

**Implications of Methadone Maintenance for Theories of Narcotic Addiction**  
by  
**Vincent P. Dole M.D.**

**On The Occasion of The Presentation of  
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Vincent P. Dole, M.D. is Professor Emeritus at The Rockefeller University, New York City.

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This article is dedicated to the memory of Marie Nyswander, M.D. who opened the modern era of treatment with her book *The Drug Addict As A Patient* (New York: Grune & Stratton, 1956). Her experience and compassion guided the development of methadone maintenance.

*Abstract*

Clinical success in rehabilitation of heroin addicts with maintenance treatment requires stability of the blood level in a pharmacologically effective range (optimally, 150 to 600 ng/mL) a phenomenon that emphasizes the central importance of narcotic receptor occupation. It is postulated that the high rate of relapse of addicts after detoxification from heroin use is due to persistent derangement of the endogenous ligand-narcotic receptor system and that methadone in an adequate daily dose compensates for this defect. Some patients with long histories of heroin use and subsequent rehabilitation on a maintenance program do well when the treatment is terminated. The majority, unfortunately, experience a return of symptoms after maintenance is stopped. The treatment, therefore, is corrective but not curative for severely addicted persons. A major challenge for future research is to identify the specific defect in receptor function and to repair it. Meanwhile, methadone maintenance provides a safe and effective way to normalize the function of otherwise intractable narcotic addicts. (JAMA 1988 260: 3025-3029)

The achievements of molecular biology in analyzing processes of cell function suggest that all diseases, including disorders of behavior, might ultimately be reduced to biochemical terms. The claim is extreme, but at least for narcotic addiction the optimism seems to be justified. Analysis of the clinical results of methadone maintenance treatment during the past 25 years, coupled with advances in the understanding of narcotic receptors and their ligands, support the view that compulsive use of narcotic stems from receptor dysfunction.

This is a departure from the traditional concept of addiction as misbehavior— a distinction of great practical consequence. As recently as four months ago the Supreme Court affirmed the denial of veteran's benefits to alcoholics on the ground that their condition is due to "willful

misconduct" (Trayner v. Turnage, 1988), an opinion that seems to be at odds with the medical tradition of basing services on need rather than on fault. The ruling made explicit the widespread prejudice against addicts, one that if carried to logical limits would deny treatment to a skier with a broken leg or a sunbather with skin cancer. For the immediate future, the harshness of the ruling has stimulated corrective action in the legislature. In the longer term, scientific understanding should displace prejudice, and attitudes toward addictive behavior should become more consistent with medical tradition. At least so one may hope, provided that the scientific community can provide a basis for rational understanding of addictions as diseases.

### **Methadone Normalizes Function**

This article, updating previous analyzes (Dole & Nyswander, 1968; Dole, 1970), is concerned mainly with the theoretical implications of methadone maintenance treatment and the direction of future work. The practical success of maintenance in rehabilitation of tens of thousands of addicts, now especially important as a measure of limiting the spread of acquired immunodeficiency syndrome, has been documented and need not be reviewed further (Dole & Joseph, 1978; Cooper, Altman, Brown et al, 1983; Newman, 1986; Kreek, 1987). The issue to be considered here is the basis of this success. The treatment is corrective, normalizing neurological and endocrinologic processes in patients whose endogenous ligand-receptor function has been deranged by long-term use of powerful narcotic drugs. Why some persons who are exposed to narcotics are more susceptible than others to this derangement and whether long-term addicts can recover normal function without maintenance therapy are questions for the future. At present, the most that can be said is that there seems to be a specific neurological basis for the compulsive use of heroin by addicts and that methadone taken in optimal doses can correct the disorder. When somatic function has been normalized, the ex-addict, supported by counseling and social service, can begin the long process of social rehabilitation.

The social rehabilitation of methadone maintenance patients and the normalization of endocrine function substantially exceed the expectation that Marie Nyswander, M.D., and I brought to the problem 25 years ago. Then, as now, it was clear that narcotic addiction could not be eliminated simply by prohibition, however severe the penalties. For a chronic user, the need for narcotic is inelastic. With tens of thousands of such persons as a market, limiting supply without reducing demand increases the price of illicit drugs to the point that black marketers are willing to take the necessary risks. The net result is a highly profitable business for the drug sellers, corruption of government officials, infiltration of legitimate business with laundered money, increase in crime committed by addicts to support their expensive habits, filling of jails, and deaths from injection of contaminated drugs of uncertain potency. The clear lesson to be learned from repeated failures of past policy is that demand must be reduced by effective treatment. The epidemic of narcotic use has not been extinguished by prohibition, civil commitment, jailing, or other punishments.

