



DRUGS

The Systematic Prohibition of U.S. Drug Science

The drug war is not and has never been based in science. Early drug warriors did not commission scientific studies to rank the most medically and socially harmful substances and then prohibit them accordingly. Science rarely played a part in deciding which drugs would be prohibited; in fact, where there was scientific research, drug warriors often denied and opposed it.

It is crucial to remember this fact when examining how governments have influenced scientific research into drugs. Unlike the subjects of other chapters in this volume, restrictions on drug research are the primary method by which the government has tilted drug science. Although those who study diet, energy, and climate science have encountered problems with funding and biased government agencies, they rarely have to deal with the outright prohibition of the objects of their research.

Drug prohibition has developed primarily from a confluence of three factors: (1) the popular perception of the race or class of the drug user, (2) the popular perception of the drug's effects, and (3) the dehumanization of the perceived drug user. Drugs have often been prohibited before any scientist had a real chance to study the effects

and before most politicians and voters had interacted with the drug in their daily lives. Rumor, myth, and prejudice explain drug prohibition, not science.

The process that leads to prohibition plays out with an almost eerie regularity—a scripted public-policy play performed in legislatures around the world and throughout the 20th and 21st centuries. First, reports begin to circulate about a disturbing new drug with a strange name like “demon weed,” “ecstasy,” “acid,” or “bath salts.” Law enforcement officials often give the first accounts of the drug’s dangerous effects, which biases the story because law enforcement officers are not usually dealing with people at their best moments (imagine if the public perception of alcohol were informed only by stories of police interacting with drunks). “It’s like nothing we’ve seen before,” police say; “the people on this drug are not only maniacs, but they are also nearly unkillable.” Tales of Hulk-like strength seem to follow every drug.

The drug is soon associated with a certain race, class, or nationality—perhaps African Americans, Chinese, Mexicans, or even hippies—and parents are warned that their children may already be taking it. Talking heads with dubious scientific credentials take to print and the airwaves to say that the drug is the most addictive drug they’ve seen and that even a single use could create a lifelong addict. Soon anyone who uses the drug, and especially those who manufacture and sell it, are dehumanized as subhuman scum, “drug fiends,” and “merchants of misery” who must be stopped no matter the cost.

After a drug is restricted or outright prohibited, any scientist who wants to study it must contend with new layers of control and bureaucracy. Those extra restrictions are significant barriers to scientific research—particularly if that research will inquire into the possibility that an illegal drug has beneficial uses. Funding also becomes relatively difficult to obtain, especially from the government. By prohibiting or increasing regulation, governments around the world bias the scientific study of drugs.

Moreover, for many scientists, even to propose studying a prohibited drug in a clinical, scientific manner could be dangerous to their career and professional standing. One politician, when asked how his views on marijuana prohibition might change if scientists came out

favorably for marijuana wondered, “Why should we use it when it has no redeeming value? The desire of someone to get out of this world by puffing on marihuana [sic] has no redeeming value.”¹ President Richard Nixon, when asked how he would react to the report of a commission that was studying marijuana, was even more direct: “As you know, there is a Commission that is supposed to make recommendations to me about this subject, and in this instance, however, I have such strong views that I will express them. I am against legalizing marijuana. Even if the Commission does recommend that it be legalized, I will not follow that recommendation.”²

Faced with headwinds like these, it’s no wonder that scientists often don’t bother researching controlled substances. Results that find beneficial uses of drugs or call into question a drug’s dangerousness can be criticized by politicians who are either dogmatic drug warriors or who do not see a political benefit to sticking their necks out to advocate for real change.

That gun-shy behavior of political actors was demonstrated in 2012 during an almost comical congressional committee hearing on Drug Enforcement Administration (DEA) oversight. Michele Leonhart, administrator of the agency, was asked by Rep. Jared Polis (D-CO) about the relative dangers of different drugs:

POLIS: Is crack worse for a person than marijuana?

LEONHART: I believe all the illegal drug —

POLIS: Is methamphetamine worse for somebody’s health than marijuana?

LEONHART: I don’t think any illegal drug —

POLIS: Is heroin worse for someone’s health than marijuana?

LEONHART: Again, all the drugs —

POLIS: I mean, either yes, no, or I don’t know. I mean, if you don’t know, you can look this up. You should know this as the chief administrator for the Drug Enforcement Agency. I’m asking you a very straightforward question. Is heroin worse for someone’s health than marijuana?

LEONHART: All the illegal drugs are bad.

POLIS: Does this mean you don’t know?

LEONHART: Heroin causes an addiction that causes many problems that's very hard to kick.

POLIS: Does that mean that the health impact is worse than marijuana, is that what you're telling me?

LEONHART: I think that you are asking a subjective question.

POLIS: No. It is objective. Just looking at the science. This is your expertise. I am a lay person, but I have read some of the studies and [am] aware of it. I am just asking you as an expert in the subject area, is heroin worse for someone's health than marijuana?

LEONHART: I am answering as a police officer and as a DEA agent that these drugs are illegal, because they are dangerous, because they are addictive, because they do hurt a person's health.

...

MR. POLIS: Well, again, this is a health-based question, and I know you obviously have a law enforcement background, but I am sure you are also familiar, given your position with the science of the matter, and I am asking, you know, again, clearly, your agency has established abuse of prescription drugs as the top priority. Is that, therefore, an indication that prescription drugs are more addictive than marijuana?

LEONHART: All illegal drugs are addictive.³

Despite serving under President Obama, Leonhart was a holdover from the George W. Bush administration, and she had become a DEA agent in late 1980, just before President Ronald Reagan ramped up the drug war.⁴ (Leonhart also reportedly once said that the day a hemp U.S. flag flew over the Capitol building was the worst day of her life.)⁵ It is perhaps understandable that Leonhart would hold unnuanced views on the relative dangers of the drugs she has dedicated her life to fighting.

But the political position of the DEA administrator demands unnuanced views on drugs. The DEA is tasked with eliminating drugs, not promoting them. It has been the policy of the U.S. government since the early 1970s that marijuana is as dangerous as heroin, LSD, MDMA (ecstasy), and bath salts. Those drugs are placed in Schedule I

of the Controlled Substances Act (CSA), meaning that, according to the government, they have a high potential for abuse, there are no currently accepted medical uses, and there is a lack of “accepted safety” standards for use of the drugs.⁶ While there are good reasons to believe that many scheduled drugs are misclassified (there are five schedules, with I deemed the most dangerous), Schedule I is truly the Hotel California of government classifications—you can check out any time you like, but you can never leave. In over 40 years, the DEA has only re-scheduled a Schedule I drug seven times: five times a Schedule I drug has been moved to Schedule II, and only twice has a Schedule I drug been descheduled entirely.⁷

This chapter discusses how the government has distorted scientific research on two Schedule I drugs, marijuana and MDMA, also known as ecstasy. Although a whole book could be written about how the government has affected drug research for a variety of illicit drugs, I focus on marijuana and MDMA for two reasons. First, government restrictions have had a unique and unmistakable effect on biasing the scientific study of these two drugs, and second, because there is mounting evidence that these drugs are both not particularly dangerous and can provide significant benefits to users suffering from a variety of ailments.

Marijuana

In August 2016, despite recreational marijuana being legal and commercially available in four states, and despite 25 states and the District of Columbia allowing at least medicinal marijuana, the DEA reviewed its scheduling of marijuana and decided that it would remain a Schedule I drug.⁸ It was the fourth time since 1972 that the DEA had denied a petition calling for the rescheduling of marijuana. The fate of those four petitions encapsulates the government’s institutional recalcitrance on neutral drug research and the difficulties faced by anyone who wants to change our outdated laws.

The CSA, signed into law by President Nixon in 1970, was supposed to make reconsideration of drug scheduling relatively straightforward, at least as straightforward as dealing with the government can be. The

law initially listed 81 substances to be placed on Schedule I, including marijuana. But in a concession to some concerned lawmakers, it also created a commission to study marijuana use.⁹ Drug classifications under the CSA can be reviewed at the behest of the attorney general, the secretary of health and human services, or an interested third party.¹⁰

Scientific and medical evidence were to be the basis for CSA classification. In fact, during the drafting of the act, an amendment was proposed that would have expressly required scientific evidence to form the basis for scheduling. But the amendment was defeated as being redundant. In the words of Bureau of Narcotics and Dangerous Drugs (the precursor to the DEA) director John Ingersoll:

The bill allows the Attorney General upon his own motion or on the petition of an interested person to bring a drug under control. However, he is authorized to do so only after requesting the advice in writing of the Secretary of Health, Education, and Welfare and the advice in writing of the Scientific Advisory Committee. . . . The intent of the amendment was to insure that the scientific and medical information necessary for a determination of whether a substance should be brought under control was available. But the legislation already insured that there would be sufficient medical and scientific input into any control decision.¹¹

The first third-party petition for marijuana rescheduling was filed in 1972 by the National Organization for the Reform of Marijuana Laws (NORML). The DEA was created the following year, and it promptly refused to consider NORML's petition. NORML went to court, and in 1974 the United States Court of Appeals for the District of Columbia Circuit ordered the DEA to comply with the statute and review the petition.¹²

In response to the court order, the DEA held a three-day hearing before an administrative law judge. The judge agreed with NORML on many counts, yet the DEA administrator entered a final order denying the petition.¹³ NORML went back to court and won again, with

the court ordering the DEA to submit the petition to the secretary of health, education, and welfare (HEW).¹⁴ The HEW secretary recommended that marijuana remain on Schedule I, and the DEA ratified that determination without further hearings. The DEA's cursory actions led NORML to bring yet another challenge to the courts. Again the court not only agreed with NORML, but found it necessary to chide the government for continually ignoring its orders: "[We] regrettably find it necessary to remind respondents [DEA and HEW] of an agency's obligation on remand not to 'do anything which is contrary to either the letter or spirit of the mandate construed in the light of the opinion of [the] court deciding the case.'"¹⁵

It wasn't until 1986, 14 years after the original petition, that the DEA agreed to hold substantive hearings on rescheduling that complied with the requirements of the CSA. From October 1987 until June 1988, administrative law judge Francis L. Young heard evidence on whether marijuana's medical applications were sufficient to demand a "demotion" to Schedule II. In his ruling, Judge Young found that marijuana should be rescheduled:

Based upon the foregoing facts and reasoning, the administrative law judge concludes that the provisions of the Act permit and require the transfer of marijuana from Schedule I to Schedule II. The Judge realizes that strong emotions are aroused on both sides of any discussion concerning the use of marijuana. Nonetheless it is essential for this Agency, and its Administrator, calmly and dispassionately to review the evidence of record, correctly apply the law, and act accordingly.

