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Trial and failure

Only the most promising AIDS gels should reach large-scale trials.

Last month saw the failure of a clinical trial of a cellulose sulphate vaginal gel as a protective measure against HIV infection (see page 12). The result was a disappointment for microbicide researchers, and a setback for millions of women in Africa and elsewhere who could benefit from such a product. The international trial, organized by CONRAD, a reproductive-health research group based in Virginia, ended when the gel in question was found not only to be ineffective, but actually to increase the risk of HIV infection.

This is the third large-scale clinical trial of a microbicidal gel for AIDS protection to fail. Naturally, it leaves researchers asking where the approach will go from here. Some counsel patience: the development of new therapies is always an arduous and unpredictable process, they argue.

The concept of microbicide gels — one of the few interventions that might allow women to protect themselves from HIV infection — has been heavily promoted by activists, particularly in the United States. Buoyed by success in raising awareness and funds, these activists want to see the product pipeline filled with as many reasonable candidates as possible.

But a continued pattern of well-publicized trial failure carries risks. This has been amply demonstrated by the history of AIDS vaccine research, where failed trials of products that hadn't even done well in animal models did little to further the development of a working vaccine. And when different groups push their favourite products into trials without taking a hard, rational look at which are most likely to succeed, the whole enterprise suffers. Multiple failures lead to a loss of public confidence. Even if donors continue funding the work, it becomes difficult to recruit volunteers for clinical trials if people think the product is doomed to failure — or worse, that it might even harm their health.

The microbicide field therefore requires a mechanism to help it make rational choices about the best candidates to move through trials. The field is already good at exchanging information. As part of this process, leaders and funders of microbicide clinical trials meet twice a year and are considering doing so more often. But they are not in the business of filtering late-stage trial candidates.

Participants need to explore ways of doing just that, however. Researchers, activists and funders of microbicide work should construct a consultative body that will have the confidence of the community, and help it reach a consensus on issues such as how best to test for efficacy and safety in animals, and how to use the results from such tests to move the best microbicide candidates into large human studies.

Ideally, this should be part of a wider discussion on how to test and roll out interventions to prevent AIDS. Several groups have recommended that researchers convene a cross-community forum to discuss issues related to all the concepts now in trials: prophylaxis with oral antiretroviral drugs; barrier methods initiated by women; treatment of HIV-infected patients who have non-infected partners; vaccines; microbicides; and male circumcision and herpes suppression, which both got a boost from positive trial results last week.

Such a discussion could also help researchers address common problems, such as how best to accommodate the high pregnancy rates in trial populations (which tend to disrupt trials, as pregnant women withdraw from them), and the fact that when counselling is provided in trials of new interventions, the rate of HIV infection plummets, potentially obscuring the effect of the intervention. Researchers also have a common interest in working out how to ensure that interventions that prove to be successful end up being used where they are most badly needed.

Researchers are supportive of such cross-community discussion. At the XVI International AIDS Conference in Toronto last August, for example, a group of about 50 researchers and activists known as the Global HIV Prevention Working Group laid out its own blueprint of challenges for AIDS prevention. On 23 February, the Forum for Collaborative HIV Research released a report that echoed the working group's findings. And a panel of the US Institute of Medicine will report later in the year on the challenges facing clinical trials of interventions to prevent HIV. There is broad and diverse agreement on the urgent need for cross-disciplinary dialogue on these questions. But all the talk must lead to active and careful coordination of AIDS prevention research, to confront the pandemic. ■

Solid foundations

In praise of those physicists who are unobtrusively revolutionizing everyday life.

The perception of physics in the minds of the public is one of esoteric exploration, elucidating the fundamentals of space, time and energy — even the nature of reality itself. And much effort is indeed devoted to articulating and exploring these deep concepts, whose grip on the public's imagination is both undeniable and entirely appropriate. But such investigations do not form the stock-in-trade for the vast majority of physicists, who have chosen instead to focus their efforts on understanding the physical properties of solid matter. Should we conclude that they have little to boast about? Or even suggest that solid-state physics is fundamentally rather mundane?

Far from it. Much of the research that underpins modern technologies — from cars to computers, televisions to telecommunications — has its roots in the physics of the solid state. Occasional debates over whether one should have confidence in science more generally have already been fundamentally won by these self-same developments.

The impact of solid-state physics on society is hard to overstate.

But it would be disingenuous to imply that the attraction of research in solid-state physics is primarily driven by a desire to benefit humanity materially. Such a motivation is undoubtedly present within the community, but for most physicists studying the solid state, the central appeal is similar to that driving their more exotically inclined brethren: intellectual richness and the excitement of the imagination. And a very large element of surprise.