On the other hand, it must be conceded that attempts to treat addicts with narcotic maintenance 70 years ago were not successful. Indeed, leaders in the medical profession and the Public Health Service cooperated with enforcement agents in closing the experimental clinics, thus effectively transferring responsibility for control of addiction to the police (Musto, 1973). When Marie Nyswander and I began our work, the position of the Federal Bureau of Narcotics was that maintenance had been tried and had failed. The argument could not be denied, but it seemed self-serving. The failure of clinics that had been organized hastily in response to the panic that followed enactment of the Harrison Narcotic Act constituted the database. Not only were physicians ill prepared to deal with the flood of desperate addicts, they had only two narcotic

drugs, morphine and heroin, to prescribe. In retrospect, a major reason for their failure is clear: the physicians were using the wrong drug.

Our objective at the onset was simply to find a medication that would keep addicts content without causing medical harm and that would be safe and effective for use over long periods in relatively stable doses. The goal of social rehabilitation of addicts was not part of the original plan. Merely satisfying addicts, although not an ideal result, seemed better than the existing policy that forced incurable addicts into criminal activity.

### **Stability Essential**

The initial studies, conducted at Rockefeller Hospital (New York) in collaboration with Mary Jeanne Kreek, M.D., examined the clinical effects of different narcotic drugs when given in various doses to long-term users of heroin. All drugs were of the opiate class that is, they were known to exhibit cross tolerance with morphine and all had been approved for human use as analgesics. The reason for failure of previous attempts to maintain addicts on morphine soon became apparent: the patients could not be stabilized on the drug. Despite frequent injections, their condition fluctuated between somnolence and agitation throughout each day, with tolerance increasing over consecutive days to the point that they were almost continuously agitated even when receiving huge doses of morphine. Similar results were obtained with heroin (which is essentially the same drug as morphine since it is rapidly converted to morphine in the body), hydromorphone, codeine, oxycodone, and meperidine. The prospect for maintenance treatment did not look promising at this point.

A remarkably different result was seen when, in the course of the scheduled testing, methadone was administered. The fluctuation in clinical state became less and then disappeared. Doses became stable. The patients seemed normal. Most remarkably, their interests shifted from the usual obsessive preoccupation with timing and dose of narcotic to more ordinary topics (Dole, Nyswander & Kreek, 1966). We had no explanation for this surprising result. Prior to our studies, methadone had been tested at the Public Health Hospital (Lexington, KY) and was found to be a typical opiate, distinguished from morphine only by greater oral effectiveness and a somewhat longer period of action (Eddy, Halbach & Breanden, 1957). However, because of the favorable response, we decided to continue administration of methadone beyond the original schedule and to observe longer-term effects. It was not until several years later that an explanation for the unusual result became apparent: the concentration of methadone in blood is stabilized by reversible absorption into tissues (Dole & Kreek, 1973), mainly the liver (Kreek, Oratz, Rothschild, 1978). The key factor is the reversibility of this absorption. Immediately after ingestion of the daily dose, 99% of the medication is bound to the tissues in equilibrium with the concentration in blood. It is released as the concentration falls, thus buffering the level. With a relatively steady concentration in blood, the narcotic receptors in critical cells remain continuously occupied and the patient becomes functionally normal. The essential feature in the treatment is the stability of receptor occupation, which permits interacting systems to function normally. The physiological and behavioral disturbances in heroin addiction apparently are consequences of the rapid changes in status of the endogenous narcotic receptor-ligand system. When the addict takes short acting narcotics, the system cycles between abstinence and narcosis several times a day. A stable state of adaptation is impossible.

Our work involved a fortunate accident that explains why the unique value of methadone for maintenance had not been discovered previously. The patients had just completed a long series of tests with other opiates and, as a consequence, had developed a high tolerance to narcotics.

Therefore, methadone was administered in exceptionally high doses, about ten times greater than is needed for analgesic action in naive patients. Injected in a single, small dose to a nontolerant patient, methadone is a relatively short-acting drug. The bulk of the dose is quickly removed from blood and later is returned to circulation at a pharmacologically insignificant level. Only when large doses of methadone have been administered repeatedly do the nonspecific binding sites come into equilibrium with a pharmacologically effective concentration in circulating blood. When this condition is reached, all that is needed for buffering the concentration at a high enough level to ensure significant occupation of receptors is a single daily dose to replace the amount of drug that has been eliminated by metabolism. Moreover, because of efficient absorption from the gastrointestinal tract, the dose can be given orally, thus eliminating needle use.

