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Biotechnology: a revolution in progress

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Introduction

It is customary for each President of the Royal Society of New South Wales (RSNSW) to write a paper for the Society's journal at the end of their term.[1] My sole instruction from journal editor, Robert Marks, was to "write something of interest on a topic of your choice." I have chosen to write about biotechnology, the field that has consumed my career.

Biotechnology harnesses nature's designs of living organisms to develop technologies and products that improve the health of people and our planet.

Needing to limit the scope of this paper because the field of biotechnology is so vast, I can only offer a few snapshots of biotechnology's transformational impacts through my lens as a physician-scientist since the 1970s.

My career expanded well beyond my initial medical and research qualifications. I have crossed and combined disciplines and sectors and worked at the intersections between them, always with a unifying theme: the importance of science and technology to our future. No wonder I was attracted to join the RSNSW with its thought leaders and innovators from across academia, industry, government, public administration, culture and civil society.

Foundations of modern biotechnology

Biotechnology has its origins in the dawn of civilisation when humans were selecting plants for cultivation, microorganisms to make bread, beer, cheese and wine, and animals for domestication. From the early 1800s until the early twentieth century, many scientists began to reveal the basis for observations made during previous millennia.

Fundamental discoveries include: the nature of cells as the functional unit of living organisms; the existence of a nucleus in human, animal, plant and some other cells; invisible internal units (later called genes) that transfer information from one generation to the next and account for observable traits; chromosomes and their role in inheritance; proteins and enzymes; microorganisms; and the concepts of vaccination and evolution.

Penicillin

Modern biotechnology emerged in the 1940s with the large-scale production of penicillin in yeast. During a recent visit to London in August this year, I visited the Alexander Fleming Laboratory Museum. Tucked away in St Mary's Hospital, the Museum celebrates Fleming's discovery of penicillin on 28 September 1928 when he recognised the antibacterial effect of an accidental contamination by mould on one of his agar plates. Fleming identified the

1 Immediate Past President of the Royal Society of New South Wales.

mould as *Penicillium notatum* and named the antibacterial agent penicillin. He published his results (Fleming, 1929).

I had always known that chance was involved in the discovery but not the entire sequence of serendipitous events. In his biography of Fleming, Gywn Macfarlane describes their almost unbelievable improbability (Macfarlane, 1984).

> First, Fleming inoculates a plate with staphylococci and it happens to become contaminated with a rare, penicillin-producing strain of mould. Second, he happens not to incubate this plate. Third, he leaves it on his bench undisturbed while he is away on holiday. Fourth, the weather during this period is at first cold and then warm. Fifth, Fleming examines the plate, sees nothing interesting and discards it, but, by chance, it escapes immersion in lysol. Sixth, Pryce [one of Fleming's former colleagues] happens to visit Fleming's room, and Fleming decides to show him some of the many plates that had piled up on the bench. Seventh, Fleming happens to pick the discarded penicillin plate out of the tray of lysol (in which it should have been immersed), and on a second inspection sees something interesting.

Despite the serendipity, Fleming is rightfully acclaimed for his prepared mind that recognised the significance of his observation. Fleming, Ernst Boris Chain and Howard Walter Florey were awarded the Nobel Prize in Physiology or Medicine jointly in 1945 for discovering penicillin, isolating the active substance from the mould, and developing methods to produce it at scale for therapeutic use. Penicillin was first used extensively and highly effectively during the WW II North Africa campaign in 1943. Introduced for public use in 1946, it represents one of the greatest medical breakthroughs of the 20th century.

DNA double helix

My second stop in August was London's Science Museum to see first-hand another great scientific breakthrough: the double helix model of DNA (deoxyribonucleic acid) created by Francis Crick and James Watson at Cambridge University. The reconstruction displayed in the museum includes some of the metal plates used in their original model.

By incorporating X-ray crystallography results from King's College London, Watson and Crick determined that the structure of DNA is spiral, consisting of two strands of DNA wound around each other in a double helix. Each strand has a backbone made of alternating sugar (deoxyribose) and phosphate groups. One of four bases — adenine (A), cytosine (C), guanine (G), or thymine (T) — is attached to each sugar. The two strands are connected by chemical bonds between the bases: A bonds with T, and C bonds with G.

In April 1953, *Nature* published a one-page article by Watson and Crick (1953) reporting their results, along with articles by Rosalind Franklin (Franklin and Gosling, 1953) and Maurice Wilkins (Wilkins et al., 1953) who were contemporaries at King's College. The iconic final sentence in Watson and Crick's paper reads: "it has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material." This heralded our modern understanding of the role of DNA in inheritance and direction of protein synthesis via messenger RNA (ribo-

nucleic acid). Watson, Crick and Wilkins were awarded the Nobel Prize in Physiology or Medicine in 1962.

