Remarkable advances have been made recently in our understanding of the molecular and genetic bases of disease. The potential therapeutic opportunities offered by these scientific findings, combined with the expanding needs of an aging population, have led to broad-based congressional support for increases in the National Institutes of Health budget. These developments have put into sharp relief the question of how to allocate growing budgetary resources among the various categories of medical research. In addition to the need to support basic-science research, investigators and policy analysts alike have recently emphasized the need to invest in translational research and clinical evaluative research. The rationale for supporting translational research, which is typically physiologic in nature, is that it is needed to convert the insights provided by basic biomedical science into new methods of diagnosis and therapy. A case in point is the research that was based on fundamental observations about how renal tubules handle sodium and that led, in turn, to the development of new diuretic agents and methods of managing sodium imbalance. The argument for supporting clinical evaluative research is that it is needed to assess the efficacy and safety of such new interventions.

There is, however, a much stronger rationale for the support of both types of research. Innovation is a learning process that takes place over time, and a fundamental aspect of learning is the reduction of uncertainty. The end of the research-and-development process does not entail the elimination of all, or even most, of the uncertainties surrounding medical innovation. Among these uncertainties are benefits that were unanticipated when the research was performed. Unanticipated uses of diagnostic and therapeutic interventions are often identified many years after their introduction. Indeed, widespread use is often an essential precondition for the identification of new applications, and clinical practice itself is thus a particularly important source of medical innovation. The unexpected and anomalous results of clinical experience thus pose new questions for basic biomedical research and enrich its ultimate payoff.

What measures might be taken to broaden the range of indications for new therapies and to accelerate their discovery and introduction? Should these measures be publicly or privately financed? It took half a century for the cardiovascular benefits of aspirin, the most widely used drug in the world, to be recognized and nearly 40 more years before it was widely used for cardiovascular indications. Could this process have been expedited? To address these questions, it is necessary to examine the pathways by which new indications for therapies are discovered.

Why Uncertainty Endures

Successful research and development puts an end to some uncertainties but opens the gate to others, not for want of methodologic acumen, but because the complexity of humans limits the ability to predict the effect of a new intervention. Alpha-adrenergic–receptor antagonists, for instance, were first tested for hypertension. At the time of their introduction, it was not known that alpha-adrenergic receptors are also present in the prostate. In fact, it took another 20 years to establish alpha-adrenergic blockade as a treatment for men with benign prostatic hyperplasia.

Clinical trials are designed to test a narrow hypothesis and
consequently do not usually reveal unexpected benefits.

The heterogeneity of patients further limits the opportunity to find benefits of new research. Randomized controlled trials do little to minimize this uncertainty, because the selection criteria often exclude many patients who might benefit (e.g., the elderly, pregnant women, children, and patients with coexisting conditions). A case in point is coronary bypass surgery; only 4 to 13 percent of the patients who now undergo this operation would meet the eligibility criteria for the randomized controlled trials that established its efficacy. How to account for this heterogeneity is a sizable challenge, given that improvements in medical interventions often expand the range of patients in whom treatments and diagnostic tests are used.

**The Post-Innovation Innovation Process**

Thus, the history of medical innovation is replete with instances in which new indications have been discovered after drugs and devices have been introduced into clinical practice. These new indications have been identified in at least three ways. First, after a drug or device has been introduced, new basic-science investigations elucidate the nature of its mechanisms of action. For example, when the first calcium-channel blocker, verapamil, was introduced in 1963 for the treatment of angina pectoris, clinicians differed as to how the drug worked. Some were convinced that the primary mechanism of action was coronary vasodilation, whereas others believed it was due to beta-adrenergic-receptor blockade. Later, verapamil was found to mimic the cardiac effects of simple calcium withdrawal. This understanding encouraged clinical investigators to explore the value of calcium-channel blockers for esophageal spasm, peripheral vascular disease, preterm labor, hypertension, and prophylaxis against migraine. Indeed, use of calcium-channel blockers for the treatment of hypertension vastly exceeded that for the original indication in terms of demand for the drug and volume of sales.

