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ARTICLE

The Birth of Naloxone: An Intellectual History of an Ambivalent Opioid

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Abstract

Naloxone, which reverses the effects of opioids, was synthesized in 1960, though the hunt for opioid antagonists began a half-century earlier. The history of this quest reveals how cultural and medical attitudes toward opioids have been marked by a polarization of discourse that belies a keen ambivalence. From 1915 to 1960, researchers were stymied in seeking a "pure" antidote to opioids, discovering instead numerous opioid molecules of mixed or paradoxical properties. At the same time, the quest for a dominant explanatory and therapeutic model for addiction was likewise unsettled. After naloxone's discovery, new dichotomizing language arose in the "War on Drugs," in increasingly divergent views between addiction medicine and palliative care, and in public debates about layperson naloxone access. Naloxone, one of the emblematic drugs of our time, highlights the ambivalence latent in public and biomedical discussions of opioids as agents of risk and relief.

Keywords: naloxone; opioids; addiction; neuroethics; palliative care; history of medicine; FDA; medical research; War on Drugs

The opioid antagonist naloxone was first synthesized in 1960, and has since inspired more ambivalence than almost any substance in the modern pharmacopeia. One of the major arcs of the palliative care movement was the transition from liberal use of naloxone in clinical practice to "rescue" end-of-life patients "succumbing" to the effects of opioids, to the condemnation of this practice with the advent of palliative care. In the public sphere, many support equipping police officers with naloxone, but others fear that the drug's widespread availability incentivizes "bad behavior" and recidivism. Myths of "Narcan parties" (in which opioid users are said to intentionally overdose, confident they will be revived) and "Narcan aggression" (in which opioid users purportedly react with almost superhuman rage and violence when administered naloxone) blend cultural fears and fantasies of outsized pleasure or outsized belligerence. Why this ambivalent love/hate affair with naloxone, and how did we get here?

One answer might be our equally ambivalent relationship with opioids. As the perception of opioids becomes ever more colored by political, socioeconomic, legal, and ethical connotations, the antidote to opioids—naloxone—becomes the arena in which we seek clarity, a way of defining *by negation* a public and medical stance toward opioids.[1] Although opioids are still controlled and dispensed by two monoliths, healthcare professionals and the black market, naloxone is being radically democratized, available and usable by nearly anyone. This fuels new, grassroots conversations not only about naloxone's function but about its social and historical meaning. Of course, naloxone carries with it all the massive contradictions that mark the historical discourse around opioids. Like a painting of dramatic *chiaroscuro* whose shadows enhance the vividness of its highlights, naloxone is the shadow-drug by which we make out with greater clarity our attitudes toward opioids, in society at large and in the biomedical professions. The play of light and shadow each do their part in highlighting these vexing binaries.

Opioids: A Primer

For as long as opioids have been recognized, the search for an "ideal" opioid—one with potent analgesia but without respiratory or dependence-forming effects—has maintained its allure for chemists and physicians, right up through today's ongoing efforts at rational molecular design.[2] From the start, American public and medical feeling about opioids has been profoundly ambivalent. Although preparations of opium, most commonly dissolved in alcohol as laudanum, were present from the early colonial period, developing in the nineteenth-century new connotations of Romanticism and political freethinking (besides the drug's more pedestrian uses as an antitussive and general "tonic"), America's first "opioid epidemic" *avant la lettre* arose in the aftermath of the Civil War, when veterans with devastating traumatic injuries found themselves dependent on one of the few efficacious analgesics then available. Terrible as this was—a "cruel bondage," wrote Confederate lieutenant Albert Wymer Henley, to a "relentless and terrible taskmaster"[3]—wounded soldiers were more likely to die of their wounds than survive to face dependence or addiction, and thus this first epidemic was self-limiting.

By the late nineteenth century, opiate preparations were liberally dispensed for use as purported improvements to quality of life—for their euphoric properties, or as aids in the management of colicky infants or unruly children. Opiate consumption rose 538% between the 1840s and the 1890s;[4] a survey in the *Saturday Evening Post* in 1872 found that 5% of New Yorkers regularly filled opiate prescriptions.[5] (By contrast, researchers estimated that in 2005, approximately 3%–4% of the adult U.S. population was prescribed long-term opioid therapy.[6])

Despite, or rather because of, this popular ubiquity, disturbing to Progressivist reformers, Congress criminalized opium trade and possession in 1909 and tightened regulations on medical manufacture and distribution of opiates through the 1914 Harrison Narcotics Tax Act. As historian of science Nancy Campbell has written, in this age before antidotes, overdoses and other adverse events "occurred at or beyond the margins of respectability," stoking fears not only of death or addiction, but also of a general corruption of social order.[7]

The 1906 Pure Food and Drug Act, a visionary piece of legislation that banned product adulteration and various forms of false advertising, might also be the first time in which federal legislation explicitly participates in some of the vexing binaries that continue to plague dialogue around substance use today: unlike "pure" foods and drugs, substances that contain opiates are associated with things that are literally or metaphorically "dirty": rotten meat, seemingly attractive fruit touched up with poisonous dye. (This abhorrence of the shadowy and foul runs through the discourse on opioids and their antagonists, as we shall see.)

