Two Centuries of Assessing Drug Risks
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The history of medicine is largely the story of medicines — a continuing tale of unfolding risks and benefits. Yet the medical world into which the Journal was born in 1812 did not systematically assess the side effects of treatments in relation to the good they did. Often, there was no understanding of the causal linkage between adverse events and the therapies that led to them. The mixed bag that was the era’s pharmacopoeia is illustrated in the first article of the Journal’s first issue, “Remarks on Angina Pectoris,” in which John Warren describes a patient with acute cardiac ischemia who “was ordered to take opium and aether, or the fetid gums; to bathe the feet in warm water; and under the direction of a physician, to lose a little blood. . . . The nitrate of silver was prescribed in solution.” Tobacco rounded out the regimen (1812; see box for cited Journal articles). There was no systematic approach for determining which treatments could be effective with an acceptable level of risk and which were merely toxic.

This confusion is illustrated by an 1814 article on arsenic noting that in the treatment of “herpetic affections,” “the beneficial effects of the remedy are not apparent until after its use has been sometime discontinued” — a perfect method for confounding assessment of efficacy (in this case nil) with side effects. The author describes a patient in whom arsenic treatment was stopped when it caused the skin eruptions that are a hallmark of its toxicity (1814a). The lesions subsided after the arsenic was discontinued, a primitive but commonsensical basis for attributing causality to drug-induced pathology. Not so fast, warned the expert, a Dr. Kinglake. “Under such circumstances, it is natural enough for the patient to deny the medicine any share in the cure, attributing the benefit rather to the discontinuance than the efficacy of the remedy.” In reality, he explained, the arsenic had had a “high stimulating effect” that “prevent[ed] its beneficial operation from being observable.” This “arsenical excitement” was “mistook for an unaltered continuance of the original affliction.” Treat on through the signs and symptoms of toxic effects for up to 3 months, Kinglake recommended. The Journal’s own commentator wisely noted, “we cannot divest ourselves of apprehension that [such continuing treatment] may lay the foundation of subsequent irreparable mischief, and should by no means recommend its general employment to such an extent.”

That same year, a case report...
from Dublin commented on the difficulty of determining whether a particularly florid syndrome was an adverse drug effect, a new unrelated disease, or — most problematic — the consequence of stopping medication too early. The patient, who been treated with mercury, developed a dramatic skin eruption, fever to 108°F, tachycardia to 130 beats per minute, headache, nausea, convulsions, blisters that discharged “an acrimonious lymph,” and desquamation so severe that large pieces “of the hand will come off, so entire as to resemble a glove.” Appropriately, the article was titled “Description of a disease produced by the use of mercury.” Helpfully, the report pointed out that “The cure of this disease is very simple. It consists, first, in removing the exciting cause and then its effects.” But the author “thought, in some cases, that continuance of mercury [is] proper.” For although this devastating syndrome could be caused by “an incautious use of mercury,” it could also “be produced in an aggravated form by a too early removal of the mineral” (1814b).

The Journal’s clinical descriptions of adverse drug effects were often detailed and apt, but there was little capacity to weigh these downsides of therapies against their usefulness. When the Journal was launched, the systematic use of randomized, controlled trials was still more than 130 years in the future; it did not become standard until after World War II. Attribution of drug-induced syndromes to a cause was therefore often confused and occasionally counterproductive. At the end of the Journal’s first century of publication, the dean of Harvard Medical School summed up the risk-benefit situation neatly: “I firmly believe that if the whole materia medica could be sunk to the bottom of the sea, it would be all the better for mankind, and all the worse for the fishes.”

Appreciation of this imbalance between toxicity and benefit was not widely shared by his medical contemporaries, but it caught the attention of their patients. By the turn of the 20th century, the proliferation of “patent medicines” had become a national scandal. Manufacturers were not even required to reveal their products’ contents, and certainly not to ensure their safety and efficacy. In the Journal, the debate became a battle between those concerned with patient safety and benefit and a powerful industry intent on protecting its profitability and autonomy from government control. A 1906 issue reported the view of H.W. Wiley, who headed a com-
mission working on the Pure Food and Drugs Act, which would lay the groundwork for today’s Food and Drug Administration (FDA). In an apparent bow to political reality, Wiley said his commission “desired to have the new law go into operation with the least possible disturbance to business and with the least possible inconvenience to the [patent medicine] manufacturers and dealers of the country” (1906).

