in any country to participate in international trade? Does he understand how that works?

The main argument for independent states—not necessarily national states—is a public choice argument related to the danger of an international Leviathan, which would be much more difficult to escape than local tyrants are. This argument is based on the intrinsic danger of the state as a monopoly of force, and on the value of individual dignity and flourishing. Don't forget individuals! The idea that a system of independent states is a less dangerous system than a world empire—at least for those who do not live under the worst tyrants—must not prevent one from dissenting against his own Leviathan. It is not a license to glorify nationalism.

The Virtue of Nationalism is anchored in the Hebrew Bible, that is, the Old Testament, and in the political history of the Jews in biblical times. "I have been a Jewish nationalist, a Zionist, all my life," the author writes in the book's introduction. We can understand and sympathize with the plight of Jews in history, from the early tribes of Israel and the kingdoms of Israel and Judah, to the diaspora, the constant discrimination against Jews, the Holocaust, and the contemporary refuge that the state of Israel represents for them. We can also admire the millennia-old Jewish traditions (when they are not too stifling), as well as the major contribution of Jewish culture to Western civilization. But that's not a reason to hold the Hebrew Bible as the ultimate book of political philosophy.

Lessons / I think that two qualified lessons can be drawn from *The Virtue of Nationalism*. First, it reminds us of the danger of a world state. A world state would likely have killed the experiments that led to the discovery of individual liberty and classical liberalism. Hazony would not weep for the latter, but perhaps he does not understand it well. Under a world tyrant, islands of liberty would be very difficult to establish and defend. But note how these islands of liberty have also been busy destroying themselves under national states with growing power.

Second, nationalism does not always turn into national socialism or other monsters. Hazony shows that nationalism can sometimes be useful. We know many Western national states under which individual liberty has flourished in different degrees. Yet, these liberty-bearing societies were probably those whose elites had the most cosmopolitan outlook. Note also how open these countries were historically to trade or immigration. Immigration constantly changed the "tribes" of America.

A more general reflection is that we—we who think that individual liberty is the main political value—must accept both that it is a universal value and that prudence requires not to trust a world state to impose and protect it. This does not preclude international treaties between national governments. Another way to express the general idea is that we must marry cosmopolitan values with the preservation of separate states, of which some will hopefully become islands of liberty. Incidentally, unilateral free trade is one way to achieve that: it would leave individuals in the unilaterally free-trading country free to import, export, or invest abroad, even if foreign states don't recognize the same liberty for their own subjects. (See "How Is Your Trade War Going?" Summer 2018.)

If there is something that could persuade a cosmopolitan intellectual of the virtue of nationalism, this book would be it. It doesn't succeed, though, because of its collectivism and romantic politics. R

Is the Era of 'Free to Choose' Medicine Upon Us?

REVIEW BY THOMAS A. HEMPHILL

Over a decade ago, Bart Madden unveiled the genesis of his "Free to Choose Medicine" concept in the pages of *Regulation* (see "Breaking the FDA Monopoly," Summer 2004). He developed those ideas in the monograph *Free to Choose Medicine*, the third edition of which was released this April. Just a few weeks later, President Trump signed "Right to Try" legislation giving terminally ill Americans greater access to investigational drug treatments that have undergone Food and Drug Administration Phase I safety and early efficacy testing but have not completed the full FDA testing regimen and are not yet available to the public.

Madden's arguments support policies like "Right to Try," but there is much more to what he proposes than simply giving terminal patients access to experimental drugs. In this review, I sketch out his proposal and offer some practical suggestions for increasing the possibility that it will one day become law.

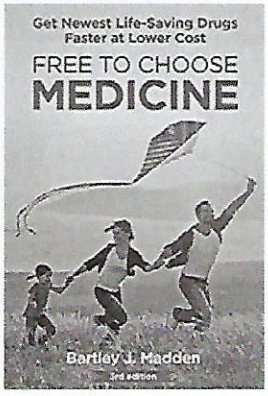
THOMAS A. HEMPHILL is the David M. French Distinguished Professor of Strategy, Innovation and Public Policy at the University of Michigan, Flint. He is an affiliate of the Heartland Institute and has discussed some of the points in this review with Madden.

Need for Free to Choose Medicine / On the first page of the first chapter, Madden states the purpose of his Free to Choose Medicine concept:

> This book makes the case that we need to be free to make informed decisions about whether to use not-yet-approved therapeutic drugs—that is, new drugs that have successfully passed initial safety trials, generated preliminary efficacy data, and may offer us the opportunity to improve our health or even save our life.