Marijuana can be harmful. Marijuana is abused. But the same is true of dozens of drugs or substances which are listed in Schedule II so that they can be employed in treatment by physicians in proper cases, despite their abuse potential.¹⁶

Amazingly, the DEA still refused to follow Judge Young's recommendation. In December 1989, DEA administrator John Lawn overruled Young and in 1994, 22 years after NORML first filed the petition, the DC Circuit upheld Lawn's decision.

NORML's ridiculous journey through the red tape of the DEA underscores the political and legal headwinds that have restricted and are restricting the implementation of a drug policy based in neutral scientific and medical research. Behind the DEA's determined foot-dragging is the dogged resistance that arises when an organization tasked with eradicating drugs is asked to make one of those drugs more accessible. This attitude toward drugs—that elimination through prohibition is the only viable solution—permeates many of the organizations that oversee both funding research and allowing researchers to access controlled substances.

What's more, NORML's petition was not the last time the DEA denied petitions to review the scheduling of marijuana. Three other times the DEA has refused to accept that marijuana has enough medical uses to be considered at most a Schedule II drug.

Unsurprisingly, the deck is stacked against marijuana when it comes to petitioning for rescheduling. Because of its Schedule I status, it is difficult for researchers to study marijuana to produce the kind of clinical evidence that could help marijuana be rescheduled. Thus, while the DEA requires "proof" of marijuana's medical effectiveness, government policies are preventing such studies from being done.

During one chapter in NORML's 22-year fight with the DEA, the DC Circuit highlighted this unfairness. When the DEA overruled Judge Young's findings, it did so partially on the grounds that marijuana had failed to meet three criteria: (1) the general availability of the substance and information regarding the substance and its use; (2) recognition of its clinical use in generally accepted pharmacopeia, medical references, journals, or textbooks; (3) recognition and use of the substance by a substantial segment of the medical practitioners in the United States.¹⁷ NORML argued, and the court agreed, that it was impossible for any drug classified as Schedule I to meet these criteria. As the court wrote:

One of the very purposes in placing a drug in Schedule I is to raise significant barriers to prevent doctors from obtaining the drugs too easily. DEA regulations require doctors who wish to use such drugs to submit a scientific research protocol to the FDA for

approval and permit use only in accordance with the protocol. And the FDA insists that a developed scientific study program be presented in order to gain approval of the protocol. The DEA regulations further impose mandatory registration with the DEA and mandatory record-keeping and safe-keeping requirements, presenting additional barriers to widespread use. We are therefore hard-pressed to understand how one could show that any Schedule I drug was in general use or generally available. We are also concerned that the fifth factor “recognition of [a drug’s] clinical use in generally accepted pharmacopeia, medical references, journals, or textbooks” might be subject to the same objection. Petitioners assert that if a drug is not widely prescribed—regardless of its safety or use—it will not appear in a pharmaceutical listing of medically useful drugs.¹⁸

The DEA eventually figured out a way around this legal snafu by subtly changing the criteria used. Yet that did not resolve the fundamental issue of government interference with marijuana research, a problem that has bedeviled marijuana researchers for decades.

Although the barriers to scientifically studying marijuana have improved in modern times, there are still significant problems. In the United States, as well as around the world, various United Nations treaties restrict drug research, including the 1961 Single Convention on Narcotic Drugs, the 1971 Convention on Psychotropic Substances, and the 1988 Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances. The 1971 treaty requires parties to “prohibit all use except for scientific and very limited medical purposes by duly authorized persons, in medical or scientific establishments which are directly under the control of their Governments or specifically approved by them.”¹⁹

The United States takes its obligations under these treaties very seriously, especially when it comes to studying marijuana. In fact, despite the fact that marijuana is by far the most commonly used illicit substance in the world and its medical applications are now recognized by 32 states and the District of Columbia, the federal government makes studying marijuana more difficult than studying other Schedule I

drugs. While it is comparatively easy for researchers to get permission from the DEA to produce and study Schedule I compounds like LSD and MDMA (although it is still very difficult), marijuana researchers must go through three different government bureaucracies. First, a license must be granted by the DEA. Second, to do clinical research, further approval by the Food Drug Administration (FDA) is required. Finally, to actually obtain marijuana, researchers must go through the National Institute on Drug Abuse (NIDA).²⁰

Yet even reviewing the steps in that cumbersome process does not adequately convey the barriers to scientifically neutral cannabis research. NIDA, after all, is an organization focused on drug abuse, not medicinal, therapeutic, or other positive uses. According to Dr. Steven Gust, former special assistant to the director of NIDA, NIDA's mission is to "support research on the causes, consequences, prevention, and treatment of drug abuse and addiction."²¹ It is not NIDA's mission, according to Dr. Gust, "to study medicinal uses of marijuana or to advocate for such research."²²

NIDA controls the only source through which researchers can legally acquire marijuana. That source is the University of Mississippi, which for nearly 50 years has had a monopoly on sanctioned marijuana production. Nothing in U.S. law mandates only a single source of marijuana production, and in fact the Controlled Substances Act requires an "adequate and uninterrupted supply of these substances under adequately competitive conditions for legitimate medical, scientific, research, and industrial purposes."²³ Nevertheless, although many research organizations have applied for permission to also grow marijuana, all have been denied.

The DEA has said that "for most of the nearly 50 years that this single marijuana grower arrangement has been in existence, the demand for research-grade marijuana in the United States was relatively limited—and the single grower was able to meet such limited demand."²⁴ Yet in 2007, the DEA's own administrative judge found that "NIDA's system for evaluating requests for marijuana research has resulted in some researchers who hold DEA registrations and the requisite approval from the Department of Health and Human Services being unable to conduct their research because NIDA has

refused to provide them with marijuana.”²⁵ For example, in 2011 the Multidisciplinary Association for Psychedelic Studies (MAPS) sought cannabis for an FDA-approved study of post-traumatic stress disorder (PTSD), but NIDA denied access because approval had not been given by the Public Health Service (this requirement was eliminated in 2015). After receiving Public Health Service approval, MAPS was told that NIDA did not have the cannabis required for the study. It wasn’t until April 2016 that the study finally moved forward.²⁶ These types of delays, if not outright obstruction, have been quite common, which may explain why the DEA perceived its supply as adequate to meet “such limited demand”—researchers simply didn’t bother wading into the DEA’s bureaucratic morass and chose other things to research instead.

MAPS has been continually stymied by the lack of an adequate supply of NIDA-produced marijuana. Although NIDA eventually provided marijuana for MAPS to study the treatment of PTSD in veterans (as of March 2017, this study had moved into phase 2 of clinical trials),²⁷ the government has simply blocked other attempts to study marijuana. Since June 2003, for example, NIDA has blocked research into whether vaporizing marijuana can effectively mitigate some of the harms cause by smoking the drug through combustion. According to MAPS:

In a prolonged triumph of drug-war politics over science, our vaporizer research has been blocked since June 2003 by the National Institute on Drug Abuse (NIDA), which has a monopoly on the supply of marijuana that can be used in research. Since 2003, NIDA has rejected and/or ignored our repeated requests (including one lawsuit for “unreasonable delay”) seeking to purchase 10 grams of marijuana to continue our studies. NIDA uses its monopoly to obstruct studies into both the beneficial medical uses of marijuana as well as into drug delivery devices that might increase the chances of FDA approval of marijuana as a prescription medicine, and might decrease the harms associated with the non-medical uses of marijuana.²⁸

In August 2016, under the Obama administration, the DEA switched course and announced it would take applications to authorize other

sources of research marijuana. Yet the effects of 50 years of government stifling marijuana research will be tough to overcome. Requirements for new applicants are stiff, and it is still easy for the DEA to simply claim that no applicant meets the requirements. Or the DEA can simply ignore the applications, which seems to be exactly what happened under the Trump administration and former attorney general Jeff Sessions, a committed drug warrior who even asked Congress for the ability to prosecute medical marijuana distributors.²⁹

In August 2017, the *Washington Post* reported that “Attorney General Jeff Sessions has effectively blocked the Drug Enforcement Administration from taking action on more than two dozen requests to grow marijuana to use in research.”³⁰ In the year after the Obama administration began accepting applications, 25 proposals were submitted. According to one law enforcement official, “They’re sitting on it. They just will not act on these things.” “[T]he Justice Department has effectively shut down this program to increase research registrations,” said a DEA official.³¹ Sens. Kamala Harris (D-CA) and Orrin Hatch (R-UT) twice sent letters to Attorney General Sessions, in April and August of 2018, arguing that it is “imperative that our nation’s brightest scientists have access to diverse types of federally-approved, research-grade marijuana to research both its adverse and therapeutic effects” and asking him to at least “put a date on when the DEA will take action on the more than two dozen pending applications.”³² As of May 2019, no applications had been approved.³³

The ease with which policies can shift between administrations underscores the need for a more permanent legislative fix. Senator Hatch and Sen. Brian Schatz (D-HI) introduced the MEDS Act in September 2017, which would “remove the administrative barriers preventing legitimate research into medical marijuana” by, among other things, making marijuana more available for legitimate research.³⁴ That is a heartening development, but the bill’s future is uncertain. And in September 2018, the House Judiciary Committee approved the Medical Cannabis Research Act, which would require the attorney general to approve at least two qualified suppliers of research-grade marijuana within a year after the act is passed, and at least three qualified suppliers

every year after that.³⁵ As of this writing, the bill will be introduced in the House of Representative, but its future is also uncertain.

