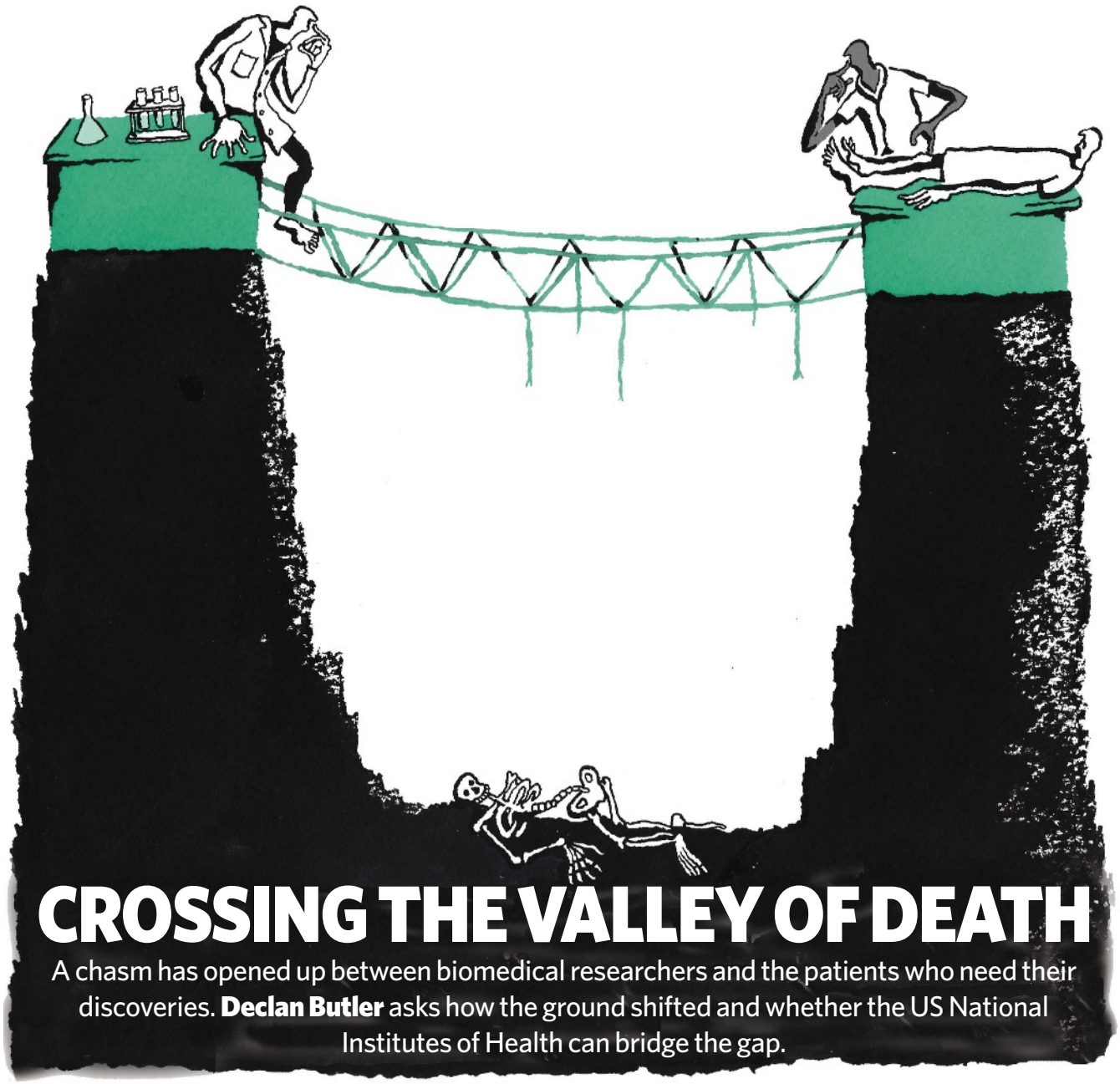


CROSSING THE VALLEY OF DEATH

A chasm has opened up between biomedical researchers and the patients who need their discoveries. **Declan Butler** asks how the ground shifted and whether the US National Institutes of Health can bridge the gap.

