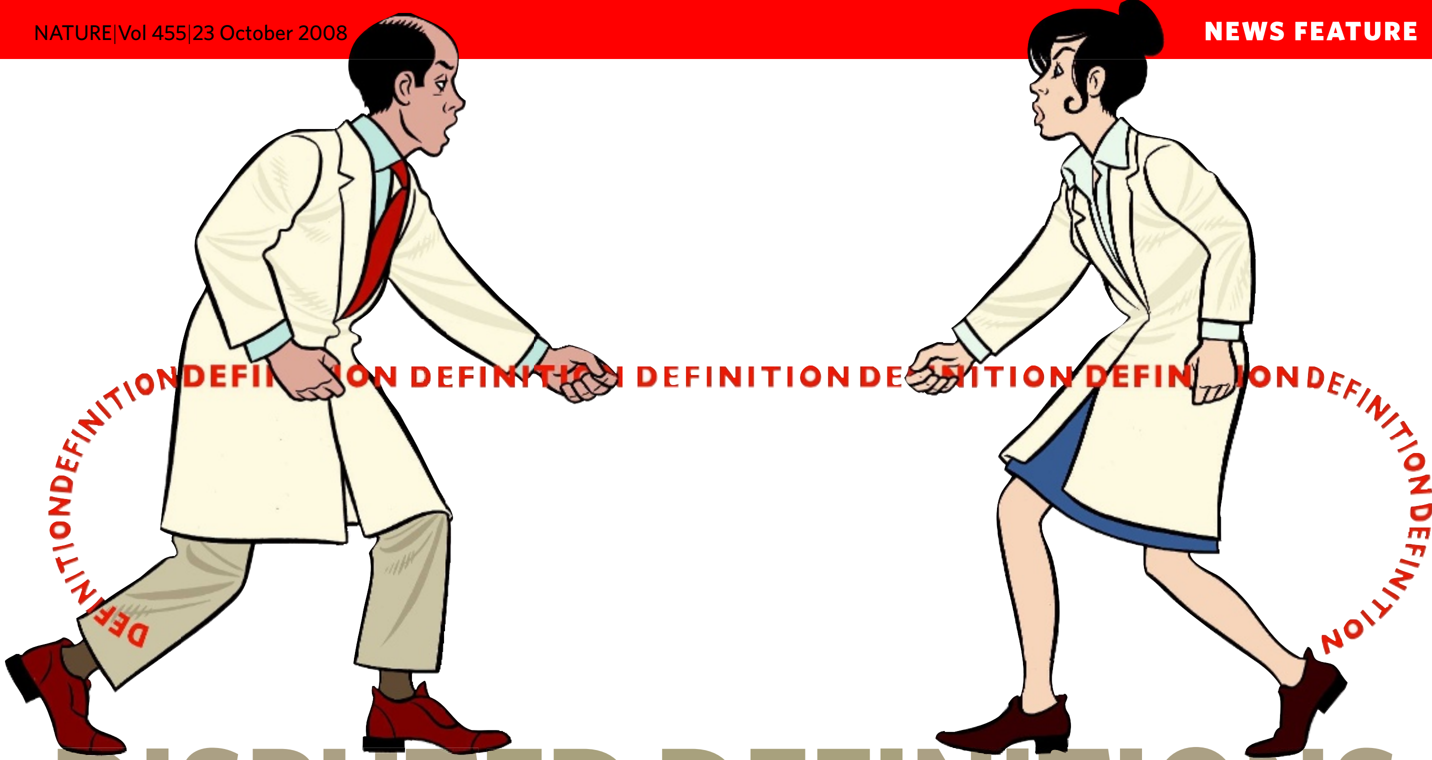


DISPUTED DEFINITIONS

If you want to start an argument, ask the person who just said 'paradigm shift' what it really means. Or 'epigenetic'. *Nature* goes in search of the terms that get scientists most worked up.

To a great extent, science is about arriving at definitions. What is a man? What is a number? Questions such as these require substantial inquiry. But where science is supposed to be precise and measured, definitions can be frustratingly vague and variable.