If either the MEDS Act or the Medical Cannabis Research Act fails to pass, and even if William Barr, Sessions's replacement as attorney general, allows the application process to move forward, the DEA may have placed a poison pill in the requirements for applicants to grow marijuana for research. Many applicants may not qualify because one "factor" the DEA will consider is "whether the applicant has previous experience handling controlled substances in a lawful manner and whether the applicant has engaged in illegal activity involving controlled substances."³⁶ This means that experienced growers who have been supplying the state-legal markets in Colorado, Washington, and elsewhere will have a difficult time being approved because "illegal activity includes any activity in violation of the CSA (regardless of whether such activity is permissible under State law)."³⁷ This bizarre requirement may stifle new applicants altogether. Owing to the costs of complying with the DEA's other requirements, such as controls to prevent diversion of the crop into the general marketplace, few funders may want to take risks on producers with no previous experience growing marijuana. "Why would anyone take a gamble in trying to meet all of these requirements had they not had prior experience with growing!?" asked Dr. Sue Sisley, who conducted a DEA-approved study on treating PTSD with cannabis.³⁸

The single-source system is and has been a severe constraint on scientifically neutral research into marijuana, but Dr. Sisley's comment points to another: funding. In fact, in the DEA's comments pertaining to new applications for official marijuana sources, the agency acknowledged in a footnote that funding is often more important than sourcing marijuana. That footnote is worth quoting in full:

Funding may actually be the most important factor in whether research with marijuana (or any other experimental drug) takes place. What appears to have been the greatest spike in marijuana research in the United States occurred shortly after the State of California enacted legislation in 1999 to fund such research. Specifically, in 1999, California enacted a law that established

the “California Marijuana Research Program” to develop and conduct studies on the potential medical utility of marijuana. The state legislature appropriated a total of \$9 million for the marijuana research studies. Over the next five years, DEA received applications for registration in connection with at least 17 State-sponsored pre-clinical or clinical studies of marijuana (all of which DEA granted). However, it appears that once the State stopped funding the research, the studies ended.³⁹

Ironically, those 17 approved California state-funded studies were cited in a 2004 order that denied a MAPS petition to qualify as an official marijuana producer.⁴⁰ The fact that NIDA’s marijuana was sufficient to supply those studies was cited as evidence that NIDA’s supply was adequate and thus no further producers needed to be authorized.

Funding for neutral marijuana research has been difficult to come by, particularly if that funding is sought from the federal government. Some marijuana-friendly states have funded studies, such as the 17 funded by California and Dr. Sisley’s PTSD study, which was funded by a \$2 million grant from the state of Colorado. Yet researchers who seek funding from a federally controlled entity are likely to come up wanting. According to one study, “\$1.1 billion of the \$1.4 billion that the National Institutes of Health spent on marijuana research from 2008 to 2014 went to study abuse and addiction,” leaving only \$297 million to spend on studies looking into “effects on the brain and potential medical benefits for those suffering from conditions like chronic pain.”⁴¹ A search of medical studies in 2013 found that only 6 percent were investigating the potential benefits of cannabis rather than its harms.⁴²

These statistics confirm the observations of David Nutt, a neuropharmacologist in the United Kingdom. As he wrote on his blog:

Scientists examining the health and social impacts of drugs are usually funded by government agencies, and they often highlight the negative effects of drugs to justify their own source of funding. If a scientist can show that a drug is harmful, then they can show that it’s important to do more research on the topic to protect society. The more harmful the drug appears to be, the more

critical it is to fund research on it, so their funding is perpetuated. By contrast, if use of a drug appears to have only benign effects, then why would the government bother spending more research money on it? This cycle has perpetuated a scientific industry intent on demonstrating the harmful effects of drugs like cannabis, precisely because doing so allows the industry to justify its own existence. Of course, one of the major consequences of this cycle is that research on the potential benefits of drugs gets sidelined, for example with not nearly enough government funding for studies on cannabis' health benefits.⁴³

It is clear that marijuana's status as a Schedule I drug is a severe hindrance to good scientific research. Our policy choices of the 1960s and 1970s are not serving us well in a modern world that is slowly, but inexorably, coming to terms with the benefits of cannabis, both recreationally and medically.

MDMA

First synthesized in 1912 and patented by Merck in 1914, 3,4-Methylenedioxymethamphetamine, better known as MDMA or ecstasy, was a relatively obscure drug for much of its history.⁴⁴ In the 1950s, the CIA dabbled in researching the drug for possible chemical warfare purposes.⁴⁵ It wasn't until the 1970s, however, when a group of psychiatrists began to use the drug to facilitate psychotherapy, that recreational use began to grow. Eventually, the drug showed up on the streets. Frightened of a new, unknown street drug with the sexualized name of "ecstasy" that could be used by children, the DEA issued a notice of proposed rulemaking in July 1984, announcing the intent to classify MDMA as a Schedule I controlled substance.⁴⁶

In response to the DEA's proposal, a group of physicians, researchers, and therapists hired DC attorney Richard Cotton to draft a letter to the DEA administrator requesting a hearing on whether and how MDMA should be scheduled.⁴⁷ This letter seems to have surprised the DEA, which, according to one DEA pharmacologist, "had no idea that psychiatrists were using it."⁴⁸ In fact, MDMA, initially called "Adam"

within the therapeutic community (possibly either as a reference to Adam and Eve or as a pseudo-anagram of the letters MDMA), had flown under the radar of the DEA for years. Given that use was usually therapeutic, and that MDMA rarely causes an adverse reaction requiring either medical treatment or law enforcement assistance, it seemed that MDMA could have flown under the radar for years more had it not hit the streets, been renamed ecstasy, and landed in the hands of teenagers. One distributor reveled in the DEA's ignorance:

One of the wonderful things is MDMA has been known as Adam and used therapeutically in thousands, tens of thousands of sessions for 10 years, since the early, early 70s, when the DEA moved to make it illegal, they had never even heard the name Adam. It wasn't listed at all. It was people who had learned of it from a therapeutic community, some of [whom] had gone on to mass market it under the name of Ecstasy.⁴⁹

An initial hearing occurred on February 1, 1985, in front of DEA administrative law judge Francis L. Young, the same judge who would later rule that marijuana should be rescheduled, only to be overruled by the DEA administrator. Young ordered that three hearings on MDMA be held, one in Washington, DC, one in Los Angeles, and one in Kansas City.

The three hearings produced ten volumes of testimony. Since the DEA was pushing to quickly ban a drug on which there had been little research done, opponents of the ban trumpeted MDMA's benefits as well as the problems that would result from hastily classifying a possibly beneficial drug as "having no recognized medical uses" under the CSA. The DEA, however, was on the warpath, with the assistant administrator, Gene Haslip, telling the *San Francisco Examiner* during the hearings, "We are going to ban Ecstasy within the next several months," because "it's extremely dangerous."⁵⁰

Ron Siegel, a star witness for the DEA, continually mischaracterized MDMA as a "hallucinogen," and told his favorite drug mania stories, including one about a psychologist who decided to direct traffic on a busy street after taking MDMA.⁵¹ The DEA also cited a University of Chicago study showing that MDA, not MDMA, caused brain damage

in rats. Although MDA and MDMA are very similar, they are chemically distinct in important ways. Opposing witnesses testified that the two drugs act on the brain in different ways, and that the MDA-damaged rats were administered the drug in highly unusual circumstances. The rats were given extremely high doses of the drug (three to five times a comparable human dose) intravenously rather than orally every 12 hours for two days.⁵²

Opponents of the ban presented evidence that MDMA is not addictive, that it rarely results in harmful side effects, and that it had helped thousands of people suffering from various psychological ailments. As such, they argued, the drug should be on Schedule III, not Schedule I. Putting it on Schedule III would allow the DEA to regulate and prohibit recreational use, but it would not keep physicians from prescribing it or hinder scientists from studying it. Schedule III would mean that a possibly truly beneficial drug that had been administered approximately 500,000 times before the DEA had even heard of it could be further studied for methods of safe and beneficial use. Schedule I would essentially be a death sentence for any further scientific research. “I would regard the scheduling of this drug as a scientific calamity,” wrote psychotherapist Nathaniel Branden in a letter to the agency. He implored the agency to “leave the door open to further research, exploration, and study in this area.”⁵³

The DEA, fully ensconced in the drug-warrior mentality of the 1980s, didn’t seem to care. In fact, the agency didn’t care that it couldn’t offer much evidence that MDMA was harmful or that it was being abused. Instead, the agency argued that *actual* harm need not be shown, just the *potential* for harm.

