for services does not bring market forces into play.

What is needed are reforms that create clear financial incentives that promote value over volume, with active engagement by both consumers and the health care sector. Market-friendly reforms require empowering individuals, armed with good information and nondistorting subsidies, to choose the type of Medicare delivery system they want. Being market-friendly means allowing seniors to buy more expensive plans if they wish, by paying the extra cost out of pocket, or to buy coverage in health plans with more tightly structured delivery systems at lower prices if that's what suits them. If market-friendly Medicare reform is your aim, a good place to look is the plan proposed by Senator Ron Wyden (D-OR) and Representative (and vice-presidential candidate) Paul Ryan (R-WI) — not the ACA.[5]

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From Project HOPE, Bethesda, MD.

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1. Centers for Medicare and Medicaid Services. 2012 Annual report of the boards of trustees of the federal hospital insurance and federal supplementary medical insurance trust funds. April 23, 2012 (http://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/ReportsTrustFunds/Downloads/TR2012.pdf).
2. Wilensky GR. Reforming Medicare's physician payment system. N Engl J Med 2009; 360:653-5.
3. Centers for Medicare and Medicaid Services. Fact sheet: bundled payments for care improvement initiative. August 23, 2011 (http://www.innovations.cms.gov/files/fact-sheet/bundled-payment-fact-sheet.pdf).
4. Emanuel EJ, Tanden N, Berwick D. The Democrats' market-friendly health-care alternative. Wall Street Journal. September 25, 2012:A19.
5. House of Representatives Committee on the Budget. Wyden and Ryan advance bipartisan plan to strengthen Medicare and expand health care choices for all. December 15, 2011 (www.budget.house.gov/bipartisanhealthoptions).

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HISTORY OF MEDICINE

Reform, Regulation, and Pharmaceuticals — The Kefauver–Harris Amendments at 50

Jeremy A. Greene, M.D., Ph.D., and Scott H. Podolsky, M.D.

Fifty years ago this month, President John F. Kennedy signed into law the Kefauver–Harris Amendments to the Federal Food, Drug, and Cosmetic Act (see photo). With the stroke of a pen, a threadbare Food and Drug Administration (FDA) was given the authority to require proof of efficacy (rather than just safety) before approving a new drug — a move that laid the groundwork for the phased system of clinical trials that has since served as the infrastructure for the production of knowledge about therapeutics in this country. We often remember the Kefauver–Harris Amendments for the thalidomide scandal that drove their passage in 1962. But there is much we have collectively forgotten about Senator Estes Kefauver (D-TN) and his hearings on administered prices in the drug industry. Many parts of the bill left on Congress's cutting-room floor in 1962 — and left out of our memories since — have not disappeared but continue to confront those who would ensure access to innovative, safe, efficacious, and affordable therapeutics.

By the time Kefauver began his investigation into the pharmaceutical industry in the late 1950s, the escalating expense of lifesaving prescription drugs was illustrating that the free-market approach to medical innovation had costs as well as benefits. From the development of insulin in the 1920s, through the "wonder drug" revolutions of sulfa drugs, steroids, antibiotics, tranquilizers, antipsychotics, and cardiovascular drugs in the ensuing decades, the American pharmaceutical industry had come to play a dominant role in the public understanding of medical science, the economics of patient care, and the rising politics of consumerism. For Kefauver, the "captivity" of the prescription-drug consumer in the face of price gouging and dubious claims of efficacy underscored the need for the state to ensure that innovative industries worked to the benefit of the average American.

President John F. Kennedy Signing the 1962 Kefauver–Harris Amendments.

After 17 months of hearings, in which pharmaceutical executives were openly berated for profiteering and doctors were portrayed as dupes of pharmaceutical

companies' marketing departments, Kefauver presented his bill, S.1552. Perhaps its least controversial components were its calls for ensuring that the FDA review claims of efficacy before drug approval, monitor pharmaceutical advertising, and ensure that all drugs had readable generic names. More radically, Kefauver proposed completely overhauling the relationship between patents and therapeutic innovation. First, he proposed a compulsory licensing provision so that all important new drugs would generate competitive markets after 3 years. Second, and more controversial still, Kefauver wanted to eliminate "me-too drugs" and "molecular modifications" by insisting that a new drug be granted a patent only if it produced a therapeutic effect "significantly greater than that of the drug before modification."[1] Proving that a drug worked, according to Kefauver, was not enough: he wanted proof that a drug worked better than its predecessors. In contemporary terms, he wanted to know its comparative effectiveness.

Kefauver's bill met strong resistance as it made its way through the Subcommittee on Antitrust and Monopoly.[2] The American Medical Association firmly opposed the regulation of efficacy by a government agency, arguing that "the only possible final determination as to the efficacy and ultimate use of a drug is the extensive clinical use of that drug by large numbers of the medical profession over a long period of time."[3] The editors of the *Journal*, on the other hand, supported the efficacy provision and the expansion of generic drug names but opposed the patent provisions (considering them an "arbitrary discrimination" against the pharmaceutical industry) and the comparative effectiveness provisions (considering "proof of superiority" necessary only if superiority was actually being "claimed by the manufacturer").[4] The pharmaceutical industry amplified such concerns about comparative effectiveness, arguing that any a priori determination of which medicines were "me-too" and which were true innovations would be arbitrary. Efficacy was hard enough to prove, they suggested; proving *comparative* efficacy would be "completely impracticable."[3]

Kefauver initially stuck to his guns on issues of compulsory licensing and patents, but his persistence ultimately cost him control of his own bill. In June of 1962, officials from the Kennedy administration and the pharmaceutical industry presented the subcommittee with an alternate bill — with no regulatory language about patents included. Kefauver cried foul, the Kennedy administration eased off its support, and S.1552 seemed to all observers to be a dead letter. It was only by chance timing that the summer of 1962 also produced a highly visible tragedy (thalidomide), a hero (Frances Kelsey), and enough ensuing public outcry to persuade Kefauver and Kennedy to embrace the gutted bill.