Here, *Nature* looks at some of the most difficult definitions in science. Some are stipulative definitions, created by scientists for their convenience, but on which the community has not found consensus. Popular though they are, not everyone agrees on what is meant by 'paradigm shift' or 'tipping point'.

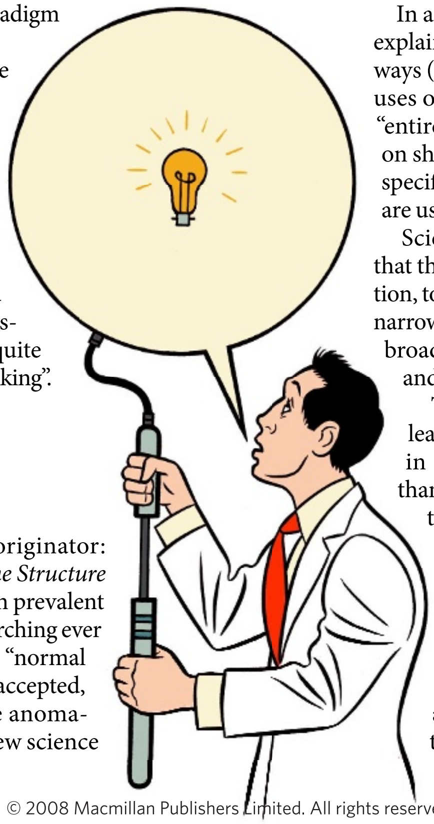
Essential definitions — those that get at the question of what makes a thing a thing — can be just as troublesome. What is race, or consciousness? And does it even matter if there is no agreed-on meaning?

The good news is that for every troublesome term there are thousands used every day with no problems. Scientists are competent, if unconscious wielders of definition, says Anil Gupta, a philosopher of science at the University of Pittsburgh in Pennsylvania, "just as one can walk quite happily without having a complete account of walking".

Paradigm shift

[ˈparədʌɪm ʃɪft] *noun.*

Paradigm shift has a definite origin and originator: Thomas Kuhn, writing in his 1962 book *The Structure of Scientific Revolutions*, argued against the then prevalent view of science as an incremental endeavour marching ever truthwards. Instead, said Kuhn, most science is "normal science", which fills in the details of a generally accepted, shared conceptual framework. Troublesome anomalies build up, however, and eventually some new science comes along and overturns the previous consensus. Voilà, a paradigm shift. The classic example, Kuhn said, is the Copernican revolution, in which Ptolemaic theory was swept away by putting the Sun at the centre of the Solar System. Post-shift, all previous observations had to be reinterpreted.



Kuhn's theory about how science works was arguably a paradigm shift of its own, by changing the way that academics think about science. And scientists have been using the phrase ever since.

In a postscript to the second edition of his book, Kuhn explained that he used the word 'paradigm' in at least two ways (noting that one "sympathetic reader" had found 22 uses of the term). In its broad form, it encompasses the "entire constellation of beliefs, values, techniques and so on shared by the members of a given community". More specifically it refers to "the concrete puzzle-solutions" that are used as models for normal science post-shift.

Scientists who use the term today don't usually mean that their field has undergone a Copernican-scale revolution, to the undying annoyance of many who hew to Kuhn's narrower definition. But their usage might qualify under his broader one. And so usage becomes a matter of opinion and, perhaps, vanity.

The use of the term in titles and abstracts of leading journals jumped from 30 papers in 1991 to 124 in 1998, yet very few of these papers garnered more than 10 citations apiece[1]. Several scientists contacted for this article who had used paradigm shift said that, in retrospect, they were having second thoughts. In 2002, Stuart Calderwood, an oncologist at Harvard Medical School in Boston, Massachusetts, used it to describe the discovery that 'heat shock proteins', crucial to cell survival, could work outside the cell as well as in[2]. "If you work in a field for a long time and everything changes, it does seem like a revolution," he says. But now he says he may have misused

ILLUSTRATIONS: N. DEWAR

the phrase because the discovery was adding to, rather than overturning, previous knowledge in the field.