Initially, the FDA’s pharmaceutical jurisdiction was limited to requiring manufacturers to accurately label the contents of their products, whose main active ingredient was often alcohol or an opiate. The agency had no authority to require that products be safe (which came 32 years later) or effective (which came 23 years after that). For decades more, therapeutics continued to be dominated by useless nostrums that posed potentially great risks. A 1937 article quotes FDA chief W.G. Campbell railing against patent medicines that claimed to cure cancer, tuberculosis, diabetes, pneumonia, influenza, gallstones, glomerulonephritis, and venereal disease — products, he complained, “that have no value whatever in the treatment of those conditions. The firms resorting to this sort of business find shelter, at least temporarily, in the requirement that the Government must prove fraud, and in the inadequate manpower of the Administration, which must cover the coast lines and State borders with a corps of inspectors numbering less than 100” (1937a).

A major movement to prevent medication-induced illness took shape in 1937, propelled — as most important drug-safety developments have been — by a crisis. More than 100 children had been fatally poisoned by the Massengill company’s preparation of the new antimicrobial sulfanilamide (see photo) dissolved in diethylene glycol, a solvent known to be lethal. An enraged public demanded that the FDA be given the right to require that manufacturers prove their products were not toxic before they could be sold.

A Journal editorial placed the sulfa disaster in the context of other drug-induced tragedies: deaths and blindness caused by dinitrophenol, fatal hepatotoxic effects from cinchophen, and “acute and chronic poisoning . . . from the improper use of thyroid and radium preparations.” “Perhaps,” the editorialist suggested, “the boyish enthusiasm with which we accept nearly anything new, and swallow hook, line, and sinker of the printed page, may be again tempered with that calm appraisement of the facts that has so long been considered a heritage of the medical fraternity” (1937b).

As reaction to the “Massengill massacre” grew, G. Philip Grabfield of Peter Bent Brigham Hospital and Harvard Medical School noted that “Under the present law the only liability of this firm lies in connection with use of the word ‘elixir,’ which is defined as an alcoholic solution. In other words, the firm cannot be indicted for manslaughter but only for misbranding.” Selling a poisonous medication was not yet illegal. He continued, “It was shown in 1930 that the toxicity of diethylene glycol was approximately that of wood alcohol. Apparently, this mixture was distributed for sale not only without being tested but without even a casual investigation of the literature on the part of its makers. This ghastly experience indicates . . . the crying need for adequate legislation to control the marketing of all medicinal substances” (1938c).

Grabfield argued that deficits in physicians’ knowledge contributed to the drug-safety problem, noting that the teaching of pharmacology and preventive medicine “is deficient in most schools. After graduation it should become the concern of the legally constituted health authorities to keep the physicians under their jurisdiction continually conscious of these pitfalls of therapeutics. . . . Education, continuous and unremitting, is the only practicable method of breaking down the hold that proprietary medicine has upon the medical and lay public.”

Critical of the proposed 1938 amendments to the law defining the FDA’s authority, and observing that “as much is spent in the United States for patent medicines as for all other types of medical service combined,” he noted, “eliminating the waste of money on patent medicines might almost make unnecessary the provision of additional facilities for the ‘medically indigent’” (1938c).
Control of pharmacologic toxicity was to be joined in the new legislation with control of informational toxicity — the outrageous and often completely untenable claims made in promoting drugs. But industry pushback was intense. In a 1938 letter to the editor, Henry Christian of Peter Bent Brigham Hospital exhorted physicians to agitate for stronger laws to protect patients: “Remember that powerful interest in the drug and food trades fight against restrictive laws; they are well organized; so there is great need that every physician express himself to those who make our laws in Washington” (1938a). This concern was echoed in an editorial criticizing the new drug-safety law: “Why was such a bill written and approved? The proper answer seems to be that powerful business interest of the trade in drugs and cosmetics saw in this method an escape from the more effective provisions of a different bill” that would have given the FDA stronger authority to monitor promotional claims (1938b).

The next major drug-safety event, the thalidomide disaster, came nearly a quarter-century later, when pregnant women who took the heavily promoted sedative–antinauseant gave birth to children with crippling limb-reduction malformations (1962). Before the drug–defect association was understood, this epidemic of congenital anomalies afflicted more than 10,000 children worldwide, but very few in the United States, where an astute FDA medical officer had prevented the drug’s approval. Like the sulfanilamide tragedy, the thalidomide debacle led to major legislative reforms, this time giving the FDA the power to require drug manufacturers to demonstrate effectiveness as well as nontoxicity.

