

THIS WEEK



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The antibiotic alarm

There is a growing recognition that action must be taken to deal with the alarming rise in the incidence of bacteria resistant to today's antibiotics, and its implications for global health.

The threat posed by the spread of antibiotic-resistant strains of bacteria is unlikely to be news to *Nature's* readers. Stories of the spread of 'superbugs' have become familiar in recent years. Yet what may come as more of a surprise is the relatively low level of recognition that this problem has received among policy-makers, especially when compared with the potentially catastrophic nature of the crisis that is unfolding. In essence, we are engaged in an arms race with pathogenic bacteria — and we are losing.

Academics, health-care professionals and campaigners have for decades warned that the misuse and over-prescription of antibiotics have led to a rise in resistant strains, a problem compounded by an alarming decline in the discovery and development of new classes of antibiotic. However, that message has grown stronger in recent years, and the previously disparate voices have begun to shout as one. Well-organized campaigns such as Antibiotic Action (a global initiative of the British Society for Antimicrobial Chemotherapy) have applied important pressure and raised the profile of the antibiotic-resistance threat with policy-makers around the world. At last, there are signs that the message is being heard.

This week saw the launch of a UK report into infections and the rise of antimicrobial resistance from Sally Davies, the UK chief medical officer. The report draws on the expertise of academics and health-care professionals to outline the burden of infectious disease in the United Kingdom and the increasing proportion of infections due to antibiotic-resistant strains. Davies makes 17 recommendations for policy and political action relating to antibiotic resistance, pathogen surveillance, prevention of infection and training for the health-care workforce. Chief among these recommendations is that antibiotic resistance should be added to the UK government's list of threats to national security, alongside pandemic influenza and terrorism, a recommendation alone that is sure to raise the profile of the issue. Importantly, Davies' report also recognizes the global nature of the challenge posed by antibiotic resistance and calls for international leadership and coordinated action. The report precedes the upcoming announcement of the UK cross-government antimicrobial-resistance strategy for 2013–18, which is supposed to make these things happen.

The call for better surveillance, better training for health-care professionals and more prudent use of antibiotics is also reflected in a second report, which was published on 5 March by the US Centers for Disease Control and Prevention and focused specifically on infections with carbapenem-resistant Enterobacteriaceae (CRE). Carbapenems are among the last options for treating many bacterial infections, and the increasing prevalence of CRE infections in the United States in the past decade is of concern, especially given that such infections are most often associated with patients undergoing serious medical procedures.

There have been many false dawns in the fight to raise the profile of antibiotic resistance and introduce meaningful policy changes.

Despite expert advice to the contrary, antibiotics remain heavily over-prescribed by doctors around the world. In many countries they are available to buy over the counter without a prescription. In addition, in both the developed and the developing world, antibiotics remain in wide use as growth supplements in livestock, a practice that has drawn much criticism.

As the recent reports show, politicians and policy-makers are beginning to pay the antibiotic issue greater attention, and scientists should

“Antibiotics remain heavily over-prescribed by doctors around the world.”

applaud them. Similarly, those individuals and groups that have campaigned to get us this far should be congratulated for their efforts. But nobody involved can afford to rest on their laurels. The next step must be to bring together all parties with a stake in the issue — researchers, health-care professionals and policy-makers, as well as representa-

tives of the pharmaceutical and agricultural industries — to draw up a plan to tackle the crisis together. This will not be an easy process, and in addition to meaningful political will, it will probably require substantial funding. In the current global financial climate, this is likely to be a sticking point. But the potential financial and human cost of not tackling this crisis will almost certainly be much greater. It was not that long ago that loss of a sibling to a now-treatable disease was a common occurrence in Britain. We must not turn the clock back. ■

Form and function

Although debate over scientific definitions is important, it risks obscuring the real issues.

Science is at the mercy of its language. It can be difficult for researchers to communicate what most excites them about the beauty, intricacy and complexity of the natural world. And when words fail, debates and arguments often arise.

One enduring debate has been resurrected by ENCODE, the Encyclopedia of DNA Elements — an ongoing multimillion-dollar project to catalogue the functional elements of the human genome. A headline-grabbing claim, first made in this publication last September, was that roughly 80% of human DNA had been ascribed some “biochemical function” thanks to the efforts of more than 440 scientists (The ENCODE Project Consortium *Nature* **489**, 57–74; 2012).

That percentage is remarkably high, in part because of a broad definition of ‘function’. The ENCODE team used the term to include binding by a regulatory protein, or transcription into RNA — activities

identified as widespread. But almost immediately, other scientists began to take this definition to task, calling it essentially meaningless.

Some background is useful. Genomes vary dramatically in size — sometimes irrespective of the complexity of the organism. Take, for example, the genome of the marbled lungfish (*Protopterus aethiopicus*), which clocks in at an excessive 133 billion base pairs. That of the pufferfish (*Takifugu rubripes*), by contrast, sports only 365 million.

For the ENCODE paper to suggest that humans have little genomic redundancy implies that the 3.2-billion-base-pair human genome hits a sweet spot in efficiency. Critics suggested, sometimes sharply, that this was both anthropocentric and ignorant of how evolution shapes the genome. Much of human DNA is non-functional, they insisted. It is a relic of history, garbled by mutation and essentially junk.

The most recent formal critique, published this week, suggests that similar analyses on organisms with very large and very small genomes would probably find the same density of functional elements (W. F. Doolittle *Proc. Natl Acad. Sci. USA* <http://doi.org/kr3>; 2013). This investigation has yet to be done.