Rosalind Franklin was ineligible to receive the Nobel Prize because she had died four years before the award at the age 37 from ovarian cancer. Brenda Maddox in her biography *Rosalind Franklin: The Dark Lady of DNA* presents a detailed account of Franklin's life and the significance of her science (Maddox, 2002). She writes:

> [b]ut could Watson and Crick have done it without the 'dark lady': Rosalind Franklin, the thirty-two-year-old physical chemist ... Her research data, which had reached them by a circuitous route and without her consent, had been crucial to their discovery. Watson's glimpse of one of her X-ray photographs of DNA gave him and Crick the final boost to the summit. From the evidence in her notebooks, it is clear that she would have got there by herself before long.

Other research during the 1950s and 1960s unlocked many more advances in biotechnology. Nobel Prizes in Physiology or Medicine, or Chemistry awarded for discoveries made during these decades track many of these revolutionary discoveries.

Recombinant DNA technologies

In 1972, Paul Berg from Stanford University reported success in splicing a piece of DNA from a bacterial virus into the DNA of a virus that infects monkeys (Jackson et al., 1972). He was awarded one half of the 1980 Nobel Prize in Chemistry for his fundamental work on the biochemistry of nucleic acids and recombinant DNAs.

In passing, I note that the other half of the 1980 Nobel Prize in Chemistry was awarded jointly to Walter Gilbert and Frederick Sanger for their contributions to the determination of base sequences in nucleic acids. An initial sequence covering about 90% of the human genome (but missing complex repeated sequences) was published in 2001 (IHGSC, 2001) and the complete sequence in 2022 (Nurk et al., 2022). The capacity to sequence nucleic acids (now very cheaply) marked a turning point in the history of medicine towards preventive healthcare and precision medicine. For example, rapid gene sequencing played a pivotal role in the global responses to the devastating COVID-19 pandemic, enabling rapid identification of and testing for the virus and its variants and development of effective vaccines.

Recombinant DNA (rDNA) technologies involve joining (recombining) pieces of DNA in a test tube, creating identical copies (cloning) in a bacterium or another organism, and expressing the DNA as a protein or ribonucleic acid (RNA) molecule. Key to this process is the ability, using enzymes (restriction enzymes, usually from bacteria), to cut DNA at a specific point (restriction site) in its sequence, produce a well-defined fragment, and then to paste it using ligating enzymes (ligases) into a specific sequence in the DNA of another organism.

When I took up my appointment in medicine and clinical pharmacology at the University of California San Francisco (UCSF) in 1977, I had a bird's eye view of the early days of the Genentech (*Gen*etic *En*gineering *Tech*nologies). This, the world's first biotechnology company and still an icon of the industry, was established in 1976 by venture capitalist Robert Swanson and Herbert Boyer (USCF) with the radical goal of using rDNA technology to produce human proteins at scale.

Earlier, in 1974, Boyer and his colleague Stanley Cohen from Stanford University had filed the first of their patents on the process and products of rDNA. They had succeeded in incorporating human genes into bacteria, thus allowing them to replicate and express the human gene as recombinant protein. Boyer and Cohen used plasmids — tiny rings of DNA that can reproduce in the cytoplasm of bacterial cells — to transport the DNA fragments into bacteria, and a restriction enzyme (EcoRI) that cut DNA predictably at a specific position and produce "sticky ends" that make it easy to paste in a second DNA fragment. They demonstrated that the engineered plasmids reproduced in bacterial cells and thus cloned the inserted foreign DNA. Plasmids were being studied for their role in the growing problem of bacterial resistance to antibiotics.

During their lifetime, the Cohen-Boyer patents, which expired in December 1997, were licensed to Genentech and hundreds of other companies and earned millions of dollars in royalties for Stanford and UCSF.

Science historian Sally Smith Hughes tells the story of Genentech's turbulent, triumphant ride (Hughes, 2009). She writes:

> Genentech's future rested on technological innovation, business acumen, human dedication, and a freewheeling, can-do culture strikingly different from anything the pharmaceutical industry offered. Its handful of irreverent scientists captured a swiftly expanding audience as they cloned and expressed three medically significant genes in three successive years: human insulin, human growth hormone, and human interferon.

In 1978, Eli Lilly licensed Genentech's rDNA technology to produce insulin. In 1982 the US Food and Drug Administration (FDA) approved the Genentech-Lilly recombinant human insulin (Humulin), the first rDNA product to reach the market. The production of pharmaceutical grade human insulin at scale represents one of the most significant accomplishments of modern medicine.

