

14. Eslamboli A, Georgievska B, Ridley RM, et al. Continuous low-level glial cell line-derived neurotrophic factor delivery using recombinant adeno-associated viral vectors provides neuroprotection and induces behavioral recovery in a primate model of Parkinson's disease. *J Neurosci* 2005;25:769–777.
15. Kotzbauer PT, Lampe PA, Heuckeroth RO, et al. Neurturin, a relative of glial-cell-line-derived neurotrophic factor. *Nature* 1996;384:467–470.
16. Choi-Lundberg DL, Lin Q, Chang YN, et al. Dopaminergic neurons protected from degeneration by GDNF gene therapy. *Science* 1997;275:838–841.
17. Kordower JH, Emborg ME, Bloch J, et al. Neurodegeneration prevented by lentiviral vector delivery of GDNF in primate models of Parkinson's disease. *Science* 2000;290:767–773.
18. Fjord-Larsen L, Johansen JL, Kusk P, et al. Efficient in vivo protection of nigral dopaminergic neurons by lentiviral gene transfer of a modified Neurturin construct. *Exp Neurol* 2005;195:49–60.
19. Tuszynski MH, Thal L, Pay M, et al. A phase 1 clinical trial of nerve growth factor gene therapy for Alzheimer disease. *Nat Med* 2005;11:551–555.
20. Borasio GD, Robberecht W, Leigh PN, et al. A placebo-controlled trial of insulin-like growth factor-I in amyotrophic lateral sclerosis. European ALS/IGF-I Study Group. *Neurology* 1998;51:583–586.
21. Lai EC, Felice KJ, Festoff BW, et al. Effect of recombinant human insulin-like growth factor-I on progression of ALS. A placebo-controlled study. The North America ALS/IGF-I Study Group. *Neurology* 1997;49:1621–1630.
22. A double-blind placebo-controlled clinical trial of subcutaneous recombinant human ciliary neurotrophic factor (rHCNTF) in amyotrophic lateral sclerosis. ALS CNTF Treatment Study Group. *Neurology* 1996;46:1244–1249.
23. A controlled trial of recombinant methionyl human BDNF in ALS: the BDNF Study Group (Phase III). *Neurology* 1999;52:1427–1433.
24. Safety of CERE-120 (AAV2-NTN) in subjects with idiopathic Parkinson's disease. Available at: <http://clinicaltrials.gov/ct/show/NCT00252850?order=1>. Accessed 1/12/06.
25. CERE-110 in subjects with mild to moderate Alzheimer's disease. Available at: <http://clinicaltrials.gov/ct/show/NCT00087789?order=1>. Accessed 1/12/06.
26. Bloch J, Bachoud-Levi AC, Deglon N, et al. Neuroprotective gene therapy for Huntington's disease, using polymer-encapsulated cells engineered to secrete human ciliary neurotrophic factor: results of a phase I study. *Hum Gene Ther* 2004;15:968–975.

Translation: Case Study in Failure

The perception that basic research has failed to meet its full promise in improving health has been widely discussed.^{1–7} In one recent analysis, less than 30% of 101 major scientific discoveries with therapeutic potential made it into clinical trials over a 20-year period, and less than 5% resulted in a licensed clinical therapy.⁸ Despite a doubling in the National Institutes of Health (NIH) budget, the number of promising novel agents

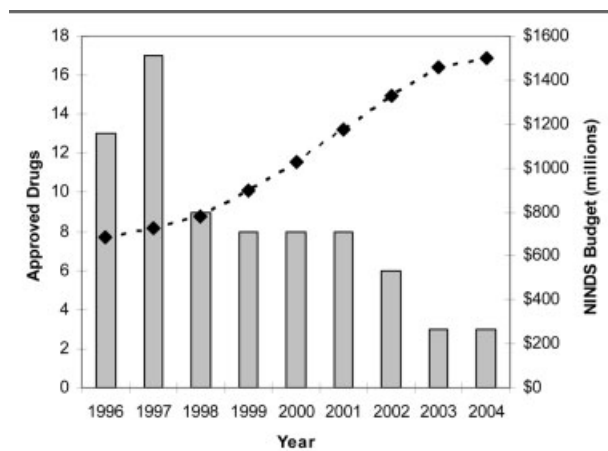


Fig. Number of drugs approved by the US Food and Drug Administration for a neurological indication (bars) and total budget for the National Institute of Neurological Disorders and Stroke (line). A neurological indication is broadly defined to include pain, insomnia, and even erectile dysfunction.¹⁰

entering clinical trials is not increasing.⁹ For neurology, the trend is particularly worrisome, with a dramatic decrease in the number of drugs approved for neurological indications by the Food and Drug Administration, from a high of 17 in 1997 to only 3 in 2004 (Fig).¹⁰ Yes, pace of advancement in understanding basic mechanisms has been exciting and fundamental research is essential to developing new therapies. However, for many clinicians and the public, the real value of scientific research is captured when discoveries are translated into new therapies. In fact, the mission of the NIH is "... to uncover new knowledge that will lead to better health for everyone."¹¹ How can we assure that this happens as efficiently as possible?

Ischemic stroke is a case study in failed translation. Understanding of the basic mechanisms of ischemic brain injury has advanced at an impressive rate.¹² Elucidation of the complex cascade of thrombosis, excitotoxicity, calcium influx, free radical formation, apoptosis, and inflammation represents a major scientific achievement. Based on these discoveries, many agents have been developed and tested in animals. Results in animals have often been encouraging, with drastic reductions in infarct volumes for some agents in some models. However, results in clinical trials have been disappointing. Of more than 100 agents tested in clinical trials, only one has been approved for clinical use, tissue plasminogen activator.

