Mastering Disease Through Discovery

CELEBRATING THE ACHIEVEMENTS OF PROFESSOR DONALD METCALF ON HIS 80TH BIRTHDAY
THE WORLD OF 1929

Meanwhile, the infant Donald Metcalf enjoys Australian country life.

The illustrious Donald Bradman hits a six…

…while the harbour is bridged in Sydney…

…and the Jazz Age hits dizzy heights.

A view of prosperous Bourke Street, Melbourne, in early 1929, looking east towards Parliament House.

Chaos on Wall Street in late 1929, with the stock market crash and the onset of the Great Depression.
How does one capture in just a few paragraphs the essence of an 80-year old icon?

I shall begin with his remarkable scientific achievements. Known the world over as ‘the father of modern haematology’, Don Metcalf’s 44-year quest to understand how blood cells are generated by the body led to the identification and purification of the CSFs, hormone-like proteins essential for white blood cell production. CSFs have now been used to treat over 8 million cancer patients, in order to replenish the vital blood cells destroyed by their chemotherapy.

Don has garnered almost every major international science prize, including the Bristol-Myer Prize for Distinguished Cancer Research (1987); Robert Koch Prize (1988); Alfred P Sloan Prize of the General Motors Cancer Research Foundation (1989); Albert Lasker Award for Clinical Medical Research (1993); Gairdner Foundation International Award (1994); Royal Medal of the Royal Society (1995) and the AACR Lifetime Achievement Award (2007). Nationally, he has received the prestigious Victoria Prize (2000) and Prime Minister’s Prize for Science (2001). His peers have elected him a Fellow of the Australian Academy of Science (1969), Fellow of the Royal Society of London (1983) and a Foreign Associate of the US National Academy of Sciences (1988).

At WEHI, the image of Don meticulously counting colonies at his microscope, challenging seminar speakers and pricking egos with a sardonic thrust in his deep slow drawl is etched into our psyches. He does not suffer either fools or theorisers. He is the quintessential ‘scientist’s scientist’, obsessed with gathering impeccable data, publishing unassailable experiments and challenging scientific fads. His rigour and determination to make discoveries that improve human health are a model to us all. He is intensely loyal to WEHI and his co-workers, a great raconteur and, under the tough shell, a very warm and sensitive human being.

I count myself very fortunate to have had Don as my colleague and mentor – and to have had the friendship of Don and his beloved Jo for over 30 years.

Happy birthday, Don!

Suzanne Cory

PROFESSOR SUZANNE CORY AC
Director, The Walter and Eliza Hall Institute of Medical Research
It gives me immense pleasure to pay tribute to Professor Donald Metcalf on his 80th birthday.

A relentless experimentalist, Professor Metcalf was awarded the Victoria Prize in 2000 and the Prime Minister’s Prize for Science in 2001 but his ability to articulate and translate his discoveries in haematology has been invaluable to more than just Victoria’s thriving biotechnology research sector.

His vast list of international accolades includes some of the highest honours in the world of contemporary science. They reinforce Professor Metcalf’s role in laying the foundation and nurturing an abundant field of research. In addition to being considered the pioneer of modern haematology, he is among the most original and influential thinkers in the biomedical field and no doubt one of Australia’s greatest scientists.

Even with this recognition, Professor Metcalf has remained committed to his roots. His longstanding association with The Walter and Eliza Hall Institute dates back to 1954, when he joined the organisation as the Carden Fellow in Cancer Research – a position he continues to hold.

Over five decades, his pioneering research in Colony Stimulating Factors has led to significant medical breakthroughs and has helped patients worldwide regenerate blood cells following cancer treatment. In this time, he has demonstrated generosity in fostering new generations of Victorian minds, and in his readiness to acknowledge the 350-plus scientists with whom he has collaborated and co-published.

My congratulations to Professor Metcalf on a stellar career and for his tremendous contribution to the Victorian community. I wish him the very best in all his future endeavours.
WHAT ARE THE CSFs?
A revolutionary discovery defined

To understand Don Metcalf’s discoveries, we first need to consider some of the basic facts about blood. There are three blood cell types: red blood cells, platelets and white blood cells. All three kinds of blood cell are produced in the bone marrow, deriving from a single type of stem cell: the haematopoietic stem cell or blood-forming cell.

Red blood cells are the most common. They travel throughout the body and deliver oxygen to the body’s tissues. Platelets are tiny circulating cells responsible for blood clotting and wound healing. White blood cells are part of the body’s immune system. Relatively few in number, being less than 1% of all blood cells, they patrol the body, ready to attack infectious agents and ‘non self’ invaders.