In 1985, Genentech received FDA approval to market its own product: human growth hormone for children with growth hormone deficiency. This was a major step forward for patients previously receiving the hormone pooled from multiple cadavers and thus at risk of developing Creutzfeldt-Jakob disease from any donor carrying the neuropathogenic protein known as a prion.[2]

Development of products based on the rDNA revolution necessitated a revolution within regulatory agencies, such as the FDA and Australia's Therapeutics Goods Administration (TGA). Divergent views about the risks and regulation of rDNA technologies have been debated ever since the meeting held in 1975 at the Asilomar Conference Grounds in California, when a group of scientists agreed on guidelines defining what experiments should and should not be done. They were concerned, for example, about the potential to create new organisms that could infect laboratory staff and the wider public. Such discussions continue today (Cobb, 2025).

When I returned to Australia in 1985, I was very much involved in these debates through my service as an independent member of many TGA Advisory Committees. Many of the initial concerns raised

2 Deaths had occurred. [Ed.]

at the Asilomar conference of 1975 never materialised. It was always a good day when, based on thorough risk-benefit analysis, we could recommend approval of the next therapeutic advance created using rDNA technologies. They continue to produce breakthrough treatments. Recent approvals by the TGA include potentially curative antibodies for metastatic cancers, including melanoma, and antibodies that appear to slow progression of Alzheimer's disease in patients in the early stages.

The AIDS epidemic

From 1980–1984 I was amongst the group of physicians at the San Francisco General Hospital (SFGH) treating patients with a new disease initially known as "gay-related immune deficiency" (GRID). In 1981, the US Centre for Disease Control (CDC) reported similar cases in New York and Los Angeles. Previously healthy young men were presenting with rare infections such as *Pneumocystis carinii Pneumonia* (PCP) and atypical tuberculosis. Some developed tumours such as Kaposi's sarcoma, a rare and aggressive cancer, and lymphomas. Many manifested unusual allergies to their medications.

The CDC used the name "acquired immunodeficiency syndrome" (AIDS) for the first time in 1982, providing as the case definition, "a disease, at least moderately predictive of a defect in cell-mediated immunity, occurring in persons with no known cause for diminished resistance to that disease." It had also become apparent that several groups of people were at risk of AIDS. Amongst them were blood transfusion recipients, injecting drug users, and babies born to mothers with AIDS.

AIDS was proving to be a death sentence, sometimes within weeks of diagnosis. The intensive-care wards at SFGH were full of AIDS patients. By 1983, the disease had affected and killed hundreds of patients in San Francisco alone. SFGH established specific wards in collaboration with the gay community — Ward 86 for outpatients and 5B for inpatients — to ensure optimal care.

AIDS was also becoming recognised as a global epidemic as reports streamed in from many other countries, including Africa where transmission was largely in heterosexual populations.

In 1984, an RNA virus, later named Human Immunodeficiency Virus (HIV), was identified as the infectious agent (Gallo et al., 1984; Barré-Sinoussi et al., 1983). Then followed four decades of research and development resulting in tests to identify patients, screen blood supplies, sequence the wide variety of viral variants, unravel the life cycle of the virus (including the many years between initial infection and clinical presentation), and introduce safe and effective anti-HIV drugs.

The first patients with AIDS in Australia were diagnosed in Sydney and Melbourne in 1982 and 1983. Australia mounted a strong, proactive and effective medical and community response to the epidemic. Key leaders included: RSNSW Fellows David Cooper and Chris Puplick; Distinguished Fellows Marie Bashir, Peter Baume, Barry Jones and Michael Kirby; as well as Neal Blewett, William Bowtell, Julian Gold and Ronald Penny. There were many more.

A Liberal NSW Senator from 1974–1990, Peter Baume held several ministerial and shadow portfolios and was member of the AIDS Parliamentary Liaison Group from 1985. In 1991, he delivered a comprehensive report on the inquiry he conducted into perceived dissatisfaction, particularly by

the AIDS community, with the timely availability of anti-HIV agents in Australia (Baume, 1991).

By that time, I had been back in Australia for six years as Professor of Medicine and Clinical Pharmacology at the University of Queensland and served on several TGA committees. In 1992, I was invited to join the "new" Australian Drug Evaluation Committee (ADEC; now known as the Advisory Committee on Prescription Medicines) established as part of the Baume recommendations. I served as Chair from 1994–1996.

During these years, we approved several breakthrough anti-HIV agents, including HIV protease and non-nucleoside reverse transcriptase inhibitors. These and many other advances led to the registration of dozens of small-molecule anti-HIV therapies, including the modern long-acting injectable drugs that provide durable suppression of HIV and enable patients to live a normal life.