B. MELLOR

"NIH stands for the National Institutes of Health, not the National Institutes of Biomedical Research, or the National Institutes of Basic Biomedical Research." This jab, by molecular biologist Alan Schechter at the NIH, is a pointed one. The organization was formally established in the United States more than half a century ago to serve the nation's public health, and its mission now is to pursue fundamental knowledge and apply it "to reduce the burdens of illness and disability". So when employees at the agency have to check their name tag, some soul searching must be taking place.

There is no question that the NIH excels in basic research. What researchers such as Schechter are asking is whether it has neglected the mandate to apply that knowledge. Outside the agency too there is a growing perception that the enormous resources being put into biomedical research, and the huge strides made in understanding disease mechanisms, are not resulting in commensurate gains in new treatments, diagnostics and prevention. "We are not seeing the breakthrough therapies that people can rightly expect," says Schechter, head of molecular biology and genetics at the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, Maryland.

Medical-research agencies worldwide are experiencing a similar awakening. Over the past 30 or so years, the ecosystems of basic and clinical research have diverged. The pharmaceutical industry, which for many years was expected to carry discoveries across the divide, is now hard pushed to do so. The abyss left behind is sometimes labelled the 'valley of death' — and neither basic researchers, busy with discoveries, nor physicians, busy with patients, are keen to venture there. "The clinical and basic scientists don't really communicate," says Barbara Alving, director of the NIH's National Center for Research Resources in Bethesda.

Alving is a key part in the NIH's attempt to bridge the gap with 'translational research'. Director Elias Zerhouni made this bridge-building a focus in his signature 'roadmap' for the agency, announced in 2003 (see *Nature* **425,** 438; 2003). Spearheading the NIH effort will be a consortium of 60 Clinical and Translational Science Centers (CTSCs) at universities and medical centres across the country, which will share some US$500 million annually when they are all in operation by 2012. Late last month, the NIH doled out the most recent grants in

this programme to 14 institutions, including Indiana University School of Medicine in Indianapolis and Harvard University, bringing the consortium up to 38 member centres since its launch in 2006.

Yet the money for the CTSCs will total only 1–2% of the NIH's annual budget of $29.5 billion, and at this early stage it is not clear how much these catalysts will be able to change the terrain. Even so, some people credit the organization and its leader for trying. "Lots of people say they hate Zerhouni. I love him. He had the courage to come forward and say that the NIH was not delivering on its promise," says Lee Nadler, head of the new CTSC at Harvard.

Ask ten people what translational research means and you're likely to get ten different answers. For basic researchers clutching a new prospective drug, it might involve medicinal chemistry along with the animal tests and reams of paperwork required to enter a first clinical trial. For groups wanting to developing diagnostics, imaging tools, or screening and prevention methods the route would be different.

New image

In some sense much translational research is just rebranding — clinical R&D by a different name. But it also involves investing in training, research and infrastructure to help researchers engage in clinical research — and cross the valley of death. Funding agencies hope that this will break down barriers in the transformation of basic-science breakthroughs into clinical applications ('bench to bedside') and enable more research on human subjects and samples to generate hypotheses that are more relevant to people than to animal models (see page 843).

The barriers to translational research are relatively recent. Back in the 1950s and 60s, basic and clinical research were fairly tightly linked in agencies such as the NIH. Medical research was largely done by physician–scientists who also treated patients. That changed with the explosion of molecular biology in the 1970s. Clinical and basic research started to separate, and biomedical research emerged as a discipline in its own right, with its own training. The bulk of biomedical research is now done by highly specialized PhD scientists (see graph), and physician–scientists are a minority.

The basic biomedical research enterprise has now evolved its own dynamic, with promotions and grants based largely on the papers scientists have published in top journals, not on how much they have advanced medicine. And many clinicians who treat patients — and earn fees for doing so — have little time or inclination to keep up with an increasingly complex basic literature, let alone do research. This has diminished the movement of knowledge and hypotheses back and forth between bedside and bench. At the same time, genomics, proteomics and all its cousins are generating such a volume of potential drug targets and other discoveries that the pharmaceutical industry is having trouble digesting them. With pharma spending more on research but delivering fewer products (see graph), it is no longer in a position to take forward most academic discoveries. "There is a real crisis in the industry," says Garrett Fitzgerald, head of the CTSC based at the University of Pennsylvania in Philadelphia.