### **Specificity**

Studies of the original six patients on our metabolic ward demonstrated the absence of acute narcotic effect in methadone maintenance patients and provided an understanding of the importance of receptor occupation. Switching the daily dose to d-methadone in place of the usual racemic mixture of d- and l- methadone was followed by the gradual appearance of abstinence symptoms, as expected from the fact that the narcotic activity of methadone is limited to the l isomer. The patients, not noticing any difference in the taste or immediate effects of the daily dose, reported on the next day that they seemed to be "getting the flu." Only on the third day did they begin to suspect the medication and asked if "something had happened to the methadone." At this point they were returned to the usual racemic mixture. All symptoms cleared immediately. The patients had responded to the fall in concentration of l-methadone in blood and the resultant dissociation of this active isomer from critical receptors. When returned to medication containing l methadone, they again became functionally normal.

The acute effect of naloxone, an antagonist that displaces narcotic ligands from receptors, shows the extreme sensitivity of physically dependent patients to the degree of occupancy of their narcotic receptors. Within a few seconds after an intravenous injection of a minute dose of naloxone (1/20 the amount that might be used in treating a nontolerant patient with narcotic overdose), a maintenance patient will be put into acute abstinence, with profound dysphoria. The subjective sensation apparently defies description in ordinary terms, being reported as a terrible feeling not like anything else. To an observer the patient appears to have been suddenly plunged into severe depression; he becomes immobile, sagging in posture, apparently grief-stricken.

Nontolerant patients are essentially unreactive to naloxone but are highly sensitive to narcotics. The classic studies of Houde et al (1960), quantitating the analgesia in pain patients following administration of a single dose of narcotic, showed a reproducible time course that depended on the dose and degree of tolerance induced by previous exposure. Subsequent studies by Berkowitz et al (1975) correlated this effect with the blood level of morphine, thus demonstrating a direct, moment-to-moment relation between analgesia and occupation of narcotic receptors. Studies by Inturrisi et al (1987) during the past 15 years have provided quantitative analyses of pain relief as a function of narcotic blood level. Clearly, the subjective experience of pain is inversely related to receptor occupation, given a constant input of sensory signals from injured tissue and dependent on the degree of narcotic tolerance.

### **Persistent Receptor Disorder**

An interpretation of these phenomena is that the narcotic receptor-ligand system acts as a modulator, adjusting the intensity of suffering and the body's hormonal response to stress. In

nontolerant patients, the reactions to tissue damage and related stresses are modulated by the natural ligands, the opioid peptides, while pain can be abolished therapeutically for a limited time by a dose of narcotic drug. However, repeated injections of narcotic lead to down-regulation of the modulating system and possibly also to suppression of endogenous ligands, thus contributing to narcotic tolerance and dependence and progressively diminishing the analgesic utility of narcotics.

This oversimplified analysis assumes a balance between activating and modulating processes. Under normal, unstimulated conditions, both processes are quiescent. When sensory stimuli activate neurological and humoral systems, the modulating processes react to protect against excessive response. With long-term administration of narcotics, the modulating system is down-regulated. The receptors become insensitive both to narcotic drugs and to their natural ligands. A new stability is achieved if methadone is given in an adequate daily dose, but at the price of continued dependence on the medication. Thus, a fundamental question in treatment of long-term users of narcotics is whether the modulating systems can return to normal function after termination of narcotic input. Ideally, methadone would be used as a stabilizing medication to provide immediate intervention, stopping the use of illicit narcotics and normalizing general metabolism. Later, after medical and social rehabilitation, the maintenance medicine would be withdrawn slowly and the patient would be totally cured.

Unfortunately, cure of chronic narcotic addiction is not that simple. Some patients do well after rehabilitation and termination of methadone maintenance, but the majority, although equally motivated, experience dysphoria, restlessness, irritability, and recurrent urges to use heroin again. The danger of relapse is great under these conditions. Objectively measurable physiological disturbances persist after detoxification from heroin or any other narcotic that has been used for a long time. These were noted by Himmelsbach (1968) in early studies of the abstinence syndrome at the Public Health Hospital. Observing signs of dependence (sympathetic nervous system hyperactivity) that persisted up to two years in prisoners serving long sentences, he surmised that the almost invariable relapse of prisoners after release was "abetted by what seem to be indelible effects of addiction on the nervous system" (Himmelsbach, 1968).

It had, of course, long been known that most long-term users of narcotics relapse after withdrawal of the drug. The Public Health Hospital was started in 1935 under the reasonable assumption that medically assisted detoxification with counseling, general medical care, and healthy living on a Kentucky farm would provide optimal conditions for cure. Nevertheless, more than 90% relapsed after return to New York City (Hunt & Odoroff, 1962). Although the hospital made major scientific contributions, using volunteers from the population of prisoners to test the addictive potential of new drugs and conducting fundamental studies of narcotic pharmacology, including the work of Wikler (1958) on conditioning, the initial goal "that of curing addicts" was never realized.