Arvid Carlsson, of the University of Gothenburg in Sweden stands by his use of the phrase. "Until a certain time, the paradigm was that cells communicate almost entirely by electrical signals," says Carlsson. "In the 1960s and '70s, this changed. They do so predominantly by chemical signals. In my opinion, this is dramatic enough to deserve the term paradigm shift." Few would disagree: base assumptions were overturned in this case, and Carlsson's own work on the chemical neurotransmitter dopamine (which was instrumental in this particular shift) earned him the 2000 Nobel Prize in Physiology or Medicine

Unless a Nobel prize is in the offing, it might be wise for scientists to adopt the caution of contemporary historians of science and think twice before using a phrase with a complex meaning and a whiff of self promotion. "Scientists all want to be the scientists that generate a new revolution," says Kuhn's biographer, Alexander Bird, a philosopher at the University of Bristol, UK. "But if Kuhn is right, most science is normal science and most people can't perform that role."

Emma Marris

'So big we don't know where to start' definitions

- Science
- Life
- Natural
- Intelligence
- Ethical
- Sustainability

NOAA GOES-7/NASA

Epigenetic

[ɛpɪdʒɪnɛtɪk] *adjective.*

No one denies that epigenetics is fashionable: its usage in PubMed papers increased by more than tenfold between 1997 and 2007. And few deny that epigenetics is important. What they do disagree on is what it is.

"The idea is that there is a clear meaning and that it's being violated by people like me who use it more loosely," says Adrian Bird at the University of Edinburgh, UK . Last year he suggested this as a definition: "the structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states"[3]. But this wide-ranging proposal, which takes on-board pretty much every physical indicator of a gene's activity is "preposterously dumb", says Mark Ptashne of Memorial Sloan–Kettering Cancer Center in New York, who has published his own take on the word's usage[4]. "I've grown to be very careful about using the term," says Bing Ren, who studies gene regulation at the University of California, San Diego.

"Epigenetics is a useful word if you don't know what's going on — if you do, you use something else."
— Adrian Bird

According to the 'traditional' definition that Ptashne favours, epigenetics describes "a change in the state of expression of a gene that does not involve a mutation, but that is nevertheless inherited in the absence of the signal or event that initiated the change". The classic example is found in a bacteriophage called Lambda, which stays dormant in the genome of generations of cells through inheritance of a regulatory protein. These sort of processes are basic to some of the most pressing questions in biology today: such mechanisms are needed to explain how a single-celled embryo can generate cells that are genetically identical, but express a different array of genes and hence take on different jobs in blood, brain or muscle for generation after generation.

Over the past few years, however, all kinds of processes associated with gene control have been subsumed under the moniker. For example, 'epigenetic' is often used to refer to the chemical modification of histones — proteins that DNA winds around — which is involved in gene regulation. This infuriates those who learned the classical definition; they say it puts these modifications at the heart of development and disease despite scant evidence that they are inherited. "Why did histone marks become epigenetic?" says Kevin Struhl at Harvard Medical School in Boston. "People decided that if they call them that it makes them interesting." Others say that it is not about making things sound important, it is more the lack of any other phrase with which to collectively refer to this type of work.

The word had dual meanings long before the current debate. In the 1940s, Conrad Waddington used it to describe how the genetic information in a 'genotype' manifests itself as a set of characteristics, or 'phenotype'. In 1958, David Nanney at the University of Michigan, Ann Arbor, borrowed the term to describe "messy" inherited phenomena that could not be explained by conventional genetics[5]. "It was controversial in 1958 and everything died down and it has come alive again," says Nanney. "It took 40 years for epigenetics to become a major word in the vocabulary of modern biology."

A lot of money can ride on whether a researcher is, or is not, studying epigenetics: the US National Institutes of Health (NIH) this month started handing out US$190 million as part of its epigenomics initiative and other countries are pouring funding into the area. (The NIH is careful to define the epigenetics it is paying for as including both heritable and non-heritable changes in gene activity, something that Ptashne describes as "a complete joke".) Bird says he remains in favour of a relaxed usage. "Epigenetics is a useful word if you don't know what's going on — if you do, you use something else," he says.

