THIS WEEK

EDITORIALS

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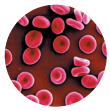

FLEXIBLE FRIENDS Red blood cells offer a new route to making plastics **p.9**

Overdose response

Information about the structure of a key brain protein could help in the development of safer prescription drugs.

The musician Tom Petty last year joined a long line of high-profile stars to hit the headlines for dying from an accidental overdose of prescription painkillers and tranquillizers. The risks of opioid painkillers dominate the news. But the other half of the deadly mixture in such overdose cases deserves attention, too. It's typically a medicine from a class of drugs called benzodiazepines or — more colloquially — benzos.

These drugs — Valium (diazepam), Xanax (alprazolam) and the like — have been prescribed as tranquillizers for decades, mainly for anxiety. And the health risks they pose, such as addiction, are well known. Yet a study published last week spells out the specific danger of mixing them with an opioid painkiller: the risk of an overdose is five times higher when people taking opioids are also prescribed a benzodiazepine (I. Hernandez *et al. JAMA Network Open* **1**, e180919; 2018). According to the US National Institutes of Health's National Institute of Drug Abuse, almost one-third of overdoses involving opioids also involve benzos.

The problems come because both opioids and benzos function as depressants on the central nervous system. Acting together, they can make it difficult to breathe — so difficult, in fact, that many overdose deaths are caused by suffocation. As a result, the US Food and Drug Administration (FDA), among other regulatory bodies, has repeatedly tried to highlight the risks of prescriptions for both types of drug. In a perspective article published last month, the FDA called for "proactive pharmacovigilance" — better tracking of the drugs that different (and sometimes the same) doctors prescribe to patients (D. C. Throckmorton *et al. N. Engl. J. Med.* http://doi.org/gdj5t4; 2018).

A better long-term solution would be safer drugs. Work is under way already to develop non-addictive opioids. Also on the radar is replacements for benzos, with the aim of finding compounds with the same calming effect but none of the risky side effects.

In *Nature* this week scientists present an advance that could help in this search: the detailed structure of a receptor known as $GABA_A$, a membrane protein that is found mainly near the brain's synapses (see page 67). The physiological effects of benzos and some other drugs are triggered by binding to this receptor. Knowing its structure might help researchers to design or identify less-risky compounds. Alternative drugs are a long way down the road, but chemists are already finding compounds that can bind to other receptors with known structures. Information about exactly how benzo drugs bind to this receptor should provide insights to help in the development of new compounds for the treatment of anxiety, epilepsy and other neurological disorders.

The structure of the $GABA_A$ receptor is so complicated that chemists had been unable to solve it using conventional structural-biology techniques. Instead, they turned to cryo-electron microscopy (cryo-EM), a technique that fires beams of electrons at proteins that have been frozen in solution, and that is rapidly overtaking conventional techniques for solving the structures of the more complicated human proteins.

The $GABA_A$ receptor comprises several subunits, which can be arranged in a number of ways in what are called isoforms; the *Nature* paper looks at the main isoform found at human brain synapses. The high-resolution structures reveal how the neurotransmitter GABA (γ-aminobutyric acid) and benzodiazepines such as flumazenil, bind to interfaces between the subunits.

"The complexity of the protein could help to explain one of its most striking features: its versatility."

The complexity of the protein could help to explain one of its most striking features: its versatility. As well as binding to benzos, the receptor is also activated by compounds such as barbiturates, alcohol, anaesthetics and steroids. So knowing the structure should help chemists to find therapeutic compounds in those fields, too. The next steps will probably involve working out the modes of action of these chemically distinct drug classes.

The original medicines have helped millions of people and, used with care, can continue to do so. But too much of a good thing can and does kill people. And that needs to stop. Fundamental structural biology — once seen as a purely theoretical pursuit — can point the way. ■

City living

Researchers must get to grips with the grave challenge of rapidly growing urbanization.

Cape Town has avoided its Day Zero, when it was due to run out of water, but has instead ended up with scenes reminiscent of the disaster film *The Day after Tomorrow*. Heavy winter rains in the South African city this week caused widespread flooding. Dry for so long, the city's storm drains have been overwhelmed, and many roads have turned to rivers. Its citizens have been forced to shift from fears of a lack of water to dealing with the chaos caused by having too much.

In some ways, the experience of the city and its residents is a parable for our times, and an example of the kinds of problems faced by city officials the world over. How can we enable our urban centres to cope with extremes of weather, including those that global warming is expected to bring? And how can planning for worst-case scenarios be aligned with increasing awareness of the need to make our cities more sustainable?

That need is great. It's well documented that humans are becoming an urban and not a rural species, and that trend is expected to continue. In 1950, less than one-third of the population lived in cities. More than 50% do so now, and by 2050 the figure is projected to be 70%. Every week, the urban population grows by around 1.5 million. By

mid-century, as many people will be living in cities as occupy the entire planet today. About one-third of this new urban population growth will be in just three countries — Nigeria, China and India.

All of those billions of city-dwellers have entirely predictable demands: food, water, and subsequent waste disposal. Realistically, most world cities will struggle to become self-sufficient when it comes to dealing with those basic needs of their citizens. High-density housing and infrastructure don't leave much space for fields and landfill. So the idea of a truly sustainable city is something of a misnomer. But to make cities more sustainable than they are now is a noble goal, and one included in the United Nations' Sustainable Development Goals (SDGs) agreed in 2015.

