Remember not the events of the past, the things of long ago consider not; see, I am doing something new! Now it springs forth, do you not perceive it?  
Is. 43: 18-19

Since hope recently centered on the ability of methadone hydrochloride to control heroin abuse in America, this chapter defines methadone maintenance treatment. What is methadone maintenance and what are its exact pharmacologic and behavioral effects? Is it different from addiction to other narcotics?

METHADONE MAINTENANCE DEFINED

Methadone (adolphine, dolophine, adanon, amidone, physeptone, althose, miadon, butalgin, diadone, polimadone) is a synthetic substitute for heroin. The drug was originally synthesized by the German firm I. G. Farben in 1941 and appropriately named "Adolphine." Since morphine was unavailable in Germany during World War II for relieving pain in battlefield injuries, methadone was developed as a synthetic substitute on orders from Hitler.

Methadone maintenance is the dispensing, for over twenty-one days, of methadone to treat dependence on heroin or other narcotics. Methadone maintenance should not be confused with use of methadone in detoxification treatment of heroin addiction; the goals and methods of the two therapies differ radically. Using methadone in detoxification from heroin is a short-term procedure whose goal is abstinence. Although methadone maintenance embodies abstinence as its ultimate goal, some individuals have been on maintenance since the 1950s.

The rhetorical obfuscation with methadone maintenance was to classify continued narcotic addiction as "success" rather than "failure." Rehabilitation thenceforth would mean more than simple abstinence, the historical goal of addiction treatment. The crucial modification was now to view continued addiction to narcotics, always considered failure before, as an indicator of "success" in maintenance therapy. Through this unbelievable mumbo-jumbo methadone maintenance gained many adherents. A patient could be "normal" and still hooked.

In the early 1970s the United States government, under the aegis of the Nixon administration,
sponsored large-scale methadone maintenance for the treatment of heroin addiction. By 1971, some 9,000 addicts nationwide were receiving methadone. In 1972 there were 25,000 in such programs. At the end of 1973, as federal grants poured into local governments and nonprofit corporations licensed to dispense methadone under strict regulatory policies, there were 73,000 clients. In 1976 Dole and Nyswander indicated that about 85,000 of the nation's estimated 500,000 to 600,000 street heroin addicts were being maintained on methadone in more than 500 outpatient programs around the country. Methadone maintenance programs now exist in Canada, Mexico, Puerto Rico, Great Britain (where they have largely replaced the system of heroin maintenance), West Germany, Sweden, Thailand, Hong Kong—in fact, in most nations of the world.

In the United States methadone is a Class II controlled substance, unavailable for maintenance except in government-licensed and inspected clinics. Private physicians are forbidden to prescribe the drug for maintenance purposes, but it may be prescribed to relieve pain in terminal cancer patients. This attests to the drug's analgesic properties. When ingested by an addict, the drug has the same effects as heroin, though its duration of effect is much longer (twenty-four hours compared to six hours for heroin). By 1970 many clinicians agreed that methadone maintenance was "...the preferred treatment for long-established heroin addiction."\(^\text{3}\)

The crux of the problem with abstinence-type treatment is that, although many addicts have been "clean" many times, both on their own and while in custody, "craving" for heroin persists. This craving has been defined variously." Spoken of in terms of desire, "yen" or "yin," or conditioning, this compulsion almost invariably leads to continued heroin use, addiction and, to varying degrees, crime to support the habit. The most important pharmacologic effect of a sufficient methadone dose is to suppress this intense craving for heroin.\(^\text{5}\)

THE DOLE/NYSWANDER RESEARCH PROJECT

Beginning in the mid-1960s Vincent Dole and Marie Nyswander published increasingly glowing scientific reports on the effectiveness of methadone maintenance. The close relationship between Dole and Nyswander (who subsequently married) began in 1963 when Dole, a researcher and prominent Rockefeller Institute for Medical Research biochemist, had a number of conversations with Nyswander, a psychiatrist, who like him had concluded that heroin addiction caused some kind of "metabolic changes" in body chemistry that made abstinence impossible.
THE METABOLIC THEORY