He believes that the result of the 1962

federal legislation expanding the FDA's monopoly authority to test drugs and judge whether they are "safe and effective" has been ever-increasing prescription drug prices. He argues this is because of the agency's continuing demand for more expensive and time-consuming clinical trials to minimize the likelihood of injury and death (and adverse publicity for the FDA) and expand understanding of the experimental drugs' effects. More importantly, he argues powerfully that these lengthy clinical trials come at a steep cost in the unreported "invisible graveyard" of patients with serious or immediately life-threatening conditions who die while the drug undergoes the extensive testing necessary to be brought to the U.S. market.



Free to Choose Medicine, 3rd ed.

By Bartley J. Madden

83 pp.; Heartland Institute, 2018

He gives four reasons why there has not been a growing grassroots movement demanding reform of the FDA in order to make experimental drugs more readily available. First, it's easier to observe (and the media report on) adverse side effects (including death) from approved drugs as well as new information from extensive trials. People assume that unapproved drugs would be even riskier, which results in political pressure for even stricter regulation. Second, the FDA and its supporters sincerely believe they possess the moral high ground; pharmaceutical companies that would be inclined to question FDA policies are, unsurprisingly, fearful of antagonizing the regulators whose decisions can mean the difference between company failure and success. Third, most Americans are unaware of what economists call the "opportunity costs" of not being free to make an informed choice about the best drug treatment for ourselves. Fourth, only a small percentage of people at any one time realize they are experiencing pain, suffering, and the prospect of death because of denied access to new drugs.

The drugs-to-patient system / Madden applies a systems theory approach in his analysis, one that elevates the goal of providing more drugs to more patients and that focuses on eliminating questionable constraints on those drugs. He believes his systems approach "produces genuine insights that reveal a path to true reform."

The existing FDA drug approval system consists of two primary stages: the pre-clinical stage and the clinical trials stage. Historically, for every 5,000 substances that drug companies initially investigate, about 250 enter the formal preclinical research and testing stage where there is basic evaluation for patient safety. This stage typically takes three to six years to complete. Only about 10 of those substances exhibit enough promise to induce a pharmaceutical company to file an Investigational New Drug (IND) Application with the FDA to move on to Phase I testing where they are safety-tested on healthy volunteers. Roughly eight of those substances then enter Phase II safety and efficacy clinical trials where they are tested on volunteers who have the condition the substance is intended to treat. Only about three of those substances move on to Phase III efficacy clinical trials, involving larger testing groups. Finally, only about one drug out of those original 5,000 substances successfully achieves FDA New Drug Application approval.

Madden views the key bottleneck in the drugs-to-patient system as "the FDA and its narrow focus on ever more refined (and expensive) clinical trials." Research shows that in 1980, the typical drug underwent 30 FDA clinical trials involving about 1,500 patients. By the mid-1990s, the typical drug had to undergo more than 60 clinical trials involving almost 5,000 patients. Because the FDA is the monopoly gatekeeper for the American market, it is able to "disregard evidence of its failure and the pleas of suffering and dying people who are being denied potentially life-saving treatments" in the later clinical phases of the seemingly interminable drug evaluation process.

The FDA's defense / FDA staffers respond to this criticism with a simple question: Do you want citizens to have safe and effective drugs and for public knowledge about drug effects to increase? Since no one would dare not answer this question affirmatively, the FDA requires that new drugs pass an extensive battery of randomized clinical trials (RCTs) in which subjects are randomly assigned to control and test groups, with the former receiving the current standard of care (or a placebo) and the latter the substance under investigation. RCTs are considered the "gold standard" in empirical testing. They also are incredibly costly in time and resources. Thus, FDA staffers successfully lobby for "greater FDA power and a bigger budget to get the job done," even as the drugs move slower and slower through the testing pipeline.

Since no drug is 100% safe, argues Madden, the FDA's goal of "safe and effective drugs" deflects attention from the fundamental tradeoff that the agency faces:

> More extensive and hugely expensive testing can reduce the probability of unanticipated adverse side effects from an approved drug. But that same mindset greatly increases drug costs to consumers and, most importantly, causes suffering and premature deaths from delayed access. That's the tradeoff dilemma.