Consider two very different examples, both of which continue to feature frequently in these pages. Just over twenty years ago, the solid-state physics community was shaken by the discovery of high-temperature superconductivity — the unanticipated realization of zero-resistance electrical transport in a family of complex copper oxides, at temperatures too high to be accommodated by the theoretical framework that already existed for explaining such phenomena. (As it happens, the classical Bardeen–Cooper–Schrieffer (BCS) theory of conventional superconductivity is itself celebrating its 50th anniversary this year.) Of course, this stimulated much anticipation about how such materials might find serious practical application — still largely wishful thinking, unfortunately, although not altogether beyond the realms of possibility. But what continues to drive interest in these fascinating materials is the fact that their properties have yet to be understood.

More recently, this same community has born witness to another unexpected development: the discovery of unusual electronic and mechanical properties in graphene — individual crystalline layers of carbon only one atom thick. The surprise in this case is that these layers, when stacked up to form their parent material, graphite, constitute a well-known and much-studied material system that, from a solid-state physics perspective, arguably does fit the description of mundane. This system, too, has potential for practical application, but let's not get ahead of ourselves — the true cause for compelling interest is that graphene provides a powerful test-bed on which to explore the validity of some of the core concepts of solid-state physics. So far, these theoretical foundations are standing up to scrutiny pretty well, but there may well be further surprises to come. Several papers in this issue highlight some of the richness of graphene and of solid-state research in other areas (see pages 36, 52–70 and www.nature.com/conferences/aps/index.html).

The next few years can be expected to bring outstanding, high-profile science as the Large Hadron Collider at CERN, the European particle-physics laboratory near Geneva, starts to explore the landscape of particles and forces at energies never before attained in a laboratory. Who knows what other surprises may be in store (see page 16) as astronomers and physicists probe the nature of the vacuum in other ways? The results will be of no obvious use to anyone, and yet they represent exactly the sort of fundamental exploration that fascinates much of humanity. At the much lower energies found in any university lab, meanwhile, solid-state physicists will carry on unobtrusively changing our lives. ■

Not saving the whale

Japan's professed interest in whale research rings rather hollow.

As the world's biggest consumer of whale meat, Japan has a special interest in whale conservation. While fighting tenaciously to protect its whaling industry, it publicly supports the need for conservation. In a statement released last June, for example, it called on the International Whaling Commission (IWC) to "protect endangered and depleted species, while allowing the sustainable utilization of abundant species under a controlled, transparent and science-based management regime".

Japan has placed considerable emphasis on research into whaling. It spends about ¥830 million (US$7 million) each year to establish whether there are enough whales to support whaling (and in the case of the minke, at least, it finds that there are). And it works hard to get support in the IWC, sometimes from member nations that have no obvious interest in whaling. Two weeks ago, many of these countries sent representatives to a meeting in Tokyo — boycotted by the Western nations most strongly opposed to whaling — at which Japan reaffirmed its commitment to the goal of sustainable whaling.

When it comes to events on the high seas, however, Japan's actions leave much to be desired. Lately, for example, there have been repeated cases of western grey whales (*Eschrichtius robustus*) being caught in Japanese fishing nets. Only about 120 of these whales, which migrate along the Pacific coasts of Asia, are thought to survive, although a much larger, sustainable population of eastern grey whales lives off the west coast of North America. The World Conservation Union (IUCN) estimates that the population of reproductive female western grey whales totals only about 30 animals. But four females have been trapped in Japanese fishing nets and accidentally killed in the past two years.

Japan has expressed concern over this issue. Its fisheries agency says it has been asking fishermen to report sightings of the whales, and to release them when trapped, instead of keeping them and selling their meat, as permitted under the law. The agency claims that its effort has worked so far, with no meat from grey whales being sold on the market.

"When it comes to events on the high seas, however, Japan's actions leave much to be desired."

However, the agency's efforts have not actually prevented the deaths, even though much could be done to that end, including supporting better research into the whales' migration and breeding habits, and the development and use of fishing nets that can release trapped animals. One might expect the Institute of Cetacean Research (ICR), which heads Japan's research whaling programme, to take charge of this effort. But it says that responsibility rests with other research institutes and with the fisheries agency. The overall result has been inaction.

The ICR is often characterized by its critics as little more than a cover for Japan's whaling industry. If it is to claim a real role in whale conservation, it could start by responding more energetically to the clear and present danger to the grey whale. ■