The debate over ENCODE's definition of function retreads some old battles, dating back perhaps to geneticist Susumu Ohno's coinage of the term junk DNA in the 1970s. The phrase has had a polarizing effect on the life-sciences community ever since, despite several revisions of its meaning. Indeed, many news reports and press releases describing ENCODE's work claimed that by showing that most of the genome was 'functional', the project had killed the concept of junk DNA. This claim annoyed both those who thought it a premature obituary and those who considered it old news.

There is a valuable and genuine debate here. To define what, if anything, the billions of non-protein-coding base pairs in the human genome do, and how they affect cellular and system-level processes, remains an important, open and debatable question. Ironically, it is a question that the language of the current debate may detract from. As Ewan Birney, co-director of the ENCODE project, noted on his blog: "Hindsight is a cruel and wonderful thing, and probably we could have achieved the same thing without generating this unneeded, confusing discussion on what we meant and how we said it" ([see go.nature.com/8xorge](http://go.nature.com/8xorge)).

"To dismiss the debate as semantics minimizes the importance of words and definitions."

The ferocity of the criticism has no doubt been fuelled by dissatisfaction over ENCODE's top-down, big-science approach and the large share of research funds that it has attracted. Many biologists have called the 80% figure more a publicity stunt than a statement of scientific fact. Nevertheless, ENCODE leaders say, the data resources that they have provided have been immensely popular. So far, papers that use the data have outnumbered those that take aim at the definition of function.

The debate sounds like a matter of definitional differences. But to dismiss it as semantics minimizes the importance of words and definitions, and of how they are used to engage in research and to communicate findings. ENCODE continues to collect data and to characterize what the 3.2 billion base pairs might be doing in our genome and whether that activity is important. If a better word than 'function' is needed to describe those activities, so be it. Suggestions on a postcard please. ■

Cancer costs

Educating patients is key, but the US National Cancer Institute must keep spending in check.

Cancer experts from 15 countries last week published their reckoning of what it would take to combat the disease on a global scale. They highlighted the need for action and the scale of the problem — 12.7 million new diagnoses a year, more than half of them in developing nations — then ticked off a laundry list of developments needed to drive down that number, and to improve care for people with cancer.

It is an ambitious set of goals. From internationally agreed standards for preclinical animal models to harmonized clinical-trial protocols, the report lays out a framework that will require resources and coordination on an unprecedented scale (H. Varmus and H. S. Kumar *Sci. Transl. Med.* 5, 175cm2; 2013).

The problem needs focus, and all involved must pull in the same direction. Yet last November, the same month that the cancer experts signed off on their recommendations, the US National Cancer Institute (NCI) resurrected a subcommittee of its advisory board to get to grips with a more local problem: the US\$381.2 million that it had spent on its Office of Communications and Education (OCE) between 2006 and 2012.

The figure is high enough to make even bureaucratically hardened Washington DC insiders gasp. On 1 March, the respected cancer-research bulletin *The Cancer Letter* pointed out that the OCE's 2012 budget of nearly \$45 million was almost double what the US Food and Drug Administration spent on communications, including drug and food safety announcements (P. Goldberg *Cancer Lett.* 39, 9; 2013).

The news comes at an already troubling time for US cancer research. Funding agencies must strip 5% from their spending as part of budgetary sequestration, a failed political ploy to force lawmakers to trim the national budget. Where that will leave cancer research is still unclear: little information has trickled out to the public about how and where

the cuts will be made. But the NCI's success rate for grant applications was already at 14%, an all-time low. At a press conference last September, director Harold Varmus predicted that the rate would fall even lower if sequestration were to take effect.

The OCE produces educational brochures for cancer patients and doctors, and runs Physician Data Query, a comprehensive database that includes clinical-trial summaries and definitions of medical terms. It also updates the NCI's websites, runs a hotline for patients and arranges the institute's exhibits at conferences.

In 2007, an external consultancy determined that the office had fallen prey to 'mission creep', losing its focus as a parade of directors shifted course repeatedly over the previous 10 years. Lack of focus, it seems, bred a behemoth. Whatever the cause of the largesse that allowed the OCE's bloated budget, it will only encourage lawmakers determined to slash access to public funds. And it is galling for those researchers who are scrambling to keep their labs alive. As *The Cancer Letter* has pointed out, the OCE's 2012 allotment would cover more than 100 coveted R01 research grants (P. Goldberg *Cancer Lett.* 38, 45; 2012).

With the revival of its advisory board's subcommittee on communications, the NCI has an opportunity to end the mission creep, focus efforts and reduce its budget. This is not the first time that Varmus has had to trim the fat from NCI programmes. He successfully tackled the cancer Biomedical Informatics Grid, which came under fire in 2011 when NCI advisers questioned its \$350-million price tag. And the institute has already taken steps to rein in the OCE's budget: its 2012 allotment, although large, reflected a 34% cut from 2006, when the office's spending topped \$68 million. The subcommittee is next scheduled to present at an advisory board meeting in June.

There is no doubt that education of patients is crucial for cancer care and for clinical-trial recruitment. But the institute can surely continue to educate while tightening its belt, perhaps by consolidating the OCE's other administrative tasks. It must evaluate outside contracts and consider partnering with philanthropic groups to produce educational materials. In an era of ambitious goals and shrinking resources, that could free up much-needed money for research. ■

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