Funding Basic Research: Continued

Three responses to my editorial of 19 July (p. 291) by Louis Ianniello, Monroe Burke, and Arthur Kornberg (Letters, 16 Aug., p. 857) are about the responsibility of all scientists to help improve and reform our own institutions to respond to the changing dynamics of national and international finances. The letters by Burke and by Kornberg contain the same imperial message: we, scientists, know better how to allocate the nation's resources. These two letters are innocent of specifics and contain little reference to the recent relevant literature. On the end-of-science issue, may I refer the letter writers to *The End of Science* by John Horgan (Abrams, New York, 1996); *Frontiers of Illusion* by Daniel Sarewitz (Temple University Press, Philadelphia, PA, 1996) and *The End of the Future* by Jean Gimpel (Praeger, Westport, CT, 1994).

Arthur Kornberg's superb credentials force us to examine his championing of the possible value of public support for bioscience research. The examples he cites of useful technologies developed are largely outside his field. In most cases the flow was from technologically useful discovery to science, not vice versa. Nor was any bureaucratic funding "process" involved.

On the matter of who should support research, however, times have changed dramatically from the era when only the government could support *relevant* basic research. I cite only one major challenge to such outmododed "golden age of science" axioms: a book by Cambridge University biochemist Terence Kealey, *The Economic Laws of Scientific Research* (St. Martin's, New York, 1995), which provides detailed technical support for the position that most *nontargeted* basic research should be privatized. Over the last 15 years, I have written two books and some two dozen papers with the same approach, giving data and argument and constructive alternatives to the present, unsustainable system. I have yet to find *one* similarly reasoned book or paper replying to these arguments.

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Keratinocytes and the Danger Model

In their report "Neonatal tolerance revisited: Turning on newborn T cells with dendritic cells" (22 Mar., p. 1723), John Paul Ridge *et al.* demonstrate that the neonatal immune system was not uniquely poised for tolerance induction upon encountering antigen, but that neonatal T cells could be primed if antigen was presented by activated professional antigen-presenting cells (APCs) such as dendritic cells (*1*). On the basis of this finding and of previous studies (*2*), they are quoted in a Research News article by Elizabeth Pennisi (22 Mar., p. 1665) on the topic of the danger model, which holds that the immune system does not provide intrinsically for self:nonself discrimination, but rather responds to activated APCs, which are found only at sites of tissue destruction and inflammation. Activated APCs are able to induce T cell responses to antigen, in part through the provision of costimulatory signals to the T cell. The degree to which the regulated provision of costimulatory signals is important in maintaining peripheral tolerance is not known, although Ridge *et al.* and others suggest that the absence of costimulatory signals on "normal, healthy peripheral tissues . . . should continuously induce T cell tolerance . . ." (*1*). This concept is illustrated in the figure in the Research News article (p. 1665), in which skin is portrayed as being unable to deliver signal two. Although

we found several aspects of this model intriguing, keratinocytes do not lack the capacity to provide costimulatory signals.

In studies of normal human keratinocytes (the principal cell type in skin), we have shown that these epithelial cells, when activated, express major histocompatability complex (MHC) class II molecules and can function as nonprofessional APCs by providing costimulatory signals to T cells that support proliferative responses to a variety of mitogens and bacterial superantigens (*3*). While keratinocytes do not appear to express either CD80 or CD86 (ligands for the T cell costimulatory pathway mediated through CD28), we have shown that they do express CD40 (*4*), a molecule also found on professional APCs and which has been proposed to have direct T cell costimulatory activity (*5*), particularly for interleukin-4 (IL-4) production (*6*).

As keratinocytes are frequently confronted and stimulated by an array of environmental toxins and allergens, this raises the question of why pathogenic immune responses are not seen more frequently. One reason may lie in the types of cytokines produced by "keratinocyte-supported" T cells and by the activated keratinocytes themselves. Activated T cells receiving accessory signals from keratinocytes produce T_H2 cytokines (IL-4, IL-5, and IL-10) almost exclusively, with minimal or absent production of the T_H1 cytokine IFN-γ (*7*). This "immune-deviation" is a result of the inability of keratinocytes to produce IL-12, because the defect in IFN-γ production by "keratinocyte-supported" T cells is reversed with exogenous IL-12 (*7*). Keratinocytes themselves produce IL-10, which inhibits the expression of CD80 and CD86 on professional APCs (*8*). This action would reinforce T_H2 responses by inhibiting the ability of professional APCs (which induce T_H1 responses) to costimulate T cells.

We have proposed that immune deviation of this type, although not classical tolerance in the sense of absence of an immune response, is likely to be an important mechanism of self-tolerance, as it is perceived on a macroscopic level (*9*). The report of 22 March (p. 1728) by T. Forsthuber *et al.*, as well as work by Chen and Field (*10*), indicate that immune deviation is an important mechanism of neonatal "tolerization." Immune deviation of this type has also been implicated in oral tolerance (*11*). It is probably not coincidental that the gut and the skin, two organs with large surface areas that regularly come into contact with potentially dangerous environmental antigens, each appear to be able to have immunologic tolerance through an active, nonpathogenic immune response, rather than through the absence of an immune response.

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β Sheets and Spider Silk

Although Alexandra H. Simmons *et al.* state that their excellent nuclear magnetic resonance work on the supramolecular structure of spider dragline silk (Reports, 5 Jan., p. 84) is inconsistent with our previous electron microscopy-based investigations (*1*), in fact it supports our findings.

From direct observations of diffracting regions in silk fibres, we concluded that the β-sheet REPEAT (approximately 13 Å for two sheets) is dictated by the inclusion of large amino acid sidegroups in the loosely conserved Gly-Gly-X (X = Tyr, Gln, Leu) sequences; we noted that this repeat falls in the range of other published data (*2*) for the *Nephila* genus. The diffracting regions are too large (and they have the wrong inter-sheet spacing) to consist solely of the available polyalanine runs. Also, they are an order of magnitude larger than the displacement lengths of the Gly-Gly-X–based sequences.

We suggested (*1*) that the diffracting regions are β-sheet crystals "made from MIXED strands of polyalanine and Gly-Gly-X," and that "it is possible that the fine-scale contrast variations present in the crystal . . . are due to such compositional/structural variations." Therefore, our description of these crystals is not correctly represented by Simons *et al.* when they state (p. 85)