Helen Pearson

Complexity
[kəmˈplɛksɪti] *noun.*

In his book *Programming the Universe*, engineer Seth Lloyd of the Massachusetts Institute of Technology in Cambridge describes how he once compiled 42 definitions of complexity — none of which encompasses everything people mean by that word. Researchers in the many institutes and programmes formed to study 'complexity' are still searching for the right way to describe their discipline. "If we're a university centre, we should be able to say what we care about," says Carl Simon, director of the Center for the Study of Complex Systems at the University of Michigan.

The quest for a rigorous definition reached a particularly intense pitch in the early 1990s, when some of the more visionary researchers at the Santa Fe Institute in New Mexico held out the hope of a universal theory of complexity — a mathematically precise set of equations that would hold for all complex systems in much the same way that the second law of thermodynamics holds for all physical systems.

James Crutchfield, head of the Complexity Sciences Center at the University of California, Davis, says that this created a problem. "New people would come into the field and start using the word 'complexity' as if it was a unitary thing" — which, as became increasingly clear, it was not. No all-encompassing theory emerged. Even within the precise world of binary code and bit strings, there was computational complexity, which describes how much memory and processing is required to carry out a calculation; algorithmic complexity, which is related to how much a digital description of something can be compressed; and any number of combinations and variations. "So my bottom line is, add an adjective to 'complexity'," Crutchfield says.

Researchers have found plenty of undeniably complex systems to study, such as economies, ecosystems, urban traffic and brains (see 'Consciousness'). And in a qualitative sense, at least, these systems do have certain features in common that might serve as a definition. They are, for instance, all composed of many independent 'agents' (consumers, species, vehicles, neurons) that are constantly interacting with, and adapting to, one another. They all display a rich array of nonlinear feedback loops among the agents, which means that small changes can have a big effect. And they never quite settle down into static equilibrium.

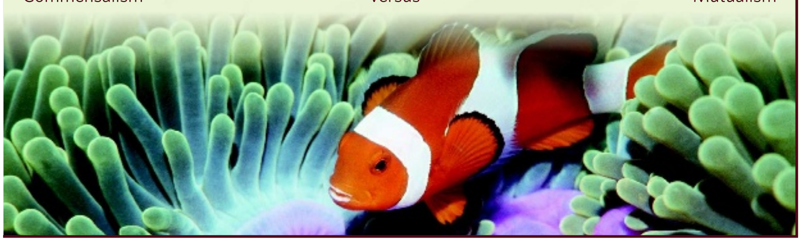
The effort to understand complex systems has led researchers to develop new analytical tools such as network theory, agent-based modelling and genetic algorithms. These tools, combined with the exponential growth in computational power, have allowed researchers to build ever more complex models of complex systems — and study the subtle but powerful phenomenon of 'emergence,' in which multiple agents exhibit collective behaviour that is a great deal more than the sum of its parts.

So even though the field seems little closer to defining its subject, says Lloyd, "in places where people can apply these conceptual and computational tools, we've made huge progress in understanding complex systems". But in a world where we are constructing ever more complex artefacts — technologies, economies, organizations and societies — even better tools are needed to keep pace.

M. Mitchell Waldrop

'There is a difference, honest' definitions

Molecular electronics	versus	Molecule-based electronics
Thermohaline circulation	versus	Meridional overturning circulation
Commensalism	versus	Mutualism



G. HOLLAND/PHOTOLIBRARY.COM

Race
[reɪs] *noun.*

If biologists had a list of four-letter words to avoid, then 'race' would be higher up than anything more conventionally vulgar. It is controversial, it lacks a clear definition and the more that genetics reveals about race, the more biologically meaningless the term seems.

Race was long used to imply a shared, distinct ancestry, as in a 1936 definition of the term in *Nature*: "It has two main connotations, one being community of descent, the other distinctness from other races." But in 1972, Harvard geneticist Richard Lewontin showed that the concept of race starts to dissolve under genetic scrutiny. He found that the vast majority of human genetic variation, which he measured in 16 genes, is found within, not between, what he called the 'classical racial groupings'[6]. Since then, studies examining hundreds or even thousands of genetic markers have confirmed Lewontin's findings[7,8].