Even though board-certified psychiatrists explained that MDMA had an “accepted medical use” in their practices, the DEA insisted that the FDA should decide what belongs in that category. They argued that the agency “need only ask the FDA whether the drug or substance in question has received FDA approval under the FDCA [Food, Drug, and Cosmetic Act of 1938] in order to ascertain the existence, *vel non*, of ‘accepted medical use.’”⁵⁴

In a carefully reasoned 90-page opinion, Judge Young concluded that MDMA should be placed on Schedule III, not Schedule I. Young

disposed of the DEA's argument that "accepted medical use" was synonymous with FDA approval. "Congress could easily have linked the phrase 'accepted medical use in treatment' in the CSA to some provision of the FDCA, and FDA's authority thereunder, had it desired to do so. It did not do so." Rather than being determined by the FDA, accepted medical use is determined "by what is actually going on within the health-care community."⁵⁵

Young reviewed "testimony in this record from reputable physicians, i.e., responsible medical authorities who constitute a respectable minority, that the use of MDMA is acceptable in the treatment of certain kinds of patients."⁵⁶ Furthermore, the drug, although it can be abused, does not have a high potential for abuse. Finally, reasoned Young, there are accepted safety standards for use under medical supervision, therefore, MDMA should be a Schedule III drug.

Just as he would do with marijuana three years later, DEA administrator John Lawn overruled Judge Young's determination. The action was immediately challenged in the United States Circuit Court of Appeals for the First Circuit, which overturned the DEA's decision on the grounds that the agency's interpretation of "accepted medical use," namely that FDA approval was the sole consideration, was not based in a proper reading of the CSA. "The opportunity for a meaningful hearing would be lost," the court wrote, if the question "turned solely on the existence of FDA approval for interstate marketing." Because the CSA requires an opportunity for a hearing, such a hearing would be "reduced to an empty formality and, for participants like Dr. Grinspoon [who brought the challenge], would amount to an exercise in futility."⁵⁷

Again, in a telling portent of what would transpire with marijuana, the DEA "reconsidered" the question and again decided that MDMA should be a Schedule I drug. In a rule published in February 1988, the DEA gave lip service to the First Circuit's ruling by stating that the "lack of FDA approval" was "not conclusive" in determining whether a drug has accepted medical uses and accepted safety standards.⁵⁸ Then, rather than relying on the FDA's determination, the agency merely applied the FDA's standards itself.

The DEA's order perfectly encapsulates the catch-22 situation of trying to prove to the government that a drug meets scientific testing hurdles. This is especially true for drugs such as MDMA, which, because it was discovered in 1912 and is in the public domain, has long since lost any ability to be patented. Pharmaceutical companies, therefore, have little interest in pursuing clinical trials. The DEA nevertheless relied on the lack of clinical trials in determining that safety standards had not been established for MDMA, writing that "very little of this information has been generated for MDMA." The psychiatrists who claimed safe use were using "anecdotal observations" that cannot "substitute for controlled studies in animals and humans." The DEA then obliquely references the rat study, claiming that "there have been studies in animals to show that MDMA produces long term serotonergic nerve terminal degeneration." Because "further testing is necessary prior to human use," MDMA would be placed on Schedule I.⁵⁹

The irony, of course, is that placing a drug on Schedule I is perhaps the best way to shut down scientific research into the drug. The immediate effect of placing MDMA on Schedule I was the "curtailment of scientific research and experimentation with a drug that held therapeutic potential." The FDA and DEA claimed to limit testing and experimentation based on concerns about the health of volunteers, meanwhile recreational use and therapeutic treatment has seen millions of MDMA doses to be taken without the literature showing "even one case of an individual suffering neurological symptoms linked to MDMA-related brain damage."⁶⁰

Five applications were submitted to the FDA to research MDMA between 1986 and 1989, and all were denied. According to MAPS, "the FDA based its rationale for rejecting all protocols and single case studies on the hypothetical risk of functional consequences of potential neurotoxicity from MDMA." Things began to improve when, in 1992, the FDA approved a phase 1 study on MDMA use in alleviating pain, anxiety, and depression in cancer patients. That study showed that MDMA posed no unusual risks and could be safely administered. Soon after, though, the FDA put "MDMA psychotherapy research on a slow track to nowhere."⁶¹

Funding is another issue. Government funding for research into psychedelics is almost nonexistent. As Tom Insel, the director of the National Institute of Mental Health (NIMH) told journalist Michael Pollan, “The NIMH is not opposed to work with psychedelics, but I doubt we would make a major investment.”⁶² Funding for research has most often come from private donors like the Beckley Foundation in the UK, the Heffter Research Institute, and MAPS.

In the limited research that has been done, however, MDMA has continually surprised researchers with its efficacy in treating certain psychological problems, particularly PTSD. In one small study of those with treatment-resistant PTSD, 80 percent of MDMA-treated patients reported benefits from the treatment; only 20 percent of the placebo group did so.⁶³ Even one year later, the majority of those treated with MDMA reported continued beneficial effects, whereas none in the placebo group did. In another small study of those suffering chronic PTSD, 10 out of 12 subjects were determined to be cured after two MDMA-assisted psychotherapy sessions.⁶⁴

David Nutt, the aforementioned British pharmacologist, was dismissed from the British government’s Advisory Council for the Misuse of Drugs when he publicly suggested that horseback riding is more dangerous than ecstasy (it is). In his book *Drugs without the Hot Air*, Nutt put the psychotherapeutic allure of MDMA in stark terms:

If we wanted to invent a drug especially designed to help enhance trauma-focused therapies, it would have the following qualities:

1. Be short-acting enough for a single session of therapy.
2. Have no significant dependency issues.
3. Be non-toxic at therapeutic doses.
4. Reduce feelings of depression that accompany PTSD.
5. Increase feelings of closeness between the patient and therapist.
6. Raise arousal to enhance motivation for therapy.
7. Paradoxically, increase relaxation and reduce hyper-vigilance.
8. Stimulate new ways of thinking to explore entrenched problems.

Ecstasy has all these qualities when used in a clinical setting, and it is extremely effective.⁶⁵

Since then, research into psychedelics, particularly MDMA, seems to have turned a corner. In November of 2016, the FDA approved a large-scale phase 3 clinical trial of MDMA-assisted psychotherapy,⁶⁶ and, in August 2017, two more phase 3 clinical trials were approved.⁶⁷ What's more, the FDA designated MDMA-assisted psychotherapy as a "breakthrough therapy" and thus will work to complete the final phase quickly. This is primarily due to the astounding effectiveness of the phase 2 trials, like previous research:

In MAPS' completed Phase 2 trials with 107 participants, 61 percent no longer qualified for PTSD after three sessions of MDMA-assisted psychotherapy two months following treatment. At the 12-month follow-up, 68 percent no longer had PTSD. All Phase 2 participants had chronic, treatment-resistant PTSD, and had suffered from PTSD for an average of 17.8 years.⁶⁸

Providing the funding for the studies is MAPS, which is "currently the only organization in the world funding clinical trials of MDMA-assisted psychotherapy."⁶⁹ Through the effort of MAPS and other organizations, we are on the cusp of seeing the approval of a bona-fide breakthrough drug for PTSD treatment. But if 40 years ago the DEA had listened to the psychologists who touted the benefits of MDMA, untold numbers of PTSD sufferers could have been helped.

The growing acceptance of research into MDMA has also helped resuscitate research into other psychedelics that were hastily banned and given a bad reputation before any meaningful scientific research could be done, particularly LSD and psilocybin. Psilocybin has been used to combat smoking addiction in small, FDA-approved studies with shocking results. In a study with 15 participants, "twelve subjects, all of whom had tried to quit multiple times, using various methods, were verified as abstinent six months after treatment, a success rate of 80 percent." Before it was stamped with the label "hippie drug" and associated with anecdotal stories of "bad trips," LSD was used to successfully treat alcoholics.⁷⁰ But getting into the story behind psilocybin

and LSD is beyond the scope of this essay. Suffice it to say that the story is largely the same as for MDMA: a fearful government, goaded on by hyperbolic media reports and frightened parents, banned something before we knew much about it. As a result, science was retarded, and those who could have benefited were forced to languish with their possibly curable disorders.

Conclusion

Drugs, especially “new” drugs, scare people. This is understandable. But that fear should not be allowed to divert public policy from its proper moorings in good science. Prohibition is sometimes thought of as the ultimate form of regulation. But this notion is mistaken. Prohibition is the absence of regulation, either for street use or for scientific studies. Prohibition means anarchy.

Placing a drug on Schedule I virtually guarantees that our knowledge about the drug’s effects and possible beneficial uses will be hampered. In the process, the true victims will be those who could have benefited from using the drug, but instead must live in a world created by the fears and trepidations of past generations. We seem to be turning a corner on marijuana and MDMA, and it can be hoped that we’ve learned some lessons about the costs of knee-jerk reactions to “drug scares.”



