Translational Research

What Does It Mean?

The National Institutes of Health has just announced the creation of the National Center for Advancing Translational Sciences. Translational research has become the buzzword in medical research. Research institutes, universities, and even journals are increasingly eager to develop their translational research credentials. So how does Anesthesiology fare when it comes to translational research? To answer this question requires some idea of what is meant by translational research. It seems all agree that translational research is worthy, and some would say desperately needed; however, there is still some confusion over what it actually is.

The term was first used in the late 1990s. Through the last decades of the 20th century, spending and discovery in the basic medical sciences increased dramatically while improvement in health outcomes remained stubbornly slow. One perceived problem was the lag between basic discovery and the appearance of new drugs and treatments. The time from discovery in basic science to drug approval ranged from 10–20 yr and, after adjusting for the costs of all the failed drugs, the cost for developing a successful drug was heading toward $1 billion. There was no shortage of basic science discovery; advances in genomics and other “omics” have paved the way for even greater capacity in basic science discovery. The challenge was how to use that knowledge efficiently and effectively to develop new effective treatments. There was a call for more research that could bridge the gap from bench to bed: a call for translational research.

One purported reason for the gap between discovery and clinical application was the decline in the number of clinician-scientists. In the early 20th century medical scientists were often clinicians. The basic science was driven by problems the clinician-scientists encountered in their clinical work, and in turn the clinician-scientists were quick to use laboratory breakthroughs in their patient management. The number of true clinician-scientists diminished as basic science became more complex and as clinicians were increasingly drawn, or pushed, toward purely clinical work. In response there has been a drive for more clinician-scientists. This should help close the gap, but as science becomes increasingly complex it is more important that clinicians and scientists in hospitals, universities, and research institutes work together in truly collaborative environments. This is one of the aims of the National Institutes of Health-supported Clinical and Translational Science Centers.

Although going from bench to bed was perhaps the original meaning of translational research, the term was soon also used to encompass the problem of translating research into practice; the gap between the development of the new treatment and the uptake and everyday clinical use of the treatment, the development of policy, and determining that treatments are indeed improving the health of the population. A drug may have proven efficacy in a tightly controlled trial in a well-circumscribed subpopulation but lack effectiveness in the broader population. The real-life effectiveness may be reduced by comorbidities, other medication, or failure in delivery. Even if a drug is proven to be effective, there are difficulties disseminating that knowledge to clinicians and problems getting clinicians to actually change prescribing practice. There is a lack of evidence-based practice. There are three approaches to increasing this aspect of translation. The information-based approach is to condense and summarize information with meta-analyses and sys-
tematic reviews (such as the Cochrane reviews), making it easier for information to be passed to clinicians. Evidence-based clinical guidelines can also be developed and published. A second approach is the clinician-based approach: to make clinicians more receptive of information by emphasizing and teaching evidence-based practice in medical training and by encouraging clinicians to continue to be engaged in academic practices. The last approach is an active systems-based approach. Poor outcomes in a healthcare setting are identified and the system delivering the care is systematically assessed to identify areas where practice may not be based on best evidence. Changes in the system are then implemented and outcomes reassessed. This is all called translation.

The step from basic science to “first in man” is sometimes called T1; the step from clinical studies to improving the health of the community has been called T2. Some have divided the process even further, defining T1 as the step of basic science discovery to potential clinical application; T2 as finding evidence of efficacy in controlled populations; T3 as testing effectiveness in a broader populations; and T4 as changing practice with evidence of improved health in the community and across populations. Other terms are also used to describe parts of this process. Dissemination, knowledge transfer, health services research, and quality improvement have all been described as part of the translation pathway.

So what actually is translational research? From the above definitions it would seem that translational research could encompass just about everything from molecular science to education and quality improvement activity. To help in the definition, an interesting exercise is to differentiate “translational research,” “research translation,” and “research into translation.” All are important.

Research translation is the process whereby knowledge is passed anywhere along the translational pathway from basic science at one end to improved community-based health outcomes at the other and, of course, vice versa. Basic research tends to be done on molecules, which leads to studies on tissues, which then leads to studies on individual humans and lastly on populations. The type of research varies depending on the stage. A key point is that knowledge generated in one mode of research informs the study or activity needed in the next mode. That is research translation. The process works both ways. Health problems identified in the community should inform the direction for basic research. Research translation is important because the ultimate goal of medical research is to improve health in the community. If knowledge gained in research cannot spur further research and activity toward this goal, then the research itself is of little value. If the knowledge could be used for activity but for whatever reason it is not, then the value of that research is diminished; that is a failure of research translation.