One crude way of tracking the rupture is to see when people developed a new rhetoric to deal with it. The term 'translational research' first appeared in PubMed in 1993, sparked by the characterization of *BRCA1* and other cancer genes, which suggested immediate applications in early detection and treatment of cancers. Use of the term remained low throughout the 1990s, in just a handful of papers annually, until around 2000, after which it has cropped up in several hundred articles each year.

"There was a widening gap between basic and clinical research."
— Elias Zerhouni

NIH

In 2000, the US Institute of Medicine convened the Clinical Research Roundtable, which held a series of meetings that are credited with putting translational research high on the agenda. The process pinpointed two blockages in the transfer of research knowledge into practice (S. H. Woolf *J. Am. Med. Assoc.* **299,** 211–213; 2008). The first was preventing laboratory advances being converted into new medical products and tests in humans; the second was stopping proven improvements in treatment — a new drug combination, for instance — becoming adopted in medical practice.

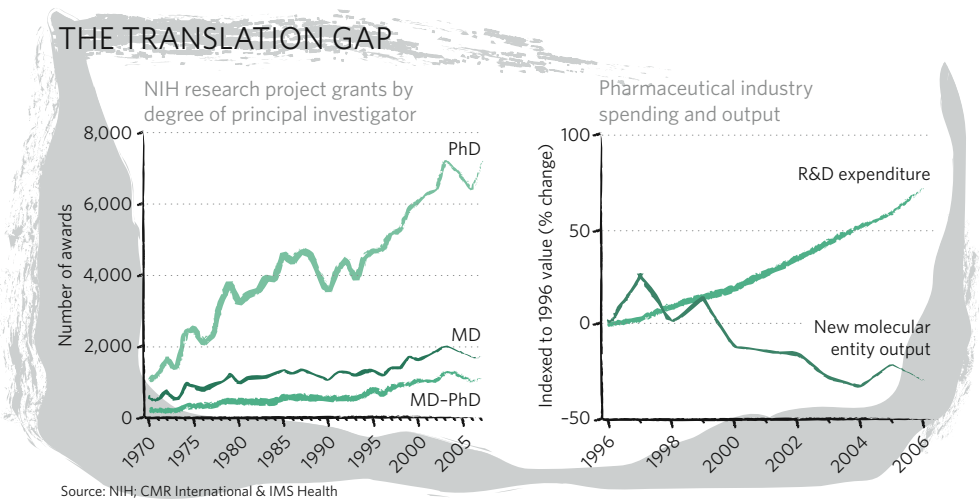
Out of the comfort zone

Biomedical research agencies are responsible for the first block. As anyone attempting translational research will testify, basic scientists have few incentives to move outside their comfort zone. It means getting involved with complex regulatory and patent issues. There is the risk of career damage to boot, because it is not the sort of research that gets published by the top journals and spurs promotion.

Publicly funded biomedical science has become disconnected from the processes that lead to cures and treatments, says Rudy Balling, a proponent of translational research at the Helmholtz Centre for Infection Research in Braunschweig, Germany. "Most biologists haven't a clue about real medical needs," he says, or about the difficulties of applying their research.

When Zerhouni became director of the NIH in 2002, "that's exactly the situation as I found it", he says. "There was a widening gap between basic and clinical research, which if left alone would have been a major barrier to progress." As head of the world's top-spending biomedical research agency, Zerhouni was under pressure to make progress. The NIH's budget had doubled since 1998 to $27 billion in 2003, and tax-payers were demanding a return on their investment. "That is the accountability factor that Congress is asking us to address," he says.

At the time, Zerhouni convened a series of whirlwind meetings with top clinicians and scientists who also realized they needed to change the way they worked so that existing



knowledge didn't end up sitting on shelves. These meetings convinced Zerhouni — a radiologist himself — that it was a priority "to get over this gap" by redesigning the agency's translational research programmes.

New lamps for old

The NIH already had projects under the old 'clinical research' label, including 78 General Clinical Research Centres (GCRCs) created in 1959 at universities and medical centres nationwide. But the centres were generally limited to providing services for conducting clinical trials. They did not tackle Zerhouni's new priority, spelt out in the roadmap, to boost the agency's ability to train physician–scientists and translational researchers capable of bridging the valley of death. The CTSCs will replace the GCRCs.