MEDICAL INNOVATION AND THE GOVERNMENT-ACADEMIC-BIOMEDICAL COMPLEX

The incentive structure for advancement in the biomedical sciences differs very little from that in other fields. Success or failure is judged through the prism of academic publications generated by outside financial support—in this case, both public and private. Here we discuss the concept of innovation in medicine and its relationship to the reward structure. We will find that the two are almost completely independent of each other. In other words, federal funding for research is not very related to progress in patient care, in the same way that public funding and private funding produce roughly the same amount of innovation in basic and applied research.

“Medical science,” a widely used term, is misleading. Without question, the study of the natural sciences has contributed to the fact we lead longer and healthier lives than previous generations. But it is *technology*—the availability of practically useful drugs, diagnostics, and medical devices—that deserves most of the credit for these improvements. The failure to recognize that distinction is the basis of a common misconception that free-ranging research by academic scientists—funded predominantly over the past half-century by the

federal government—is the main basis of medical advances. This chapter reviews the historical reasons why this idea is false.

The First Era of Medical Innovation

Substantive medical progress emerged in an innovation era that began in the middle of the 19th century. Fueled by the capital of the Industrial Revolution, medical research proliferated. Discoveries by Louis Pasteur, Robert Koch, Ignaz Semmelweis, John Snow, Joseph Goldberger, Walter Reed, and many others gradually ushered in a range of technologies, including vaccination against infectious diseases, antiseptics, anesthesia, sanitation, treatment of vitamin deficiencies, and elimination of insect disease vectors, all of which contributed to the prolongation of life.

In the early years of the first innovation era, these discoveries often emanated from state-funded European universities and research institutes. Subsequently, a few private institutions in North America such as Johns Hopkins Medical School and the Rockefeller Institute engaged in medical research supported by private philanthropy. Their work was later supplemented by associations dedicated to specific maladies such as heart disease, rheumatism, and cancer. Medical innovation also arose from drug discovery generated by partnerships between academic physicians and the German dyestuffs industry. These led to aspirin to treat pain and fever, and to antimicrobial therapies such as arsenicals (for syphilis and parasitic disease), sulfonamides, penicillin, and streptomycin.¹

In America, until early in the 20th century, proprietary apprenticeships competed with and overshadowed the European tradition of university-based education of physicians. The 1910 Flexner Report, however, enabled organized medicine, eager to restrict professional access and reduce competition, to collude with universities to have states only license physicians who had graduated from accredited academic medical schools.² An important criterion for academic advancement in these institutions was the performance and publication of research. This resulted in election of medical researchers to elite professional

societies such as the Association of American Physicians, the American Society for Clinical Investigation, the Interurban Clinical Club, and the Clinical and Climatological Society that convened gatherings to share research results. Sinclair Lewis's Pulitzer Prize-winning novel *Arrowsmith*, published in 1925, along with other contemporary accounts, describes how doing research in medical schools conferred prestige on its practitioners and the tension between research and nonresearch physicians who felt demeaned by them.³

Although the number of American medical researchers was relatively small during the first innovation era, they made important advances, such as treatments for pernicious anemia, hormone replacement therapies, and surgical treatments for heart valve disorders or to remove blood clots from occluded vessels.⁴ During World War II, academic medical researchers' contributions to the war effort resulted in the development of anti-malarials, mass production of antibiotics, and blood transfusion therapy.⁵

The Second Era of Medical Innovation

The role of technological superiority as a decisive factor in the Allied victory was a transformative element that ushered in the current era of medical innovation. The principal architect of that transformation was Vannevar Bush (1890–1974). An engineer, entrepreneur, and academic administrator, Bush came to head the entire research-and-development organization of the American war effort, culminating in the Manhattan Project and the atomic age.⁶

At the behest of Franklin Roosevelt, Bush wrote a treatise—*Science: The Endless Frontier*—making the case for lavish government funding for research.⁷ A central element of Bush's plan was the idea that basic research, or research for research's sake—"the free play of free intellects"—was the best path toward progress. The emerging Cold War, with its mandate for achieving nuclear superiority, was a prime mover in ensuring a political embrace of Bush's vision. But on the medical front, influential university officials and researchers invoked the recent success of a vaccine to combat frightening polio epidemics and other

achievements to argue for applying Bush's ideas to medical innovation. Congress enthusiastically complied with a massive buildup of the National Institutes of Health (NIH).

The NIH's predecessors originated in 1798 with the Marine Hospital Service to care for merchant seamen (the NIH logo still features an anchor!). It evolved into a public health organization, the Hygienic Laboratory, to address infectious diseases and in 1930 acquired the title of NIH (Institute in the singular), which expanded to include multiple institutes during World War II.⁸

As an ultimate result of Bush's proposal, through postwar congressional initiatives, the NIH began receiving much larger appropriations.⁹ It constructed a laboratory research facility and a hospital dedicated entirely to research on a spacious tract of land in the Washington, DC, suburb of Bethesda, Maryland. Most of the NIH's funds, however, began to flow "extramurally" to universities and independent research institutes. Thus began the second era of medical innovation, giving birth to what is best called the government-academic-biomedical complex (GABC), which remains the dominant bankroller of medical research in American academic medicine.

The Growth of Academic Medical Research

The premium on research as the route to advancement in academic medicine conspired with the availability of money to recruit more and more faculty members to that endeavor. Medical schools not previously counted among the elite achieved sudden prominence. The University of Texas-Southwestern in Dallas evolved in the late 1940s from a collection of former military barracks into a major academic powerhouse, culminating in the 1985 Nobel Prize in Physiology or Medicine awarded to Michael Brown and Joseph Goldstein for their work on cholesterol metabolism.¹⁰

The Korean and Vietnam Wars' drafting of physicians in postgraduate training into the military additionally contributed to the medical research workforce.¹¹ Those with academic ambitions could fulfill their military obligation in the Public Health Service and obtain positions at the NIH (or at the newly founded Centers for Disease

Control) facilities to receive research training. Competition for these slots—facetiously named “the yellow berets”—was stiff and resulted in the rapid population of the NIH “intramural” Bethesda facility with young trainees, many of whom became career medical investigators.¹² The emphasis on research led medical specialties’ accreditation boards to stipulate research training as a requirement for specialist certification. Physicians training to be specialists had to spend time in research programs whether or not they wanted to. The NIH provided stipends for such training both to academic departments and to individual trainees, who were cheap labor for university research programs. NIH funds were also made available to universities to encourage undergraduates to obtain research experience and to subsidize graduate training programs.

Money went begging in the startup phase of GABC-fueled extramural granting. NIH officials solicited universities for research grant applications. But this vacuum filled rapidly. Medical school departments, such as surgery, that had traditionally done little research, soon initiated laboratory-based research programs. Since surgeons spend so much time in the operating theater, they hired basic scientists with PhD degrees to work in their laboratories. The emerging research programs needed expensive equipment, glassware, chemicals, and experimental animal facilities. Most heads of research laboratories spent their time reading research papers and designing experiments, leaving the execution of those experiments to researchers in training (graduate students, interns, residents, and technical assistants). Grant applications and research papers—all typewritten in those days—required secretarial support. The NIH underwrote it all. In the late 1940s, the American Cancer Society was the largest funder of medical research. By the mid-1950s, its contributions lagged far behind the government’s.

An especially attractive feature of NIH funding for universities and research institutes was that it provided much more generous indirect (overhead) support than private philanthropists, who preferred to see their donations underwrite research and researchers rather than institutional infrastructure such as building construction and maintenance and administrative costs.

This bounteous federal research funding party lasted only about a decade and a half, up to the late 1970s. Congressional NIH appropriations did not decrease thereafter but rather, as discretionary budget items, could not rise in proportion to the demands by academic centers for more and more externally funded research. Despite general congressional enthusiasm for the NIH mission, the Johnson administration's Great Society programs and Vietnam War spending precluded further expansion of the NIH. Congress and the NIH's management began to impose restrictions on the use of NIH funds, such as disallowing payments for secretarial services and requiring training grant recipients to spend post-training time in bona-fide academic research programs or else pay back the funds they had received.

Financial constraints increasingly became a serious problem within the GABC. But even beginning with the first signs of fiscal distress, the GABC's beneficiaries—universities and their guilds, research institutes, professional societies, patient advocacy groups, and voluntary health agencies—lobbied Congress strenuously for more NIH funding. Unsurprisingly, their efforts at persuasion centered on the premise that such subsidy is essential for medical innovation.

This plausible hypothesis is wrong. Whereas others have provided cogent critiques of the role of government in science and of Vannevar Bush's enthusiastic promotion of basic research, this analysis drills down more specifically on the problem of *medical* innovation, which has—I believe—unique features that differentiate it from other research-based endeavors.¹³

Medical Innovation versus Basic Research in the GABC

Assessing contributions to “medical innovation” demands a precise definition of that term. Unfortunately, innovation gets muddled with novelty. Clearly, novelty has its benefits—most palpable in the arenas of fashion and entertainment. What matters in healthcare, however, is what improves longevity and life quality by promoting health and combating disease. The definition of medical innovation should be restricted to the technologies that accomplish those ends. Innovation requires the intermediary step of having a research result suggest a

practical possibility, an outcome I define as “invention.” When an invention comes to practical use, innovation occurs.

Attesting eloquently to the divide between GABC-based research and innovation is an examination of 25,000-plus publications in prestigious biomedical research journals. Only 100 even *mentioned* invention, a practical implication of the reported findings.¹⁴ Also telling was the passage in 1980 of the Bayh-Dole Act to encourage universities to license technologies to companies for practical development, prompted by the observation that discoveries were either not being patented or patents were not resulting in licensing.¹⁵

Almost three decades after Bayh-Dole was enacted, university income from all licensed inventions—not just medical innovations—remains a minor sum in comparison with the totality of healthcare revenues—or for that matter university revenues, being less than three billion dollars a year.¹⁶ In fact most universities lose money on innovation efforts because their revenues do not even cover the administrative costs of licensing.¹⁷ Clearly government funded basic research is not generating a significant number of useful medical innovations.

