

Coagulation and Adulteration — Building on Science and Policy Lessons from 1905

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It's always instructive and often painful to contrast the impressive development of medical science with the more fitful evolution of health policy. The former marches forward more or less systematically; well-developed rules of evidence determine what works, and practical methods build on established facts and test new paradigms. Data and concepts proven true are rarely discarded or forgotten.

Not so with health policy. Although the field's evaluation tools can be rigorous, in practice what is proclaimed "true" often depends on who's doing the proclaiming and whose interests are being represented. As a result, though medical science has progressed fairly steadily, pushing back the frontiers of our ignorance, the application of our collective wisdom in health policy, at least in the United States, has more closely resembled the movements of a planarian swimming through a solution of LSD.

Consider blood coagulation. In 1905, the German internist and physiologist Paul Morawitz published a seminal article on coagulation, including an exposition of how tissue factor leads to the generation of thrombin.¹ In the ensuing years, other researchers extended these observations.² Progress accelerated, with developments in pharmacology and molecular biology building on these foundations to produce new generations of drugs to accelerate

or inhibit the coagulation cascade in ever more useful ways. A particularly elegant demonstration of the progress of that science is the elucidation by Kishimoto et al. in this issue of the *Journal* (pages 2457–2467) of the mechanisms by which the oversulfated chondroitin sulfate contaminating batches of heparin made in China can activate the kinin-kallikrein pathway to generate bradykinin as well as activate the complement system. This research clarifies precisely how the contaminant caused anaphylactoid reactions in many patients in the United States and Europe and draws an uninterrupted line connecting the biochemical and clinical data "from breach to bench to bedside."

The year that brought the world Morawitz's insights into coagulation also saw important developments in U.S. health policy. Several publications ran exposés of the unregulated patent-medicine industry. Because manufacturers did not have to indicate what was in their remedies, patients and doctors had no way of knowing what was being consumed. Often the secret ingredient was merely alcohol, with one popular medicine consisting only of 28% ethanol mixed with water. Many "soothing syrups" contained addictive compounds such as cocaine and opium, as well as other substances that were merely toxic.³ Contamination with impurities

was common and usually undetected. These exposés helped to fuel the Progressive Movement, which envisioned a more activist role for government in protecting the public welfare. The same year that Morawitz published his coagulation paper, President Theodore Roosevelt called for a law to ensure the safety of the drug and food supply. Congress responded the following year by passing the first Pure Food and Drug Act, creating the forerunner of today's Food and Drug Administration (FDA).

The logic behind that law was as elegant and compelling as the early studies of thrombin generation. Proponents of the law argued that only surveillance by the federal government could ensure that medicines would be accurately labeled and free from any adulteration — a "poisonous or other added deleterious ingredient which may render such article injurious to health."³ As Philip Hiltz has noted, "The change in policy that came with this law was a fundamental one. It was an assertion that it was the job of the government to protect citizens from some kinds of commerce rather than just to protect commerce."³

For several decades, additional work built on the foundations of the Pure Food and Drug Act. That first law did not compel manufacturers to demonstrate their products' safety or efficacy; those re-

quirements were added in 1938 and 1962, respectively. But in recent decades, while developments in biology were further extending our capacity to understand and control physiology, less wholesome policy developments began to undercut the country's capacity to ensure the purity and safety of its drug supply.

The first of these was gradual erosion of the belief that government must play the central role in protecting the public's health, accompanied by a backing away from many of the values and goals of the Progressive Movement. "Big government" was painted as a major evil, and deregulation was put forward as the best way to protect Americans' interests related to air travel, financial policy, workers' rights, medical care, and other areas of life. Beginning in the 1980s, reliance on the government to protect the population's health began to be undercut by a belief that the marketplace could ensure quality and value in various sensitive health-related areas, including the drug supply. In its most extreme form, this logic would suggest that companies selling contaminated heparin, for example, would eventually fail economically and be supplanted by companies that sold purer heparin (though it's unclear how the market would help patients who had fatal allergic reactions before its invisible hand managed to work its magic). Regulatory agencies were not dismantled — they just had their funding severely constrained. Function follows funding, and the anti-Progressive ideology became reified in inadequate inspection and surveillance budgets for the FDA, reflecting

and perpetuating the reduced expectations of government. Anti-Progressive policies were presented as a way to lower taxes, so that, like the patent medicine elixirs of the early 20th century, these feel-good solutions didn't cure anything yet quickly became addictive.

By the 1990s, globalization was further eroding efforts to ensure the safety of our drug supply. Most medications that Americans ingest are now manufactured outside the United States — which makes them somewhat less expensive, moderating rising drug prices. But we forgot the Progressive Era lesson that, if left unchecked, human nature often favors a quick buck over a pure product. In a system in which cheaper is better and drug manufacturing is disseminated around the globe (and, for a product like heparin, further decentralized to workshops of Chinese peasants processing pig entrails in their households), it's not surprising that quality control will lose out. The likelihood that the heparin contamination was done intentionally to increase profits makes the problem even more sinister and portentous.

The international production of medications isn't going away. But we cannot embrace the low cost of global pharmaceutical manufacture without following through with its obvious complement of global pharmaceutical inspection. We've been in similar situations before — ceding government responsibility over an essential health-related function and then failing to adequately implement the proposed replacement solution. In the 1960s, the

plan was to shut down expensive and horrible state mental hospitals and replace them with a well-supported network of community-based mental health centers. The first part of the plan was put into place, but not the second. In the 1990s, the plan was to shorten drug-approval times and then follow up with a more robust system of postmarketing safety surveillance. Again, we did the first part but not the second. And here we are again.

It would be wrong to view the heparin debacle as primarily an FDA failure. An agency can do only what it is staffed to do, and the FDA's budget for surveillance of foreign drug manufacturers is an order of magnitude or two too small.⁴ It has been estimated that at current funding levels, it would take the FDA more than 13 years to inspect all foreign plants exporting prescription drugs to the United States and 27 years to inspect all foreign plants exporting medical devices.^{4,5} Criticizing the FDA for failing to stay on top of such inspections when it doesn't have the requisite funds is victim blaming, not policy analysis.

Teddy Roosevelt, a Republican, knew that commerce without enlightened regulation can have potentially devastating consequences for individuals and societies. The burgeoning federal deficit will make it difficult to implement the surveillance responsibilities that a globalized pharmaceutical industry requires, but if we fail to do so, more disasters surely await.

Our colleagues in physiology and pharmacology have built impressively on the scientific discoveries of the past hundred years.

It's time for health policy to build on the evidence and insights of its own history. Remembering the lessons of 1905 would be a good place to start.

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1. Morawitz P. Die chemie der blutgerinnung. *Ergebn Physiol* 1905;4:307-422.
2. Owen CR. A history of blood coagulation. Rochester, MN: Mayo Foundation for Medical Education and Research, 2001.
3. Hiltz PJ. Protecting America's health: the FDA, business, and one hundred years of regulation. New York: Alfred A. Knopf, 2003.

4. Crosse M. Drug safety: preliminary findings suggest recent FDA initiatives have potential, but do not fully address weaknesses in its foreign drug inspection program. Washington, DC: Government Accountability Office, April 22, 2008. (Publication no. GAO-08-701T.) (Accessed May 15, 2008, at <http://www.gao.gov/new.items/d08701t.pdf>.)
5. Harris G. U.S. identifies tainted heparin in 11 countries. *New York Times*. April 22, 2008.

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