Science and innovation have become too complex for any nostalgic return to the physician–scientist on their own as the motor of health research. Reinventing that culture is therefore the focus of the CTSCs, in the form of larger, multidisciplinary groups, including both basic scientists and clinicians, but also bioinformaticians, statisticians, engineers and industry experts. Zerhouni says he expects them to be breeding grounds for a new corps of researchers who will effectively stand on the bridge and help others across. Scientists at the centres will be evaluated with business techniques, such as milestones and the ability to work in multidisciplinary groups, rather than by their publications alone.

NCRR/NIH

"The clinical and basic scientists don't really communicate."
— Barbara Alving

Since 2006, Fitzgerald's centre in Philadelphia is using its CTSC money to pull together 400 or so staff who were previously scattered across research centres and hospitals and install them in a new bricks-and-mortar institute. For researchers with work to translate, the new centre offers support with regulatory issues, patents and clinical trial design. Fitzgerald would ultimately like 20% of new medical-school graduates to follow translational research courses, and the centre also offers master's and other degrees in the new discipline for MDs and PhDs. One of Fitzgerald's programmes is exploring the aftermath of painkillers called COX2 inhibitors, which were more or less abandoned by the pharmaceutical industry after they were found to increase the risk of heart attack and stroke. Researchers at the centre are looking for biomarkers that might identify those who escape these side effects and salvage a future for the drugs.

Scientists in other countries are watching the NIH flagship effort with interest. In Britain, which is second only to the United States in biomedical research output, the government last year announced a doubling of the Medical Research Council's budget to almost £700 million (US$1.3 billion) by 2010, largely to finance a new focus on translational research. In Europe, around 20 national research and government agencies are exploring a European version of the CTSCs. Coordinated by Balling, the European Advanced Translational Infrastructure in Medicine wants to create a multimillion-euro network of biomedical translation hubs across Europe, based on existing research centres.

J. IDE/HARVARD UNIV. NEWS OFFICE

A new breed of researchers will aim to bridge the translational divide.

Time will tell whether the NIH's translational centres can come up with the goods. Gary Pisano, an expert in innovation at Harvard Business School, calls them "an experiment worth doing". Government support has been used with some success to further application of other research fields, he points out, such as defence funding that supported applied research in electronics, communications and the Internet.

Measuring the outcomes of translational research is notoriously difficult, as they do not lend themselves to the simplistic bean counting of publications. Because drug development can take up to 20 years, the eventual impact of such efforts on the drug pipeline will only emerge with time. At the NIH, Alving has set up a commission to advise how the CTSCs should be evaluated. This might be done by tracking researchers' career paths and surveying productivity by, for example, counting patents, clinical trials and collaborations with industry. But until patients see a benefit, the aims of the programme risk appearing laudable but vague.

Some basic scientists baulk at the $500 million annual costs of the centres when the NIH budget is under extreme pressure. But Zerhouni says there will be no significant diversion of resources to translational research and that the CTSCs will be funded largely by absorbing the $290 million budget of the old GCRCs. Some $95 million will come from the NIH's Common Fund, and the rest will be redirected from other clinical projects. Zerhouni says the NIH has a current balance of 60% basic and 30% clinical and argues that it needs more, not less, basic research to feed the translational pipeline. Others assert that the 30% clinical figure is artificially inflated because it classifies a proportion of work — such as that on animal models — as clinical that others would call basic, something Zerhouni denies.

With a tiny fraction of the NIH budget, and much of that shuffled from existing clinical programmes, critics might charge that the CTSCs are little more than business as usual. Schechter thinks that the NIH needs to go further down the translation road by reforming the monopoly of investigator-driven research grants as the agency's main funding mechanism. This system rewards individual success and does little to encourage the type of collaboration that translational research demands. He points to alternative models for doing translational research, such as the Multiple Myeloma Research Foundation, based in Norwalk, Connecticut, and other charitable groups that operate more like businesses in their drive to get research into clinical trials. "There are other structures for doing biomedical research than that which the NIH has hewed to for 40 years."

Zerhouni is sensitive to the need for reform, and points to new awards for multiple investigators. He acknowledges there is no 'right' model for translational research, but he is confident that the NIH will learn about the best ones by giving the CTSCs the freedom to explore a diversity of approaches. As to what the NIH stands for — National Institutes of Health, National Institutes of Biomedical Research or National Institutes of Basic Biomedical Research — "we are all of the above", says Zerhouni. And perhaps it will take many aliases and many attempts to cross this particular chasm. ■

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See also pages 823 and 843, and online at http://tinyurl.com/3tt3y3.