

## Books & arts

Perhaps the most important theme that emerges is that although clear continuities exist between childhood and later well-being, these links are far from exact. Human development is probabilistic rather than deterministic, and continues well beyond the first decade of life. Many different processes are likely to underlie such long-term continuities. We see here, for example, instances of the ways in which childhood characteristics can 'select' individuals into later environments, so reinforcing early tendencies. Tracked to early adulthood, for example, people who were socially inhibited as toddlers had smaller social circles and less social support than their peers, whereas those who had been impulsive in early childhood often evoked negative responses from family, friends and partners, and in the workplace. Early adversities such as maltreatment, social isolation and bullying can become embedded in our biology, influencing inflammatory processes and stress responses in ways that might, later in life, increase the risk of conditions such as diabetes and poor mental health.

But we also see that change is possible throughout life, and that some individuals are resilient even in the face of quite severe early adversity. Teasing out the factors that contribute to strengths, whether they lie in the family, the neighbourhood, society or genetic inheritance, can be especially valuable in pointing to targets for intervention – such as investment in school meals or education.

### Long game

Alongside the specific findings, what shines through is the power of the longitudinal method. The three projects that are explored here form part of a larger body of studies, mostly initiated since the Second World War, tracking individuals across their lives. Their findings are now revolutionizing our understanding of the determinants of health and social capital, and, in the case of the long-est-running studies, of ageing and decline.



A child takes part in a 1940 development study.

Each represents an extraordinary investment – by researchers, participants and, of course, funders – in documenting lives in real time.

It's true that essentially 'observational' studies might not give the tight purchase on causality that could be achieved by an experiment. Instead, they offer something in many ways richer and more valuable: insights into the processes that shape human development. Given the tricks that memory can play, issues of this kind cannot be studied retrospectively. We need to observe lives as they unfold. And as this book shows, the value of such data increases exponentially with time, illuminating issues undreamt of when the studies began.

For those new to cohort literature, *The Origins of You* is an engaging introduction. For those familiar with this work, it is a chance to hear the authors thinking aloud, debating the best approaches and pondering what to study next. We can be certain that those conversations will now include how best to use these rich longitudinal resources to understand the effects of COVID-19.

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# The poisonous history of chemotherapy

A Second World War disaster drove a crusade for cancer treatment argues Jennet Conant. **By Heidi Ledford**

**O**n 2 December 1943, German forces attacked the Italian port town of Bari. The onslaught cost at least 1,000 lives and sunk 17 ships. One was carrying 2,000 bombs loaded with deadly mustard gas.

The gas – which was actually in liquid form – mixed with oil from the sinking tankers to create a deadly slick that clung to sailors' skin as they swam to safety. Many who made it to the local hospital were greeted with blankets to wrap around their poison-soaked clothing, sealing their fate as they awaited care. The agony set in hours or days later. Stunned nurses found themselves with wards full of swollen, blistered patients, temporarily blinded.

*The Great Secret* brings that harrowing night to life, and then follows the military physician who fought to uncover the truth about the chemical weapons. His efforts contributed to the development of chemotherapy, seeding the cancer-research juggernaut that dominates drug discovery to this day, argues writer Jennet Conant in her latest history of war-era science.

That hard-working and brilliant physician is the first of the book's two heroes. Stewart Alexander, an American expert on chemical weapons, is called in to explain the mysterious ailments plaguing the Bari survivors. The possibilities offer a harrowing tour through the chemical arms race of the early twentieth century. Could it have been chlorine or mustard, the causes of the chemical massacres of

the First World War? Or was it lewisite, a blistering agent that quickly penetrated the skin? Or one of the new blends such as 'Winterlost', a combination of nitrogen mustard and lewisite that featured a low freezing point to ensure effectiveness at the frigid Russian front?

### Chemical secret

The deadly cargo in Bari's harbour was a fiercely guarded secret. The Geneva Protocol had banned the use of chemical warfare in 1925, but the shipment was there in case of the need to retaliate if Hitler had resorted to chemical weapons. Alexander struggles to treat his ailing patients while battling military officials who are intent on keeping the incident quiet.