Persistent after effects of narcotic exposure also have been found in experimental animals. Physiological disturbances were demonstrated by Martin et al (1963) and Cochin and Kornetsky (1964) months after treatment of rats with morphine. Brase and associates (1976) have used a small priming injection of morphine followed by naloxone as a probe to unmask residual abnormalities in rats long after exposure to narcotic drugs. Surprisingly, little new clinical research has been directed to the phenomenon of protracted abstinence despite the fact that relapse after completion of treatment is the central problem of narcotic addiction. With the present availability of sensitive analytic techniques, including specific ligands for analysis of receptor binding, the problem seems ripe for renewed investigation. What is needed now are

methods to assess the kind and degree of receptor derangement in addicts and a better understanding of the function of this modulating system in response to physiological stress. With a more detailed understanding of addiction in molecular terms, a fundamental cure may be possible. Indeed, progress may come from work on other conditions in which chronic exposure to powerful nonnarcotic drugs leads, in susceptible persons, to persistent derangement of neurological (Gunne & Barany, 1976; Gunne & Haggstrom, 1984) or endocrine (Williams, Dluhy & Thorn, 1980) function.

### **Practical Considerations**

None of these theoretical speculations should divert attention from the fact that methadone maintenance is an available treatment for otherwise intractable addicts. It is effective under a wide variety of conditions provided that an adequate, constant daily dose is given. Like digitalis, methadone can be lifesaving. Although it is now possible to provide a theoretical explanation for their beneficial actions, in practical terms, the justification for use of either methadone or digitalis, and the details of how they should be used, stem from experience.

The comparison goes deeper. No one questions the need for efforts to prevent the cardiac damage that ultimately leads to congestive failure or the importance of protecting young people from exposure to narcotic drugs. Prevention is fundamental in limiting the prevalence of these conditions. In principle, there should be no conflict between prevention of a disease and treatment of an established disability, and in the case of heart disease there is none. But with drug addiction, a serious dilemma arises: limiting the supply of a dangerous drug, which is an essential part of prevention, can cause more damage to society than the addiction itself if extremes of enforcement promote criminal behavior. There is no simple answer to this dilemma. Obviously there should be a balance between enforcement and treatment, reducing both supply and demand proportionally. With heroin and related narcotics, methadone maintenance has by far the greatest immediate potential for reducing demand. It is therefore important that the medical profession understand its pharmacology, its indications, and its limitations.

The optimal daily dose of methadone for maintenance is the quantity that will hold the blood level in the 150 to 600 ng/mL range. This concentration range is consistent with binding to narcotic receptors when allowance is made for binding of methadone to plasma proteins and reduction in sensitivity of receptors with narcotic tolerance. As a general rule, 60 to 80 mg of oral d-methadone hydrochloride a day (reached by gradual increase over four to six weeks) is adequate and not excessive, although in exceptional cases substantially higher doses may be needed. If the activity of the hepatic microsomal enzyme oxidizing system has been increased by interaction with other medications being taken concurrently (Kreek, Garfield, Gutjahr et al, 1976; Tong, Pond, Kreek et al, 1981), or for unknown reasons (Tennant, 1987), the elimination of methadone will be accelerated. In extreme cases, even 100 mg/d may fail to hold the blood methadone level within the therapeutic range for the full 24 hours and a higher divided dose will be needed for optimal results. However, these cases are unusual. Usually patients after stabilization for some months on a 60 to 80 mg/d dose can be lowered to the 40 to 60 mg/d range without difficulty. Some can be maintained successfully with even lower doses but, except the rare cases in which full tolerance to the narcotic effects of methadone may not be developed, there is no compelling reason for prescribing doses that are only marginally adequate. As with antibiotics, the prudent policy is give enough medication to ensure success.

This perhaps is too casual an answer to the question of optimal dosage. If the instruments and funding required for repeated measurement of methadone blood levels were generally available

(which they are not) it would be apparent that any rigid set of dosing guidelines would be misleading. The levels vary substantially from patient to patient receiving the same daily doses (Kreek, 1973; Holmstead, Anggard & Gunne, 1978). Analytic data, if available, would permit a fine-tuned adjustment of doses to optimal amounts for individual patients. Fortunately, this laboratory support is not needed. An experienced clinician can judge the adequacy of the dose from the effects. Symptoms of abstinence can be distinguished from anxiety, and narcosis from neurasthenia, by carefully listening to the symptoms, considering their timing in relation to the daily dose of methadone, noting the patient's response to a change in dose, and evaluating his or her emotional stability. The patient's clinical state is correlated reliably with the blood level and the degree of tolerance.

