W e use the term \textit{reversal} to signify the phenomenon of a new trial—superior to predecessors because of better design, increased power, or more appropriate controls—contradicting current clinical practice. In recent years, a number of such reversals have occurred. Use of hormone therapy,\textsuperscript{1} the class IC antiarrhythmic agents,\textsuperscript{2} and the pulmonary artery catheter\textsuperscript{3} have decreased when trials demonstrated that they are either less effective than previously thought or harmful.

\textbf{See also page 1636}

Reversal not only affects medications and diagnostic tests. Previously accepted indications for surgical and medical procedures have also been contradicted. In 2007, the \textit{Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE)}\textsuperscript{4} trial found no benefit to support percutaneous coronary intervention (vs optimal medical therapy) in many patients with stable coronary artery disease, an indication that was previously accepted. The implications of reversal are notable. Reversal implies error or harm to patients who underwent the practice in question, during the years it was considered effective. Reversal also undermines trust in the medical system. We sought to estimate the frequency of reversal by examining 1 year of original publications in the \textit{New England Journal of Medicine}.

Other researchers have studied the rate of reversal in medical research.\textsuperscript{5} Studies of medical interventions are often followed by studies that either reach the opposite result or suggest the magnitude of effect was initially overestimated. Among high-citation count publications, Ioannidis\textsuperscript{6} found that 16\% were contradicted by future studies, and another 16\% were found to have smaller effects than initially thought. Herein, we focused on existing practices that were contradicted in a given period in high-impact literature. Knowing the rate of, and predisposing factors for, reversal may have implications for the approval of medical therapies.

\textbf{Methods.} We reviewed all Original Articles in the \textit{New England Journal of Medicine} in 2009 (the last complete year of the publication at the time of our investigation).

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|}
\hline
\textbf{Article} & \textbf{Date of Publication} & \textbf{Why We Got It Wrong Initially} \\
\hline
Oral Prednisolone for Preschool Children With Acute Virus-Induced Wheezing & Jan 22, 2009 & Extrapolating study results to an age group not studied \\
Quality of Life After Late Invasive Therapy for Occluded Arteries & Jan 19, 2009 & Confidence that the pathophysiologic concepts underlying the practice were rational, and minimal change in practice after the original Occluded Artery Trial (OAT) \\
Intensive Versus Convensional Glucose Control in Critically Ill Patients & Mar 26, 2009 & Excessive confidence in a single-center trial, and confidence that the pathophysiologic concepts underlying the practice were rational \\
Mortality Results From a Randomized Prostate-Cancer Screening Trial & Mar 26, 2009 & Confidence that the pathophysiologic concepts underlying the practice were rational \\
Rosuvastatin and Cardiovascular Events in Patients Undergoing Hemodialysis & Apr 2, 2009 & Confidence that the pathophysiologic concepts underlying the practice were rational, extrapolating study results to a group not explicitly studied \\
Efficacy of Esomeprazole for Treatment of Poorly Controlled Asthma & Apr 9, 2009 & Confidence that the pathophysiologic concepts underlying the practice were rational \\
Cognitive Function at 3 Years of Age After Fetal Exposure to Antiepileptic Drugs & Apr 16, 2009 & Confidence that the pathophysiologic concepts underlying the practice were rational \\
Early Versus Delayed, Provisional Eptifibatide in Acute Coronary Syndromes & May 21, 2009 & Confidence that the pathophysiologic concepts underlying the practice were rational, and minimal change in practice after the original Occluded Artery Trial (OAT) \\
Endoscopic Versus Open Vein-Graft Harvesting in Coronary-Artery Bypass Surgery & Jul 16, 2010 & Confidence that the pathophysiologic concepts underlying the practice were rational \\
A Randomized Trial of Vertebroplasty for Painful Osteoporotic Vertebral Fractures & Aug 6, 2009 & Confidence that the pathophysiologic concepts underlying the practice were rational \\
A Randomized Trial of Vertebroplasty for Osteoporotic Spinal Fractures & Aug 6, 2009 & Confidence that the pathophysiologic concepts underlying the practice were rational \\
Weight Lifting in Women With Breast-Cancer-Related Lymphedema & Aug 13, 2009 & Confidence that the pathophysiologic concepts underlying the practice were rational \\
Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients & Oct 22, 2009 & Confidence that the pathophysiologic concepts underlying the practice were rational \\
Revascularization Versus Medical Therapy for Renal-Artery Stenosis & Nov 12, 2009 & Confidence that the pathophysiologic concepts underlying the practice were rational \\
A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease & Nov 12, 2009 & Confidence that the pathophysiologic concepts underlying the practice were rational \\
Extended-Release Niacin or Ezetimibe and Carotid Intima–Media Thickness & Nov 26, 2009 & Confidence that the pathophysiologic concepts underlying the practice were rational \\
\hline
\end{tabular}
\caption{A table of reversals and why we erred initially.}
\end{table}
Articles were classified on the basis of whether they addressed a medical practice, whether that practice that was new or already in place, and whether the studies’ results were positive or negative. Two reviewers independently classified these articles (V.P. and V.G.). This yielded a highly similar profile (weighted Cohen $\kappa=0.94$). Where there was disagreement, a third reviewer (A.C.) adjudicated those discrepancies. Next, we studied the precondition(s) that permitted reversal in each case. Two reviewers independently articulated the precondition (V.P. and A.C.), and these results were combined. This again yielded a highly similar profile (weighted Cohen $\kappa=0.85$).

**Results.** There were 212 original articles published in the *New England Journal of Medicine* in 2009, 124 (58%) of which made some claim with respect to a medical practice. The remainder was predominantly descriptive, molecular science publications. Of these 124 articles, 89 (72%) investigated a new medical practice, while 35 (28%) studied a practice already in adoption; 91 (73%) were randomized controlled trials; 19 (15%) were prospective cohort studies; 13 (10%) were retrospective cohort; and 1 was a case-control study. Of the 124 studies, 82 (66%) reported positive results and 42 (33%) reported negative findings; 61 (49%) reported a new practice surpassing current care; 12 (10%) reported a new practice failing to improve on current practice; 16 (13%) reported an existing practice that was upheld as beneficial and 16 (13%) constituted reversal; and 19 (15%) were classified as inconclusive.

The eFigure (http://www.archinternmed.com) details all 16 reversals that appeared in 2009, and how each article contradicted current medical practice. Reversals included medical therapies (prednisone use among preschool-aged children with viral wheezing, tight glycemic control in intensive care unit patients, and the routine use of statins in hemodialysis patients), invasive procedures (endoscopic vein harvesting for coronary artery bypass graft surgery and percutaneous coronary intervention for chronic total artery occlusions and ath erosclerotic renal artery disease), and screening tests. In several cases, current guidelines were contradicted by the study in question, as indicated in the third column of the eFigure. The **Figure** is an attempt to identify the underlying reason that permitted reversal. Confidence in physiologic models as the prime reason to adopt a practice initially was the most common precondition for reversal.

**Comment.** The reversal of medical practice is not uncommon in high-impact literature: 13% of articles that were published in the *New England Journal of Medicine*, we believe that the results reported are more likely to be enduring. The reversal of medical practice is an important subject with far-reaching consequences. Further study is necessary and of profound importance.

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**Deaths Involving Drugs in Vermont, 2004 Through 2010**

In 2009, the National Center for Health Statistics at the Centers for Disease Control and Prevention identified Vermont as having one of the highest rates of death due to overdoses (both accidental and suicide) involving opioid analgesics based on 1 year of data (2006). Given this disconcerting finding, we sought to examine deaths involving opioid analgesics over time to obtain a clearer picture of the problem.