use in children.




Another strategy for limiting the harm done by doxorubicin is to give it only to patients with the right genetics to handle it safely. For children with a particular genetic variant of *CBR3*, a gene that regulates doxorubicin metabolism, the cure may be worse than the disease. For these children, "there seems to be no safe dose" of doxorubicin, researchers say[3].

## LATER IN LIFE

Patients who dodge the late effects of radiation and chemotherapy are not necessarily out of danger. They may still face other risks if their treatment includes bone-marrow transplantation. "There is a whole set of issues that are unique, and some of them are quite long-term," says David Avigan, a haematologist and oncologist at Beth Israel Deaconess Medical Center in Boston, Massachusetts.

As with all transplants, bone-marrow transplants carry a risk that immune cells in the donor tissue will recognize the recipient as 'foreign' and attack the body. This can have serious consequences, including long-term damage to the liver, lungs, skin and gastrointestinal tract. A more surprising late effect in leukaemia survivors who have had bone-marrow transplants is the replacement of lean muscle mass with fat. This process is a natural part of ageing, but after a bone-marrow transplant, it seems to be accelerated, says Baker. His team has shown that those who have bone-marrow transplants also develop insulin resistance, which is linked to diabetes, cardiovascular disease, and other problems that fall under the broad category known as 'metabolic syndrome' — a condition for which ALL survivors are already at increased risk.

Given how widespread late effects are, the problem has received surprisingly little study, especially in survivors of leukaemias other than paediatric ALL. The Childhood Cancer Survivors Study, led by Robison, tracked more than 20,000 children and has provided a wealth of data on them. But such studies require a huge investment of time and money, and the first long-term study[4] of survivors of paediatric acute myeloid leukaemia was not published until 2008.

There are also few data on late effects in leukaemia survivors diagnosed as adults. "The paediatricians have been way ahead of us," says Ann Partridge, a medical oncologist at Dana-Farber who studies adult survivorship. "It's clear we need to do better for our adult survivors, now that we have adult survivors."

Those patients historically exposed to the harshest treatment — Jolene Hanson's generation — are now aged 40 or 50 and may develop a wave of late effects that mimic premature ageing. Diller has warned[5], for example, that loss of bone density in paediatric ALL survivors may lead to increased risk of fractures in middle age.

Robert Hayashi, a paediatric haematologist and oncologist at St Louis Children's Hospital in Missouri, is concerned that intense steroid chemotherapy (such as the prednisone Hanson received) can put children at risk of premature arthritis. And Robison has discovered a group of survivors in their 30s and 40s who have surprisingly high blood pressure in the lungs for their age, resulting in breathing difficulties.

Sallan says that some children whose hearts are damaged by anthracyclines may avoid congestive heart failure for their first few decades, only to suffer it in later life. "There are late effects," he says, "and there are very late effects."

In Hanson's case, there certainly are. A few years ago, she says, she had a spell of good health, but in late 2012 she developed a brain tumour behind her right eye that required surgery. She might have preferred radiation to destroy the tumour — but radiation may have caused the tumour in the first place, and she has had too much already. Hanson says she's prepared for yet another round of late effects. "But I'm really hoping my body will leave me alone for a while." ■

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1. Zhang, S. *et al. Nature Med.* **18,** 1639–1642 (2012).
2. Sacco, G. *et al. Vasc. Pharmacol.* **50,** 166–170 (2009).
3. Blanco, J. G. *et al. J. Clin. Oncol.* **30,** 1415–1421 (2011).
4. Mulrooney, D. A. *et al.* Cancer **112,** 2071–2079 (2008).
5. Diller, L. *N. Engl. J. Med.* **365,** 1417–1424 (2011).