While he agrees that the RCT is a powerful tool in determining if drugs are safe and effective, it is only one tool of many in the growing medical knowledge base. He also notes that many physicians and medical ethicists consider RCTs unethical because they require the participation of ill individuals. In essence, the control group is barred from receiving a potentially superior treatment. Madden makes a case for using observational data versus RCTs. As

evidence, he points out that observational data, or "real-world data," are contained in physician communications when considering the "pros" and "cons" of off-label use of FDA-approved drugs. Observational data and the associated inferences of cause-and-effect expand the knowledge base through daily life experiences.

What are the costs of the FDA's reliance on RCTs? It can take up to 12 years, on average, for a new drug to successfully complete the FDA review process. In addition, according to a 2014 Tufts University study, total development costs of a new drug are estimated at $2.9 billion. Madden believes that the FDA needs competition to its existing monopoly regulatory position to eliminate this "critical bottleneck" in the nation's health care system.

Two tracks / As a solution, Madden offers a "dual approval track" plan. Under the first track, patients choose to only use drugs that have gained approval through the traditional FDA approval process. Under the second track, the Free to Choose track, the FDA would have "competition," which I'll describe below. Madden's hope is that this competition will provoke the agency to streamline its clinical testing and approval requirements, thus allowing smaller, cash-strapped pharmaceutical companies to bring their drugs to market much sooner.

The Free to Choose track would allow patients (under the care of their physicians) to access not-yet-approved drugs. Specifically, this would provide access to drugs in Phase II of FDA clinical trials after the drug's completion of one or two trials.

In the drug discovery stage, which precedes the Phase I trials, basic safety of the drug is established. In Phase I of clinical trials, 20–80 healthy volunteers are used to establish a drug's safety profile; this process usually takes one year. In Phase II of clinical trials, 100–300 patient volunteers with the condition the drug is intended to treat are used to better assess the drug's safety. Because these trials are randomized, researchers find indications of its efficacy; this phase can take up to two years to complete. Phase III (involving further testing of 1,000–3,000 volunteers afflicted with the condition) better assesses efficacy and gathers other information about the drug's effects, and can easily take up to five additional years before the FDA grants final approval. All told, that's 12 years of evaluation. In contrast, Madden believes the Free to Choose track can reduce the evaluation period to just six years.

As an integral part of the Free to Choose track, physicians would be required to input treatment results anonymously (although including pertinent genetic data and biomarker information) into an internet-based Tradeoff Evaluation Drug Database (TEDD). TEDD would become a valuable database of up-to-date information about the risks and effectiveness of drugs qualified for early access on the Free to Choose track, enabling patients and their physicians to make informed decisions about what is in a patient's best interests. Madden believes that TEDD would be invaluable for medical researchers, greatly accelerating further pharmaceutical innovation through faster learning and more effective allocation of research and development funds. TEDD would be operated independently of the FDA within a public/private organizational structure.

TEDD would be useful. The question is, would it provide anywhere near the information on drug effects that Phase III RCTs do. The great value of RCTs is that they control for unobserved differences in test subjects that cannot be controlled for in observational studies. The resulting information is important, and there have been many cases where it has been out outright revelatory.

To attain it, the current FDA system uses coercion—people can't obtain an experimental drug unless they participate in a trial, and then they still may be assigned to a control group. The Cato Institute's Michael Cannon has proposed that, instead of coercion, test administrators pay subjects to participate in RCTs (and maybe receive the experimental drug). With the Free to Choose track, Madden risks losing a significant chunk of this information, though TEDD may provide some of it and the traditional tract may ultimately provide all of it (if enough desperate patients don't select the Free to Choose track). In essence, he makes a values choice to increase access at the risk of less information—but then, Congress and the FDA made a values choice to increase information at the loss of some access, and Cannon makes a values choice to increase information and access at a public financial cost.

Drug developers would have the choice to use either track, or both, to bring their drugs to market. To institute the Free to Choose track, Madden argues that new federal legislation would be needed to provide drug developers sufficient immunity from strict product liability laws to ensure their active participation in this track. There is also a strong assumption that health insurance companies would respond favorably to a drug that has a low price and shows safety and effectiveness under the Free to Choose track, and that these drugs would likely receive insurance reimbursement. As to patient safety, Madden notes that technological advances make preclinical testing by drug developers, as well as the FDA's Phase I safety trials, far superior to the testing used during the 1960s when the thalidomide disaster took place in the United Kingdom.

