



POLARIS/EVINE

Timothy Brown was cured of HIV after a bone-marrow transplant for leukaemia.

## VIROLOGY

# Vanquishing HIV

Sharon Lewin welcomes a book tracing how two men with HIV were functionally cured.

In the 30 years since HIV was identified as the cause of AIDS, antiretroviral treatment has changed the infection from a death sentence to a chronic, manageable disease. Now, treatment is lifelong but often consists of just a tablet a day; resistance to the drugs is rare; and side effects are infrequent. However, the virus integrates into the patient's DNA and becomes silenced, in what is known as latency, and no tools have yet been found to eliminate it. When the antiretrovirals are stopped, infectious virus re-emerges.

But since at least 2009, a cure for HIV has been widely accepted as possible, thanks to a handful of reported cases. Members of this select group are functionally cured, often in unusual circumstances: the virus is detectable at low levels, but is under control without antiretrovirals. Now, in *Cured*, Nathalia Holt — an immunologist who has done groundbreaking research on gene therapy as a cure strategy — traces the fascinating cases of two people who have effectively vanquished HIV.

The Berlin patients, both diagnosed in the city, are 'Christian' (not his real name), and Timothy Brown, an American. *Cured* covers their personal stories and the science that their cases inspired, as well as the scientific

and political history of HIV.

Christian, Holt tells us, was functionally cured after receiving antiretroviral treatment and a fairly toxic cancer drug, hydroxyurea, within days of infection. Brown was cured of HIV after a bone-marrow transplant for leukaemia; the donor lacked the CCR5 receptor, which normally ushers HIV into human cells, and so was naturally resistant to the virus. Both cases were reported in *The New England Journal of Medicine* (*NEJM*), in 1999 and 2009 respectively.

The cases are similar in many details, as Holt relates. Both men were diagnosed in the mid-1990s — when infection with HIV heralded a real prospect of early death. Both were cared for at some time by the same dedicated family doctor, Heiko Jessen. Both had access to life-saving antiretrovirals. Both their identities were initially hidden. And



**Cured: How the Berlin Patients Defeated HIV and Forever Changed Medical Science**  
NATHALIA HOLT  
Dutton: 2014.

both cases became the focus of media stories claiming that a cure had been found, even though the treating physicians had carefully avoided using that word in interviews.

The Berlin patients also highlight the often vicious and competitive nature of science — rife with big egos, high stakes and a reluctance to brook unexpected findings from outsiders. Much of the innovation in how they were managed came from two unknown German physicians: Jessen and Gero Hütter, Brown's haematologist, who tested unconventional treatments outside formal clinical trials. The big science, which demanded an analysis of how much virus was left and why it was under control, was driven largely by well-known US investigators. The tensions between the two cultures are telling.

Jessen, for example, ended up as fourth author of the 1999 *NEJM* paper on Christian's case; as Holt explains, he no longer works with any of his US-based collaborators. Hütter's initial submission to *NEJM* was rejected, and his presentation of Brown's case at the 2008 Conference on Retroviruses and Opportunistic Infections in Boston, Massachusetts — the premier meeting for HIV scientists — was largely ignored. In Holt's view, it was only

when the American Foundation for AIDS Research started to take an interest that Hütter engaged well-recognized names, and *NEJM* eventually accepted his paper.

More importantly, the Berlin patients' cases have inspired new scientific ideas. We still do not know what led to either cure. Many researchers think that Christian is probably an 'elite controller', one of the 1% of people with HIV whose genetic make-up gives them an effective immune response to the virus. So he may have controlled his virus at the outset. However, his case raised the possibility that very early treatment could reduce or prevent the formation of long-lived reservoirs, as was demonstrated last year in 14 people with HIV in the VISCONTI (Viro-Immunological Sustained Control after Treatment Interruption) study in France. Christian's case also revealed the importance of the role of the T-cell immune response in controlling the virus — a major stimulus to HIV vaccine development.

With Brown, was the cure a reaction of the donor marrow against his immune system, a process called graft-versus-host disease? Was it down to the intensive conditioning treatment he received before the transplant? Or was it that the donor marrow was CCR5-negative? A promising treatment based on eliminating CCR5 using gene therapy was developed in a mouse model by a team including Holt, and is now being tested in clinical trials.

