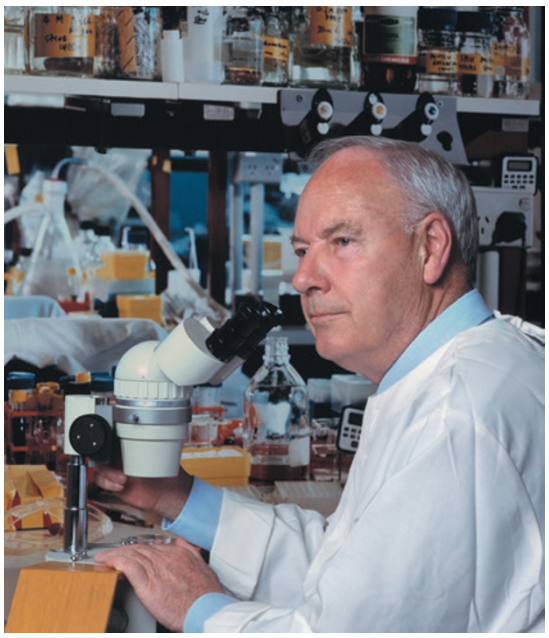
Donald Metcalf

(1929–2014)

Discoverer of hormones that regulate blood-cell proliferation.



WALTER AND ELIZA HALL INSTITUTE

Donald Metcalf established which blood cells give rise to which, and identified the hormones that regulate the cells' proliferation and differentiation. His work, which shed light on how to boost people's supplies of white blood cells, has benefited millions.

Metcalf — Don to nearly everyone who worked with him — died on 15 December 2014. He was born in 1929 in Mittagong in the Southern Highlands of New South Wales, Australia, to schoolteachers. During his medical degree at the University of Sydney, Metcalf's passion for research was ignited when he spent a year studying the ectromelia virus, which causes 'mousepox'.

Metcalf received his degree in 1953 and moved to Melbourne in 1954 to join the Walter and Eliza Hall Institute of Medical Research (WEHI). Aside from brief trips to Europe and the United States, he spent his 60-year career at the institute, supported throughout by the Carden Fellowship of the Anti-Cancer Council of Victoria (now the Cancer Council).

Metcalf's arrival at the WEHI was not smooth. Its then director, Frank Macfarlane Burnet, who was later awarded the Nobel Prize in Physiology or Medicine for his work on immunity, was not a fan of cancer research. According to Metcalf, Burnet, like many others at the time, viewed cancer as "an inevitable disease", and cancer researchers as either "rogues or fools". Metcalf was undeterred.

For ten years he worked on cell turnover in an immune organ called the thymus, until a chance finding changed his focus. Metcalf, with Ray Bradley of the University of Melbourne, discovered that he could grow colonies of blood cells in agar, provided that the right stimulus was added.

Metcalf's genius lay in realizing that he could use this system to work out how cell types are related, and also to characterize the hormones that regulate the cells' proliferation and differentiation. He named these hormones colony-stimulating factors (CSFs). Over the next 50 years, Metcalf made the blood-cell system the model for understanding the regulation of cell growth in body tissue.

Early on, Metcalf realized that to purify CSFs, and to clone the genes that encoded them, he would need collaborators. He recruited young faculty members with the required biochemical and biophysical skills to work with him at the WEHI. The group later collaborated with several molecular biologists who came to work at the Melbourne branch of the international Ludwig Institute for Cancer Research. The branch was directed by Tony Burgess, previously a laboratory head in Metcalf's WEHI Cancer Research Unit.

From 1965 to 1985, Metcalf and his team identified and purified four colony-stimulating factors: granulocyte-macrophage CSF (GM-CSF), granulocyte CSF (G-CSF), macrophage CSF (M-CSF) and multi-CSF, now known as interleukin-3. The team also cloned the gene for one of these, GM-CSF; the other genes were cloned by groups around the world.

This work paved the way for mass production of the hormones and the experiment that Metcalf had long dreamed of: injecting CSFs into animals. His niggling doubt was that the factors — purified using a contrived *in vitro* assay — might be irrelevant to normal physiology. He needn't have worried. In mice, the CSFs triggered a spectacular rise in the number of white blood cells in the bone marrow and peripheral blood.

Clinical applications soon followed. The most widespread use of CSFs has been to ameliorate leukopenia, a decline in the number of white blood cells associated with chemotherapy. During phase I clinical trials of G-CSF conducted in the late 1980s, Metcalf and his collaborators noticed that administering the hormone prompted large numbers of haemopoietic stem cells — precursor cells that give rise to all types of blood cell — to move from a person's bone marrow into their peripheral blood.

The finding allowed clinicians to harvest stem cells simply by injecting people with G-CSF and taking their blood, rather than by extracting the cells from bone marrow — a more painful and complicated procedure. The new method made the transplantation of blood stem cells safer, easier, more effective and ultimately more widely used. In the past 20 years, 20 million people are thought to have benefitted from Metcalf's discoveries.

None of the many prizes that Don received conveys the degree to which he was a scientist's scientist. He distrusted researchers who had turned their back on the bench; he always worked in the laboratory, assisted by one or two research assistants and an occasional graduate student or postdoctoral fellow. He had an incredible work ethic. Having worked in the lab for eight or nine hours, Don would write papers or books at home. He also detested spin. His inclination was to produce one paragraph of discussion for each page of results — not a word more.

The only thing that Don valued more than his science was his family — Jo, his wife of more than 60 years, his four daughters and six grandchildren. Last August, when Don was diagnosed with incurable metastatic pancreatic cancer, he faced a dilemma: how could he continue to do experiments and spend as much time as possible with his beloved Jo? He found a solution: he had his microscope moved to his dining-room table. Don continued to work, surrounded by his loved ones, until early November — exactly as he wanted it. ■

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