A consensus now exists across the social and biological sciences: regardless of appearance or heritage, groups of human beings are overwhelmingly more genetically similar to each other than different. This doesn't mean race does not exist or is meaningless in society — far from it. But it does mean that an individual's race is not a particularly useful or predictive indicator of biological traits or medical vulnerabilities. Race is "the social interpretation of how we look, in a race-conscious society", says Camara Phyllis Jones, the research director on the Social Determinants of Health and Equity programme at the US Centers for Disease

Control and Prevention in Atlanta, Georgia. Lewontin says that assigned races are essentially arbitrary. "It means essentially a group of related people, and where you draw the line depends on where you are in history."

Some argue that severing biology from the definition of race risks jettisoning medically meaningful information. Patterns of genetic variation can be used to classify people from different geographical regions into clusters that sometimes mimic the classical racial groupings, and geneticists say that members of these groups seem to have distinctive disease prevalences and drug metabolism. So race could serve as a cheap, albeit imperfect, surrogate for defining groups for clinical trials or medical interventions.

But genetics is turning up ever more examples of how race obscures relevant information. A study published in April showed that a mutation found in 40% of African Americans acts like an endogenous beta blocker to protect patients with heart failure from death[9]. It also suggested why previous research had found conflicting evidence about the response of African Americans to beta blockers: those studies had lumped all African Americans into one group, obscuring the effects of mutations that confer protection or vulnerability.

A person's perception of his or her race can still serve to capture life experiences relevant to behavioural and clinical research, such as the stress of lifelong discrimination that may contribute to health disparities. But in other contexts researchers are abandoning the term in favour of other ways to group humans, by 'population,' genetic ancestry' or 'geographic ancestry'.

Erika Check Hayden

Makeovers

Before	After
Nuclear magnetic resonance	Magnetic resonance imaging
Clinical research	Translational medicine
Cloning	Somatic cell nuclear transfer
Genetic engineering	Synthetic biology
Lots of [genes; transcriptions; citations; etc]	[gen-; transcripto-; biblio-; etc-]omics

BLUESTONE/SPL

Tipping point

[tɪpɪŋ pɔɪnt] *noun.*

In July 2006, scientists running the RealClimate blog ironically headlined one of their posts 'Runaway tipping points of no return'. The post laments that usage of the phrase 'tipping point' in climate-change and ecosystem discussions had reached, well — a tipping point.

It's not the frequency of the word that bothers researchers. It's the lack of one clear definition and the confusing way in which the concept is being used, among scientists and in the public discourse, often to imply that global warming-induced changes will propel Earth into irreversible and catastrophic climate change. "There is no convincing theoretical argument or model that at some point the planet as a whole will snap into a second state of system," says Timothy Lenton, an Earth scientist at the University of East Anglia, UK.

The term was originally coined in 1958 by sociologist Morton Grodzins in the context of studies on the racial makeup of US neighbourhoods. He found that when the migration of African-Americans into traditionally white neighbourhoods had reached a certain level, whites began to move out. In the 1970s, epidemiologists adopted tipping point to describe the threshold at which, mathematically, an infectious disease's 'reproductive rate' goes above one. This means that each infected person infects more than one other and the disease starts growing into an epidemic.

The phrase reached its own tipping point in 2000 when Malcolm Gladwell, a staff writer at *The New Yorker*, published his successful book *The Tipping Point: How Little Things Can Make a Big Difference*. It also acquired a worrisome — some say alarmist — flavour courtesy of its frequent usage in the context of climate change.

Regarding climate, the term is commonly defined as the critical threshold at which a slow gradual change qualitatively alters the state of an entire system. This is different to a 'point of no return' which is, by definition, irreversible. Only if internal forcing will cause a runaway effect is a tipping point also a point of no return.

The idea that positive feedbacks — such as the melting of polar ice reducing surface reflectivity, thereby causing yet more solar absorption, warming and melting — could amplify climate change to a point of fundamentally altering the global system has been around for decades. The debate now is about where those tipping points lie, and what will happen when they are crossed.