Unquestionably, medical innovation proceeded apace during the early GABC era, but not at any increasing rate, though funding for basic research did grow substantially. A benchmark for innovation is the regulatory approval of drugs and medical devices. The average number of such approvals has been constant for the past half-century despite the introduction and continuous operation of the GABC over that interval.¹⁸ Moreover, independent analyses have concluded that over 80 percent of the drug approvals arose solely from research and development in private industry.¹⁹

The Revealing Case of Heart Disease

In addition, an examination of some particular innovations during the GABC era raises questions regarding the GABC’s specific contributions. Over the first half of the 20th century, deaths from heart attacks and strokes had risen steadily, reaching their highest peak at the GABC’s onset in the 1950s.²⁰ Today, six decades later, cardiovascular mortality has fallen by over 60 percent.²¹

Many factors account for this improvement. Risk factors for vascular disease, such as smoking, high blood pressure, abnormal blood cholesterol levels, and genetic predisposition were unknown in the middle of the 20th century; research identified them and led to efforts to mitigate them. But does the GABC deserve most of the credit for this accomplishment?

A principal source of cardiovascular disease risk identification was the NIH-sponsored Framingham Study that correlated the existence of heart disease with the presence of such factors in the population of the Massachusetts city for which the epidemiologic project was named.²² Although the Framingham Study began before the extensive expansion of the GABC, it clearly deserves recognition for its contributions.

How this knowledge translated into innovation is complex. When the Framingham parameters associated with heart disease emerged, whether they were causal or merely correlative was unclear. In fact, other NIH-funded epidemiologic studies that purported to link dietary fat intake to heart disease were ultimately deemed flawed and uninformative.²³

Medications—produced by companies—to treat high blood pressure existed before recognition of its association with heart disease. Their principal use was to combat “malignant hypertension,” extremely high pressures that acutely damage the heart, brain, and kidneys, because these drugs were too toxic to apply to milder cases of hypertension. Once companies developed more tolerable blood-pressure-reducing agents, large population studies demonstrated that lowering blood pressure diminished the incidence of heart attacks.²⁴

Similarly, whether elevated blood cholesterol levels truly caused heart attacks and strokes was also a topic of debate. Only the development of cholesterol-lowering “statin” drugs—an effort solely driven by industry research—established that high blood cholesterol is a bona-fide heart disease risk factor and that reducing it has preventive value.²⁵

Another key contribution to the reduction of heart disease mortality has been the introduction of imaging techniques to diagnose

narrowing and closure of arteries that feed blood to the heart and of devices and drugs to restore blood flow. With the exception of the clinical trials that have established the effectiveness and safety of these interventions, the preponderance of effort underlying these innovations took place in private industry with the important input of entrepreneurial physicians. A similar argument applies to the development of joint replacements, which have markedly mitigated the pain and immobilization inflicted by arthritic conditions.

The Case of the Genetic Revolution

Space limitations preclude examining the universe of innovation that has appeared during the GABC era. But worth mentioning is the highly touted genetic revolution. This effort spawned the biotechnology industry that accomplished the discovery and application of potent “biological” therapies. It also generated the “genome project” that elucidated the sequences of the human genes and those of other species. One oft-cited example of seemingly impractical “basic” research that strongly abetted this genetic technology was the discovery of “restriction enzymes,” compounds produced by bacteria that cut up DNA in specific ways that enable researchers to define and manipulate genes.

Though unequivocally useful, work on restriction enzymes and other discoveries leading to elucidating the structure of DNA was subsidized by sources such as the American Cancer Society rather than the government long before the buildup of the GABC.²⁶ And by credible accounts, although the GABC initiated the genome sequencing project, without its rescue by what started as competition from the private sector, its completion would have been markedly delayed.²⁷

These examples—especially the decoding of the human genome—contradict the passionate advocacy for the GABC’s essential role in medical innovation by its academic beneficiaries. The naiveté of the facile assumption that basic research is the progenitor of innovation is also discussed in Chapter 1 by Kealey and Michaels.

Subjective Attempts to Defend Academic Medical Research

As concerns began to arise in academic institutions regarding the sustainability of government funding for basic research, two physician-researchers, Julius Comroe and James Dripps, attempted to counter an inconvenient finding that emerged in the 1960s. A study dubbed Project Hindsight had examined weapons technology innovation and posited that the vast predominance of progress in weaponry was the result of work directly related to the subject at hand, not basic research.²⁸ In an influential paper published in the journal *Science*, Comroe and Dripps came to the opposite conclusion: that advances in the treatment of cardiovascular disease management—their area of clinical specialization—originated from research findings with no direct connections to the ultimate technological achievements.²⁹

But rather than meticulously documenting the steps involved in the evolution of specific military technologies as was done by Project Hindsight, Comroe and Dripps relied on the indirect approach of having “experts” opine about the provenance of medical innovations, an exercise fraught with subjectivity and potential inaccuracy.³⁰

Innovation is inherently nonlinear and routinely depends on adaptation and serendipity to exploit findings applicable to practical problem solving. Although some such results arise from undirected basic research, this fact does not in and of itself justify a massive investment in research for research’s sake. The Comroe-Dripps compilation also failed to quantify the large denominator of research results that contributed nothing to innovation, an important element of any cost-benefit analysis.

A more recent attempt to give the credit for drug discovery to university research also recruited “experts” to opine on what they considered to be the “most transformative” drugs developed between 1984 and 2009.³¹ The authors concluded that the most impactful drugs arose from academic research.

It is logical that communities that have benefited so much from the GABC will fiercely proclaim its virtues, even resorting to substantial rhetorical and logical leaps. Like the Comroe study, the more recent experts’ drug selections also involve subjective opinions, and the focus

on “transformative” drugs reflects the academic obsession with what is novel and impressive. In the real world, any given patient wants a drug that *works*. A medication that relieves a headache effectively is “transformative” for that individual. Also, most of the drug approvals cited in that study took place early in the study interval, too soon for the GABC to have had a major influence.

Finally, and most important, the study’s authors’ casual anecdotal descriptions of drug development were skewed—often inaccurately or inappropriately—to overemphasize the importance of academic contributions. For example, the narrative implies that a highly effective anti-leukemia drug, inatimib, was discovered by an academic physician grounded in basic science principles.

The truth is that a company discovered the drug looking to treat diseases other than leukemia, and while the academic researcher’s contribution was material, the drug never would have helped patients in the absence of industry efforts.³² The article reporting the study neglected to cite most of the previous research that more meticulously analyzed the development histories of important drugs. Most telling, a separate and far greater in-depth analysis of the provenance of the same “transformational” drugs covered in the study ascribed the dominant influence to the private sector.

The Flawed GABC Incentives

If the march of medical innovation has not benefited from the GABC as much as advertised, what could be the explanation? The principal answer is misaligned incentives. If history teaches anything, it is that incentives and rewards work far better than good intentions, especially those dictated by authorities. The GABC’s incentive misalignment relates to the definitions discussed above: the GABC rewards “research” more than it does “innovation.”

Producers of goods and services dependent on revenues must innovate in order to survive. Because sales monopolies enjoyed by manufacturers of brand pharmaceuticals and medical devices are temporary, a thriving enterprise producing follow-on generic products mandates that the innovative brand industry maintain a pipeline that

addresses previously unmet medical needs or provides better management than what is currently on the market.

Researchers outside of industry have been happy to advertise that they have high-minded intentions—improving mankind’s lot by increasing knowledge and providing practical innovation. This propaganda impulse is understandable in view of the fact that such researchers depend heavily on public philanthropy for their livelihoods. To unlock that purse, researchers have created the impression that they promote material progress by operating in a universe of higher—“objective”—reality than purveyors of mere business. The opacity of science to most nonscientists plays into that message.

But historians of science have documented that researchers work predominantly for recognition of their accomplishments by influential peers, and that they fight tooth and nail for that attention.³³ Nothing attests more powerfully to this conclusion than the profound importance the establishment of scientific journals in the 17th century had on the advance of science.³⁴ By providing an institutional repository for scientists to claim credit for discoveries, journals overcame scientists’ reluctance to publicize their work for fear of intellectual pilferage.³⁵ In addition, scholars have challenged the conceit that science reveals absolute, “objective” “truths.” Rather, it is a very social activity that depends on a very mutable interpersonal consensus influenced by personal preferences, career ambitions, and political power.³⁶

A prime example of the different incentives for “medical innovation” and academic “medical research” is that the former receives its rewards for achieving regulatory approval of new products for clinical use. The latter seeks recognition through publication of research papers, awarding of research grants, academic promotion, admission into scientific elite organizations, and receipt of prizes. If these academic rewards accrued to researchers because they promoted innovation, the GABC’s incentives could be appropriate. Instead, historians and sociologists of science have concluded that academics value and reward elegant solutions for complex scientific puzzles more than they do innovation that saves or enhances life.³⁷

Interesting versus Useful

One articulation of what constitutes value in science lists “accuracy, intrinsic interest and general relevance.”³⁸ Ironically, whereas the criterion of “accuracy”—also definable as reproducibility—would seem to go without saying as an essential criterion of value, the bar set for academic research is that observations need only achieve minimal statistical validity without independent corroboration to justify publication. It is the norm that companies attempting to exploit academic findings as possible product candidates are often unable to replicate the academic results.