Around the same time, the Flexner Report, Abraham Flexner's 1910 survey of American medical training and institutions, offered at times a frightening glimpse of vast and wild differences in knowledge base among the trainees and medical centers of the United States, with some unfortunately being mere dens of quackery. A sense of moral sternness and a need to return to probity colored the dealings of the American Medical Association toward its physician members, which in turn colored the way that physicians conceived of patients with "unclean" or iniquitous habits. The *chiaroscuro* nature of opioids was already a matter of public discussion: as enhancer of life and reliever of pain, but also as something dark, dirty, and disreputable.

Moreover, the Flexner Report's emphasis on curricular standardization and modernization also made pharmacology a new and vaunted biomedical discipline at the forefront of physician education.[8] Whereas students had been exposed to traditional *materia medica,* lists of remedies and how to prepare them, this was supplanted by a new emphasis on chemistry, eager to put medicine on the same footing as the "pure" sciences. Centering pharmacology piqued the interest of physicians eager to incorporate drug development into their careers, and indeed to see it as part of medicine's core pursuits.

In this milieu, the public pressure and the promise of acclaim helped ripen the moment for the first opioid antagonist to be discovered by the German chemist J. Pohl in 1915. His discovery even predates the now-familiar, near-ubiquitous scientific consensus of addiction as a disease. Despite the fact that Enlightenment physicians had proposed a disease model of addiction centuries earlier, this model was not taken up by the American Medical Association until the 1950s, and then only for alcohol.[9]

Naloxone and its earlier cousins have thus been with us for as long as addiction has been understood as a chronic disease. Examining these antagonists, we come to know our relationship with opioids better—and thereby see more clearly our own attitudes toward pain and palliation, addiction and recovery, medical authority, and grassroots activism. Of course, there is no single cultural or medical perception of these antagonists in any point in their history; rather, their competing shades of light and dark are precisely what galvanized medical innovation and public fascination throughout the twentieth century.

The *Forme Fruste*: Opioid Antagonists 1915–1960

Nalodeine

J. Pohl's name on an obscure 1915 biochemistry paper was excavated from obscurity generations later by physician Louis Lasagna in 1954 for initiating the "dramatic" and "exciting" pharmacological creativity that led to the development of opioid antagonists and mixed agonists.[10] Pohl's article, "Uber das N-allylnorcodeine, einem Antagonisten des Morphins," recounts his synthesis of what would come to be called N-allylnorcodeine (Nalodeine). As a mixed agonist/antagonist, Nalodeine could reverse the respiratory depressive effects of morphine in rabbits and dogs but did not appear to interfere with analgesia, confusing Pohl.[11] This new mystery drug appeared to be neither an opiate nor an antidote—curious, but perhaps not useful.

Lasagna, who trained under the famed Henry K. Beecher (of whom we shall see more later), was a physician best known for rewriting the Hippocratic Oath for contemporary trainees, and for shaping modern FDA policy in the regulation of drug trials. He was a model of probity, not one to rush the sober process of research. Nevertheless, one can almost hear his impatience when he writes that "For over 25 years this exciting fact"—a compound with some antagonist properties—"lay buried in the literature."[12] The tantalizing promise of an opioid antagonist would wait another generation to reach a large public. Although Nalodeine never came to market, its existence gave concrete hope to the 1920 Committee on Drug Addiction formed by the Bureau of Social Hygiene.[13] This group now had good reason to believe it technically possible for biochemists to create new, nonaddictive analgesics, and new antagonists to existing opiates.

This was a period, like our own, with multiple narratives of addiction in circulation. The final book-length report of the Committee on Drug Addiction, published in 1928 as *The Opium Problem,* contains forward-thinking language about the epidemiology of addiction: that "this condition is not restricted to any social, economic, mental, or other group: that there is no type which may be called the habitual user of opium, but that all types are actually or potentially users."[14] Moreover, it championed open-mindedness and pragmatism, hoping to:

> reduce the evils of opium use to the minimum consistent with its proper therapeutic employment. Until such time, we should look with disfavor upon dogmatic statements and arbitrary and unscientific rulings to either groups or individuals.