In this issue of the *Annals*, O'Collins and colleagues systematically address the connection between results of studies in animals and selection of agents for testing in patients with or at risk for ischemic stroke.¹³ They ask the question, have the correct agents been chosen to take forward to clinical trials? Their review of the literature identified 1,026 agents studied in animals with

a 25% average reduction in infarct volume in various animal models. Those taken to clinical trials showed no greater reduction in infarct volume in animals compared with those not taken to clinical trials. Thus, there was no evidence that more promising agents were taken into clinical trials.

As the authors acknowledge, their analysis has several limitations, and these may have led to the appearance of greater arbitrariness in the selection of agents for clinical trials. First, the methods they used to identify animal studies in the literature were incomplete. They certainly missed some published studies. Second, results of negative animal studies may never have been published. An investigator studying a group of agents may not bother to seek publication of negative results, particularly given the bias against their publication by journal reviewers and editors. Third, much industry research is unpublished. Industry scientists are not necessarily motivated or even permitted to publish, so we do not know how well studied proprietary agents are. Finally, planning clinical trials takes years, with one analysis showing a median delay of 7 years between publication of major initial scientific findings, often in animal models, and the first relevant randomized trial.⁸ Many of the neuroprotective agents have been tested only in the last few years, and it is not realistic to expect results to have led to clinical trials in this time frame. The end result of all these limitations is noise in the analysis, and this noise could obscure a real association between results in animals and further testing in humans.

In spite of its limitations, the study of O'Collins and colleagues is very important. Specifically, the study may be useful for stroke researchers. It may be helpful in identifying the most promising agents to test in the next clinical trial and in showing where animal research is lacking or unresponsive. More broadly, the study is important as a demonstration of the potential utility of applying rigorous methods to studying research. As scientists, we should demand vigilant introspection into our methods, not just for individual studies but also between studies. Only with careful study of the processes of scientific discovery and translation will we identify potential problems and address them. A careful study of translation of basic science findings to therapies may allow us to consolidate knowledge and process it in much more useful ways. In clinical medicine, a similar move from traditional subject reviews to meta-analysis has improved the quality of evidence for practitioners. Why shouldn't the same be done for translational research?

Introspection into the science of science is rare. Thirty years after its publication, for example, an analysis of research contributing to major medical advances remains a frequent citation in support of funding for basic science even though it is now 30 years old⁷ and has been widely criticized.^{14,15} There are many ques-

tions that could be answered with careful objective analysis. Is current allocation of resources to translational research appropriate? Is peer review working? Are research funds distributed reasonably and equitably across diseases? Has society seen a return on the research investment? These are the sorts of questions that should be addressed as rigorously and as scientifically as possible. With the huge public investment in medical research, if we do not address these questions ourselves, politicians will do it for us,¹⁶ and we may not be so pleased with the outcome. Science must be used to address its own policy and funding.

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References

1. Frist WH. Federal funding for biomedical research: commitment and benefits. *JAMA* 2002;287:1722–1724.
2. Stamler JS, Taber RL, Califf RM. Translation of academic discovery into societal benefit: proposal for a balanced approach—part 1. *Am J Med* 2003;115:596–599.
3. Stamler JS, Taber RL, Califf RM. Translation of academic discovery into societal benefit: proposal for a balanced approach—part 2. *Am J Med* 2003;115:683–688.
4. Schechter AN, Rettig RA. Funding priorities for medical research. *JAMA* 2002;288:832; author reply, 832.
5. Pound P, Ebrahim S, Sandercock P, et al. Where is the evidence that animal research benefits humans? *Br Med J* 2004;328:514–517.
6. Stewart PM. Improving clinical research. *Br Med J* 2003;327:999–1000.
7. Comroe JH Jr, Dripps RD. Scientific basis for the support of biomedical science. *Science* 1976;192:105–111.
8. Contopoulos-Ioannidis DG, Ntzani E, Ioannidis JP. Translation of highly promising basic science research into clinical applications. *Am J Med* 2003;114:477–484.
9. Pollack A. Despite billions for discoveries, pipeline of drugs is far from full. *The New York Times*, 2002:C1.
10. Approved drugs for neurology. CenterWatch Web site. Available at: <http://www.centerwatch.com/cgi-bin/cl.pl?p=patient/drugs/area10.html>. Accessed October 11, 2005.
11. NIH Public Access Background Information. National Institutes of Health (NIH) Web site. Available at: http://www.nih.gov/about/publicaccess/publicaccess_background.htm. Accessed October 11, 2005.
12. Endres M, Dirnagl U. Ischemia and stroke. *Adv Exp Med Biol* 2002;513:455–473.
13. O'Collins TE, Macleod MR, Donnan GA, et al. 1026 experimental treatments in acute stroke. *Ann Neurol* 2005;58:00–00.
14. Grant J, Green L, Mason B. From bedside to bench: Comroe and Dripps revisited: Health Economics Research Group, Brunel University, Uxbridge, Middlesex, UK, 2003:1–48.
15. Smith R. Comroe and Dripps revisited. *Br Med J (Clin Res Ed)* 1987;295:1404–1407.
16. Neugebauer serves up a victory for important mental health research and fiscal responsibility. Congressman Randy Neugebauer Web site. Available at: http://www.house.gov/apps/list/press/tx19_neugebauer/NIMH062405.html. Accessed October 11, 2005.

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