



Methadone Treatment Marks 40 Years

Bridget M. Kuehn

FORTY YEARS AND COUNTLESS political firestorms after it was first introduced, methadone maintenance for the treatment of opioid addiction remains a standard therapy in the field of addiction treatment.

The publication on August 23, 1965, of positive results from a small clinical trial of methadone as a treatment for heroin addiction in *JAMA* marked a sea change in the treatment of addiction (Dole and Nyswander. *JAMA*. 1965; 193:646-650). The study, conducted at Rockefeller University in New York City by Vincent P. Dole, MD, and the late Marie E. Nyswander, MD, suggested that a medication could be used to control the cravings and withdrawal that often lead to relapse in individuals with opioid addiction who attempt to quit.

The work, along with subsequent research by Dole, an endocrinologist, Nyswander, a psychiatrist, and colleagues established the concept of opioid addiction as a chronic disease, similar to diabetes, that as such required long-term treatment. The researchers also emphasized the need for psychotherapy in combination with methadone treatment.

The research has had a tremendous impact on the treatment of individuals addicted to opioids and on the larger field of addiction treatment, said Thomas Kosten, MD, professor of psychiatry at Yale University, New Haven, Conn, in an interview. "It may be equivalent to the kind of impact penicillin had on infectious diseases," Kosten said.

Mary Jeanne Kreek, MD, who was a resident in internal medicine working in the Dole laboratory in 1965 and is

now head of the Laboratory of the Biology of Addictive Diseases at Rockefeller University, explained that work conducted by the group in 1964 and published in 1966 established that methadone blocked the effects of heroin and stabilized patients, who prior to treatment oscillated between feeling

done treatment, the approach has always struggled for acceptance against the forces of public opinion and politics. "There is a stigma against addictions, addicts, and—sadly—treatment providers," said Kreek, an outspoken supporter of the methadone therapy.

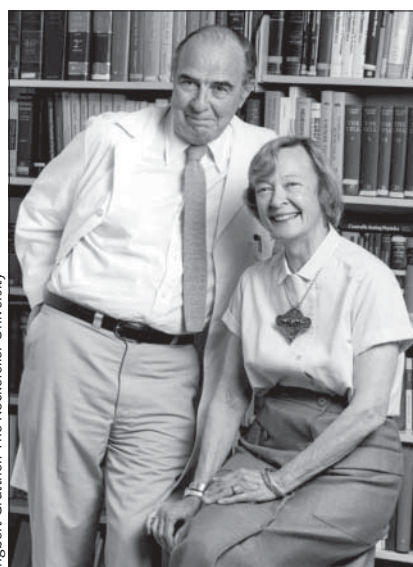
"THE FARM"

Methadone maintenance therapy represented a reversal of the traditional US approach to treating drug addiction, said David F. Musto, MD, history lecturer at Yale and expert on US drug policy. A 1919 Supreme Court decision had established that addiction alone did not justify physicians treating addicts with opioids. Before that decision, some physicians had used short-acting opioids to treat individuals with opioid addiction.

The Drug Enforcement Administration, in fact, considered Dole's research illegal and had threatened to prosecute him prior to the 1965 publication. "To defy the US government was an act of political courage," said Jerome Jaffe, MD, who became the first national drug czar under President Nixon in 1971.

When the paper came out, Dole and Nyswander, his wife, faced skepticism from physicians who believed methadone maintenance wasn't a treatment at all but merely substituted one addiction for another. Dole forcefully defended the treatment from such criticism at a meeting of the Association of American Physicians in 1966.

"In providing medication, we are guided by the same considerations that you and the rest of us have when we use substitute therapy for an endocrine disorder; we don't shrink from the fact that it may in some conditions be necessary to give medicine chronically," he said.



Forty years ago, a landmark study by Vincent P. Dole, MD, and the late Marie E. Nyswander, MD, published in *JAMA*, changed the landscape of treatment for opioid addiction.

high and being ill and seeking heroin (Dole, Nyswander, and Kreek. *Arch Intern Med*. 1966;118:304-309). Once stabilized on methadone, a long-acting opioid agonist, individuals whose lives had been consumed by perpetually seeking a heroin-induced high were able to resume normal productive lives.

"Little by little, their thoughts [over 1-3 months] changed," she said.

Despite ongoing advances in the understanding of addiction and strong evidence of the effectiveness of metha-



Others criticized the lack of controls in the study. However, Dole pointed out that in Nyswander's more than 20 years of experience treating individuals with heroin addictions, she had made many efforts to treat her patients without medication, some of whom she later successfully treated with methadone. "She had very little doubt that the medication plays an essential role," Dole said.

The scientists also faced some resistance from within the addiction treatment community, which would compete with the methadone maintenance approach for funds and political support, Jaffe said. An array of treatments were in use at the time, including therapeutic communities and detoxification. Civil commitment, which was essentially prison camp, was a popular treatment. One such program, known as "the Farm," was operated by the US Public Health Service, in Lexington, Ky. Despite growing political and popular support for such programs, however, relapse rates were high after release.