In a paper published in February, a team led by Lenton looked at 15 potential tipping 'elements' (things that could reach tipping points) in Earth's climate system[10]. Arctic sea-ice and the Greenland ice sheet were those most at risk from 'tipping' within the twenty-first century, the authors concluded.

But researchers accept that most known tipping points seem to be reversible on human timescales. Melting of the complete Arctic summer ice sheet, for example, could probably be reversed within a few years or so in a cooler world. Melting of the extremely thick Greenland and Antarctic ice sheets are a possible exception because, once melted, new ice would have to form at lower, warmer altitudes with less snowfall.

Claims that global warming could reach an irreversible tipping point by 2016, as made last year by James Hansen, director of NASA's Goddard Institute for Space Studies in New York, refer to the trajectory of greenhouse-gas emissions, not to changes in the climate system. Even if greenhouse-gas concentrations reach a point at which they cannot be restored to pre-industrial levels, it will not inevitably push the world's climate over a catastrophic tipping point.

Quirin Schiermeier

Stem cell

[stɛm sɛl] *noun.*

Ask a group of stem-cell biologists to define stem cell, and they'll say roughly the same thing: a cell that can, long term, divide to make more copies of itself as well as cells with more specialized identities. Ask the same scientists to list the most disputed terms in the field, however, and 'stem cell' will be top of that list.

The problem here is an operational one: reasonable people disagree on which cells qualify under the definition. "It's not unusual to pick up a paper and see someone call something a stem cell and the evidence that it is, is just not there," says Lawrence Goldstein, who directs the stem-cell research programme at the University of California, San Diego.

Alleged 'stem cells' can fail to meet the definition on many counts. Stem cells should persist long term, yet many 'stem cells' exist only in the fetus. Multipotency — the ability to generate multiple cell types — is a criterion for a haematopoietic, or blood-forming, stem cell, but spermatagonial stem cells only produce sperm. Stem cells specific to tissue such as cartilage, the kidney and the cornea have been reported, with varying degrees of acceptance. The quest for a 'stemness signature', a collection of markers common to all stem cells, has been met with frustration.

Debate erupts most commonly over whether a particular cell should be considered a stem cell, which can divide indefinitely, or a progenitor cell, which can differentiate into fewer cell types and is thought to burn itself out after a certain number of divisions.

The only way to be really sure of what a cell can, and cannot do, is to observe it, but it is difficult to study cells *in vivo*, and putting them in a dish might change their behaviour. Haematopoietic stem cells were the first to be identified and have, to some extent, set default standards. Putative stem cells are isolated, then placed into animals whose own haematopoietic stem cells have been destroyed by radiation. If the blood-forming system is restored, the transplant is assumed to have contained stem cells. But such an assay is impossible when working with other cell types, such as neural stem cells, which are harder to transplant and assess in disease models. And it is difficult to pin the label to one cell type, when studies commonly involve a mixed population. "It is perhaps not realistic to come up with a generally applicable definition of an adult stem cell," says Thomas Graf of the Centre for Genomic Regulation in Barcelona.

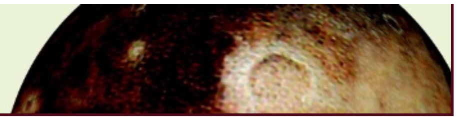
"Some of this just breaks down. That's biology. It wasn't designed to fit the language."
— Lawrence Goldstein

Some researchers are side-stepping the debate by referring in their papers to 'stem/progenitor cells'. Fully understanding what each cell can do is more important than knowing what to call them all, says Goldstein. "Some of this just breaks down," he says. "That's biology. It wasn't designed to fit the language."