Alexander is struck by how the mustard-oil mixture obliterated his patients' white blood cells. He scrambles to make sense of data from different treatments given in different hospitals, with different standards of care and no control groups. (There are uncomfortable parallels with the flurry of uninterpretable observational studies and uncontrolled clinical trials during the first months of the COVID-19 pandemic.)

Alexander had seen similar effects of such agents in animal studies before the war. These had conjured up hopes that the chemicals could be used to rein in cancerous blood cells in leukaemia and lymphoma. Flood the body with toxic substances, the theory went, and the disease could be snuffed out or at least beaten back. Alexander's detailed report of



Rescuers work sift through the debris left by the explosion of a munitions ship in Bari harbour, Italy, in 1945.

his findings in Bari, initially classified but circulated among some military researchers, spurred efforts to find a chemical treatment for cancer.

On this point, Conant has to labour to connect the dots. The inspiration for chemotherapy did not come from Bari. Yale University researchers in New Haven, Connecticut, first treated cancer with nitrogen mustard in 1942; the patient died of lymphosarcoma a year before the Germans attacked the Italian harbour. But Conant argues that Alexander's report of his observations helped to convince researchers of the value and robustness of the approach.

The book's second protagonist is physician Cornelius 'Dusty' Rhoads. He is much harder to like. Fiercely driven and passionate about curing cancer, Rhoads oversold preliminary research results and rushed into clinical trials. Before the war, Rhoads worked at Rockefeller University in New York City, and he travelled to Puerto Rico to study conditions such as anaemia and tropical sprue. There, he penned a hideously racist letter – unsent but discovered by his office staff – claiming to have transplanted cancer cells into healthy Puerto Ricans, whom he compared to animals. Rhoads later said the claim was a joke; subsequent investigations found no evidence that he carried out such "experiments".

Nevertheless, Rhoads continued to wield significant influence in military and academic science. He applied that influence with full force to the search for chemotherapies. Scepticism

from other physicians was rampant. Cancer treatment, Conant reminds us, had changed little since Hippocrates (460–370 BC) named the disease and proclaimed "what drugs will not cure, the knife will". Surgery and radiation were nearly the only options, and cancer was so lethal and stigmatized that patients often were not told of their diagnosis.

### Hope and heartbreak

After the war, Rhoads advocated fiercely for chemotherapy – inspired in part by Alexander's report, Conant argues. Rhoads's leadership and aggressive fundraising led, by the mid-1950s, to the first large-scale efforts to screen for new cancer drugs and to test promising candidates in people. Conant brings to life the exhilaration and hope that physicians felt when the first patients responded to chemotherapy – followed by the heart-wrenching dismay when, time and again, initial success was followed a few weeks or months later by the cancer's resurgence.

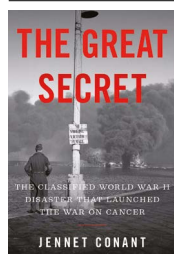
Opponents were horrified by the toxicity

of chemotherapies and unimpressed by the ephemeral reprieves that most offered. US physician William Woglom captured the challenge: "It is almost, not quite, but almost as hard as finding some agent that will dissolve away the left ear, say, but leave the right ear unharmed; so slight is the difference between the cancer cell and its normal ancestor."

Despite that challenge, Rhoads planted the seeds for the cancer-research enterprise that continues today. There are now reams of DNA sequence data detailing the genetic differences between our 'left and right ears'. Drug-screening efforts are more sophisticated, and the chemical libraries that they trawl are orders of magnitude larger and more complex.

For a science-hungry reader, *The Great Secret* has a few too many excursions into the strategies, personalities and troop movements of the Second World War. And I yearned for more on the development of ethical boundaries between experimentation and treatment, which remain fuzzy in cancer research. But the book succeeds as a history of chemotherapy's origins.

Today, chemotherapy has advanced; some drugs are less toxic, given at lower doses, or more-targeted in their effects. But the benefits are still too often transient. "For a short period of time the patient was delighted," says one researcher of the first mustard chemotherapy trial. "But it was a short period of time."



**The Great Secret: The Classified World War II Disaster that Launched the War on Cancer**  
Jennet Conant

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