At the same time, a competing model of addiction, emphasizing its relation to other negative character traits, was also in currency, as when a speaker at the 1931 National Conference of Social work called addiction a "maladjustment or inadequacy" in the individual, like "unemployment, desertion, alcoholism…, and any of the host of other problems present in case work practice."[15] As Caroline Jean Acker has shown, the psychiatrist Lawrence Kolb of the U.S. Public Health Service had done much to circulate this novel idea of the "addictive personality" in the 1920s and the 1930s.[16] The "morphinist" was a "psychoneurotic individual whose preexisting defects of personality structure predisposed him or her to intractable addiction"—an idea with ready uptake in a middle-class invested in the idea that civic order would prevail if only individuals with disorderly "traits" could be kept apart from the catalyzing drug.[17] These warring disease models paralleled a similar bifurcation emerging in early psychiatry, with

psychodynamic and somatic approaches differing even so far as the ontology of mental illness itself. The heterogeneity of theories as to who might succumb to addiction reflected the heterogeneity of opinion as to what addiction was—disease or social ill?—and the protean effects of opioids themselves.

Narcosan

The early twentieth century was a time of frequently odd bedfellows, unimpeachable medical luminaries, and shadier quacks, making common cause in pursuing research on opioids and addiction. When a compound called *Narcosan* (not actually an opioid agonist or antagonist, but a bizarre solution of "lipoids, nonspecific proteins, and water-solution vitamins" made from soy, millet, and other seeds) was said to prevent withdrawal and stop cravings and dependence, physicians at Bellevue Hospital and New York's Department of Correction were eager to collaborate in experimenting with the concoction on 366 prisoners on Welfare Island (now Roosevelt Island) in 1926.[18]

The mixing of eminence and notoriety among the experiment's principle investigators is striking: inventor A.S. Horovitz, a self-styled but unaccredited "doctor"; Alexander Lambert, professor of medicine at Cornell University Medical College, former personal physician to President Theodore Roosevelt, and former president of the American Medical Association; and Frederick Tilney, Professor of Neurology at Columbia University's College of Physicians and Surgeons, and director of the Neurological Institute of New York. Lambert and Tilney were about as eminent as physicians could be. Moreover, in the Flexner era, medical professional societies were wary of allopathic physicians rubbing elbows with possible charlatans. In a time of heightened anxiety to demonstrate the legitimacy of mainstream allopathic medicine, their collaboration with Horovitz on Narcosan is hard to understand—unless, that is, one takes into account the extraordinary seduction of this search for opioid antagonism, which would lead many more researchers into murky territory.

The editors of the *Journal of the American Medical Association* were appalled to see Lambert and Tilney in such company, and wrote an editorial in *Science*, noting that "Horovitz has been continuously identified with attempts to promulgate cures for all sorts of disorders… the Horovitz-Beebe "cure" for cancer, the Merrell Proteogens for the cure of practically everything."[19] *JAMA*'s editors wanted to make clear that the Narcosan findings would not be published in their pages, "because the clinical investigations are not set forth in such a manner as to indicate even ordinary controls, such as might have been secured by treating an equal number of patients with the nonspecific proteins alone."[20]

The Narcosan project pressed on, and the lay public loved it. Preliminary results leaked to the press were said to be a roaring success, a "blessing" to "rescue mankind from the tyranny of poppy and mandragora and all the 'drowsy syrups of the world.'"[21] Letters flooded the prison from individuals demanding access to the experimental drug. In 1929, the research group finally reported their negative findings to *JAMA* (which finally deigned to publish them), noting in fact that withdrawal symptoms, and relapse, seemed to be worse in those exposed to Narcosan.[22] The public outcry was enormous. Similarly unsuccessful studies with belladonna, scopolamine, "autohemotherapy," and other treatments dampened a generation's belief that a pharmacologic solution could be found to the problems of addiction or overdose. From a period of bright optimism in the 1920s, the pendulum swung again in the 1930s toward a dark despair of finding a counterweight to the powerful effects of opiates.

Nalorphine

In the 1940s, interest slowly began to revive in Pohl's earlier experiments with adding allyl groups to opioid molecules. Investigators from Jefferson Medical College and the University of California, San Francisco, published their findings in synthesizing another allyl-modified opioid: nalorphine (Nalodeine), which reversed respiratory depression in animal subjects on morphine.[23] The race was on.

In 1953, Murray Strober, internist at Kings County Hospital in Brooklyn, published a case report stating that he had successfully revived a "mulatto" waitress who had been brought to the hospital after a heroin overdose, by giving nalorphine—the first known instance of treating heroin overdose this way.[24]

Strober was clearly curious about the possibilities of this relatively recent new substance, nalorphine, but also felt an ambivalence and even guilt—prescient for his time—about having gambled with the welfare of another person with this little-studied new drug. Terms like "research subjects" and "informed consent" had yet to be codified in this era, but Strober appears to be of mixed conscience. For all the case report's triumph, it does at moments read as somewhat defensive, referring multiple times to the woman's race, that she had recently left her husband, and that she was sexually active, as though some or all of these would abrogate her ability to accept or decline treatment, or would give her doctor even more reason to make unilateral decisions on her behalf and pursue investigative work under the aegis of beneficent treatment. Although nalorphine came and went, the mood and implications of Strober's case report—pensive, wrestling with the classic model of paternalistic medicine but without a clear alternative yet in sight—mark a moment in which societal ambivalence around opiates, and the medical profession's ambivalence about the source of therapeutic norms and authority, coincide and forecast the explosive changes yet to come.

