

Narcotic Blockade

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i. Introduction

Heroin, as used by addicts, produces quite different effects than are seen with use of narcotic drugs in ordinary medical practice. Addicts inject themselves repeatedly with larger doses of a narcotic than are usually prescribed for analgesia, and develop modified responses to the drug. In particular, the euphoric effect appears to be a learned phenomenon, like pleasure from smoking; the first shots of heroin taken by a curious adolescent are more likely to cause nausea than pleasure. Later, the euphoric experience becomes central to the addict's life and leaves little room for other interests. With continued use of narcotics, however, the addict finds it progressively more difficult to achieve euphoria, because a chronic exposure to narcotic drug induces a state of tolerance that diminishes the euphoric response. At the same time the increase in physical dependence obliges the subject to continue drug use or suffer abstinence. An advanced state of addiction thus presents the paradoxical combination of resistance to narcotic effects and need for repeated injections.

Obviously, the addict's compulsive use of heroin and obsessive concern with euphoria must be stopped before he can be employed in a responsible job. In principle, it would seem that the removal of physical dependence by gradual withdrawal of drug - which is easy - followed by psychiatric treatment would enable a significant fraction of addicts to become normal members of society. In practice, this approach has consistently failed as a treatment for chronic addiction to heroin. It has not failed because of lack of effort or facilities; devoted and well-trained physicians - assisted by competent nurses, social workers, probation and enforcement agents - working in special facilities both in the city and removed from the city, have tested this approach for 30 years. A careful search of the literature has failed to disclose a single report in which withdrawal of drug and psychotherapy has enabled a significant fraction of the patients to return to the community and live as normal individuals.

It thus seemed reasonable to look for some medication to block the abnormal reactions of addicts to heroin and permit them to live as normal citizens in

the community. Any such medication, to be of practical value, must meet a number of stringent conditions: it must eliminate the euphoric appeal of heroin and the abstinence symptoms that draw addicts back to drug use; it must be sufficiently free from toxic or dysphoric effects that patients will continue with treatment; it must be orally effective, long acting, medically safe, and compatible with normal performance in work and at school and with responsible behavior in society.

The search for such an agent must start with an understanding of the pharmacological state of an addict using heroin on the street. Most of the time he is functionally disabled. Although he has some periods of normal alertness and well-being, which he calls "straight," the typical addict spends a major part of his day in two other conditions-"high" and "sick"-that are not part of normal experience. When "high" or euphoric- he is sedated, tranquilized, absorbed in himself, and lost to responsibilities. When "sick" - or abstinent - he is desperate in his need for narcotic drug, with symptoms of general malaise, nausea, lacrimation and perspiration, tremors, and cramps. Because of the short period of action of heroin, he oscillates between the limits of "high" and "sick" with insufficient time in the normal condition of "straight" to hold a steady job. Addiction leaves little time for a normal life.

Figure 1 (*not shown here*) illustrates the variability in functional state of a typical heroin- using addict. As shown schematically in the first day of the Figure, he awakens with some degree of "sickness," and takes a shot of heroin, if available. If he has sufficient drug, and if his tolerance is not too great, he will inject himself repeatedly, striving to be "high" as much as possible. The second day shown in the figure illustrates his problem (perhaps a few days or weeks later) when he has insufficient drug and too great a tolerance for euphoric response. Then he spends much of his time in misery, with relief only when heroin gives him brief periods of feeling "straight." The final episode illustrated on this diagram is sudden death from "overdose" not well understood medically, but a familiar phenomenon in the world of street addicts.

Figure 2 (*not shown here*) illustrates the effect of blockade with methadone. When properly stabilized, the patient is firmly buffered in the zone of normal function. He is protected against both abstinence and euphoria. If he takes heroin, he does not get "high," as he otherwise would, nor is such an experiment followed by the "sick" feeling that in the past had forced him to seek relief with repeated injections of heroin. To maintain the state of blockade, he is given a constant, daily oral dose of methadone. Patients have been maintained on methadone for more than two years without escalation of dose.

This medication, given in fixed dose to tolerant subjects, does not make patients "high" or cause any other narcotic effects. On the contrary it eliminates the abnormal euphoric response of addicts to narcotic drugs. The absence of any significant drug sensation on taking the daily dose of

methadone has been verified by experiments in which, unknown to the patient, d-methadone (a pharmacologically inactive isomer) was substituted for the usual morning dose of racemic drug. The patients not only failed to notice the substitution, but when mild symptoms began to appear about 36 hours later they even failed to identify the symptoms with abstinence. Unaware of any change in their medication, the patients believed that they had caught cold.

The present report outlines a technique for bringing patients into the condition of stable blockade, without production of disabling side-effects, and describes a series of experiments in which the blockade has been challenged by intravenous injections of various narcotic drugs.

