Haematopoietic growth factors

SIR — May we add some important points to those made by T.M. Dexter in his News and Views article on haematopoietic growth factors[1]. The development of blood cells requires a programme for the multiplication of stem cells and their differentiation to various types of mature cells with different functions. The mature cells no longer multiply. The normal developmental programme also has to include a mechanism for coupling the induction of multiplication in stem cells to the induction of differentiation, so as to maintain the normal balance between undifferentiated and mature cells. The points we wish to add are that multiplication (growth) and differentiation of blood cells are induced by different proteins, those that induce growth and those that induce differentiation, and that coupling between growth and differentiation can be achieved by a growth factor switching on production of a differentiation factor.

In cells of the myeloid series there are four different growth-inducing proteins. These are now called colony stimulating factors (CSF), or macrophage and granulocyte inducers — types 1 (MGI-1)[1-4]. Of the four growth factors, one (M7) induces the development of clones with macrophages, another (G7) clones with granulocytes, the third (GM) clones with both macrophages and granulocytes, and the fourth (also called interleukin-3), clones with macrophages, granulocytes, eosinophils, mast cells, erythroid cells, or megakaryocytes. This multigene family represents a hierarchy of growth factors for different stages of blood cell development as the precursor cells become more restricted in their developmental programme. How do normal myeloid precursor cells induced to multiply by these growth factors develop into clones that contain mature differentiated cells that stop multiplying when they terminally differentiate? This has been a answered by experiments that complement those discussed by Dexter[1].

Normal myeloid precursors require addition of one of the myeloid growth factors for cell viability and multiplication. But there are myeloid leukaemic cells that are viable and multiply without adding growth factor, and that can be induced to differentiate to non-malignant terminally differentiated macrophages or granulocytes by proteins which are different from the growth factors called CSF or MGI-1[2,3]. These differentiation-inducing proteins, which also induce differentiation of normal myeloid cells[2,3], have been called MGI-2[2,5] or differentiation factors (DF)[6,7]. The injection of these MGI-2 proteins into leukaemic mice inhibits the development of myeloid leukaemia[3,8]. Normal myeloid precursor cells cultured with one of the myeloid growth factors endogenously produce the differentiation factor MGI-2[2,3,9] and this serves as an efficient mechanism to couple growth and differentiation. Differences in the time of the switch-on of the differentiation factor can produce differences in the amount of multiplication before differentation. There is more than one type of MGI-2[5,10]. Different growth factors may switch on different differentiation factors and this may determine the differentiated cell type.

It has been suggested from experiments with WEHI-3B myeloid leukaemia cells that one of the myeloid growth factors (MGI-1G = G-CSF) can also act as a differentiation factor for these leukaemic cells[4]. This has not so far been found with other clones of myeloid leukaemic cells, and studies with these other clones have identified MGI-2 proteins that have no MGI-1G activity[3,5-7]. In addition, MGI-2 but not MGI-1 binds to double stranded DNA[11]. The form of MGI-1G used in the experiments with WEHI-3B may be a hybrid molecule, but there is also a different explanation. WEHI-3B cells constitutively produce their own growth factor and under appropriate conditions can be induced to endogenously produce their own differentiation factor[11]. As with normal myeloid precursors, WEHI-3B cells may thus be induced to differentiate indirectly by the growth factor MGI-1G (G-CSF). In addition to these results with myeloid cells, different proteins that induce growth and differentiation have been found with B lymphocytes[12] and this presumably also applies to the other types of blood cells. Induction of differentiation factor may also play a role in the normal developmental programme of other cell types.

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Calibrations for nuclear winter

SIR — In their recent complaint[1] about John Maddox's criticisms[2,3] of their climate modelling work on the 'nuclear winter' concept[4], Turco *et al.* attempt to buttress their case by stating that the climate model they used was partly calibrated by (1) 12 years of research on martian dust storms, (2) the climatic consequences of volcanic explosions on Earth, and (3) the possible collision of an asteroid or cometary nucleus with Earth at the time of the Cretaceous/Tertiary extinctions. In addition, they say that their work was reviewed by a large number of experts and that it referred to many previous studies. If these reasons are indeed the basis for their confidence, the criticism they received was well justified.

To begin with, what good is a technique that is only *partly* calibrated? And how can a model be calibrated against a *possible* phenomenon which may or may not have actually occurred, and at that in the distant past? With respect to the climatic consequences of volcanic explosions, Turco *et al.* indicate in their complaint that these are caused primarily by sulphuric acid aerosols and not by the smoke and dust that is supposed to operate in the nuclear winter scenario. So how can this comparison be of any use? In addition, of what real comparative value is the planet Mars? It has no liquid water on ts surface, while Earth is 70% covered by seas; and its atmospheric mass is miniscule. Dust there operates almost as if it were in a vacuum; and, again Turco *et al.* claim that it is not dust but rather sooty smoke from fires that is the major cause of nuclear winter. And as for citing lots of background material and getting the opinions of a large number of experts, what does that *prove*? Absolutely nothing, which is precisely the point made by John Maddox, and one which I heartily endorse.

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DNA methylation and G+C rich DNA

SIR — In a recent "News and Views" article, Max collated evidence showing that the 5′ region of certain genes is undermethylated in the cells of all tissues examined including sperm[1]. This was used to explain the recent observations[2] that CG dinucleotides are present in unusually high amounts in certain regions of some genes. Where cytosine methylation does not occur, deamination of a cytosine base in DNA will produce uracil which can be removed from the DNA and the original sequence re-established. However, the occasional deamination of methylcytosine to thymine in DNA will lead, over many generations, to the loss of CG dinucleotides from the genome — so called CG suppression[3]. McClelland and Ivarie[4] found a reduced suppression in the 5′ flanking regions of some vertebrate genes which might imply that these regions are