I enjoyed the book but I do have quibbles. Holt's discussions can be dense and detailed. Her interviews, which tend to focus on US-based leaders in HIV science, make it seem as if little discovery was being led from elsewhere, even though there have been significant contributions from many other countries, not least France, where the initial discovery of the virus was made. This is an important book, nevertheless.

Although the Berlin patients' case reports are anecdotes, they convinced a sceptical scientific world that a cure was possible, and inspired lines of enquiry and investment. On World AIDS Day 2013, US President Barack Obama announced that his administration would give an extra US\$100 million to research towards a cure. Most importantly, the cases belong to a significant handful that is giving hope to millions of people living with HIV. ■

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## PHYSICS

# Inside utter strangeness

David Seery applauds a primer on the incongruous world of quantum mechanics.

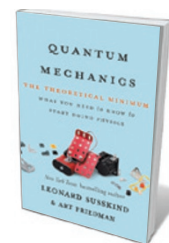
It is all too easy to compound the perplexities of quantum mechanics. Monographs are often weighed down by abstruse mathematics; other treatments struggle to separate physics from formalism. The problem is to communicate the subject's intrinsic strangeness without burdensome mathematical demands — but also without resorting to gee-whiz platitudes that assert, but do not explain, the incongruities between the quantum world and everyday experience.

Leonard Susskind and Art Friedman's *Quantum Mechanics* is the second entry in Susskind's *Theoretical Minimum* series, based on an Internet course of the same name and designed to satisfy a mathematically literate audience looking for more detail than can be found in a popular-science offering. The authors set their aims at the outset: "the goal", they say, "is not to hide the utter strangeness of quantum logic but to bring it out into the light of day".

To achieve this, Susskind, a physicist, and Friedman, a data engineer, eschew the analogies and qualitative descriptions typically used to explain quantum mechanics to a lay audience. Instead, readers are expected to invest time in getting to grips with mathematical concepts such as complex numbers, vector spaces, linear operators and tensor products, all of which are deftly explained in a series of interludes. In return, the authors offer self-contained chapters that vividly articulate aspects of the theory: the space of states, time evolution, uncertainty, entanglement, particle dynamics and so on, leading eventually to the harmonic oscillator, a quantized mechanical spring. This is the most important of all simple quantum systems because quantum field theory, the discipline's description of the forces in nature, interprets particles as harmonic oscillators.

The selection of concepts is close to what would be found in a typical undergraduate course. It steers clear of the philosophical morass surrounding interpretation and focuses on how quantum mechanics is used and understood today, rather than its development or the human stories behind it. This is a book about physics, not history.

The writing is fresh and immediate, with plenty of detail packaged into the smooth narrative. It will not teach anyone to carry out complex calculations, and it may leave the reader with questions that can be resolved



**Quantum Mechanics: The Theoretical Minimum: What You Need to Know to Start Doing Physics**

LEONARD SUSSKIND  
AND ART FRIEDMAN  
*Basic Books/Allen Lane: 2014.*

only by digging into more conventional textbooks. But on their own terms, I found Susskind and Friedman's explanations crisp and satisfying. The chapters on entanglement — in which particles interact in such a way that they cannot be described independently — are especially clear, taking pains to draw out the distinction between quantum entanglement and correlation. In either case, we can predict something

about the relationship between measurements in different parts of a composite system. The puzzling feature of entanglement is that, although we may know everything about the state, it might be impossible to predict anything about the outcome of these measurements individually.

Susskind and Friedman's choices will suit their intended readership, but might make the book less attractive to others. Those with the determination to navigate the complexities of Hermitian operators, normalizable wavefunctions or creation-annihilation operators will struggle to find a book that serves them better. Secondary-school pupils, however, may find the more detailed passages too demanding; university students might find that the early chapters proceed slowly, and that overall the book is too light on detail to serve as a principal text.

Still, I maintain a clear recollection of the bewilderment with which I struggled through my own university quantum-mechanics courses. For students in a similar position, trying to draw together the fragments of formalism into a clear conceptual whole, Susskind and Friedman's persuasive overview — and their insistence on explaining, with sharp mathematical detail, exactly what it is that is strange about quantum mechanics — may be just what is needed. ■

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