The amendments granted the FDA the power to demand proof of efficacy — in the form of "adequate and well-controlled investigations" — before approving a new drug for the U.S. market. They also led to a retrospective review of all drugs approved between 1938 and 1962 (the Drug Efficacy Study Implementation program), which by the early 1970s had categorized approximately 600 medicines as "ineffective" and forced their removal from the market. These market-making and unmaking powers were also tied to a new structure of knowledge generation: the orderly sequence of phase 1, phase 2, and phase 3 trials now seen as a natural part of any pharmaceutical life cycle.

However, a well-circulated grievance pointed to one unanticipated consequence of the amendments: the new burden of proof appeared to make the process of drug development both more expensive and much longer, leading to increasing drug prices and a "drug lag" in which innovative compounds reached markets in Europe long before they reached the U.S. market. Industry agitation surrounding the "drug lag" finally led to modification of the drug patenting system in the Drug Price Competition and Patent Term Restoration Act of 1984 — through further extension of drug patents. Indirectly, then, Kefauver's amendments ultimately affected both pharmaceutical pricing and patenting — in a manner diametrically opposed to the one he intended.

Another unintended consequence of the amendments was that the new structures of proof changed not only the behavior of the pharmaceutical industry but also the conceptual categories used by biomedical researchers around the world.[5] Pharmaceutical research came to be overwhelmingly organized around the placebo-controlled, randomized, controlled trial. Although this system has greatly helped researchers gauge the efficacy of an individual drug, it has also rendered data on comparative efficacy much more difficult — and much more expensive — to find or produce.

Renewed attention to comparative effectiveness research in the 21st century illustrates the consequences of sidelining Kefauver's

initial demand for comparative data for evaluating the promotion of novel therapeutics. By 2000, pharmaceutical expenditures had become one of the fastest-growing parts of the budget of many U.S. states and third-party insurers. But the kind of knowledge required for entry into the U.S. drug market offers consumers and payers little information relevant to choosing between subtly different "me-too" drugs within the same therapeutic class — whose therapeutic effect may or may not be the same. Only in the past decade, through the action of the Reforming States Group, the Drug Effectiveness Review Project, and most recently funding of comparative effectiveness research through the American Recovery and Reinvestment Act, the Affordable Care Act, and now the Patient-Centered Outcomes Research Institute, have we begun to catch up on the vital project of comparing therapeutics so that American consumers and their physicians can make meaningful treatment decisions — the project that motivated Kefauver's original investigations a half century ago.

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1. Congressional Record. Washington, DC: United States Senate, 1961;107:5639.
2. Tobbell D. Pills, power, and policy: the struggle for drug reform in Cold War America and its consequences. Berkeley: University of California Press, 2012.
3. Drug Industry Antitrust Act. 87th Congress, Session 1, 1961.
4. Ethical drugs — reflections on the inquiry. N Engl J Med 1961;265:1015-6.
5. Carpenter D. Reputation and power: organizational image and pharmaceutical regulation at the FDA. Princeton, NJ: Princeton University Press, 2010.

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Liver Transplantation — A Vision Realized

Jules L. Dienstag, M.D., and A. Benedict Cosimi, M.D.

The history of medicine is that what was inconceivable yesterday and barely achievable today often becomes routine tomorrow.[1]

Little more than a generation ago, treatment options for end-stage liver disease were few and of limited durable utility. Little could be done to stem the decline of affected patients, who would ultimately go on to have liver failure and portal hypertension — variceal bleeding, intractable ascites, peritonitis, jaundice, hepatic encephalopathy, and coagulopathy — culminating in multisystem failure.

All that changed in 1983, when successes in experimental liver transplantation justified the procedure's generalization as standard treatment. In a tribute to the pioneers who shepherded liver transplantation from barely imagined concept to fully implemented reality, the 2012 Lasker–DeBakey Clinical Medical Research Award honors Thomas Starzl of the University of Pittsburgh and Roy Calne of Cambridge University. Together, these physician-scientists bridged an intellectual and technical chasm as wide and forbidding as the ocean that separated them.

The era of solid-organ transplantation was inaugurated in 1954 with a successful kidney transplantation between identical twin brothers. But while nascent approaches to immunosuppression permitted renal transplantation to flourish, early efforts at liver transplantation stagnated, despite observations in pigs and dogs suggesting that the liver might be an "immunologically privileged" organ. Preliminary work on experimental canine liver transplantation was reported initially in the 1950s, heralding a disappointing foray into auxiliary liver transplantation (insertion of a donor liver without removal of the native liver), after which orthotopic liver transplantation (replacement of the native liver by the donor liver; see illustration) gained traction.[2]

By the early 1960s, in the laboratories of Starzl, then at the University of Colorado, and Calne, at Cambridge, acquisition of the technical expertise for replacing the liver and the availability of early-generation immunosuppressive drugs converged, setting the stage for success in experimental animals, followed by Starzl's first attempted human liver transplantation in 1963.[1,2] The recipient, a 3-year-old boy with biliary atresia, bled to death on the table. In the ensuing year, Starzl tried five more times, but none of the recipients — or two others elsewhere — survived longer than 23 days. Although these early deaths were not attributed to rejection, poor initial graft function resulting from ischemic damage, in concert with limited options for immunosuppression (azathioprine and prednisone), led to what appeared to be insurmountable obstacles of uncontrolled coagulopathy, infection, and multiorgan failure. Accordingly, a nearly 4-year mor-