Traversing the public policy gauntlet / When evaluating Madden's proposal, it is important to begin the process with clear parameters on what the author is not proposing. First, he is not calling for the elimination of the FDA; instead, he wants to reform the agency. The FDA status quo is, in fact, a complement to his proposal because the agency's drug approval process would remain in place. Second, to reinforce the first point, RCTs would be an integral part of the Free to Choose proposal up through the early part of Phase II. This includes through all of the basic safety protocols and initial testing for effectiveness of the drug on the affected population. Third, Madden's proposal does not eliminate mandatory

reporting of the affected population after initial Phase II testing. TEDD requires physicians to report to a designated third party on the effects of Free to Choose–track pharmaceuticals on their patients.

Yet reforming the FDA (a laudable and challenging undertaking) and getting the "newest life-saving drugs faster at lower cost" to Americans vulnerable and in need would require confronting and ameliorating formidable public policy challenges involving a myriad of stakeholders. Toward that end, here's a five-point strategy:

- ***Define the target population.*** While Madden relates deeply moving examples of people with life-threatening diseases who are not able to access experimental drugs, his Free to Choose track leaves the decision on patient eligibility entirely up to the patients (in consultation with their physicians). This is a position entirely in line with a libertarian philosophy supporting the broadest freedom of individual choice; however, from a public policy perspective, acceptable eligibility limitation is essential to successfully enacting this federal legislation.

  For example, FDA Commissioner Scott Gottlieb recommended to Congress that Right to Try legislation define the term "terminal illness" as "a stage of disease in which there is a reasonable likelihood that death will occur within a matter of months." Similarly, since his proposal is especially intended to help alleviate suffering from "life-threatening" diseases, federal legislation should emphasize developing a workable definition of such diseases—that is, one that includes reasonable and politically justifiable qualifications for patient eligibility.

  An example of such a disease would be ALS, better known as Lou Gehrig's Disease, a "life-threatening" neuromuscular disease with no known cure. The overwhelming majority of people diagnosed with ALS die from respiratory failure within three to five years of diagnosis. In contrast, many chronic diseases can be "life-threatening" yet medically managed through existing treatments, e.g., diabetes. Therefore, a proposed rubric useful for "defining a life-threatening" disease may be "reasonable likelihood" of death within 10 years of diagnosis with no known treatment available to successfully manage the disease and prevent death. This would coincide with potential patient benefits accruing from the Free to Choose track, which is expected to reduce the length of time required for drug approval by six years.

- ***Tort liability reform.*** Pharmaceutical manufacturers are held to strict product liability for adverse effects on patients under U.S. tort law (with the exception of in Michigan, where citizens do not have the right to sue pharmaceutical companies unless the drug maker withheld or misrepresented information to the FDA that would have led to non-approval, or bribery was involved). Strict liability is the imposition of liability on a party without finding of fault, such as negligence or tortious intent. In other words, the aggrieved party—i.e., the patient—need only prove that the tort occurred and the drug company was responsible. Madden correctly argues that the trial bar would lobby intensely against a patient waiving liability by explicitly consenting to engage in what can be reasonably construed as "a risky activity."

  Establishing a written waiver of "consent" releasing the pharmaceutical company from any liability—short of gross negligence or willful misconduct—would require the establishment of a legislative tort liability "safe harbor" for participating pharmaceutical companies. Realistically, to create this safe harbor would require that Free to Choose drugs be made available only to patients having serious, life-threatening diseases without a known cure. Expanding the definition of patient eligibility would require widening the safe harbor, potentially nullifying the legal protection of strict liability and thus making it exponentially more difficult to acquire congressional support for legislative passage.

- ***Physician liability.*** Physicians whose patients want to use Free to Choose medicines may worry that they could still be held liable for negligence under "duty of care" obligations. Since physician licensure is regulated at the state level, a state authority could declare physician complicity contrary to ethical standards ("physician do no harm") for medical practice, thus placing a physician's licensure in jeopardy. Physicians would need a clear legal standing regarding their personal liability. While establishing a similar safe harbor (through model state legislation) allowing for a defense of willful consent by the patient may eliminate civil negligence liability, the question of ethical conduct is one that could play out differently among 50 state licensing boards.