Dole and Nyswander suggested a physiological conception of heroin addiction in place of the older concepts that addiction was symptomatic of an underlying psychological disorder or attributable to environmental factors like poverty. In their view addiction leads to a "metabolic deficiency" that contributes to the high relapse rate associated with traditional treatment. They presented their addiction theory as a kind of flow chart, tracing a possible sequence of involvement with, and addiction to, heroin. The Theory suggested that "curiosity" and "availability of the drug" led to "experimental drug use" which, in turn, led either to a "normal"—no addiction—state or through the intermediary condition of a "neurological susceptibility" to an "altered response to narcotics," and finally to "addiction." Any attempt to leave the condition of "addiction" through "detoxification" leads to "recurrent symptoms of abstinence" and subsequently back to addiction. What they mean is that addicts like dope.

Dole and Nyswander were aware of this well-known heroin cycle and teamed up for research. Five individuals were experimentally addicted to injected morphine to make "enzymatic tests." They found, however, that they could not continue the tests because their subjects were always "on the nod" from the morphine injections. so they decided to detoxify them using gradually decreasing dosages of methadone over a fifteen-day period. This technique of withdrawal treatment of heroin addiction had been developed by Nyswander and others at Lexington in the early 1950s. During the detoxification regimen they found that the subjects were no longer "nodding-out," that they were alert and that the enzymatic tests could be completed. While performing these tests Dole and Nyswander found they could "stabilize" their subjects on methadone for a prolonged period of time at a fixed dosage, which varied between 120 mg and 180 mg per day. Weight-for-weight this represents about three grains of morphine a day, or an "average" heroin habit.

THE DOLE-NYSWANDER CONCLUSIONS

This work, performed in 1963, seemed to confirm the following:

1. In sufficient doses methadone produces physiological cross-tolerance to other opiates. Methadone-tolerant addicts are not susceptible to the effects of equal amounts of parenterally injected heroin;

2. Methadone is orally effective for about twenty-four hours (and newer forms for seventy-two hours), compared with four to six hours for heroin. A clinic system for dispensing was therefore
3. The Physiology of Methadone Maintenance

Written by David Bellis
Thursday, 15 November 2012 00:00

a logistic possibility;

3. Methadone maintenance showed some potential for reducing criminal behavior among experimental addict-patients, leading to "social rehabilitation," usually defined as discontinued heroin use, decreased criminal activity and holding a job of some kind;

4. Methadone seemed to have a fairly low diversion potential due to its longer duration of effect (clients do not have to be given "take-home" doses) and the government-regulated clinic system for its distribution (addicts are tested at the clinic to make sure they are taking methadone and not using other drugs);

5. Methadone maintenance, compared to other drug-free treatment modalities, appeared to be a cost-effective form of therapy. Yearly cost per client in methadone maintenance is about $1,500, compared to $6,000 a year in residential treatment, $3,000 for a year in aftercare counseling, $1,500 for each inpatient detoxification attempt, and more than $20,000 a year to keep an addict in prison.

Nyswander describes "typical" behavior of their early addict-patients receiving from 110 mg to 180 mg of methadone a day:

Striking alterations in behavior and appearance were taking place in the . . . patients. We sent them off to school, outside the hospital grounds. . . . [None] copped heroin on the outside. . . . they turned from slugabeds into dynamos of activity. . . . We found that methadone blocked out all other narcotics. They couldn't feel the effect of another narcotic when they were on methadone. Accordingly, there was no craving for heroin. We found out that methadone could be given only once per day. . . . As for tolerance, there was no escalation problem. The dosage remained stable. . . . Methadone had no deleterious effects anywhere.'

FAVORABLE RESULTS SPUR PROGRAM EXPANSION

In 1964 the Dole/Nyswander program had only twenty-two addict-patients enrolled. By 1965, with a grant from New York City, they expanded their outpatient maintenance project at the Morris J. Bernstein Institute of the Beth Israel Medical Center. It included an inpatient "induction center" and an outpatient maintenance clinic. By spring 1967 there were three methadone clinics in New York: Bernstein, Harlem Hospital, and Van Etten Hospital in the Bronx. About 350 outpatients were enrolled in them, with long waiting lists developing.