Regarding Don Metcalf’s work, it’s the white blood cells that are of particular interest to us. To maintain its defences against infection, the body needs to produce up to 5 billion white blood cells every day. We now know that the regulation of white blood cell production is the responsibility of naturally occurring hormones (chemical messengers) that Metcalf called the Colony Stimulating Factors or CSFs – but this was unknown to anyone right up to the mid 1960s.

You may be aware that the CSFs are of special relevance to cancer patients who are being treated by chemotherapy. Usually, chemotherapy takes the form of a fluid that is infused into the bloodstream. The fluid contains chemical (chemo) agents or drugs that search for rapidly dividing cells, which are typical of cancer tumours. The chemo drugs attack and attempt to destroy those rapidly dividing cancer cells.

Unfortunately, the chemo drugs are unable to distinguish the rapidly dividing cells of cancer tumours from the rapidly dividing blood cells of the bone marrow. Consequently, an undesirable side effect of chemotherapy is the progressive destruction of the bone marrow. This leads to a rapid decline in the production of all blood cell types. With severely diminished numbers of white blood cells, the cancer patient can become easy prey to serious and sometimes fatal opportunistic infections.

At The Walter and Eliza Hall Institute in the early 1960s, Don Metcalf speculated that there must be a biological mechanism – one or more hormones – that controlled white blood cell production. The existence of this unknown mechanism was suggested by the fact that patients suffering from infections experienced rapid increases in white blood cell production; and after damage to the bone marrow by chemotherapy in cancer patients, there was eventually a rise in blood cell numbers. If the naturally occurring hormones of blood cell production could be found, then perhaps they could be artificially mass-produced and administered to cancer patients to rapidly restore normal blood cell production. In the case of white blood cells, this quick restoration would enable cancer patients to effectively fight off otherwise potentially fatal infections while their chemotherapy programs continued at full pace.

Over a laborious period of fifteen years, Metcalf and his team did indeed find and purify four hormones that regulate blood cell production. These were dubbed Colony Stimulating Factors because they were the biological products (or growth factors) that stimulated the production of groups (or colonies) of white blood cells and other blood cells. By the late 1980s, the genes encoding the CSFs were isolated and gene cloning enabled the mass production of the CSFs to proceed. Since that time, the CSFs have moved into the clinic all around the globe. To date, more than eight million chemotherapy patients worldwide have had their essential immune functions – and, hopefully, their normal lives – rapidly restored to them, thanks to the CSFs.
I first met Don Metcalf 58 years ago when he was a Sydney University medical student who had recently completed a year of research in virology. The meeting is sharply etched in my mind. Don was witty, laconic, slow of speech (then with a broad, somewhat countrified Australian accent) but quick of mind. He gave me great courage to pursue a research apprenticeship in the same laboratory. We became close colleagues in 1958 as young blades within The Walter and Eliza Hall Institute. Though he worked on an organ, the thymus, full of lymphocyte cells, he would have none of the new vogue of immunology. Always the independent thinker, he was going to ‘crack’ the problem of leukaemia as the lone cancer researcher within the Institute. His little team was confined to an annexe, infelicitously located above the smelly animal house and made more unpleasant by the fact that the inbred mice on which he worked had to be bred right there on the spot. Discovering the extraordinary amount of white cell division going on in the thymus made him ask what molecular forces drove this multiplication. Hence an abiding fascination with white cell growth factors.

From bench to bedside

The definitive saga of the CSFs began through a collaboration with Ray Bradley in 1965. Bradley had learnt how to grow certain bone marrow cells in jellified growth media, much like growing bacteria from a throat swab. Colonies of hundreds to thousands of cells arose from a single progenitor, but only if the cells were ‘fed’ in the right way. Progress would only be possible if the postulated ‘colony stimulating factor’ (CSF) could be purified. This turned out to be a monumental task. I was appointed Director of the Institute in that year and was able to provide much better accommodation, but the harder part was to assemble the needed scientific skills. Over the years, Don worked with biochemists to find the needle in the haystack, the rare protein CSF molecule among the myriad proteins in the feeding soup. It turned out that there were four different CSFs at work. Don then had to persuade genetic engineers to ‘clone’ these molecules and
to provide enough material to study their effects in living mice. Finally, if the CSFs were to help patients with low white cell counts, clinicians had to join the team and validate usefulness in clinical trials. At each of these steps, Don encountered delays, frustrations, tough international competition and straight research setbacks. Yet he persisted, and thus became one of the few investigators to follow a discovery all the way from a basic finding at the laboratory bench to a finished product benefiting millions of people.