The criteria of “intrinsic interest and general relevance” raise the question: of interest and relevance to whom? Experience reviewing research papers submitted to journals for publication and grant applications reveals that new (“novel”) and unexpected findings elicit maximal interest. General relevance, such as laws that predict the behavior of moving objects, commands the highest adulation. But notably, practical utility is not on the list. In the case of biomedical science at the outset of the GABC era, Vannevar Bush’s lionization of basic research played seamlessly into this value system.

The Case of Reductionism versus Innovation

Even as medical innovation accelerated in the first, pre-GABC, innovation era, medical practitioners had little or no idea how most of their beneficial tools worked. Trial and error identified malfunction of the pancreas as a cause of diabetes and subsequently the existence of insulin, the hormone it produced, and the deficiency of which resulted in the disease. Even then, in keeping with the fact that only industry had the wherewithal to exploit such information for innovation, the University of Toronto researchers who discovered insulin tried and failed to do more than demonstrate its clinical efficacy to treat diabetes in a few patients. Insulin therapy did not have a major clinical impact until the Eli Lilly Company took over the problem and mass-produced the hormone.³⁹

But as the GABC expanded and new technologies for analyzing the structure and function of body components and subcomponents at ever more fundamental (molecular) levels came on line, the plausible but empirically largely unsupported idea that more detailed knowledge concerning how derangements of these processes cause disease and how addressing them produces cures held sway. The reductionist science that had so profoundly advanced physics and chemistry had great appeal for the biologists previously mired in empiricism—and more and more physicists and chemists seduced by GABC resources moved into basic biological science.

The reductionist paradigm, warmly embraced by the GABC, creates endless research questions, few of which, as recognized by others, lead to medical innovation and progress.⁴⁰ One aspect of the primacy of reductionism is an obsession with “molecular mechanisms.” The fact, for example, that aspirin reduces fever became less compelling than the “molecular basis” of *how* it happens.

Bush Was Right: Research Becomes Endless

Perversely, the expansion of the menu of “intrinsically interesting” phenomena unearthed by basic research over time presents far more opportunities for researchers to follow up with adequate depth or breadth. Instead of the finite endpoint of approval of a practical innovation by regulators persuaded that something works with acceptable risks, the basic research system accommodates open-ended wheel spinning. Editorial commentary concerning research published in journals inevitably concludes that “more studies are necessary,” as if a bottomless supply of researchers exists to advance the knowledge frontier closer to a never-receding illusory goal. This attitude brings to mind the scenario described by Herman Hesse in his 1943 novel *The Glass Bead Game*, in which abstract cerebral virtuosity divorced from any real-world activity has become the ultimate end of intellectual activity.⁴¹

For all its pretensions to research that abets innovation, the GABC ignores and dismisses a vast repertoire of essential but academically unsung skill sets required to achieve innovation. One of hundreds of

these tasks is “formulation.” A drug candidate may work spectacularly in a test tube to, say, kill cancer cells, but if it cannot be prepared in a form amenable to absorption by the body following oral or parenteral administration that persists long enough to get to the body sites where its action is desired and do what it is supposed to do, its test tube performance has no practical utility.

Economic Impacts

Separate from whatever damage the GABC’s emphasis on basic research has inflicted on medical innovation, its economic impact has arguably compromised it. Although compelling arguments—usually citing national defense—justified the postwar infusion of government support’s transformation of universities from bucolic bastions of predominantly ivory tower contemplation into more diverse institutions contributing practical inventions as well as abstract knowledge and educated citizens to society,⁴² the financial dependence on government support that accompanied this transformation inflicted deleterious consequences customarily associated with addiction.

One way to track whether the GABC kept pace with innovation opportunity is to compare its investment with the accrual of individuals living beyond 65 years of age, a figure easily obtained from census data.⁴³ The comparison reveals that both figures rose proportionately, and exponentially, until the late 1970s when, as NIH appropriations remained essentially flat, the longevity curve diverged steadily upward away from it.⁴⁴

This discrepancy raised two issues, one stridently engaged by the academic community, and the other ignored by it. The one that received attention was the fact that the NIH appropriations were rising more slowly than in the past, predictably lowering the success rate of grant applications. Academic officials raised alarms about the effect this austerity was having on the recruitment of physicians into medical research, thus encouraging a diaspora of physician-researchers from research activities into clinical or administrative efforts.⁴⁵ The ignored issue was to ask why population survival rose unabated despite the constrained GABC investment. The obvious answer was that private

investment continued to increase and, in fact, has grown precisely in parallel to the data on aging.⁴⁶

In response to slowing growth of NIH funding appropriations during the 1980s and early 1990s, academic distress escalated. Biomedical research societies and voluntary health organizations exhorted their adherents to lobby Congress for greater generosity. The arcane nature of research, the ineptness of the biomedical community in explaining it, and the competing political agendas of welfare, other entitlements, and defense made for a difficult challenge. Except for a brief five-year period in the mid-1990s during which Congress doubled the NIH budget appropriation, the gap between public and private investment in biomedical research has continued to widen.

The financial hardship in universities dependent on external research subsidies and other developments altered the demographics of the academic medical workforce. The earlier lamented decline in the number of physicians involved in research accelerated markedly.⁴⁷ For the most part, the only physicians seeking research careers had also obtained PhD degrees during an overly long training sojourn—often doing so to take advantage of tuition subsidies rather than a deep commitment to research, as evidenced by a high post-training dropout rate.⁴⁸ Hence, individuals with PhDs but no medical training came to dominate the research effort.

The researchers who had obtained faculty positions and research support defining them as “principal investigators” depended heavily on NIH salary support, because many academic institutions had recruited such individuals without setting aside funds to pay their salaries. In an effort to counter this trend and to increase the efficiency of research grants by having them cover research, equipment, supplies, and technical assistants rather than subsidizing principal investigators, the NIH capped salary budgets. One result of these developments has been that academic tenure, at one time a sinecure, has become relatively meaningless in research-intensive universities. Principal investigators unable to obtain NIH grants leave research for medical administration, clinical practice, or industry.

The average age of researchers able to obtain grants has increased markedly because only applicants with established track records and

in possession of an entourage of trainees and younger colleagues can generate enough new data that may rise to the level of intrinsic interest for sufficiently favorable review opinions to surmount the high funding priority bar.⁴⁹

Paradoxically, the GABC's straitened financial circumstances have undermined the cliché that undirected basic research addresses wide-ranging long-term scientific goals in contrast to commercial research and development allegedly committed to immediate problem solving and fast profits. Faced with ever-shortened NIH funding intervals (now three to four years), GABC applicants must operate with narrowly focused efforts tightly linked to previous accomplishments in hopes of surmounting the aforementioned bar.

The prospects for the successful principal investigators' entourage rising to the status of their superiors are vanishingly slim; they may orbit from one postdoctoral fellowship to another until they give up and leave academe for research jobs in industry—which are finite—or teaching positions or some other endeavor.

One might imagine that the leaders of academic institutions would be in the forefront of advocacy for more government research funding. Although these managers articulate such sentiments, their major concerns, reflected by the principal lobbying emphasis of the Association of American Medical Colleges that represents them, is the continuation and, if possible, expansion of government subsidies for clinical training of interns, residents, and fellows who, as a result of this welfare, represent cheap labor for providing medical services.

Left to fill the vacuum of special pleading for the GABC is advocacy entrepreneurship engaged by an organization called Research!America. Funded to some extent by universities but principally by the pharmaceutical industry, Research!America relentlessly exhorts biomedical researchers to plead with their legislators for more NIH funding. But what it does best is collect celebrities for gala events, conferring awards on them and on high-paid biomedical bureaucrats. Although absent this group's efforts things might have been worse in theory, NIH funding adjusted for inflation has declined since its founding in the 1980s.

Dysfunctional Pharmaphobia

Of all of its counter-innovative elements, the GABC's worst is arrogance. The principal manifestation of this hubris is that GABC has inverted the reality that it is private enterprise: it is the pharmaceutical and medical device industry, not the GABC, that has been accountable for most medical innovation over the past half-century.

The principal instigators of this misconception are entrepreneurial academics who have built careers not only by exploiting public ignorance of the facts by overstating the contributions of NIH-sponsored research but also by engaging in a wholesale demonization of the industry as corrupt. I refer to this activity as "pharmaphobia";⁵⁰ a signature characteristic of its acolytes is that none have made substantive contributions to medical innovation. Their critical narrative plays into the hands of sensation-seeking media, populist politicians, and predatory litigators who profit from charging real or imagined corruption.

The idea of bias induced by commercially driven funding has become a separate area of research in the GABC world. Commercial funding is viewed with suspicion, as somehow intrinsically evil, despite the fact that this is where medical innovation comes from. That government funding might be even more pernicious is not ever considered. This discriminatory research supports pharmaphobia, creating a guilt-by-association barrier to making academic research useful. So does the extensive use of so-called conflict of interest disclosure requirements. Here the implication is that any funding from a commercial firm somehow taints the research. This makes it very hard for GABC researchers to work on innovation.