After Strober's n-of-one success, nalorphine was used more regularly to reverse overdoses. Another study at the University of Pennsylvania administered nalorphine intravenously just before delivery to women who had received opiates in labor, and was found to improve newborns' respiratory status.[25] At the same time, nalorphine's pharmacologic properties were further clarified by the finding that it would also precipitate withdrawal in regular opioid users. Nalorphine, like Nalodeine before it, is now known to be a mixed agonist/antagonist, explaining these contradictory results.

Henry K. Beecher, pioneering anesthesiologist and medical ethicist at Harvard Medical School (whose legacy is both rich and nuanced)[26] and his then-fellow, the aforementioned Louis Lasagna, found that nalorphine's partially analgesic properties made it as potent at relieving postsurgical pain as morphine.[27] Unfortunately, its other antagonist properties meant that if a patient were already accustomed to receiving morphine, it could send that patient into acute withdrawal.

The dual effects of nalorphine could be clinically thorny, but the physician-scientist Gavril Pasternak, who wrote extensively about the history of pharmacology, thought that nalorphine's mixed properties was part of its virtue in the eyes of researchers at that time, who were drawn to the duality of a substance that could provide analgesia while remaining distinct from full agonists, which were beginning to be widely recognized as iatrogenic forces of addiction.[28]

In fact, a 1954 unsigned editorial in *JAMA* proposed that since nalorphine reliably precipitates withdrawal in people addicted to opioids, it could be used to detect addiction. The authors added hastily that this "should never be carried out without full explanation to the patient, and written consent should always be obtained," although it is hard to imagine many patients agreeing to such an unpleasant test, not least since "a positive diagnosis of addiction may have serious legal implications."[29] Notably, this era was marked by several areas in which clinical practice veered troublingly toward law enforcement, from psychosurgery to sterilization.[30,31,32,33]

The article goes on to describe the detection protocol then in use at the U.S. Public Health Service Hospital in Lexington, Kentucky. Notably, this was not an idle side-project at a peripheral medical backwater, but part of the central concerns of what Campbell has called "the heyday of the world's premier addiction research unit."[34] The patient is given 3 mg of subcutaneous nalorphine. The examiners watch for "profuse perspiration, pupillary dilatation, hyperpnea, 'gooseflesh,' nausea, vomiting, and defecation." If none occur, the examiners give additional doses until either a positive result is obtained (i.e., evidence of withdrawal) or three rounds of medication have been given. Patients might expect to experience mood alterations, delirium, and hallucinations. This array of untoward effects, along with the potential for coercive and punitive practice, consigned nalorphine first to the margins of pharmacotherapy and later to obsolescence.

What is interesting about both Strober's nalorphine case report and the Lexington protocol is that both articles imply a growing anxiety, almost an incipient guilt, about their lack of robustly informed consent—a decade before such concepts were codified and disseminated. That the U.S. Public Health Service was gathering consent of any kind for their nalorphine "challenge" was somewhat forward thinking, given the article's publication a dozen years before Beecher's scandalizing 1966 report on the

devastating ubiquity of research on uninformed and unconsenting subjects throughout American biomedicine.[35]

In some ways, the ambivalence intrinsic to nalorphine seems to have brought out the curiosity, even prescience, in such researchers around still-inchoate conceptions of consent and the rights of people who would eventually be identified as research subjects. Indeed, Campbell has shown that researchers in Lexington were attempting nascent versions of contemporary research ethics and protocols, such as a "clearly demarcated division between clinical and research units," and monitoring for effects not just in the immediate setting of drug administration, but also more holistically as they continued to follow those subjects living on the research ward.[36] Moreover, nalorphine's intrinsically ambiguous properties seemed to correspond to the oddly dual nature of the work of these physician-scientists, who found themselves in shadowy hinterlands between research and therapy.

Other historians of science and chemistry have framed the work in Lexington, Kentucky, and similar research sites differently, less as a liminal space between past orthodoxies and future therapeutic and ethical progress, and more squarely rooted in the moral and therapeutic paradigms of the past. As Campbell has written, "the logic of unmasking the underlying conditions was akin to the clinical logic of nineteenth-century heroic medicine, with its high dosages and purgatives" bordering on the primitive and barbaric.[37] Moreover, James Swartz has pointed out that the Lexington facility was comanaged by the U.S. Public Health Service and the Federal Bureau of Prisons,[38] blurring the status of voluntary patients and incarcerated inmates, with all the power dynamics that this distinction implies. This conflation inevitably led to both categories being thought of as potentially dangerous and criminal elements within society, both in need of authoritative and repressive management. Those receiving addiction treatment, acting as research subjects, or both, collectively experienced rates of relapse and overdose ranging from 70% to 90%,[39] further compounding regressive ideologies that cast these patient-subjects as incorrigible or degenerate. They experienced the era's simultaneously fervid expectation of scientific progress and dismal assessments of their own status as therapeutic subjects and members of society.