The qualities of success

What qualities of mind and spirit allowed this triumph? It certainly required tenacity and focus. Diligence also helped: Don’s unrelenting 10-hour days at the microscope (bad back notwithstanding) have become legendary. Breadth of knowledge was required. Don gradually established himself as the king of the new field of molecular haematology. He knew everyone in the game and therefore everything that was going on. Stability comes into the picture. Don has worked in the one institution with one major grant provider, Cancer Council Victoria, for 55 years. Also high on my list is loyalty. As the team gradually grew, Don was intensely loyal to everyone who put a shoulder to the wheel. Perhaps the biggest single factor was devotion to the primary data. Don participated personally in most experiments and saw the results not as digested by a colleague, but at first hand. Don is somewhat impatient with too much theorising; he is intensely evidence driven. This has given his laboratory’s work a remarkable solidity.

Onward

So at eighty, Don Metcalf continues his Odyssey of creativity, 15 years after what used to be considered retirement age, still mining the deep seams which remain in the expanding field that he established. Most of the several hundred scientists who came within his orbit are doing so, as well. This rare legacy is unlikely to be repeated in the annals of The Walter and Eliza Hall Institute.

SIR GUSTAV NOSSAL AC CBE
Director, The Walter and Eliza Hall Institute of Medical Research, 1965-1996
DON ON DON

When the legend becomes fact, print the legend


Don Metcalf has an individualistic, perhaps even idiosyncratic, outlook on life and science. It could also be argued that Don is somewhat taciturn by nature, given more to the arch remark than the rhetorical flourish. But fortunately for posterity, Don has gone ‘on the record’ in several comprehensive landmark interviews. Here, in extracts from classic interviews recorded in 1998 and 2007, he reflects upon his scientific career, in the process revealing his character and thoughts in ways that are sometimes outlandish and always entertaining.

Tell me about it

I don’t have time to read the [scientific] literature. I have no interest in finding out what Joe Blow did. And therefore I’m very ignorant and dependent on my colleagues for news or of new things now able to be done. I may well be able to think of how to do them properly.

Only 999 to go

Yes, I am a workaholic. If you present me with one thousand culture dishes, I will sit there until I have counted all the colonies on them. Will I say, “Hey, this is getting nowhere. I think I’ll clone a gene”? No, I won’t. I have always depended on being in a team of colleagues who say, “Listen, this is stupid. It makes no sense. Let’s do something else instead.”

Move over - let me drive

Restricted knowledge, I think, gets worse with age. You tend to become impatient. I dislike refereeing manuscripts that journals send me. I can’t be bothered reading what someone else did. I’m realising that I’m running out of time. I’ve only got time for a few more experiments and I want to do them and not be stuffed around and deviated onto other projects.
Haven’t I seen you somewhere before?

I want to do my own experiments, which I feel are probably going to be novel enough that I won’t accidentally repeat what somebody else has done. There’s a bigger risk that I will accidentally do something that I’ve done previously but forgotten. My colleagues take great joy from the fact that I forget so much. On four occasions now I’ve actually done experiments, repeated them with growing excitement, drawn up figures and got ready to write them up – only to discover that not only had I done the experiments before, but that I had already written them up and published them. I have no memory: I can read a novel and three weeks later not remember the plot at all.

*The preceding extracts are from an interview with Max Blythe for the Australian Academy of Science, Interviews with Australian Scientists, 1998.*
*The full AAS interview is available on the CD in the back of the book.*

Modesty forbids me

It’s a bit naïve to think that it’s me that did all this discovering and all this creativity. It was really several hundred people. I didn’t isolate the genes, I didn’t mass produce them, I didn’t make that bottle of stuff that [José Carreras] was given. So why parade around saying, ‘It was me. It wasn’t hard. It was me.’? You work every step of the way but, you know, it was a team. I didn’t do all that alone. Anyone who claims that is a nitwit.

Scientific Santa

I can’t wait to get to work. It’s like Christmas, isn’t it? Opening the incubator door every morning and getting out tray loads of cultures and saying, ‘Well, I wonder what’s happened.’ Now, if it hasn’t worked again, well, another day, tomorrow, we’ll try again.
What, me worry?