I. Induction of Tolerance

The essential condition for establishing a narcotic blockade without producing euphoria or other disabling effects is that the dose of methadone always be small in relation to the tolerance of the patient. Methadone is potent agent; if a large amount is given in a single dose to a nontolerant subject, it will, like any other narcotic drug, cause narcotic effects. (1,2) Such effects occur when addicts use this drug without medical control, or if physicians, not understanding the pharmacology of methadone, prescribe excessive doses. These effects are easily avoided by starting treatment with small, divided oral doses and increasing the amount gradually, as tolerance increases, over a period of 6 to 8 weeks.

The process of induction is shown schematically in Fig 3 (*not shown here*). Patients with little or no tolerance at the beginning of treatment should be given small initial doses (5 to 10 mg orally, twice daily). They can be continued at this level for 1 to 2 weeks, and then increased by steps of 5 to 10 mg added to either the morning or evening dose at intervals of 4 to 7 days until a total daily dose of 80 to 100 mg is reached. At this stage the total daily dose is held constant while the distribution is shifted to a single morning dose by transfer of medication from evening to morning in units of 5 to 10 mg at intervals of 4 to 7 days. If a patient starts treatment with a considerable degree of tolerance, he can of course be started on larger doses of methadone (15 to 20 mg twice daily), but in any case the increase to stabilization level should be a gradual process.

Tolerance is a heterogeneous phenomenon; the patient becomes refractory to the various effects of narcotic drugs at unequal rates. A considerable degree of resistance to the narcotic and euphoric action can be established within 3 to 6 weeks, but tolerances to the autonomic effects (constipation, slowness in starting the urinary stream, reduction in libido and potency, perspiration) develop more slowly. For this reason it is important to start treatment with moderate dosages, and increase slowly, even when patients come with a large heroin habit. A steady state of maintenance, apparently necessary for induction of tolerance to autonomic effects, is never achieved

by an addict taking heroin on the street. With proper use of methadone, however, patients return to normal genitourinary function, and normal bowel function (some take hydrophilic colloid), and female patients have regular menses. Some patients perspire more heavily in hot weather than they had before treatment.

It is perhaps unnecessary to add that the methadone blockade is specific for opiate-type drugs. As is well known, tolerance to opiates does not diminish the effects of barbiturates, alcohol, tranquilizers, amphetamines, or tobacco. Methadone, therefore, would not be a rational treatment for nonopiate drug abuse.

II. Test of the Blockade

Seven patients, in different stages of induction of narcotic tolerance, were challenged by intravenous injections of heroin, hydromorphone hydrochloride (Dilaudid), morphine, methadone, or saline. The physician who injected each test dose observed the patient for visible signs of drug effects (flush, sedation, drooping of eyelids, change of voice and respiration, change in mood or behavior) and questioned him systematically to record subjective symptoms.

To make the determination of drug effect as objective as possible, neither the patient nor the physician conducting the test knew the nature of the drug injected or the dose. A second physician, acting as safety monitor, supervised the dosage, but remained in the background so as not to influence the tests. The intravenous injections were given by the same physician at 1 to 2 p.m. each day, approximately five hours after the morning dose of oral methadone. The four drugs and the saline blank were injected on consecutive weekdays for four weeks in an arbitrary order derived from the sequence of letters in the rows of a 5 X 5 Latin square. The order of injection each week was permuted, according to the letter order in successive rows of the square. Injections were replicated for four weeks, omitted for one week, and then resumed with the administration of heroin in various doses for more detailed titration of heroin effect.

The dose of two drugs (morphine, 30 mg; methadone, 40 mg) remained constant during the initial series of injections. The dose of the other two drugs (heroin, hydromorphone hydrochloride) was varied, subject to the condition that no patient was given a dose larger than 20 mg of either drug unless he had been shown to be refractory to this amount. Likewise, when the higher doses of heroin were tested in the second series of experiments, patients were exposed to the large doses only after their tolerance to 40 and 80 mg doses had been established. To minimize interaction between subjects, patients received different doses of test drug on any given day; to minimize interaction between physicians, the test physician stored all data without further analysis or discussion with the safety monitor until all injections had been completed.

At the end of the period of testing, both physicians studied the accumulated data independently and scored the record of each injection for euphoric effects and drug sensation (Table) without knowledge of the drug or dose represented. These indices were averaged and then related to the records of drug injected. As a check on the reliability of the patients' reports, the records of visible signs of drug effects were compared with reports of subjective effects. It was found that the subjective scores were more sensitive, and more consistently related to the drug injected, than the visible signs. There was, therefore, no evidence of deception by the patients. As a further check, the scores for euphoric response (which the patients might be inclined to deny) were correlated with the scores for noneuphoric sensation (which might be more freely admitted). The two indices correlated well (Fig 4--*not shown*).

The euphoric effects of heroin, and other narcotic drugs tested, were found to be markedly attenuated by the blockade. Tolerance appeared to blunt the euphoric response before it abolished other drug sensations (gastrointestinal and vasomotor effects). A clear illustration of the dissociation of drug effects was the consistent report of "needles and pins" sensation following injection of morphine, 30 mg. This response (presumably due to histamine release) was reported even by subjects who were completely refractory to all other effects of morphine and who had reported no subjective effects after larger doses of heroin.