Monya Baker

Don't get us started

- Planet
- Species
- Fitness
- *Nature*



F. SAURER/SPL

Significant

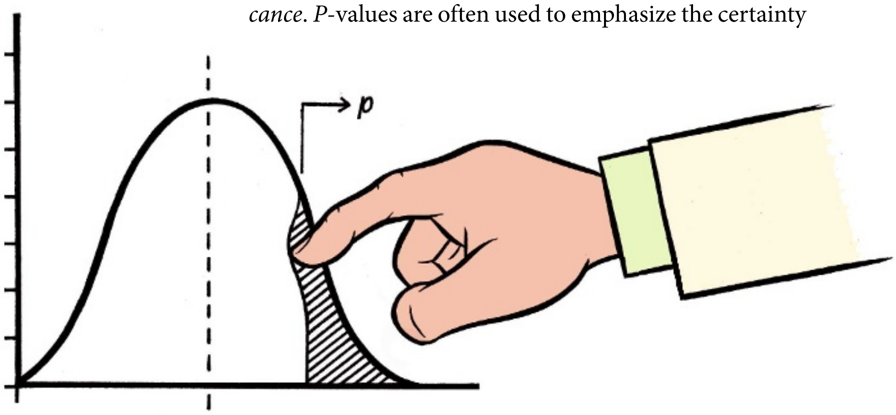
[sɪɡˈnɪfɪk(ə)nt] *adjective.*

Few words in the scientific lexicon are as confusing, or as loaded, as 'significant'. Statisticians wring their hands over its cavalier use to describe scientific validity. And backed by statistics or not, researchers commonly employ the word to illustrate the importance of their latest finding.

The very definition of statistical significance is misunderstood by most scientists, says Steven Goodman, a biostatistician at the Johns Hopkins School of Medicine in Baltimore, Maryland, and associate editor on *Annals of Internal Medicine*. Typically, researchers take a result to be statistically significant based on 'p-values'. This parameter is used, for example, to reveal whether a drug lowers cholesterol based on promising data collected in a clinical trial.

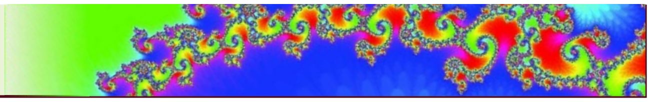
According to the common interpretation, a 'significant' result with a p-value of 0.05 or less means that there is a 5% or less chance that the drug is ineffective. According to the statistically accurate definition, there is a 5% or less chance of seeing the observed data even though the drug is, indeed, ineffective. Rhetorically, the difference may seem imperceptible; mathematically, say statisticians, it is crucial. In situations in which the data is somewhat ambiguous, there is a chance that results can be misinterpreted. "It's diabolically tricky," Goodman says.

Most statisticians resign themselves to abuse of the term's strict definition. But more grievous trespasses abound. "Statistical significance is neither a necessary nor a sufficient condition for proving a scientific result," says Stephen Ziliak, an economist at Roosevelt University in Chicago, Illinois, and co-author of *The Cult of Statistical Significance*. P-values are often used to emphasize the certainty



Yes, they do have scientific meanings: no, we don't expect anyone to listen

- Quantum leap
- Organic
- Chaos



of data, but they are only a passive read-out of a statistical test and do not take into account how well an experiment was designed. A *p*-value would not reveal, for example, that everyone was taking different doses of that cholesterol drug. In many experiments, Ziliak says, "there are so many different errors that they tend to swamp the *p*-value errors".

Even if a result is a genuinely statistically significant one, it can be virtually meaningless in the real world. A new cancer treatment may 'significantly' extend life by a month, but many terminally ill patients would not consider that outcome significant. A scientific finding may be 'significant' without having any major impact on a field; conversely, the significance of a discovery might not become apparent until years after it is made. "One has to reserve for history the judgement of whether something is significant with a capital S," says Steven Block, a biophysicist at Stanford University in California.

In some situations other statistical methods can substitute, but Goodman believes that trying to use them in the scientific literature would be like "talking Swahili in Louisiana". He says he and other editors do their best to keep the term out of *Annals* though. "We ask them to use words like 'statistically detectable' or 'statistically discernable,'" he says.

Geoff Brumfiel

Consciousness

[ˈkɒnʃəsnɪs] *noun.*

Psychologists, philosophers, neurobiologists and doctors all grapple with the term consciousness. For clinicians, the definition is of life or death importance; for some others, it is a matter of determining how the brain's interconnecting tissues collectively create a sense of self. "How can this three-pound piece of meat inside my head give rise to something like being me?" sums up Gerald Edelman, director of the Neurosciences Institute in La Jolla, California.