I’m never influenced by what the rest of the world thinks. If the rest of the world says, ‘That’s a stupid idea’, I don’t believe it for a moment. If anything, I’ll just work harder at it... I will try to think of an experiment that will prove them wrong and me right. And that’s the way you go.

Advanced recruitment policies

Be careful when you’re picking the next lot of students. Don’t just go for their academic record. Check where they grew up, where they went to school... And if the answers are ‘deprived suburb’ or ‘the country’, they’re probably going to be winners. That I grew up in the country has nothing to do with that. I distrust anyone who tops the year. Why? Because they’ve got a photographic memory and they will believe anything they read and can regurgitate it. Those that I look for can often be troublesome - but they know enough. And then if they’ve got bright eyes, I’ll pick them.

Are we there yet?

I really do think I’ll be found dead at the microscope. I hope that’s what happens. Why stop? Why stop if you’re competent enough to be doing something? There’s absolutely no point: there’s an infinity of stuff to discover. And if you can keep discovering things, why stop? I’ve got an enormous backlog of stuff to do...

The preceding extracts are from an interview with Robin Hughes for Film Australia Australian Biography, 2006.
A LIFE IN PICTURES

Professor Donald Metcalf's 80th Birthday Celebrations
DON METCALF – AN UNDULY MODEST AUSTRALIAN ICON

Barry Jones provides a global perspective

Don Metcalf, or to give him his full field rank, Professor Emeritus Donald Metcalf, AC, FAA, FRS, was born in 1929 in Mittagong, New South Wales, the son of teachers who were regularly on the move.

After studying at four high schools in the country, he entered the faculty of medicine at the University of Sydney, like his colleagues Gustav Nossal and Jacques Miller, with whom he later worked in Melbourne.

He was awarded the Carden Fellowship of the (then) Anti-Cancer Council of Victoria at The Walter and Eliza Hall Institute in 1954, a position he has held for more than 50 years. In the same year he married Josephine Lentaigne, a nurse, and they have four daughters.

When Don Metcalf joined the Hall Institute in 1954, the director was Macfarlane Burnet, a pre-eminent virologist, who made the dramatic decision in 1957 that the Institute should concentrate on immunology. Don Metcalf, whose interest was in cancer research, especially in leukaemia, had to struggle for resources. Metcalf noted of Burnet, ‘To him, cancer was an inevitable disease of ageing and therefore neither preventable nor curable…He knew virology backwards and was making important contributions. It just so happened that he didn’t know anything about cells or the blood-forming system…’ So Metcalf faced some difficult years at WEHI to demonstrate the importance of his work. But tenacity has always been one of his great strengths.

His book Summon up the Blood: In dogged pursuit of the blood cell regulators (AlphaMed Press, Ohio, 2000) is dedicated to ‘the 329 able scientists and clinicians who worked together in our studies on the colony-stimulating factors and to our colleagues and competitors in the field’. He described ‘a 35-year saga’ in which he worked with single-minded determination, despite having an allergy to mice.

In 1965, in Melbourne, Ray Bradley had observed that blood-forming cells could be developed as colonies. Metcalf’s great insight was the realisation that the growth of the colonies required the addition of a stimulating factor and he devoted years to purifying the ‘colony stimulating factor’ (CSF) from urine and tissue.

Don Metcalf’s work with Nick Nicola, Tony Burgess and others at The Walter and Eliza Hall Institute, The Ludwig Institute and The Royal Melbourne Hospital indicated that there were several distinct ‘colony stimulating factors’ or CSFs that could stimulate the production of different white blood cells and controlled their survival, proliferation, maturation and function.

Two of the CSFs, G-CSF (granulocyte CSF) and GM-CSF (granulocyte-macrophage CSF) are now in extensive clinical use after chemotherapy. Metcalf and his colleagues discovered that these cytokines raise the levels of haemopoietic stem cells in the blood and now bone marrow transplantation has been largely supplanted by blood stem cell transplantation as a means to replace the vital blood cells destroyed by chemotherapy. The CSFs are also used in treating arthritis, other autoimmune diseases and neonatal infections.
One of the first cancer patients to benefit from Don Metcalf’s work was the Spanish tenor José Carreras who has paid repeated tributes to the development of CSFs, which have now treated over eight million patients.

In 1966, Metcalf became Assistant Director of WEHI and Head of the Cancer Research Unit until he retired, theoretically, in 1996. He was elected FAA in 1969 and FRS in 1983. In Australia he received an AO in 1976, upgraded to AC in 1993. In 2000 he received the Victoria Prize, followed in 2001 by the Prime Minister’s Science Prize, the highest Australian award for research.