Some maintenance programs, committed philosophically to low-dose regimens, expose their patients to a significant degree of abstinence each day, as the blood level falls into the low range (Dole & Nyswander, 1983). Other programs, seeing the medication as psychological rather than pharmacological treatment, give methadone as a reward for good behavior and withhold it for drug abuse and other infractions of rules. The results are generally poor, as might be expected from the fact that limiting or withholding medication that reduces drug hunger increases the need for illicit narcotics.

### **Alternative Theory**

The hypothesis suggested herein- that narcotic-seeking behavior is a symptom of deranged receptor function- is most directly challenged by treatment of addicts with an antagonist such as naltrexone to block all narcotic actions. Use of antagonists stems from traditional views of addiction as a pleasure-seeking escape from reality employed by persons of weak will who are living in a stressful environment. Add to this the postulated influence of conditioned reflexes that generate an irresistible craving for narcotic when the addict is in the company of other drug users, and one has a theory of addiction (Wilker, 1958). The escapist-conditioning explanation is so plausible that it has influenced medical thinking and public health policy for three decades. Although this conception has never led to a treatment with consistent success, the failure has been excused by the practical difficulty of removing stress and bad companions from the environment of an addict and by the inability of counselors to eliminate character defects.

According to the conditioning theory, antagonist treatment, which blocks the narcotic effects of heroin and related drugs, should insulate the addict from temptation, especially after he has found them to be unrewarding. With no reinforcement, the interest in the narcotic should subside and the patient should become responsive to counseling. Again, there is an explanation for the repeated failures of antagonist treatment to stop heroin use during the past ten years: addicts can easily quit treatment and return to the illicit drug. Current research in some laboratories, aimed at development of implantable preparations of antagonist, is intended to close this loophole.

From the perspective of the receptor derangement theory, this approach is pharmacologically wrong. Antagonist drugs block the action of natural ligands as well as that of illicit narcotics. If the basic problem leading to relapse is a failure of the modulating system to return to normal function after withdrawal of narcotic, than antagonist treatment adds to the problem. The issue, therefore, is clearly drawn. If long-lasting, implantable preparations of narcotic antagonists prove to be as successful as methadone maintenance treatment in rehabilitation of addicts, this certainly would be a useful result. Further research is needed to determine whether the result was in fact due to deconditioning or to a positive interaction with endogenous opioid processes. On the other hand, if the treatment with implanted antagonist fails, then proponents of the conditioning theory

should reconsider their position. This important experiment, if conducted, should be well documented and independently evaluated.

### **The Future**

Apart from theory, the most striking fact is the physiological normality of maintenance patients. Persons who have taken a constant daily dose over a period of months to years are indistinguishable from normal peers. Despite a daily dose that would induce a coma in a naive patient, the patients are normally alert and functional; they live active lives, hold responsible jobs, succeed in school, care for families, have normal sexual activity and normal children, and have no greater incidence of psychopathology or general medical problems than their drug-free peers. Surprisingly, considering the constant input of narcotic, they have a normal response to painful stimuli, including specifically the warning symptoms of surgical emergencies.

All this does not fit neatly into the pharmacology learned from experiments involving single injections of narcotic drugs. The molecular biology of adaptation to chronic narcotic input must be better defined before we can fully understand the pharmacology of maintenance. Somehow the receptors adapt to a steady level of occupancy. They react to a change in conditions, either in degree of receptor occupation by ligands or in the intensity of sensory stimuli, while being adapted to a constant high level of narcotic in tissue fluids.

Here, then, are basic questions to be answered by molecular biologists: How can this system function normally under such abnormal conditions? Why is stability of narcotic concentration more important than the absolute level? Are chronic adaptive changes completely reversible?

Needless to say, any attempt to relate behavioral disorders to molecular processes must start with an oversimplified model. Much more work is needed to take account of the diversity of narcotic receptors and endogenous ligands, the dynamics of receptor formation and internalization, the release of second messengers, and the interactions of modulating processes with other parts of the nervous system (Snyder, 1979; Ariena, 1984). Nevertheless, the broad outline of a metabolic theory of narcotic addiction is coming into view. Two general conclusions emerge from the experience to date: it is not necessary to await an ultimate reduction of addictive behavior to molecular terms before effective treatment can be provided. On the contrary, effective treatment, empirically found, can lead to a better understanding of molecular processes.

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