In the realm of medical devices, an important innovation is the laser, one of the most powerful and versatile advances in technology in the 20th century. The widening range of applications in the 35 years since the laser was patented at Bell Laboratories is breathtaking; it includes precise measurement instruments, chemical research, computer printers, bar-code scanners, and telecommunications. The possibility of using the laser for eye and skin disorders became apparent soon after its introduction. However, fundamental research questions about the properties of light transmission, scatter, reflection, and absorption needed to be answered before the laser could be used for clinical conditions such as refractory angina pectoris, which involve more complex tissue structures.

Second, translational research identifies new uses of a drug either in the laboratory or at the bedside. When the mechanisms of action of existing chemical compounds (e.g., receptor or enzyme inhibition) are well understood, researchers often look for applications to other conditions in which the same pathophysiologic mechanisms have a role (e.g., use of beta-adrenergic antagonists for performance anxiety and essential tremor). Even when its mechanism of action is unknown, a drug often proves to benefit patients with disorders closely related to that for which the drug was developed (e.g., antidepressant drugs for bulimia and anxiety).

For most medical devices, new uses result from their application to other organ systems, although these transfers often require design modifications. The first endoscopes, for example, were used for cystoscopy early in this century. In the 1960s, after the development and introduction of fiber optics, gastrointestinal endoscopy and gynecologic laparoscopy became well established. A further application of endoscopy depended on the eventual attachment of a television camera to the endoscope.

Finally, postmarketing discoveries are often made as a result of clinical observations about previously unrecognized uses of drugs or causes of disease. For example, antibiotics, which have been used for over 50 years, are now prescribed for the treatment of peptic ulcer disease, which followed the remarkable clinical discovery in 1983 that some peptic ulcers were caused by a bacterium, *Helicobacter pylori*. Similarly, bupropion, introduced as an antidepressant drug, was incidentally found to be an effective smoking-cessation aid. Although it is unlikely that a device highly engineered for use in one part of the body could be used without modification in another part of the body, such cases do exist — for example, use of the gynecologic laparoscope for gallbladder excision, starting in the early 1990s.
These three pathways are distinct in principle, but the evolution of clinical interventions may involve more than one of them. Thalidomide, a sedative drug widely banned in the early 1960s because of its devastating side effects during pregnancy, remained in controlled use for selected groups of patients. Subsequently used as a sedative in patients with erythema nodosum leprosum, the drug was found to have totally unexpected and dramatic therapeutic effects. The suspected antiinflammatory and immunosuppressive actions of thalidomide led to its evaluation in patients with other diseases and also stimulated bench research, which in 1989 revealed that thalidomide inhibited the formation of tumor necrosis factor α, a cytokine that mediates host defense and immune regulation. The recognition of this effect led to the use of thalidomide for painful ulcers in patients with AIDS and prompted its evaluation in patients with tumors or rheumatoid arthritis.

One may inquire whether the empirical evidence cited here involves phenomena of great cumulative importance or merely a collection of curiosities. In an attempt to answer this question, we examined the drugs that were "blockbusters" in 1993 (in terms of sales) as well as two major classes of medical devices. Although some of the drugs had been introduced only recently, nearly 90 percent had important indications for use in addition to those for which they were originally approved, and by 1995, sales for secondary uses accounted for more than 40 percent of total sales (Table 1). The pattern for medical devices is similar (Table 2). These secondary uses will probably increase in the future.

View this table:  Table 1. Original and Secondary Indications for "Blockbuster" Drugs, 1993.
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View this table:  Table 2. Original and Secondary Indications for Medical Devices, 1993.
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Policy Implications

Granting the importance of the secondary uses of new drugs and devices, do the processes through which these uses are identified need to be improved? We believe that both society at large and the medical-product industries could gain substantial incremental benefits if new indications for use could be identified sooner after the development of a drug or device. Earlier use of gynecologic laparoscopes for general surgery and earlier use of alpha-adrenergic antagonists in men with benign prostatic hyperplasia would have been of immense social benefit.

What steps can be taken to accelerate the discovery and introduction of new uses for drugs and devices? And what roles should the public and private sectors assume in providing support? Our review of the three research pathways — basic, translational, and clinical — suggests that rapid discovery of unexpected clinical effects presupposes close communication among disciplines. This is difficult to accomplish, however, given the specialization that fuels the growth of medical knowledge. The central issue is how to establish institutional arrangements that promote dialogue and cooperation among academic disciplines and departments, especially in the face of possible organizational disincentives. Even in industry, in which product-related research and development is highly interdisciplinary, development teams should resist the temptation to focus narrowly on expected indications. In the recent case of sildenafil (Viagra), a drug originally tested for use in patients with coronary artery disease, the discovery of the "side effect" of improved erectile function could easily have been dismissed as empirical "noise," had the drug not been found ineffective for its original intended use. This case, once again, shows the considerable potential of broadening the scope of inquiry.