Initial reports8 suggested that these early programs retained well over 90 percent of all addicts admitted to them, a dramatic reversal from the results of drug-free treatment modalities.
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Noting these impressive short-term results for the high-dose experimental program, in late 1967 New York City allocated enough money to treat 2,000 addicts with methadone. Other cities and states expressed increasing interest in the New York experiment. Nyswander called for rapid and massive program expansion outside the umbrella of a "research protocol" (which requires that dispensing agencies run elaborate research programs according to specified protocols) making the drug available to clinics which would function strictly as treatment programs.

HEROIN "BLOCKADE"

Dole was an aggressive public fighter determined to alleviate suffering among addicts. To get support for methadone maintenance, he deliberately turned to the popular media, giving interviews in The New Yorker. There were books written about him, and he made himself very accessible to journalists, making some nontechnical statements which attracted public attention to his and Nyswander's work.

One such statement was that methadone creates a physiologic "blockade" against the effects of heroin.9 Nyswander also referred to "the methadone blockage procedure for treatment of heroin addiction. . . ."19 This blockade supposedly extinguishes the desire to use heroin and makes addicts receptive to "rehabilitation." Others also commented on the drug's "blockade" abilities. Harvey Gollance, then associate director of Beth Israel Medical Center, noted: ". . . The methadone blockade against opiates frees the addict from his hunger so that he becomes receptive to rehabilitation."

No Blockade

Methadone, however, does not physiologically block the effects of heroin or any other opiate. Dole, Nyswander and Gollance, among others, used the term "blockade" incorrectly. W. J. Russell Taylor, director of the Clinical Pharmacology and Toxicology Center at Philadelphia General Hospital, stated:

Methadone has no blockade effect; it doesn't exist; pharmacologically its not a truth. When you're talking to medical people and you put the word "blockade" beside the name of a drug, it should be used to mean an actual pharmacologic blockade."
Methadone does produce what is called cross-tolerance. Methadone-tolerant addicts are not susceptible to the effects of equal amounts of other opiates. The methadone addict, however, can always use enough heroin to break through this cross-tolerance and achieve a greater "high." Larger dosages of heroin always bring on narcotic euphoria in the methadone addict, particularly if his methadone dosage is low (under 50 mg a day). Methadone itself produces a "high." Later, Dole said he should have used the correct term, cross-tolerance, rather than blockade, but that political persuasion was more important than scientific precision when he claimed in a scientific paper that methadone blocks the effects of heroin or other narcotics.

Dole's medical colleagues spotted this error and labeled his misrepresentation of methadone's blockage capabilities "sloppy reporting of medical research." Jaffe himself wrote: "Pharmacologists are amazed by [Dole's use of] the term "blockade" because it is not the classical way to use it. It's actually cross-tolerance induced reduction of effect."14

Narcotic antagonists do physiologically and pharmacologically block the effects of narcotics. These drugs, like cyclazocine, naltrexone and nalaxone, are unpopular with addicts, however, since they block the pleasurable effects that heroin users seek. The hope that antagonists would somehow become a workable "vaccine" against heroin addiction (their use was recommended in the early 1970s for grade school children in Harlem) vanished with the question: What addict would want an antagonist? Antagonists are therefore not widely used today in addiction treatment, except in emergency medical treatment of narcotic overdose.

PHARMACOLOGIC EFFECTS OF METHADONE MAINTENANCE

Smith and Bentel said that "Patients on regular doses of oral methadone are virtually unimpaired in physical and mental functioning [emphasis added]." Kreek noted that ". . . after oral ingestion of methadone, no euphoria or narcotic effect is experienced. . . ." Nysswander said methadone ". . . has no deleterious effects anywhere."

A survey of the medical literature, however, indicates that these statements are incorrect. A growing body if evidence supports the conclusion that there are physiological side effects associated with methadone addiction, just as there are with addiction to heroin. In fact, there are more pharmacological similarities than differences between methadone and heroin addiction.
SIDE EFFECTS OF METHADONE MAINTENANCE

Do toxic side effects accompany methadone maintenance? There is disagreement in the scientific literature on this point. Dole and Nyswander said, "Patients have shown no major ill effects from the use of methadone." In one paper Kreek flatly stated that methadone maintenance is "... medically safe, with minimal side effects and with no toxicity." But in another research paper she observed that:

. . . side effects of methadone maintenance treatment . . . [include] euphoria or "high," drowsiness, somnolence, "nodding," constipation, excessive sweating, and insomnia . . . interference in sexual functioning and menstrual irregularities. [Other side effects include] edema, transient joint pains and swelling, upper gastrointestinal symptoms including pain, nausea, and vomiting, and bradycardia and hypotension. Transient skin rashes have [also] been reported.21

Are these minimal side effects?
My experience with over 2,000 methadone-maintained addicts indicates there are methadone side effects, and they closely resemble what Yaffe and others described in a clinical study of addict-patients in the St. Louis Methadone Program:

Constipation was reported by 57% of all patients surveyed; excessive sweating, 47%; loss of interest in sex, 26%; nausea, 25%; sleepiness and drowsiness, 23%; insomnia, 23%; being jittery and tense, 23%; loss of appetite, 19%; headache, 12%; body aches and pains, 11%; and chills, 10%. Average severity ratings were all at or above the midpoint on a seven-point scale.2

Salmon and Schrier noted similar side effects including "... constipation, weight gain, decreased sexual desire and potency, dry mouth, persistent thirst, drowsiness, nasal catarrh and nervousness." Cuskey, in a study of clients on methadone, reported that "... about 15% of addict patients developed minor side effects."24

Martin noted "... persistent physiological and metabolic changes associated with chronic methadone administration."25
Whether early "no side effect" reports were part of a snow job—an attempt to build broader support for maintenance therapy—or whether their conclusions were based on insufficient clinical experience with the drug, hard facts stand out: Methadone is not a simple "medicine," devoid of side effects. In sufficient doses it is a powerful narcotic whose effects are qualitatively and quantitatively similar to morphine and heroin, although oral administration delays onset of symptoms.

MIND-ALTERING EFFECTS OF METHADONE

Does methadone maintenance interfere with the client's ability to live what the average person would call a "normal" life? Is mental functioning of methadone addicts impaired to any degree? Dole reported that among methadone clients ". . . the cognitive and other emotional and intellectual faculties of the mind are normal."26 Cushman testified in court that he had seen thousands of methadone maintenance clients, they were basically "indistinguishable" from "comparable non-drug people," and there is "no difference between a normal subject and the methadone-maintained patient after he has been stabilized on methadone."27 Lowinson concluded that there ". . . is no way of distinguishing a person on methadone from a person who is not on methadone," and that a methadone addict ". . . is in no way changed, and is no different after he has taken his medication."28 One doubts, however, whether these highly trained physicians have ever been on methadone maintenance.

I have found personally and other addicts have told me that the drug does change one's mood or sensations, just like any narcotic. It does produce a "high." The most prominent effects of methadone involve central nervous system depression. The principal pharmacological actions of methadone, like other opiates, are analgesia and sedation. In the tolerant addict, of course, these effects are less pronounced, but methadone does produce the long-lasting, slow-developing narcotic effect that is identified by addicts as a feeling of repose, suffusing warmth and relaxation. When administered parentally, methadone produces this effect immediately; taken orally, the onset is slower but basically the same.

"The behavior of the methadone addict," observes Jaffe, "is strikingly similar to that of the heroin addict."29 William Burroughs, heir to the adding machine fortune and an old-time addict whose judgement on such matters is well informed, said ". . . methadone is completely satisfying to the addict, an excellent pain killer at least as addicting as morphine."30

Comparisons of Methadone and Morphine
Vogel and his colleagues reported that the "high" that methadone produces is" . . . equal to that of morphine, so that its habituation liability is high."3 Julian Villarreal stated, "With regard to analgesic activity, methadone and morphine are practically equivalent in potency and duration."32 Isbell described the behavior of hospitalized methadone addicts:

The behavior of the men addicted to methadone was similar to the behavior seen during morphine addiction. The patients ceased all productive activity, neglected their persons and their quarters, and spent most of the time in bed in a semi-somnolent state which they regarded as very pleasurable. During addiction to methadone, patients continually required increased dosage.33

The early studies by Vogel and associates and Isbell, however, differed from Dole and Nyswander's later outpatient program. Isbell and Vogel and associates administered increasing doses of methadone over a very brief period to hospitalized subjects maintained under circumstances that might have caused them to become "stoned" more readily. This contrasts with the gradual dosage increase in Dole and Nyswander's outpatient program, in which the subjects were much more active than those in the Vogel and colleagues or Isbell studies.