Out of the Shadows: 1960–1971

Naloxone

Naloxone was first described in 1960 by chemist Harold Blumberg of Endo Laboratories in Long Island, NY.[40] A 30-year-old biochemist named Jack Fishman, who worked two jobs to make ends meet, one at the Sloan-Kettering Institute for Cancer Research and one at a private pharmaceutical lab called Endo, heard about Blumberg's hypothesis at the lab from their mutual colleague Mozes Lewenstein. Fishman devised a way to synthesize the naloxone Blumberg had described, and together the three men investigated the drug's properties in animals. Results were exciting: the first true opioid antagonist of any notable potency, and without the inelegance of any mixed agonist properties.

A full antagonist with no agonist properties, naloxone, was found in animal studies by investigators at the University of Illinois to be 10 times as potent as nalorphine, and twice as potent as another recently developed but weak antagonist (levallorphan) at counteracting respiratory depression in animals. The Chicago group then tested naloxone on young, healthy volunteers, who received IV doses of opioids while sequential measurements of respiratory status were made.[41] They were then given naloxone, which successfully reversed the opioids' depressive effects.

However, the investigators had a prescient intuition about some of naloxone's drawbacks, noticing that naloxone appeared to peak sooner than the opioids had worn off, potentially giving patients and physicians the false security of an antidote. The relatively short half-life of naloxone compared to the sometimes long half-life of various opioids would continue to be a source of concern right up to the present day, and in fact remains one argument often mustered as to why the lay public, with no knowledge of pharmacokinetics, cannot be trusted with naloxone. Although naloxone was a "pure" antagonist with clearly demonstrable properties within the cocoon of carefully controlled clinical

trials, it would be only imperfectly able to reverse the mélange of opioids and intoxicants encountered in real life.

Some of this research, while providing the safety and efficacy data necessary to propel naloxone toward FDA approval, also raised more questions. For example, one study in 1971 gave volunteers with ongoing opioid use disorders varying doses of naloxone, in conjunction with varying doses of heroin, over a period of weeks.[42] Most combinations did block some or all of the agonist effects of the heroin, although temporarily. The researchers knew from other studies that they had an antidote on their hands. But their study design indicates that what they still wanted—to no avail—was a drug that would both prevent the full agonist effects of the heroin but also, ideally "to 'immunize' subjects against the effects of opiates,"[43] which would also require preventing or allaying the withdrawal and cravings that provide such a potent foundation for addiction. This chimeric set of aspirations for naloxone was closer, in fact, to the actual properties of methadone, the long-acting opioid released commercially in the United States in 1947, and first studied as a treatment for addiction by Mary Jeanne Kreek and colleagues at Rockefeller University in 1966.[44]

Naloxone was approved by the FDA in 1971 for intravenous or intramuscular use by trained healthcare professionals. Fixed-dose "kits" explicitly intended for laypeople would only be approved in 2014. In addition, intranasal naloxone, the format most familiar today, would not be approved until 2015. Ease of use and dissemination were definitively de-emphasized: for naloxone to be a beacon of "respectable" medicine, it would largely be used inside hospitals. Its ability to reverse overdoses brought out an ambivalence in the social and political attitudes toward opioids that were difficult to face head-on.

Weaponry in the "War on Drugs": 1971–1996

On June 17, 1971, Richard Nixon spoke on television to the American people. "America's public enemy number one in the United States is drug abuse," he said, requiring the government "to wage a new, all-out offensive," not just at home but "worldwide."[45] He installed psychiatrist Jerome Jaffe as first drug czar in the War on Drugs. The approval of naloxone that same year sparked a range of ambitions about ways that it could be put to use in this domestic war. True, some grassroots and community-centered lobbies argued to liberalize the availability of naloxone in the public arena. But in the spirit of war, other researchers and policymakers were more interested in weaponizing naloxone, using it as a harsh deterrent.

Unsurprisingly, the language and imagery around opioids' molecular antagonists was frequently martial, evoking a problem geopolitical in scope. Like the "War on Cancer," likewise declared by Nixon in 1971, or Johnson's 1964 declaration of "War on Poverty," part of the goal was to create an aggressively ambitious public–private complex of researchers, with an emphasis on all-out offensives. Representatives of the pharmaceutical industry told Congress in 1971 that they would welcome collaboration with the Defense Department in developing new opioid antagonists, given that the Pentagon was known to be developing both weapons of chemical warfare and their antidotes. In an article called "Chemical Warfare Drugs Called Possible Aid to Heroin Addicts," the *New York Times* reported that Jaffe and a Congressional study group was requesting that Pentagon research be expeditiously declassified, so that public–private partnerships in the War on Drugs—including much more potent versions of naloxone—could flourish.[46]

In a similarly hybrid effort, the City of New York and the Ford Foundation pooled resources to look into using opioid antagonists as deterrents, in the hope that patients exposed repeatedly would "decondition" themselves from opioid use.[47] Fishman was one of the grant recipients for this purpose. As the authors of one animal-behavior study of naloxone noted, naloxone could be a powerful "punishing stimulus,"[48] similar to the effects of disulfiram, or Antabuse, approved in 1951 as a deterrent to alcohol consumption.