The Journal played a central role in two prominent drug-safety developments of the 21st century, involving the cyclooxygenase-2 inhibitor rofecoxib (Vioxx) and the oral hypoglycemic agent rosiglitazone (Avandia). According to the pivotal study promoting rofecoxib, the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial (2000), patients given that drug had significantly fewer episodes of gastrointestinal bleeding than those taking naproxen. The authors also reported an incidental finding: naproxen users had one fourth as many myocardial infarctions as patients in the rofecoxib group. They speculated that the cause was a cardioprotective antiplatelet effect of naproxen.

The VIGOR article became notorious, for several reasons. In 2004, another randomized trial of rofecoxib was stopped early because the drug, as compared with placebo, nearly doubled the risk of myocardial infarction and stroke (2005a). Accumulating evidence clarified that the VIGOR findings on myocardial infarction were not attributable to a cardio-protective effect of naproxen but to a cardiotoxic effect of rofecoxib. Follow-up publications drew attention to other important problems with the depiction of adverse events in that trial, including the selective omission of key adverse events caused by the sponsor’s drug and an earlier cutoff date for recording side effects that cast the product in an unfavorable light (myocardial infarctions) than for those revealing its clinical advantage (gastrointestinal bleeding events). This selective reporting prompted the editors to write two “Expressions of Concern” about the reporting of risk data in that trial (2005b, 2006).

Recent years have seen the growth of a new mechanism for the study of adverse drug events: court action forcing the release of raw clinical trial data held by the companies that funded the studies. Years after publication of the original Vioxx studies, such re-analyses of their underlying trial reports have found clear evidence, from 3 years before the drug’s withdrawal, of an increased risk of cardiovascular death, as well as evidence that its gastroprotective advantage for most patients was greatly overstated. The advent of mandatory adverse-event reporting at ClinicalTrials.gov is likely in the coming years to provide an additional means of ensuring more timely detection of drug-safety problems (2011a).

Rofecoxib became another milestone in the punctuated evolution of drug-safety science and
policy. In the wake of its withdrawal, influential reports from the Institute of Medicine and the Government Accountability Office, along with Congressional hearings, questioned how a drug that nearly doubled the risk of myocardial infarction or stroke could have been used by more than 20 million Americans over 5 years without that risk being widely appreciated. The debate highlighted the inadequacy of the FDA's reliance on spontaneously reported adverse events as a main method of ongoing drug-safety surveillance. In the resulting FDA Amendments Act of 2007, Congress required the FDA to develop a near-real-time surveillance system capable of scanning the electronic records of more than 100 million Americans by 2012. This “Sentinel System” is now operational (2011b).

The past two decades have also seen the widespread application of newer quantitative methods for analyzing drug risks. In a meta-analysis of publicly available data from the clinical trials of rosiglitazone, Nissen and Wolski reported a 43% increase in the incidence of myocardial infarction among patients randomly assigned to receive that drug versus several comparators (2007). This finding, initially contested by rosiglitazone's manufacturer, was similar to results of analyses conducted by both the company and the FDA, which had not previously been made public. The drug was effectively removed from the market in late 2010 (2010).

The latest development affecting our understanding of drug risks is the use of a computer-based review of records from thousands (or millions) of patients, combined with advanced pharmacoepidemiologic methods, to accurately quantify the rates of specific adverse effects. These tools permit assessment of risk in relation to a drug's benefits. For example, in 2008, the Journal published two observational studies designed to determine whether using the procoagulant aprotinin (Trasylol) in cardiac surgery increased the risk of thrombotic events. Scanning the records of more than 88,000 patients given aprotinin or a comparator agent, the two teams of investigators found a significant increase in the risk of death associated with aprotinin, after adjustment for underlying differences between the groups (2008a, 2008b). The larger of the two studies had been funded by the drug’s manufacturer to inform an FDA advisory committee meeting, but the company didn't provide its findings in time for inclusion in those deliberations, and the committee determined that there wasn’t enough information to warrant withdrawing the drug from the market. However, when these articles and findings from a randomized trial with similar results were published (2008c), aprotinin was withdrawn from routine use; it has since been reintroduced in Europe and Canada.

Thus, two centuries after the Journal cited experts recommending that physicians “treat through” the side effects of arsenic and mercury therapy, the assessment of drug risks has become considerably more sophisticated. Throughout this history, the study and management of this inevitable aspect of therapeutics have involved a complex interplay of clinical practice, pharmacology, epidemiology, policy, and politics. Greater access to data and the application of modern information technology and sophisticated epidemiologic approaches are finally providing a valuable and potentially lifesaving way to balance the good that medications can do against the harm that they sometimes cause.

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

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