Better interdisciplinary communication in academic medical centers and industrial firms is not enough, however. Equally important is better communication between the two realms. Manufacturers of drugs and devices might rely more fully on panels of academic experts for advice on how a new therapy or diagnostic tool that is useful for one purpose could prove useful (if modified) for another purpose. Moreover, the process of developing hypotheses about new indications for use or gathering evidence to support them would be greatly improved if our rich sources of data on episodes of illness (hospital records), drug use (pharmacy
records), and follow-up care (outpatient records) were connected and accessible to investigators. This would require us to link the information systems of academic medical centers, managed-care organizations, and pharmaceutical firms.

In view of the importance of different types of research in postmarketing discoveries, should the public or private sector support such research? The degree of uncertainty, the expected market value, and the potential social benefit are key elements in investment decisions. In view of the fact that some expansions of use have depended on new biologic insights (e.g., in the case of calcium-channel antagonists) that could not have been anticipated, it is important to support basic biomedical research. This is, in fact, the classic case for public investment (i.e., a high level of uncertainty combined with potentially large social benefits in the absence of sufficient patent protection).

Many new uses, however, are based on translational research, which involves a level of uncertainty that can range from low to relatively high (although not as high as that associated with basic research). The level of uncertainty is comparatively low when a technique developed for one organ system is transferred to another (e.g., peripheral to coronary angioplasty) and is comparatively high when technological breakthroughs are required for the transfer (e.g., plain films to computed tomographic scans). If translational research involves a low expected market value but a high social value, one can also make a strong case for public support. If the expected market value is high and if future uses are relatively easy to anticipate (i.e., there is little uncertainty), then private-sector support is probably adequate (e.g., in the case of additional indications for erythropoietin). Even if there is considerable uncertainty, however, the private sector may be willing to make such investments, as pharmaceutical companies and venture-capital groups are currently doing in the field of biotechnology. In this gray zone, collaborative research arrangements between drug and device companies and publicly supported academic medical centers are worth considering, with some sharing of risks and profits.

Finally, clinical evaluative research is necessary to substantiate the new indications. If the expected market value is low, the public sector may be the only source of support. For example, the National Institutes of Health had to support the trials that evaluated the use of aspirin to prevent myocardial infarction, because pharmaceutical companies were not prepared to do so in the light of the difficulty of obtaining exclusive economic benefits from the trials. Public-sector support for this type of research has, unfortunately, been limited. According to a recent report by the Panel on Clinical Research of the National Institutes of Health, only 27 percent of all research funds awarded in fiscal year 1996 were partly or completely earmarked for clinical research, a category that includes but is not limited to clinical evaluative research. Incentives to conduct clinical research in the private sector should be strengthened. Recent changes in Food and Drug Administration (FDA) regulations are a step in the right direction. Since the passage of the 1991 User Fee Act, the time required for the FDA to review drug applications has decreased substantially, and for the approval of secondary indications, the FDA often does not require duplication of safety studies. Moreover, the 1997 FDA Modernization Act allows companies planning to conduct clinical studies within five years to distribute information about off-label uses to clinicians. However, it may still be difficult to find private-sector support if the patent on a product is about to expire. An extension of the patent for a limited period (e.g., 12 months) would strengthen the incentive to conduct clinical research. This would involve a cost to society, at least in the short term, with consumers having to pay higher prices than would be the case if the generic drug were introduced earlier, but at the same time, it might drastically reduce the high social costs of delays in the widespread application of new indications for use.

Medical research, like medical practice, is increasingly, and reasonably, challenged to show value for money. This challenge may put new pressure on research operations in universities and industry and will entail difficult choices in allocating research funds across the entire research enterprise. Under these circumstances, an attitude of "business as usual" that focuses on the usual research-and-development process but neglects the more dispersed and subtle clinical findings that emerge in the later stages of clinical innovation could be costly to researchers, health care providers, and above all, society.

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