Nevertheless, the Vogel/Isbell and the Dole/Nyswander groups disagree over whether or not:

1. Methadone maintenance creates the same escalation problem as heroin—addicts need more and more of the drug to overcome tolerance (Vogel/Isabell yes; Dole/Nyswander no)
2. Methadone produces euphoria or "high" (Vogel/Isabell yes; Dole/Nyswander no)
3. Methadone produces side effects (Vogel /Isabell and many others yes; Dole/Nyswander no)

Who is correct? After exhaustive comparisons of the two drugs in an experimental setting, Isbell could only conclude that methadone addiction was more debilitating than morphine addiction:

The degree of somnolence and lack of activity was greater [with methadone] than that seen during morphine addiction. The men complained about this, and said that while addicted to methadone, they could do little but stay in bed. . . . The patients stated . . . that when they were
receiving morphine at least they thought they were ambitious, but when they were taking methadone they know that they were lazy.34

With these contradictory reports, based on personal experience with heroin, morphine and methadone (oral and injected), my conclusion is that methadone does get patients "loaded," although the degree of central nervous system depression and narcotic euphoria produced by methadone (and by other narcotics) is dependent on dosage and tolerance. Thus, there are many similarities between methadone and heroin addiction (given two pharmaceutically pure preparations administered in equivalent dosages at regular intervals). The main difference, it appears, is that methadone is legal and heroin is not.

METHADONE ABSTINENCE SYNDROME

What are the acute physiological and psychological effects of the methadone abstinence syndrome? Is it similar to heroin withdrawal? Personal experience with methadone withdrawal indicates it is qualitatively similar to heroin withdrawal and quantitatively more severe, although onset of symptoms is slower. Symptoms are the same as those experienced during heroin withdrawal: lightheadedness, dizziness, sedation, nausea, vomiting and sweating. Other reactions commonly include euphoria, dysphoria, weakness, headache, insomnia, agitation, disorientation and visual disturbances. Lipkowitz and his colleagues commented on experimental methadone withdrawal:

Without the controls present in a prison setting such as the one in which these observations were made, there is little doubt that each of these men [withdrawing from methadone addiction] would have made immediate attempts to acquire narcotics illicitly. Symptoms are severe: sweating, restlessness, lacrimation, muscle cramps, lightheadedness, dizziness, drowsiness, mental clouding, puritis, nausea and vomiting."

Severity of Methadone Withdrawal

Most addicts insist methadone abstinence syndrome is more severe than heroin withdrawal. The course of withdrawal from methadone, they contend, is more prolonged and painful because street heroin that addicts obtain is a low-dose (1 to 5 percent), adulterated substance used at irregular intervals. Clinic-supplied methadone, on the other hand, is a fairly high-dose
pharmaceutical preparation ingested like clockwork at regular intervals. The result is that clinic methadone addicts literally are more "hooked" or "strung out" than street heroin addicts. Their withdrawal symptoms are consequently more severe.

OVERALL EFFECTS OF METHADONE MAINTENANCE

Methadone not only reduces heroin hunger. It affects respiration, digestion and sexual behavior. Like any opiate, it affects social and psychological behavior; it slows and reduces perception and responsiveness, reduces somatic and visceral sensations, and narrows the range of human experience.

Methadone affects not only the person taking it but everyone in close contact with him: children, spouse, parents and friends. Maintenance places those who share the social life of the addict in a relationship with an individual who uses a potent narcotic. The addict's family and associates thus live with the limitations in responsiveness, alertness and potential for feeling that the drug imposes on the methadone client.

NOTES


10. Quoted in Hentoff, Doctor Among the Addicts, p. 123.


27. Cushman's testimony is quoted in ibid., p. 362.
28. Lowinson quoted in ibid.
34. Harris Isbell, "Liability of Addiction of 6-dimethyl-amino-4-4- diphenyl-3-heptanone (Methadone, 'Amidone,' or '10920') in Man: Experimental Addiction to Methadone," Archives of Internal Medicine 82 (October 1948): 362.