- ***Combat FDA resistance.*** "We're going to be cutting regulations at a level that nobody's ever seen before," President Trump vowed in a meeting with pharmaceutical industry executives in January 2017. So would Commissioner Gottlieb support a decision contrary to the existing agency philosophy for a drug made available to a non-FDA participating trial patient before extensive testing for efficacy (in Phase III trials)? If he is not supportive, and if Free to Choose legislation were enacted over FDA protest, would pharmaceutical companies be willing participants in making access available to patients? The agency could, after all, sanction participating drug makers by slowing approval of drugs the makers have submitted to the traditional process. Perhaps such risk was behind PhRMA, the major drug industry association, saying it was "neutral" on Madden's Free to Choose idea.

In addition, would health care insurers be as open to patient eligibility (and thus financial remuneration) of such pharmaceuticals (after one or two Phase II trials) knowing that many of the drugs will ultimately prove to be ineffective and some may have adverse effects? Furthermore, could an adverse effect from an investigative drug potentially leave a patient without health insurance coverage, resulting in unpaid medical bills?

- ***Promote and continue to improve the Expanded Access Program.*** The FDA has a lengthy history of supporting patient access to investigational new treatments through the agency's Expanded Access Program. (The seminal regulations for the program were issued in 1987.) In 2009, after enactment of amendments to the Federal Food, Drug, and Cosmetics Act, the FDA revised its regulations to consolidate the provisions concerning the use of investigational drugs and biologics for expanded patient access where no existing FDA approved alternatives exist. The FDA reports that, in recent years, the agency has received over 1,000 applications annually for expanded access to treat patients with these investigational drugs and biologics, and subsequently authorized 99% of the requests. In addition, the agency makes "meaningful changes" in approximately 10% of these cases to enhance patient safety.

  Yet program critics note that, in the past, physicians were required to file full investigational new drug (IND) applications with the FDA, as if they were company sponsors undertaking clinical trials. The FDA reported that it took an estimated 100 hours to complete this paperwork, a daunting task for physicians who are time-strapped. (Because of this, we should qualify the 99% authorization statistic; many potential applicants likely were discouraged by the onerous paperwork demands.) Obviously, the small number of actual applicants—as well as anecdotal stories of Americans traveling abroad to acquire unapproved drugs—offer support for this criticism.

  However, the FDA recently announced revisions to the Expanded Access Program, as required in the FDA Reauthorization Act of 2017 and the 21st Century Cures Act. Such revisions will ostensibly allow the prescribing physician to submit a "single patient IND," which the FDA claims will take as little as 45 minutes to complete, and the subsequent agency review will usually be completed within 24 hours of submission. The FDA's performance on this will need close monitoring by Congress, health care interest groups, and the executive branch.

Unlike the Right to Try legislation, which was characterized as "toothless" by many critics (as pharmaceutical companies have little incentive to provide access to experimental drugs that have not been approved by the FDA), Free to Choose Medicine could be "game changing" for eligible patients. In this well-written monograph, Madden advocates convincingly for his approach. Yet Free to Choose Medicine has many hurdles to vault before it becomes a viable regulatory solution to alleged FDA government failure. Many vulnerable patients must hope that Madden and other Free to Choose advocates "get it right" on both the policy and the politics. R

Did FDR Default on U.S. Debt?

REVIEW BY GARY RICHARDSON

The risk-free rate of return on investments is often considered to be the yield on U.S. government debt. "The risk-free rate is hypothetical," *Investopedia* states, "as every investment has some type of risk associated with it. However, T-bills [U.S. Treasury debt obligations with a maturity of 52 weeks or less] are the closest investment possible to being risk-free." One of the reasons for this is "the U.S. government has never defaulted on its debt obligations, even in times of severe economic stress." Similar statements appear in *Wikipedia*'s entry on the risk-free interest rate as well as in scores of economics and finance textbooks used around the world.

University of California, Los Angeles economist Sebastián Edwards's new book, *American Default: The Untold Story of FDR, the Supreme Court, and the Battle over Gold*, challenges this assertion. Edwards argues that the United States defaulted on federal debt during the 1930s when it withdrew monetary gold from circulation and abrogated the gold clause in both public and private contracts.

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Overview / Before I delve into the details of Edwards's insightful study, I want to give you an overall assessment of the book: It is fascinating, well-written, and thoroughly researched. It provides new perspective on an important era of American history. It discusses the ideas, personalities, politics, economics, and finance underlying the principal policies by which the Franklin D. Roosevelt administration resuscitated the U.S. economy after the catastrophic contraction of 1929–1933. An academic press published the book, but the clarity of its prose and vividness of its narrative make it