Despite these successes, there remains no effective anti-HIV vaccine. The many strategies designed and tested have been foiled by complexities of the virus, including its high genetic diversity and its interactions with the host, such as integrating into cellular DNA thus becoming "hidden" from any immunologic response.

In 1997, I entered the second phase of my career, joining Johnson & Johnson Research (JJR), an Australian-based subsidiary of Johnson & Johnson Inc (J&J) established to design and build RNA or DNA molecules that can target and cut specific nucleic acid sequences. JJR had licensed the patents on the discovery of naturally occurring RNA enzymes (ribozymes) in plants from the CSIRO spin-out Gene Shears Pty Ltd to investigate their therapeutic applications in humans.

One of JJR's projects was to develop a once-only treatment for patients infected with HIV that reduces viral load, preserves the immune system, and avoids a lifetime of antiretroviral therapy: the equivalent of a vaccine. We harvested bone marrow stem cells from patients, introduced the anti-HIV ribozyme gene using recombinant technology, then returned the modified stem cells to the patient to engraft, divide, and differentiate into a pool of mature immune cells that would be protected from HIV infection, in theory.

We designed and conducted the first ever randomised, placebo-controlled Phase II trial of this cell and gene therapy by recruiting 75 patients infected with HIV in Sydney, at Stanford University and the University of California Los Angeles. The trial was conducted under the regulatory auspices of the TGA in Australia and the FDA in the USA. David Cooper was the principal investigator at our clinical trial site in Sydney. Leaders at JJR included Louise Evans (medical), Janet Macpherson (cell and gene manufacturing), and Geoffrey Symonds (scientific). We filed many patents along the way and published the results in *Nature Medicine*, reporting that our cell and gene therapy approach was safe but did not achieve a sufficient population of protected cells to reduce viral load (Mitsuyasu et al., 2009). Nonetheless, it was a promising start.

When JJR closed in 2009, we formed two companies. The molecular diagnostics technologies that had been invented to underpin the clinical trial were spun out by Alison Todd and Elisa Mokany into the venture-capital-backed company, SpeeDx. It continues today as a successful company

at the Australian Technology Park. Calimmune Australia was formed as a division of the US parent, Calimmune, to continue work on the stem cell gene therapy platform. The entire company was acquired by CSL Behring in 2017 to complement its gene and stem-cell based therapies portfolio.[3]

As for me, increasingly concerned about the well-being of our planet, I took up a position in industrial biotechnology in the newly established Dow Sustainability Program at the United States Studies Centre (USSC) at the University of Sydney. There I developed and led the Alternative Transport Fuels Initiative. From its inception, this program was framed as a national and international collaboration between the wide variety of partners required to improve the environmental performance of all transport modes, but especially aviation.

Aviation must join the global transition to low-carbon emissions but has fewer options than road transport, given its dependence on jet fuel from fossil oil, which is high-energy-dense, light, low-freezing-point, relatively inexpensive, and safe. Sustainable aviation fuels with similar properties to conventional jet fuels can be produced using industrial biotechnology processes, but the challenge is to reach scale (Pond, 2017).

I will leave this story here to be told another day, except to note the recent commitment by the Australian Government of $1.1 billion to support the production of low-carbon liquid fuels in Australia for industries such as aviation, heavy freight and mining.[4]

The future of biotechnology

By covering but a tiny sliver of the field, I hope nonetheless to have given an inkling of the power of biotechnology to enhance our understanding of nature and deploy it for the benefit of ourselves and our biosphere.

The biotechnology revolution will accelerate exponentially, given present-day capacities to read (sequence), write (synthesise), and edit (add, remove or change a single base) DNA, and converge the biological with other rapidly advancing technologies, such as artificial intelligence,[5] information technologies, materials science and engineering, nanotechnology, quantum computing, and robotics.

Risks and unanticipated consequences always stem from new technologies. We must remain vigilant to any new threats that they pose to public health, individual safety and national security. The RSNSW will continue to lead multidisciplinary debate and engage the wider public with the aim of driving the brightest possible future for humanity.

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3 https://investors.csl.com/PDF/f00cb92f-cb30-4ed5-a5db-40a2c960f233/CSLBehringAcquiresUSBiotechCompanyCalimmune

4 https://www.dcceew.gov.au/about/news/new-prod-incentive-low-carbon-liquid-fuels

5 The 2024 Nobel Prize for Chemistry was awarded partly for the development of an AI model to solve a 50-year-old problem: predicting proteins' complex structures. [Ed.]

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