At the same time, some thought that naloxone ought to be weaponized in another way—as a coercive kind of biomarker, not unlike the problematic U.S. Public Health Service experiments conducted in

Lexington 20 years earlier. In *JAMA*, Paul Blachly, psychiatrist at the University of Oregon, argued that naloxone should be used to "distinguish a person who is physically dependent from one who is an occasional user," to prevent individuals without "true" addictions from enrolling in methadone clinics.[49] A clinic could administer a dose of naloxone to each new patient as a provocation trial, Blachly argued. If the patient experienced withdrawal, he or she truly was a chronic opioid user and warranted methadone; if not, his or her request should be declined. (Problematic dimensions aside, this test is not even quite functional on its face: someone could have an addiction but not have a critical concentration of opioid in his/her bloodstream at the moment of testing; one could also *not* have an addiction and yet have recently used, and thus withdraw.)

Blachly argued that the notion of a respectful therapeutic alliance was moot in the case of "addicts": "if the physician simply accepts the patient's word," he may be deceived by someone who either merely "thinks he is addicted" or has "ulterior reasons." The idea of such a provocation trial seems from a contemporary perspective wrongheaded in two ways: one, in the harm it might cause; two, in that it gives only a simplistic, dichotomous answer—in this case, the presence or absence of withdrawal, which may have nothing to do with a patient's addiction, motivation, values, or intentions.

In addition to its potentially vengeful or punitive connotations and its foreignization or "othering" of drug users, at least two additional aspects of the "War on Drugs" formulation were problematic. First, combatants on "our" side of the war—that is, research subjects in the "War on Drugs"—often had their rights and bodily integrity abrogated in the process. Second, the War on Drugs began experiencing what war journalists refer to as "mission creep": the expansion of an intervention beyond its initial scope or intention—in this case, becoming an all-out culture war. As Scott Vrecko has argued, "addiction neuropolitics" emerged in precisely this milieu, as addiction neuroscience went from "a marginal, almost nonexistent field, to a well-funded, state-sponsored specialty" accelerating the "molecular revolution" in psychiatry.[50]

From the early 1950s, the Armed Forces Medical Council began making plans for use of military and civilian employees in experimental research.[51] Such individuals, as a consequence of the surrounding military culture and its emphasis on duties and obligations, were at risk of being unaware of pertinent protections owed them, including protection from retribution for nonparticipation. Moreover, no assurance of compensation or treatment was provided against injuries incurred beyond simple acute emergency care.[52] Military employees, therefore, could be subject to experiments relating to opioids, addiction, overdose, and their antidotes, without guarantee of the ability to decline or withdraw their participation, and without guarantee of adequate care if things went awry. As one of us has noted elsewhere, this new and troubling avenue of research further solidified the "rise of big science and the 'garrison state.'"[53]

We see in the Blachly protocol at Lexington, for "unmasking" addiction via the use of naloxone, a characteristic conflation of its time: addiction was an undesirable and difficult condition to have; by the same token, people with addictions were also undesirable and difficult to encounter and treat. If the drugs themselves were "enemy number one," the patients who used them were often treated like hostile civilians: not exactly the opponents, but not exactly allies either. Soon, the emerging field of palliative care would urge the more liberal use of opioids in clinical practice—an opposite but equally stark viewpoint, which would face its own crisis of ambivalence in the 1980s and the 1990s.

The Height of Chiaroscuro: Palliative Care and Naloxone, 1980s–1990s

The term "palliative care"—the subspecialty dedicated to relief of suffering and improvement of quality of life for patients with life-limiting illnesses—was coined in the 1970s and recognized by the World Health Organization as a distinct field of practice in 1990.[54,55] With this movement came greater clinician expertise in the use of opioids to manage a variety of symptoms. By the end of the 1990s, a stark contrast had developed between two clinical conceptions of opioids: as one of us wrote in 1999, the palliative-care worldview held that "opioids are the gift of the god Morpheus," bringing "relief to those in

great distress and solace to their loved ones," whereas the addiction-medicine worldview held that true care for patients meant avoiding drugs that bore such high risk of addiction and mortality.[56] There was a keen irony in these contrasting views: namely, that both sides centered clinicians' fiduciary obligations to patients—but this sense of faithful obligation could lead to diametrically opposed therapeutic decisions."[57]

Yet even within the field of palliative care, many practitioners had profound concerns about the field's optimism and liberality with opioids. A case history from M.D. Anderson Cancer Center in 1996 was emblematic: a 67-year-old man with multiple myeloma taking chronic opioids was found to be drowsy (likely due to disease progression), but otherwise quite stable.[58] Nevertheless, he was promptly transferred to the hospital and given intravenous naloxone, whereupon he became confused, agitated, and in pain, and vomited repeatedly. He required several days' admission for these sequelae of naloxone to be corrected and for his pain to again be appropriately managed. The case report authors were scandalized by what their hospital had done: give a maleficent and clinically inappropriate drug to an already vulnerable and dying man.