Figure 5 (*not shown*) relates the euphoria scores to log dose of heroin injected. The cluster of points designated with a single plus show the responses of two patients who, at the beginning of the experiment, had been under treatment for two weeks. The cluster labeled + + to + + + are the responses of three patients who had four to six weeks of treatment - and consequently more tolerance - and the + + + + group refers to two patients with four months of treatment and a stable blockade.

Although the scatter in this diagram is too great for a precise titration of euphoric response, the practical effect of the blockade is demonstrated. A low blockade, established during the first few weeks of treatment, diminishes the euphoric effect of heroin but does not abolish it. This degree of blockade, therefore, would not effectively eliminate the appeal of heroin if the drug were available on the streets in sufficient quantity. With the development of + + + + blockade, heroin, even in massive doses, produced little or no euphoria. These findings can be related to the 10 to 30 mg of heroin contained in an illegal "bag" costing \$3 to \$5 (this is a rough estimate of a variable quantity; the total solids in a "bag" weigh about 300 mg and the concentration of heroin varies from 0 to 10%). It can be seen that a significant degree of euphoria could be obtained with the equivalent of one or two "bags" if the blockade was low (+), but that with development of a higher blockade (+ + + +) the equivalent of five or more "bags" had lost euphorogenic action.

An incidental finding of practical interest was the absence of euphoria or other drug effects on intravenous injection of methadone, 40 mg, into patients who were receiving daily oral doses of methadone, 40 mg or more. A substantial tolerance to the maintenance drug is necessary for success with blockade treatment; absence of euphoria removes any temptation to abuse the medication, and the tolerance protects patients against accidental overdosage. On two occasions patients have received a double ration in a single day without feeling any narcotic effect or showing any signs of drug action.

III. Clinical Test of Blockade Treatment

A pilot study, using blockade as an adjunct in rehabilitation of chronic heroin addicts, was started two years ago and is continuing. Details of the treatment procedure and the results have been reported periodically.^(3,4) To summarize briefly the present state of the program (May 3, 1966) : A total of 128 chronic heroin users have been admitted to treatment. Of these, 114 continue with regular maintenance (a retention rate of 89%); 14 were dropped from the program, 13 of whom were discharged for behavioral problems unrelated to heroin use (psychopathic behavior, violence, intractable alcoholism or use of barbiturates, hallucinatory schizophrenia) and 1 left voluntarily. Each of the 13 discharged patients has applied for readmission to the program. Every patient admitted to the program had had the usual treatment for heroin addiction on numerous previous occasions; patients have been treated by "detoxification" and psychotherapy in federal, state, and city hospitals, in jails and in halfway houses, in therapeutic communities, and on the street. Their histories of repeated relapse left very little hope that these individuals would be able to live as normal citizens in a community without additional medical help. The present state of these patients is so dramatically improved over their previous condition, and the improvement began so soon after entry into the program, that there can be no doubt that these patients have made a significant response to treatment. Patients who had spent the preceding 5 to 15 years in jail or as addicts on the street are now steadily employed, well dressed, in good health, responsible for families, and saving money. Heroin use has been stopped, except for intermittent experiments made by some patients in the early stages of treatment. No patient has become readdicted to heroin. It might be argued that stopping of heroin use and obtaining jobs (Fig 6) was merely coincidental, but no one who had known these patients before the blockade doubts the value of medication for them. Indeed, physicians with long experience in detoxification - including physicians who had made unsuccessful efforts to rehabilitate some of the patients now on the maintenance program - have become the most enthusiastic supporters of this procedure.

The clinical demonstration, however, is not yet complete. Although the results are encouraging, success in the long range goal of rehabilitation - which necessarily requires several years - cannot be evaluated on the basis

of only two years' experience. Moreover, further therapeutic trials with different selections of patients and with different clinical staffs will be necessary to define the range of applicability of blockade treatment. What can be said at the present time is that this treatment has a rational basis and that the clinical success to date justifies further trial by qualified physicians.

IV. Summary

A stable blockade against the narcotic effects of heroin can be maintained by a single daily oral dose of methadone. Blockade is established by gradual increase in dosage to a stabilization level; thereafter the dose of methadone remains constant.

With a blockade produced by a maintenance dose of 100 mg methadone, patients become refractory to the euphoric action of 80 mg or more of heroin - an amount equivalent to the drug contained in several illegal "bags" in New York.

This procedure is being tested as an adjunct in rehabilitation of "mainline" addicts who had repeatedly relapsed after previous attempts at withdrawal and psychotherapy. With the maintenance treatment the patients have lost their craving for heroin. No patient has become readdicted to heroin. A majority of the patients are now steadily employed. The therapeutic trial, started 2 1/4 years ago, is continuing.

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Generic and Trade Names for Drugs Methadone HCl-Dolopine HCl, Adanon HCl, Althose HCl, Amidone HCl. Hydromorphone HCl - Diluadid, Hymorphane.

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