Specifically, SDG 11 pledges to "make cities and human settlements inclusive, safe, resilient and sustainable". Progress towards that goal will be discussed at a meeting — the High-Level Political Forum on Sustainable Development — at UN headquarters in New York City later this month. Experts in the field will also meet in Singapore next week for a one-day Springer Nature event on Science and the Sustainable City (go.nature.com/2mluyjd).

In a World View article this week (see page 7), one of the conference speakers makes the case for city leaders to take an 'ecosystem' approach to urban environmental management. Most cities have exploited the surrounding ecosystems to support their needs, but efforts to make this relationship less damaging — and so more sustainable — are crucial. Cities are ecosystems, too, of course, and the explosion of urban science to model and understand these systems — another topic to be discussed at the Singapore meeting — demonstrates one important way in which research can contribute.

It's clear that approaches, including research, must be tailored to the individual needs of cities and the regions around them, wherever they are. But, in every case, rampant urbanization demands integrated and multidisciplinary thinking.

Delegates to the New York meeting need only look around them to see one emerging problem with SDG 11 that demonstrates the point. Experts are questioning whether "resilient" and "sustainable" are as complementary as they at first seem, or whether they might instead conflict. To help make the Big Apple more resilient to rising sea levels, plans for a massive, retractable storm-surge barrier across New York Harbor were floated after the devastation caused by Hurricane Sandy in 2012. But others have pointed out that a US$20-billion project that could damage ecosystems, and that would almost never be used, can hardly be classed as sustainable. The same debate is unfolding in Cape Town. Although many blame climate change for the drought there, experts argue that the root cause of the problem is more straightforward: reluctance among policymakers to invest in a new reservoir system. In part, this failure to make the city more resilient was caused by concerns that the dams required were not a sustainable way to do it.

"Rampant urbanization demands integrated and multidisciplinary thinking."

Such decisions and choices are difficult because they require weighing up often conflicting demands and priorities. Science can help by gathering and analysing data to define risks and benefits. Researchers can thus help to tackle these thorny problems, and to ensure that cities continue to offer a home to people — and to much of science itself. ■

Opening remarks

Nature*'s eighth editor-in-chief extends a welcome to readers and outlines her vision.*

Last week, Philip Campbell stepped down as the editor-in-chief of *Nature* after 22 years, and he passed the baton to me.

It is with great honour and sense of responsibility that I take on this unique role, as only the eighth editor-in-chief in *Nature*'s history. I am excited by the prospect of serving the scientific community from this new perspective, bringing to it my own varied editorial experience.

Phil began his parting words in last week's issue by restating that *Nature*'s editorial role has been consistently about support for outstanding science. True to our mission, we continue to enable dissemination of science. It has always been at the very heart of everything we do to facilitate communication of outstanding discoveries that are important and relevant to society and the world, as well as to the scientific community itself.

We will continue to widen our horizons at *Nature*, to be the venue for not only the established, but also emerging fields and discoveries that defy traditional discipline boundaries. There will always be room for the publication and coverage of fundamental discoveries and cutting-edge applications alike. And through our primary research papers, news and analyses, we will continue to further the societal impact of science.

Tomorrow's discoveries will be made by today's early-career researchers. I believe we at *Nature* have an important part to play in their mentorship. We hope to engage them more fully in the dissemination and vetting of the scientific record — for example, by promoting peer-review mentorship. We also hope to be guided by them, so that we can meet their needs when it comes to publishing their work, as research becomes more data-rich and computationally heavy.

In the past, *Nature* has adapted to accommodate the evolving nature of discoveries. In future, I will be keen to explore ways in which our formats can adapt further as research requirements continue to evolve.

The journal will continue to work with research communities to enhance reproducibility and transparency in science. As researchers aim for more transparency in how they both design studies and generate and analyse data, I hope we will make our own processes increasingly transparent, with the aim of demystifying the way we work.

Much has already been made of my being the first female editor-in-chief of *Nature*. Although this may well have been overdue, it is a reflection of greater diversity in the research community, and not just in terms of gender. With human diversity comes diversity of priorities, views and interests, all of which deserve equal prominence. We will continue to strive towards equal representation of all groups among our authors, reviewers and staff. Diversity of collaborators will enhance diversity in our coverage of topics. We know we have some way to go — for example, to increase the number of female reviewers — and we will continue to make it our priority.

The fact that I am one of only two life scientists to hold the title of editor-in-chief of this journal has attracted less attention. My background undoubtedly means that I bring a particular perspective on the sciences, although my focus will remain broad. To my eyes as a geneticist, the most influential work published in *Nature*'s pages under the watch of my predecessor — a physicist — must surely be the reporting of the human genome sequence. Under my watch, I look forward to publishing equally influential findings quite removed from my own area of research expertise.

The role of editor-in-chief is not unlike that of an orchestra's conductor. Behind every piece of journalism and every paper there are dedicated and talented professionals; experts who know how to play their part. I very much look forward to enhancing this well-honed performance, not just at *Nature* magazine itself but also in the broader family of Nature Research journals.

Nature is your journal. Without the scientific community, we have no authors, no reviewers and no readers. I look forward to learning from you all, so that I and *Nature* may serve you better. **Magdalena Skipper**