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Introduction for Donald Metcalf

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It is a personal pleasure to introduce my friend and former colleague, Donald Metcalf. He is best recognized as one of the founding fathers of modern experimental hematology, but we should not forget his pioneering work on the thymus. From 1956 and the decade thereafter, Don undertook a series of elegant studies on thymic cell kinetics and was one of the first to analyze the impact of thymectomy and thymic grafting on lymphopoiesis. Indeed, he should be considered the first to demonstrate the effects of thymectomy on lymphoid tissue and the autonomous control of lymphocyte proliferation within the thymus. In addition, his analysis of leukemogenesis in AKR mice is still considered definitive, revealing his ability to compare and contrast the cellular biology of the normal and neoplastic to gain insight into the etiology and pathogenesis of leukemia. The same consummate skills as an experimentalist, and the same insight and interest, were to mark his subsequent investigations into myelopoiesis and myeloid leukemia that have occupied the last two decades.

I had known and admired Don's work during his "thymic phase," since I also began my research career on thymic development, and it was this area that led me to move from England to Australia in 1967 to begin what was to be a 7-year collaboration with Don. Why, you may ask, did Don move out of the thymus area at the very time that it became a major preoccupation of immunologists? To understand this you must understand the environment, the man, and the interplay of chance and the prepared mind. In 1965 the Nobel Laureate, Sir Macfarlane Burnet, retired as Director of the Walter and Eliza Hall Institute for Medical Research (WEHI), appointing as his successors his two protégés, Gus Nossal as Director and Don Metcalf as Assistant Director and Head of the Cancer Research Unit. This was a wise decision, since Don remained relatively unburdened by administrative responsibilities, which he naturally finds irksome, and was able to pursue his scientific interests. The "golden age of immunology" can be considered to have begun in the mid-1960s and the Hall Institute was very much at the forefront. Don has always disliked the "bandwagon" concept of research, choosing instead to move in his own directions and as much as possible into uncharted territory.

At this time, experimental hematology was emerging from its lowly status as a descriptive morphological discipline, helped by radioisotope labeling kinetics and the first stem cell assay (CFU-S), as well as some knowledge about erythropoietin and regulation of erythropoiesis. While vision and concepts are necessary to move a field, there is a third essential, the catalyst of methodology. Hematology lacked in vitro systems for quantitation of hematopoietic cell proliferation and differentiation, and so an important milestone was reached in 1965 when Don, with Dr. Ray Bradley, developed a semisolid culture technique, permitting the clonal growth and maturation of granulocytes and macrophages, from committed precursors in the bone marrow. This tech-

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nique was subsequently modified by him and his colleagues to permit the clonal culture of eosinophils, megakaryocytes, B-lymphocytes and multipotential cells. With the use of these clonal culture techniques and cell separation procedures, he and his collaborators succeeded in characterizing hematopoietic stem cells and progenitor cells. His analysis of the growth requirements of granulocytes and macrophages led to the discovery of a group of specific glycoprotein regulators, the colony stimulating factors (CSFs). All four murine CSFs have been purified by his group, and work by his group and others has now led to the cloning of cDNAs for all four murine and human CSFs. His recent work, using bacterially synthesized recombinant CSFs, has shown that the CSFs' function in vivo is to control the production and function of granulocytes, monocytes, and related blood cells. In this era of megabuck science, it is instructive to remember that much of the pioneering work and the seminal observations were made in agar cultures using tools no more sophisticated than a microscope, a handheld micropipette, glass slides, and orcein stain.

To the requirements of vision, technical expertise, and powers of observation, there must be added "Chance, Fortune, Luck, Destiny, Fate, Providence which determine whether you walk to the right or left of a particular tree ..." I think this is best illustrated by recalling the circumstances surrounding the murine myelomonocytic leukemia WEHI-3. This tumor arose very early in a very large experiment on mineral oil induction of plasmacytomas in BALB/c mice, being carried out by Noel Warner and myself. Not only was this tumor unique among all the hundreds of tumors that subsequently developed, it was exactly the right tumor (myelomonocytic leukemia), with the right properties (responded to CSFs by proliferation or differentiation, produced CSFs, cloned in agar), in the right place (Cancer Research Unit, WEHI), at the right time (1968–1969), when our interests were extending from the role of growth factors in normal myelopoiesis to regulatory aberrations in myeloid leukemia.

Studies on WEHI-3 led to subsequent studies in which human myeloid leukemic populations were shown to remain CSF-dependent for cell proliferation, but one CSF, G-CSF, also had the property of suppressing myeloid leukemic cells by enforced differentiation. While showing that myeloid leukemia development need not involve autocrine mechanisms, Don and his group have recently shown that the genes for GM-CSF and interleukin-3 (IL-3) can function as proto-oncogenes. It is exceedingly unlikely that WEHI-3 would have been analyzed to the extent it was if it had developed elsewhere and one wonders without it how long it would have taken to "discover," purify, and clone IL-3 and G-CSF, since both growth factors were discovered as a direct result of the use of the WEHI-3 cell lines as constitutive sources of IL-3 and as specific responders to G-CSF.

Early in 1986 I had the pleasure of attending a Birthday Party Symposium at the Hall Institute to celebrate the 21st anniversary of the discovery of the in vitro hematopoietic colony assay. It was very much a coming-of-age party for experimental hematology, heralding its own golden age, which Don was so instrumental in creating. For those who attended the final party, the image of Don Metcalf, Ray Bradley, Leo Sachs, and Bun McCulloch, festooned with colored balloons of varying sizes representing the cellular and regulatory aspects of their respective contributions to hematology, was a vision better seen than described. What was also evident was the contribution that Don has made in inspiring the second, and what is now the third generation of "new wave" experimental hematologists.

Don's contributions were recognized by his recent award of the Wellcome Prize of the Royal Society which is, I am sure, just the beginning of a succession of recognitions for his pioneering role in the modern era of hematology and leukemia research. Your work has not only led to the discovery and characterization of hematopoietic growth factors, but as a former clinician (1953, Royal Prince Alfred Hospital, Sydney), the initiation of clinical trials with recombinant growth factors must be a source of satisfaction to you – ("Only if they are done right," I hear you say). With these words, ladies and gentlemen, it is my distinct personal pleasure to present to you an extraordinary scientist, Dr. Donald Metcalf.