The last unknown fact

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The recorded history of declaring that "all of substance is now known" goes back even further than the Roman military engineer Sextus Julius Frontinus, as quoted in Silverstein's article "The end of immunology"[1]. In one of the treatises of the Hippocratic Corpus, written around 400 BC, an unknown Greek doctor remarked:

> *Medicine in its present state is, it seems to me, by now completely discovered, insofar as it teaches in each instance the particular details and the correct measures. For anyone who has an understanding of medicine in this way depends very little upon good luck, but is able to do good with or without luck. For the whole of medicine has been established, and the excellent principles discovered in it clearly have very little need of good luck*[2].

Who can doubt that countless individuals, stretching back eons into the unrecorded history of human consciousness, have probably reached a similar conclusion. In recorded history, the conclusion has been publicly declared on numerous occasions, often by eminent persons[3].

It is widely recognized as amusing to watch eminent persons make silly statements in public, especially when they yield to the temptation of pomposity. In this regard, Silverstein's collection of (in retrospect) absurd pronouncements on the completeness of various branches of science, by some of the greatest scientists of the last one or two centuries, is excellent[3]. However, we should be wary of selective quotation. For example, after the discovery of Pluto, several planetary scientists are likely to have opined that the broad structure of the solar system has finally been established. These brave seers are (so far) correct.

There is a powerful sense that a time will come when our understanding of the universe, in a descriptive sense, will be complete. Scientists have always accepted that the foundations of their discipline are likely to be extended and might one day be overturned. But that it is inevitable would be a daunting thought. Pure research would be reduced to a process destined never to succeed, an endless journey to nowhere. And if it is not inevitable, when should we risk our hand and make the declaration?

To take the question of antibody formation raised by Silverstein[1], we shall soon know all the genes that exist in mouse and man, we know the primary structure and the crystal structure of many antibody molecules and the antibody response in many situations has been analyzed in great detail. Is it not possible to say that we truly understand antibodies and perhaps even the basics of the antibody response? It seems inconceivable that future generations will be able to discard B lymphocytes and immunoglobulin as absurd interpretations of reality, in much the same way as we today discard the four humors of Hippocratic medicine. And beyond antibodies and B lymphocytes, is it not conceivable that we shall also understand the basics of T cell function in the next few decades? And as the islands of true understanding in other disciplines coalesce with one another and with immunology, are we not moving inexorably forward to the unimaginable day when all is known?

Dante, in his devout quest for paradise, was unequivocal:

> *Mad is he who hopes that our intellect can reach the end of the unending road*[4].

But Dante was speaking not of science as a descriptive discipline, which is all science can be, but of the why and wherefore of existence. These latter aspects are outside science's legitimate sphere, however prominent are those who seek God in their scientific theories[5].

There will always be an infinity of trivial facts: the number of blades of grass in a field, the precise motion of each blade of grass as the wind sweeps through the field. But will a time ever come when everyone is waiting expectantly for that last paper to describe the last fact of substance? Will it be published in *Nature*, or will it (by the lightning speed of the grapevine or the stunning synchronization of scientific thought) be published simultaneously in many journals by many different groups, in one last gasp for pure research? We shall probably not live to see that happy day. In any case, whether we have arduously scaled a mole-hill or find ourselves on the rarified peaks of Everest is something that we cannot know except in retrospect, and therefore never with certainty. That is our problem. We shall not know for sure that we have made it, even when we have done so.

1. Silverstein, A. M. *Nature Immunol.* **2**, 893–895 (2001).
2. Potter, P. *Hippocrates* vol. 8, p. 93 (Loeb Classical Library, Harvard University Press, 1995).
3. Silverstein, A. M. *Hist. Sci.* **37**, 407–425 (1999).
4. Mandelbaum, A. *The Divine Comedy of Dante Alighieri* Purgatorio, Canto III, Lines 34–35 (Bantam Books, London, 1988).
5. Hawking, S. A brief history of time: From the big bang to black holes (Bantam Books, London, 1988).

Interaction of DAP3 and FADD only after cellular disruption

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In their recent contribution to *Nature Immunology*[1], Miyazaki and Reed propose an "adapter" function for the death-associated protein 3 (DAP3) between the death receptors DR4, DR5 and the death receptor–associated protein Fas-associated death domain (FADD). Their findings are primarily based on yeast two-hybrid experiments and immunprecipitation (IP) studies that were usually done after overexpression of the analyzed proteins. For the IP experiments whole-cell lysates were used, in which the different subcellular compartments were disrupted before analysis. In light of our recent publication concerning the subcellular targeting of murine DAP3[2], which is found exclusively in the mitochondrial matrix, maintenance of intracellular localization is key to these studies. Mitochondrial localization of DAP3 has been confirmed by others. Human DAP3 (hDAP3) was shown to be in the mitochondria by colocalization of green-fluorescence protein–tagged hDAP3 with MitoTracker[3]. Two groups[4–6] identified bovine DAP3 as a mitochondrial ribosomal protein, which confines DAP3 localization to the mitochondrial matrix. We described functional complementation of the yeast DAP3