

INTRODUCTION

What Don't We Know?

At *Science*, we tend to get excited about new discoveries that lift the veil a little on how things work, from cells to the universe. That puts our focus firmly on what has been added to our stock of knowledge. For this anniversary issue, we decided to shift our frame of reference, to look instead at what we *don't* know: the scientific puzzles that are driving basic scientific research.

We began by asking *Science's* Senior Editorial Board, our Board of Reviewing Editors, and our own editors and writers to suggest questions that point to critical knowledge gaps. The ground rules: Scientists should have a good shot at answering the questions over the next 25 years, or they should at least know how to go about answering them. We intended simply to choose 25 of these suggestions and turn them into a survey of the big questions facing science. But when a group of editors and writers sat down to select those big questions, we quickly realized that 25 simply wouldn't convey the grand sweep of cutting-edge research that lies behind the responses we received. So we have ended up with 125 questions, a fitting number for *Science's* 125th anniversary.

First, a note on what this special issue is not: It is not a survey of the big societal challenges that science can help solve, nor is it a forecast of what science might achieve. Think of it instead as a survey of our scientific ignorance, a broad swath of questions that scientists themselves are asking. As Tom Siegfried puts it in his introductory essay, they are "opportunities to be exploited."

We selected 25 of the 125 questions to highlight based on several criteria: how fundamental they are, how broad-ranging, and whether their solutions will impact other scientific disciplines. Some have few immediate practical implications—the composition of the universe, for example. Others we chose because the answers will have enormous societal impact—whether an effective HIV vaccine is feasible, or how much the carbon dioxide we are pumping into the atmosphere will warm our planet, for example. Some, such as the nature of dark energy, have come to prominence only recently; others, such as the mechanism behind limb regeneration in amphibians, have intrigued scientists for more than a century. We listed the 25 highlighted questions in no special order, but we did group the 100 additional questions roughly by discipline.

Our sister online publications are also devoting special issues to *Science's* 125th anniversary. The Science of Aging Knowledge Environment, SAGE KE (www.sageke.org), is surveying several big questions confronting researchers on aging. The Signal Transduction Knowledge Environment, STKE (www.stke.org), has selected classic *Science* articles that have had a high impact in the field of cell signaling and is highlighting them in an editorial guide. And *Science's* Next Wave (www.nextwave.org) is looking at the careers of scientists grappling with some of the questions *Science* has identified.

We are acutely aware that even 125 unknowns encompass only a partial answer to the question that heads this special section: What Don't We Know? So we invite you to participate in a special forum on *Science's* Web site (www.sciencemag.org/sciext/eletters/125th), in which you can comment on our 125 questions or nominate topics we missed—and we apologize if they are the very questions you are working on.

—DONALD KENNEDY AND COLIN NORMAN

Contents >> NEWS

- | | |
|---|---|
| 76 In Praise of Hard Questions | 92 How Are Memories Stored and Retrieved? |
| 78 What Is the Universe Made Of? | 93 How Did Cooperative Behavior Evolve? |
| 79 What Is the Biological Basis of Consciousness? | 94 How Will Big Pictures Emerge From a Sea of Biological Data? |
| 80 Why Do Humans Have So Few Genes? | 95 How Far Can We Push Chemical Self-Assembly? |
| 81 To What Extent Are Genetic Variation and Personal Health Linked? | 96 What Are the Limits of Conventional Computing? |
| 82 Can the Laws of Physics Be Unified? | 97 Can We Selectively Shut Off Immune Responses? |
| 83 How Much Can Human Life Span Be Extended? | 98 Do Deeper Principles Underlie Quantum Uncertainty and Nonlocality? |
| 84 What Controls Organ Regeneration? | 99 Is an Effective HIV Vaccine Feasible? |
| 85 How Can a Skin Cell Become a Nerve Cell? | 100 How Hot Will the Greenhouse World Be? |
| 86 How Does a Single Somatic Cell Become a Whole Plant? | 101 What Can Replace Cheap Oil—and When? |
| 87 How Does Earth's Interior Work? | 102 Will Malthus Continue to Be Wrong? |
| 88 Are We Alone in the Universe? | 78 So Much More to Know ... |
| 89 How and Where Did Life on Earth Arise? | |
| 90 What Determines Species Diversity? | |
| 91 What Genetic Changes Made Us Uniquely Human? | |

See also Editorial on p. 19 and www.sciencemag.org/sciext/125th