Translational research could be regarded as any type of research that leads to knowledge translation; this is not a particularly helpful definition as it would be hoped that all medical research could lead to knowledge translation, albeit some more than others. Research that has a high capacity for translation and research that addresses particular gaps in translation is translational research that is particularly valued.

Research into translation may be seen as discovering how best to link the knowledge, or how to best progress along the translational pathway. Research into translation is important as it seeks to make the medical research process more efficient. It is looking for new ways to ensure that basic science discovery leads to new drugs, or the most effective way of getting clinicians to assimilate new knowledge and adopt evidence-based practice. This may involve a radical overhaul in how basic and clinical research is conducted and governed. Therefore, the focus of the new National Center for Advancing Translational Sciences is to “catalyze the generation of innovative methods and technologies that will enhance the development, testing, and implementation diagnostics and therapeutics across a wide range of diseases and conditions.” It is hoped that it will “reengineer the process of developing diagnostics, devices and therapeutics.” This may involve virtual drug design, developing better biomarkers of disease and response, developing better ways to identify toxicity, and more efficient clinical trial designs. Overall, knowledge in all phases could be better synthesized using modern informatics. Research into translation also involves determining how best to disseminate information to clinicians and discovering what drives the way clinicians make decisions. Research into translation is an exciting enterprise.

So does ANESTHESIOLOGY publish translational research? In this issue Murphy et al. describe how use of acceleromyography monitoring was associated with a decreased incidence of residual neuromuscular blockade and attenuated severity of patient-perceived muscle weakness in the postanesthesia care unit. There is a clear potential for widespread clinical application. This is translational research. The next steps in the translational pathway are disseminating this knowledge and encouraging clinicians to actually use acceleromyography.

Also in this issue Kodama et al. describe how desflurane causes more neuronal apoptosis in the neonatal mouse brain compared with sevoflurane or isoflurane. This is also translational research, albeit the next step in translation is less clear. How will the results in this study be interpreted clinically and how will they be used to design human and primate trials investigating anesthesia related neurotoxicity? Results from neonatal animal models are difficult to translate to humans and primate studies are prohibitively expensive, we do not have a good biomarker of brain injury in the neonate, human trials in neonates looking at neurodevelopment are difficult to perform, and cohort studies are bedeviled with confounding factors. This is an example where research into translation is desperately needed. How can we better translate findings of toxicity in neonatal animal models to human neonates?

The mission of ANESTHESIOLOGY is “Promoting scientific discovery and knowledge in perioperative, critical care, and pain medicine to advance patient care.” With “advancing patient care” in the mission it is not surprising that ANESTHESIOLOGY publishes a large amount of translational research. With the publication of high-quality clinical reviews and a dedicated education section the journal also specifically pursues research translation. It is hoped that ANESTHESIOLOGY will receive and publish even more of the paradigm-shifting papers looking at research into translation.
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References
1. Collins FS: Reengineering translational science: The time is right. Sci Transl Med 2011; 3:90cm17

ANESTHESIOLOGY REFLECTIONS

The Ohio Military Model 685A: “The Pig”

As World War II grew to a close, the Heidbrink Division of the Ohio Chemical and Manufacturing Company was fine-tuning a new anesthesia machine for field use by the U.S. military—the Ohio 685A. This machine included an ether vaporizer attached to a nitrous oxide–oxygen apparatus. When military anesthesiologists unpacked this machine and rested it without pedestal or tanks on top of its crate, it was quite a squat, compact device. Perhaps for this reason, they affectionately nicknamed it “The Pig.” The Ohio 685A was used through the Korean War and even at the beginning of the Vietnam War. The 685A pictured (above) is part of the Wood Library-Museum’s Roderick K. Calverley Memorial Military Collection. (Copyright © the American Society of Anesthesiologists, Inc. This image also appears in the Anesthesiology Reflections online collection available at www.anesthesiology.org.)

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