In another case, a patient with "70% burns" was noted by his naively optimistic physicians to have "improved mental status" after receiving naloxone.[59] In a scathing letter to the *Lancet* following the case report's publication, one anesthesiologist retorted that this "hyperarousal" was hardly a good thing. "If endorphin release during extreme stress has evolved to provide analgesia and detachment, are doctors to dictate that such effects are to be denied in a last ditch attempt to maintain vital function…?"[60] In cases like these, clinicians' outsized fear of opioids had triggered outsized zeal for naloxone, with the distressed patient caught in the middle. It is as though the sheer idea of opioids, and opioid antagonism, loomed so large in the clinical imagination that the empiric facts at the bedside were in danger of disappearing entirely.

To the extent that such struggles did take the individual patient into account, often this was overwhelmingly through the lens of fear. A 1988 article in the *Canadian Medical Association Journal* named what many clinicians were feeling: "frightened that we are going to turn the patient into an addict."[61] Naloxone was seen as the one potent antidote that could keep physicians from becoming complicit in transforming the patient into that dreaded category. Although medical consensus around a disease model of addiction was fairly well secured by the 1980s, this existential dread on the part of some physicians clearly was not wholly explicable by the rational disease model alone. Rather, the fierceness with which some physicians, fearful of iatrogenic addiction and overdose, clung to naloxone, tells us much about how naloxone exemplified by our greatest hopes and our worst fears about the role that opioids would play in clinical care.

At the same time, naloxone's place in medical and neurological intensive care units in the United States remained debated but central. In cases of shock, one prevailing theory of the 1980s held that a patient's endogenous endorphins played a key role in patients' autonomic regulation, whether or not pain (or opioids, or overdose) was implicated in the actual etiology of their shock. According to this theory, treating septic, cardiogenic, or neurogenic shock patients with naloxone was thought to bolster blood pressure along with other conventional therapies such as fluids and antibiotics. This theory, supported by case reports and small case series, was never replicable in larger, evidence-based studies. However, it was unfortunately durable as a treatment practice throughout the 1980s,[62,63] likely leading to both misplaced hopes and a failure or absence of analgesia in patients who did indeed have pain, in addition to shock.

Across the Atlantic, other experimental therapeutics with naloxone, even more far-fetched compared to contemporary practice, were being performed. In Germany in the 1980s and the 1990s, some physicians favored a regimen whereby patients were placed under general anesthesia and then given very high doses of intravenous naloxone to produce a "rapid detoxification" that was thought to lead to fewer relapses than traditional methods, although very high risk given the strong sympathetic response experienced by patients abruptly subject to such rapid opioid antagonism.[64] This turned the relationship between naloxone and the intensive care unit on its head, from the former being in service to the latter's ambitions as a therapeutic site, to the latter being the space in which the former could be used in ever

more experimental ways. Both the American ICU use of naloxone in shock, and the German use of ICUs in order to administer very high-dose naloxone, point to the wild and sometimes self-contradictory hopes about the ways that naloxone could be incorporated into the modern hospital outside of addiction medicine.

Solidarity and the Public Square, 1996–Present

As is well known, opioid prescriptions within the United States began to rise sharply in the late 1990s,[65] fueled in part by aggressive pharmaceutical marketing aimed at physicians, which in turn gradually altered professional norms and ways of practicing (such as the infamous "fifth vital sign" of pain).[66] What is less often described is how quickly naloxone rose to further prominence alongside this latest "epidemic," and in particular, how despite its obviously pharmaceutical nature, it became held up as an example of a social strategy and a community philosophy, rather than a biomedical product. As Rachel Faulkner-Gurstein has argued, in this period, naloxone developed a "social logic," gaining potency as a tool by creating and strengthening complex interdependencies and networks of care among users and other community members.[67]

"Take-home naloxone," available by outpatient prescription and administered by nonprofessionals, was first approved by the FDA in 1996, although grassroots activists had found ways to obtain and deploy naloxone years earlier as a harm-reduction strategy.[68]

Since that time, new formulations and dissemination strategies have brought naloxone more and more into the public square. Post-FDA approval, its first successes as a layperson tool in American cities occurred in 1999 in Chicago, 2001 in New Mexico, and 2003 in Baltimore.[69,70] In reality, since the 1980s, it had been relatively obtainable to nonhealthcare workers in parts of Italy, Germany, and the United Kingdom[71,72,73]—experiences that likely hastened and amplified the call for similar provisions in the United States.[74]

Today, it is one of the most avidly discussed topics in public health, drawing the attention and innovation of physicians and policymakers alike. One of naloxone's most perplexing properties is that which was noted so presciently in 1963: powerfully effective for a short period of time (with a half-life of about an hour), it thereafter wanes, whereas many opioids last longer than an hour, and can therefore reintoxicate and even kill. For many, this is all the more reason to expand dissemination since multiple, sequential doses could be needed. For others, this complexity speaks to a need for re-centering clinical expertise rather than letting naloxone, and addiction medicine itself, drift too far into the layperson arena.