The approach also met resistance by some minority communities, which were suspicious that the treatment was an attempt to damage or kill minorities, Musto said.

As expanded clinical trials showed more positive results and more physicians gained experience with the treatment, methadone maintenance gained some momentum. But while thousands of heroin addicts were being treated with methadone by 1970, the approach was still considered experimental and the federal government began establishing strict controls of methadone treatment programs, according to Jaffe.

In 1971, however, growing public concern over the numbers of Vietnam veterans returning to the United States addicted to heroin prompted the government to establish the Special Action Office of Drug Abuse Prevention and appoint Jaffe to lead the organization. Over the next 3 years, Jaffe established a nationwide network of methadone treatment clinics.

The emergence of AIDS in the 1980s gave new urgency to the need to treat individuals with opioid addictions, among whom the infection spread by sharing contaminated needles. Kreek's laboratory was the first to identify HIV among heroin users. Using blood samples dating back to 1969, collected to study hepatitis B, her group found that the virus had begun circulating among intravenous heroin users by 1978; by 1981, half of those seeking treatment for heroin addiction at Rockefeller University were HIV-positive, Kreek said. A July 13, 1984, report detailed the high prevalence of HIV among intravenous heroin users in New York and noted that rates were lower among those in long-term methadone treatment (*MMWR Morb Mortal Wkly Rep.* 1984;33:377-379).

Public support for methadone treatment had waned somewhat in the years before AIDS emerged, but because methadone treatment is seen as one of the more effective ways to curb the spread of HIV infection by reducing intravenous drug use, some support has returned, Musto said.

BRAIN DISORDER

Detoxification remains a common treatment for opioid addiction, despite high dropout rates and patient discomfort. (The results of a clinical trial of anesthesia-assisted detoxification and an accompanying editorial appear in this issue of *JAMA* [see pages 903 and 961].) However, since the publication of the 1965 methadone trial, the field of addiction treatment has advanced considerably. Scientists now have remarkably detailed knowledge of the biology of drug addiction, down to the chemical structure of opioid drugs and the brain receptors they bind to.

"We know the agent, we know the part in your brain that it hits, we know it in exquisite molecular detail, and it makes intelligent hypothesis-driven medicine very feasible," Kosten said.

While methadone continues to be an important treatment for opiate addiction, other therapies have emerged. Buprenorphine, a opioid partial agonist,

is available through a special program allowing office-based physicians to prescribe an abuse-resistant formulation of the medication. Naltrexone, an opioid antagonist that prevents relapse, has proven to be particularly useful for treating certain groups, including physicians, nurses, and pharmacists, said Charles O'Brien, MD, PhD, professor of psychiatry at the University of Pennsylvania in Philadelphia. Naltrexone has also been found to reduce relapse rates among parolees. A monthly injectable formulation of naltrexone is being considered for approval by the Food and Drug Administration and a decision is expected by September, O'Brien said.

Scientists have been able to elucidate the key role that the endogenous opioid receptor system plays in addiction and are beginning to understand how genetic and environmental factors contribute to addiction.

"We have very good evidence now that addiction is a chronic disease," O'Brien said. He explained that brain imaging studies have shown that the brain is altered by addiction and remains altered for some time after a person stops taking drugs.

Some individuals who develop opioid addictions require long-term treatment. Kosten said some of his patients have been on methadone for decades and live productive lives, but if they stop therapy, "their life becomes chaos."

For other individuals, brain changes caused by addiction or other factors may be reversible. Animal studies have demonstrated that addiction alters the brain at the molecular level. With time and treatment, those changes can be reversed. "You've changed the neurobiology, and it takes time to get that back to normal," Kosten said.

The discovery that opioid receptors are also involved in alcoholism led to a new treatment for that disorder. For some alcoholics, particularly those with a family history of alcoholism, naltrexone has proven to be an effective treatment (see *JAMA.* 2005;293:1617-1625). O'Brien explained, "There are certain people when they drink alcohol it's almost as though they took



heroin because it releases endorphins or endogenous opioids. That's why naltrexone helps them because naltrexone blocks those endorphins and prevents them from getting high on alcohol."

Genetic differences appear to play an important role in addictions; certain individuals may have genes that make them more vulnerable to devel-

oping addictions, while others may have genes that are protective, Kreek said. She said that an estimated 30% to 50% of the risk of developing an addiction is genetic and that several groups of scientists are searching for the responsible genes.

Understanding these genetic differences will likely revolutionize the way addiction is treated. "We'll be able to

treat the patients according to their own genotype," O'Brien said.

While the discoveries by Dole's laboratory clearly laid the groundwork for many subsequent scientific advances, some in the field say the work itself wasn't the only legacy.

"It wasn't just science," said Jaffe. "It was the courage and commitment of Vincent Dole." □