I should declare an interest.

In 1990, as Minister for Science, I established the Australia Prize as an international award (and the Japan Prize was an obvious model). However in the year 2000 the title was changed to the Prime Minister’s Prize for Science. I sent a respectful protest to John Howard pointing out that the world had 120 Prime Ministers but only one Australia. I asked him, as a cricket tragic, would he rather be a member of the Prime Minister’s First XI or the Australian First XI? Although normally very courteous with correspondence, he failed to reply.

Don Metcalf was immortalised as an Australian Legend in 2002 when Australia Post dedicated a stamp to him. His modest Wikipedia entry (13 lines) has no free image, and asks, plaintively, ‘Do you own one? If so, please click here’.

He commented to Max Blythe that his children ‘moved as far away from science as they could think of’. As a self-confessed workaholic, he is miserly in hoarding time that can be used for more experiments, rather than reviewing the literature, or playing chess. I am relieved that he makes an exception for music. He taught through example, not by exposition, let alone declamation.

BARRY JONES AO
Federal Minister for Science, 1983-1990
REFLECTIONS OF A LIFE IN SCIENCE

By Professor Donald Metcalf

It is hard to believe that 54 years have passed since I first joined the Institute. Much has been discovered around the world in this eventful period but we still have barely scratched the surface of what remains to be discovered – to garner information that hopefully can be used to make an impact on disease.

I am quite aware that, even with the help of colleagues, in the time remaining to me, I am not likely to make too many of the major discoveries that are so badly needed. I have therefore made for myself a short list of what I assess to be quite important questions that may be possible for me to tackle successfully. Oddly enough, neither my colleagues nor my competitors appear to have much interest in these questions, so I am in the happy position of having a clear field.

I have had the great good fortune to have worked in The Walter and Eliza Hall Institute of Medical Research and to have had sustained research support. More important, I have had the luck to have had skilled colleagues able to exploit emerging technologies that permitted us to complete some important studies. I trust that this luck will continue, knowing that ‘luck’ is often merely the result of persistent careful work coupled with astute observation.

May my luck continue with agreeable colleagues and projects that yield consistent results! May each of you continue to experience the excitement and joy of the hunt!

A selection of Don Metcalf’s honours and awards

Grand Hamdan International Award 2008 UAE
Prime Minister’s Prize for Science 2001 Australia
Royal Medal Royal Society 1995 UK
Gairdner Foundation International Award 1994 Canada

Wellcome Medal 1986 UK
Kovalenko Medal US Academy of Sciences 1994 USA
Robert Koch Prize 1988 Germany
Sloan Prize – General Motors Cancer Research Foundation 1989 USA
Companion of the Order of Australia 1993 Australia
Albert Lasker Clinical Medical Research Award 1993 USA
Donald Metcalf was born in February 1929 in Mittagong, New South Wales, Australia. He was educated at the University of Sydney, where in 1951 he received a BSc (Med). In 1953, he earned an MB BS for his work on the ectromelia virus – the beginning of his interest in haematology. He received his MD in 1961. Metcalf was a resident medical officer at the Royal Prince Alfred Hospital in Sydney, when in 1954 he accepted a Carden Fellowship in cancer research from the (then) Anti-Cancer Council of Victoria. He moved to Melbourne’s Walter and Eliza Hall Institute of Medical Research (WEHI), where under Sir Macfarlane Burnet he initially studied vaccinia virus. Metcalf was a postdoctoral student at Harvard Medical School 1956-1958, returning to WEHI as Head of the Cancer Research Laboratory in 1958. From that time to this day, Metcalf has remained actively engaged in research at WEHI – his official ‘retirement’ in 1996 notwithstanding. Metcalf’s and his colleagues’ pioneering discovery of blood cell regulators - the ‘Colony Stimulating Factors’ – was the result of thirty years’ painstaking experimentation, leading to international clinical application for the benefit of eight million cancer patients, so far.

The front and back cover images show haemopoietic colonies with the maturing cells migrating outwards in the agar gel.

Acknowledgements

Produced by WEHI’s Communications Department
Editor: Brad Allan
Designer: Simon Taplin
Project Support: Peter Maltezos and Czesia Markiewicz
©2009 The Walter and Eliza Hall Institute of Medical Research
1G Royal Parade
Parkville Victoria 3052 Australia