Medical journal managers have enthusiastically joined the pharmaphobia bandwagon because it allows them to sell the false idea that their periodical products embody the most reliable information, which they improperly contrast with pharmaceutical marketing. In fact, as the poor reproducibility of published results attests, the vetting of industry's research and development work by professional regulators is far more rigorous than the relatively casual oversight of research published in journals, and companies can only publicize what the regulators have

approved. The overwhelming majority of published journal articles retracted because of fraud are of academic origin and have no industry association.⁵¹

In addition to discounting the value contributions of industry, the pharmaphobia narrative denies the difficulty and expense of innovation that has increased 80-fold since the onset of the GABC.⁵² The origin of this rise is tightened regulatory requirements engrafted on the fundamental unpredictability of biology. On the positive side, biological irregularity is what has enabled us to survive against trillions of rapidly evolving microorganisms that utilize our body components to sicken us. The downside of this adaptation is that more than nine out of ten drugs that seem promising in laboratory experiments or inbred animals fail in clinical trials, and therefore the one success must pay for the nine losers.⁵³

This grim economic reality mandates that the industry must achieve sufficient profitability to sustain innovation. The pharmaphobia narrative's misguided denial of this fact underlies calls by poorly informed activists to confer price controls on American drug manufacturers.⁵⁴ American consumers, who live in the only country lacking such controls, subsidize the entire world's medical innovation.⁵⁵

The pharmaphobia narrative detracts from medical innovation in many ways. Regulations it has spawned in academic health centers and in state and federal governments, designed to root out speculative corruption, at worst complicate, delay, or outright prevent relationships between academic researchers and industry that historically have promoted innovation. At a minimum, they divert scarce resources from actual innovation to bureaucratic management.

The most extreme example of this dysfunctional regulation is "sunshine legislation" embedded in the 2010 Affordable Care Act, which mandates that companies report to the government payments ("exchanges of value") of cash or in kind exceeding ten dollars to licensed healthcare practitioners for public dissemination. The reporting (at a cost of hundreds of millions of dollars) has predictably had no impact on patient care or patients' trust in their healthcare providers, but its potential for shaming has steadily increased, to 36 percent, the proportion of clinical practices that refuse to give company representatives

access to their practitioners, thereby depriving physicians of reliable medical information. What is particularly unfortunate about the pharmaphobia narrative is that it stands in the way of reconfiguring the GABC to make it more compatible with medical innovation.

Reforming the GABC

According to Socrates, “admitting ignorance is the beginning of wisdom.” The GABC equivalent of this insight is to jettison the “bench-to-bedside” legend that academics promote, claiming that basic research reliably generates discoveries that seamlessly flow down the development pipeline into inventions that become innovations. For the most part, GABC behavior remains at the bench, piling up often nonreproducible and nontranslatable reductionist findings. Here, briefly, are some reform options:

1. Supplant the legend with the reality of how innovation actually occurs. The truth is that, almost invariably, innovations come to pass in fits and starts, overcoming myriad obstacles and succeeding only if moved forward by committed champions.⁵⁶
2. Exploit the competitive advantage conferred by the fact that many healthcare workers are more interested in *care* than in research. The fact is that most healthcare providers will never be excellent researchers or innovators because the work does not interest them. Recognition of this fact could stop the venerable but increasingly anachronistic tradition of force-feeding healthcare trainees with “scientific” information that has little relevance to everyday practice and could shorten healthcare professional training and reduce the medical school science faculty population and the financial burden it creates.

Such an attitude change could also nudge the emphasis in medical schools toward practical problem solving, especially if promotion and recognition rewarded it rather than the publication of arcane papers in prestigious journals and acquisition of basic research grants as the vehicle for advancement. Since problem solving is the major goal of the medical products

industry, such an attitude change could set the stage for industry to shore up the declining financial contributions to research by the GABC.

3. Understand that industry should not and will not simply supplant the GABC model of subsidizing research for research's sake. Basic research has value and will persist in academia, though, as Terence Kealey explains in Chapter 2 in this volume, it does not require massive public funding. In addition, downsizing the basic research enterprise to a level that academic institutions can responsibly and sustainably support would make a far more persuasive case for some public supplementation than arguing that government should be almost wholly responsible for academic biomedical research as an entitlement.

4. Accept that the cultural elements that reward the pursuit of intrinsic interest and general relevance in scientific endeavor seem to be hard-wired and will no doubt persist among basic researchers. However, academic officials can help to level the playing field by promoting and honoring individuals who engage in the efforts required for innovation. Successful prosecution of intellectual property and licensing of technologies to industry should have as much cachet as publication in high-profile journals and awarding of grants.

The NIH currently supports such activities through its Small Business Innovation Research (SBIR) program. A problem with this system is that (predictably) the NIH tends to convene review panels that emphasize basic science expertise rather than the technological competence required to promote innovation proposed by the projects. The result is that these grants receive low ratings and are funded only because the number of applications is far lower than the number of standard research grant requests.

These changes would ameliorate the pharmaphobic attitude and perhaps raise the possibility that private industry will take a serious interest in partnering with academia to promote innovation. This might actually make the GABC an engine of innovation.

Medical Innovation and the Cost of Health

In a slim volume published in 1952 entitled *The Cost of Health*, Ffrangcon Roberts, a British physician, documented an exponential rise in health spending in the United Kingdom (since 1900) and correctly ascribed it to the fact that instead of dying prematurely of previously unmanageable diseases, many people were benefiting from what he eloquently characterized as “medicated survival.”⁵⁷ Although the expense figures Roberts compiled were a mere blip on the ascending cost curve that followed, its upward trajectory has not changed since.

Roberts concluded that the only possible remedies for the Malthusian expansion of medical costs were to ration healthcare or for a nation’s economic productivity to grow sufficiently to accommodate the costs. Over the past decade, relatively slow economic growth has rendered this second alternative extremely challenging.

The implication of Roberts’s analysis was that medicated survival axiomatically increases healthcare costs. If these costs exceed society’s ability to sustain them, is investment in medical innovation ultimately, as some aver, detrimental to society?⁵⁸ A difference between Roberts’s 1950s perspective and today’s is that medicated survival is now far more compatible with economic productivity. Arthritis, for example, owing to diverse etiologies, in Roberts’s time often precluded gainful employment and limited consumption of other than medical goods and services. Thanks to medical innovation, joint disease is far more manageable and consistent with an active lifestyle conducive to material production and consumption.

Many other examples exist, documenting a positive impact of medical innovation on formerly chronic debilitating diseases. This fact, plus the declining birthrate in developed countries, implies that on balance medical innovation, and its effect on longevity, is economically beneficial. Breakthroughs in the management of unmet medical needs, such as dementia, will confer even greater value.⁵⁹

Conclusion

If, as argued here, the government-academic-biomedical complex is a relatively poor system for medical innovation, why has it lasted so long and received so little critical scrutiny? The retrospective analysis provided in this chapter provides unpredictable—and predictable—reasons.

Unpredictable, in part, was how the system changed. At the GABC's onset, medical research took place in a few institutions such as New York's Rockefeller Institute or in not-for-profit hospitals affiliated with universities. The hospitals were nonprofit because little profit was possible. The relatively limited availability of medical technology relegated clinical care predominantly to observing hospitalized patients whose illnesses did or did not resolve spontaneously or responded to limited available treatments. Therefore the physicians staffing these hospitals had abundant free time to pursue research in their laboratories, often making measurements on blood or other body fluids taken from patients. Thanks to this leisure and the prestige associated with research, clinician-researchers were willing to sacrifice some income for providing clinical services. The lack of reimbursement restraints at that time still enabled these individuals to sustain comfortable incomes. The bounty of insights yielded by the first medical innovation era meant that researchers working under these relatively leisurely circumstances could only perceive an influx of federal research funding as a great opportunity to amplify their efforts and increase their chances of making discoveries that would advance their careers. The incipient GABC amply supported that perception.

But the system changed. The very success of medical innovation transformed university hospitals into intensive service providers, drove up costs, and accrued an expensive bureaucratic apparatus to manage the service business. Hospital survival, dependent on financial success in providing services, put research on the back burner. One aspect of the bureaucracy—warmly embraced by the GABC—was ever-increasing regulatory oversight, such as over the ethics of experimentation with humans and animals, over the performance of laboratory tests, and over researchers' interactions with industry. These

regulations addressed some real but often theoretical concerns and have impeded research.

Predictable, on the other hand, has been the institutional response to these systemic changes based on the fundamentals of human nature and on a consequence of the history of medicine itself.

The human element is that the bureaucracy created by the massive corporate expansion of the biomedical enterprise has created a managerial class with few incentives to challenge the system—and strong incentives to suppress dissent, because disruptions threaten managerial security. Most researchers have no financial or political wherewithal to express dissent. Unlike most business leaders, medical managers have relatively little accountability because the metrics of success in healthcare are so vague and unpredictable. The few investigators who have played the GABC successfully determine what research topics are fashionable and thereby exert regulatory capture of the granting and publication system based on peer review.

Even the leadership of the medical products industry has little motivation to challenge the GABC. It may not enjoy the rhetorical attacks of pharmaphobia, but absent price controls—something its lobbyists have managed to prevent so far—they represent no serious challenge to the industry's profitability. The industry's investors don't care where the science resulting in profitable products originates.

The esoteric nature of science in general and medical innovation in particular has helped to accommodate the widely held conceit that government-supported academic research is the source of most medical innovation. Enactment of the reform recommendations summarized here will require public education concerning the fallacy of that view. Arguably, those who ought to be most motivated to promote those reforms are individuals who personally suffer from diseases that are currently poorly managed by available medical technologies or who have friends or relatives in that circumstance.