Since the advent of take-home naloxone, the movements toward popular dissemination of naloxone have made strides in many regions of the United States and abroad. In addition, the public face of naloxone has made way for access to related skills and services pertaining to addiction and overdose. Multiple studies and public health initiatives were careful to pair naloxone distribution with trainings such as rescue breathing.[75] Campbell has dubbed naloxone "a technology of solidarity," pointing to the emergence of clothing and accessories that speak proudly about naloxone's role—and by extension, the wearer's role—in curbing this most "unnatural disaster" of the opioid epidemic.[76] "Keep calm and carry naloxone" shirts, "HERO" bracelets, and silver ribbons modeled on those used for HIV and cancer awareness—all these testify to the lifting of naloxone's taboo. This democratization of therapeutic responsibility mirrored other public transformations, such as the "citizen scientist" movement, a phrase coined and described in the 1990s by sociologist Alan Irwin.[77]

Among all the cheering, a few aspects of naloxone's contemporary life in the world remain problematic. For one, despite the legality and theoretical availability of naloxone, true access remains a problem for many. For example, despite the major public health effort in Baltimore to improve take-home naloxone access, a third of people who use opioids reported no access, whereas some who did report having naloxone nonetheless reported fear of adverse events such as aggression on the part of the naloxone recipient, threats by police, or simply misusing the drug.[78]

A Consequential Drug

Until the tide begins to turn, naloxone remains one of the superdrugs of our time, a WHO "essential medicine." Its global importance tells us volumes about the literal and figurative antagonism to opioids that remains a dominant current in American medical consensus.[79] But as we have seen, naloxone and its precursors have had so many more mixed and contradictory valences since their inception a century ago. In the quarter-century span from naloxone's public, "street" use and today, the United States has gone from a love affair with opioids to a bitter divorce. The early promise of the palliative care movement—that disease, death, and dying could all occur without pain—rapidly spiraled into extrapolations beyond these early visionaries' intentions or control, to a world of overprescription and addiction. In response to this reality, the use of opioids is now stigmatized, when it had been so abundantly extolled just a generation earlier. We live now in what might be called naloxone's postmodern era, with access to all the mixed signals and ambiguities that colored its twentieth-century history and still shade our understanding today.

The palliative care movement of the 1970s onward, along with the death-and-dying movement of the late twentieth century, offers a compelling prequel to today's concerns about the proper limitations to be placed around opioids and their antagonists. Paved by good intentions, the inroads of this movement, by emphasizing the need to illuminate taboo topics such as death and physical suffering, momentarily cast into shadow the reality of opioids as socially destructive substances. Even now, early advocates of these palliative movements seek to better understand, add nuance, and make amends for that era's complicity in the dark story of rapid opioid oversupply from the 1990s to today. As old polarities between the cordoned worlds of "science" and "society" break down, and we are better able to see how the two have always informed and infiltrated one another, the dichotomous thinking about opioids (or naloxone itself) as "good" or "bad," "safe" or "dangerous," and "drug" or "antidote" seems too reductive to fit our multidimensional reality.

The bitter contradictions of opioids' more recent history—one of good intentions and pharmaceutical malfeasance—are well known and often told. But the earlier chapters of this story—that of scientists and physicians fumbling in the dark, grasping for opioid antagonists and antidotes, and learning hastily and by improvisation—are much less known or discussed. If we, as a society, are ever to arrive at a full and clear understanding of these ambiguities, then we must also bring these more obscure episodes in medical history out of the shadows. By reflecting on the ways in which naloxone, and opioid antagonism more generally, was both conceived and misconceived, we can become more observant analysts of contemporary discourse around naloxone and opioids, alert to its nuances and contradictions.

As medical and public fears have shifted over time, so has naloxone seemed to change before our eyes. But perhaps a wiser and more salubrious appraisal of naloxone would dispense with dichotomies and recognize that naloxone is neither bane nor panacea, but something consequential, although subtler than a simple dichotomy. As a drug which is briefly but powerfully active, it brings to the fore how risk itself has temporal dimensions: that which confers protection in the short term might not be able to prevent long-term danger. This property of naloxone stands as a metaphorical representation of all opioids, which are appealing for the succor they bring but create liabilities over the longer term. Our contemporary vision of opioids is, by now, irreversibly refracted by our values, beliefs, and politics. Contemplation of naloxone might, at least, give us the chance to see the story of opioids more clearly.

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