In 2006, neuroscientist Adrian Owen, at the Medical Research Council Cognition and Brain Sciences Unit in Cambridge, UK, reported that a woman who had been diagnosed as being in a vegetative state had shown signs of brain activity associated with consciousness[11]. The activity was picked up with functional magnetic resonance imaging (fMRI), which can reveal changes in brain blood flow.

The finding rattled the clinical definition of consciousness, which is determined by using a series of behavioural tests to see if the patient can make voluntary movements in response to commands. The outcome can determine whether a patient needs pain medication, or whether it is time to switch off life support, but clinicians readily acknowledge that the tests break down when patients are unable to move. Doctors now find themselves in an uncomfortable limbo, because it is not clear whether cortical activity measured on fMRI is enough to redefine those decision points. "What do we do as a community as long as this method is not yet validated?" asks Steven Laureys, a neurologist with the Coma Science Group at the University of Liége in Belgium.

> **"You don't waste your time defining the thing. You just go out there and study it."**
> — Michael Gazzaniga

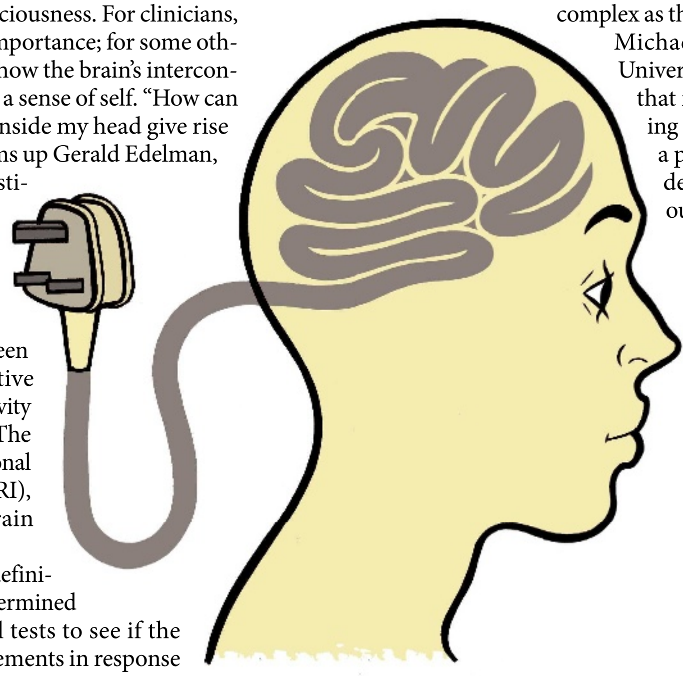
The French philosopher René Descartes declared that consciousness was a fundamental property that fell beyond the rules of the physical world. Most scientists, says Edelman, are not satisfied with that answer. "There must be some physical basis for consciousness," he says. "The difficulty is, how does that arise?"

Philosophers David Chalmers of the Australian National University in Canberra, explored what he called the "hard problem" of consciousness by pondering 'qualia', the subjective properties of experiences. Scientists and philosophers alike have struggled to explain how the physical properties of the world around us — such as colour and temperature — give rise to the experiences of 'red', or 'warm'. Chalmers has argued that the functional organization of the brain rather than its chemical or molecular properties makes these experiences possible.

Many definitions of consciousness include the ability to sort through the relentless onslaught of incoming data to create and respond to an internal model of the external world. And some believe that simply gathering data about neurons and behaviours will not be enough. "What we need is a 'theory of consciousness'. Then we'll be in a better position to define it," says professor of biology and engineering Christof Koch of the California Institute of Technology in Pasadena. Koch thinks that information theory could provide the solution by determining whether consciousness might be an inherent by-product of a system as enormously complex as the brain (see 'Complexity').

Michael Gazzaniga, a neuroscientist at the University of California, Santa Barbara, argues that researchers need only develop a working definition to explore consciousness, not a precise one. "You don't waste your time defining the thing," he says. "You just go out there and study it." ■

Heidi Ledford



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See Essay, page 1040.

Discuss definitions online at http://tinyurl.com/4afapl.