U. S. TREASURY DEPARTMENT
PUBLIC HEALTH SERVICE

EXPERIMENTS ON THE TOLERANCE AND ADDICTION POTENTIALITIES OF DIHYDRODESOXYMORPHINE-D ("DESOMORPHINE")

SUPPLEMENT No. 118

U. S. TREASURY DEPARTMENT
HENRY MORGENTHAU, Jr., *Secretary*
PUBLIC HEALTH SERVICE
THOMAS PARRAN, *Surgeon General*

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BY

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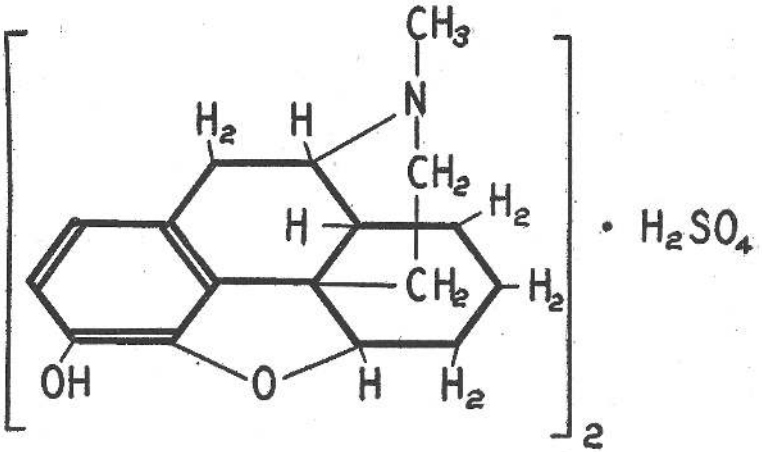
EXPERIMENTS ON THE TOLERANCE AND ADDICTION POTENTIALITIES OF DIHYDRODESOXYMORPHINE–D ("DESOMORPHINE")[1]

By NATHAN B. EDDY, *Consultant Biologist in Alkaloids*, and C. K. HIMMELSBACH, *Passed Assistant Surgeon, United States Public Health Service*

I. Introduction

On account of the remarkable activity and possible advantages of dihydrodesoxymorphine–D ("desomorphine") in relation to other morphine derivatives, described in previous papers (*1*, *2*, *3*), it seemed very desirable to attempt to ascertain the tolerance and addiction potentialities of the substance. Very briefly stated, desomorphine in comparison with morphine is at least 15 times more effective as a general depressant, more than 10 times as effective as an analgesic, and only 3 times more toxic. Krueger and Howes (*1*) report that desomorphine is more powerful in its action on the intestine than morphine, and Wright and Barbour (*2*) report that it is more effective than morphine as a respiratory depressant.

Both the dihydrodesoxymorphine–D sulphate and the morphine sulphate used in these studies were prepared by Dr. Lyndon F. Small at the University of Virginia; the percentages of alkaloidal base contained in the salts are 80.2 and 75.2, respectively. Dihydrodesoxymorphine–D differs in chemical structure from morphine in that the alcoholic hydroxyl has been replaced by H and the adjacent double bond in the aliphatic ring has been saturated with H. Its structural formula is represented thus:



Dihydrodesoxymorphine–D sulphate

[1] The work reported herein is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are the Rockefeller Foundation, the National Research Council, the United States Public Health Service, the United States Bureau of Narcotics, the University of Virginia, and the University of Michigan.

The true nature of drug addiction is not known, and any attempt to determine and evaluate the presence of addictive liability in a compound of unknown potentiality must be based upon the limited extent of our present knowledge. Drug addiction is considered to be an altered condition of the individual, man or animal, which has resulted from the regular administration of a drug, to the extent that normal function depends upon the presence of the compound in the organism in adequate amount, and that a characteristic syndrome of abstinence phenomena occurs in its absence. The appearance of abstinence phenomena, subsequent to withdrawal of the drug which has produced or is maintaining the "addicted state", is the sine qua non of addiction. The specificity of these manifestations of abrupt drug deprivation is proved by their prompt disappearance following the readministration of the substance which produced the addiction.

With this conception of the problem in mind, the laboratory work has been continued by a series of experiments which it was hoped would determine whether or not desomorphine would develop tolerance and addiction, and clinical studies have been carried out with the same end in view. This involved the daily administration of desomorphine in different doses and for different times to dogs, cats, monkeys, rats, and men, usually accompanied by similar daily administration of morphine to others of the same species. The procedures have varied in method and results and are described as separate experiments.

II. Animal Experiments[2]

EXPERIMENT 1

The four dogs, one male (no. 1) and three females (nos. 2, 7, and 8), which were used were taken from their cage each morning, weighed, and allowed to run loose in a small room. Rectal temperature and pulse and respiratory rates were taken, and then the drug was injected subcutaneously. One hour later, temperature, pulse, and respiratory rates were again taken, and in the interval observations were made on behavior, degree of narcosis, emetic effect, salivation, etc. No. 1 was given 2 milligrams per kilogram and no. 2, 5 milligrams per kilogram of dihydrodesoxymorphine–D sulphate. Nos. 7 and 8 received 10 and 50 milligrams per kilogram, respectively, of morphine sulphate. The doses and observations were repeated daily except Sunday. The first dose was given on October 23 and the last December 28, 1933, during which time the size of the doses was not changed. After the injections had been stopped the dogs were observed daily for 2 weeks for withdrawal manifestations. The

[2] All of the animal experiments (nos. 1 to 4) have been carried out in the laboratory of pharmacology of the University of Michigan, with the assistance of Mr. John G. Reid and Mr. Homer A. Howes.

morphine injections were given to facilitate direct comparisons, but the results in the morphinized dogs did not differ in any important particular from those described by various observers (*4*, *5*, *6*), and so they need not be described again here and will be referred to only sufficiently to bring out differences.

Dogs 1 and 2 went to sleep in about 15 minutes following the first injection and were aroused only with great difficulty during the period of observation. When aroused they would try to rise but the hind quarters were too weak to support their weight. The intensity of effect—that is, the depth of depression—produced by the first dose of desomorphine appeared to be between that of the two initial doses of morphine. Nos. 1 and 2 became slightly easier to arouse from day to day but still slept when undisturbed. No. 1 first began to show some control over its hind legs in the third week; it walked a little when forced to get up, but after a few steps its hind legs dragged and it gave up the effort. It began to walk spontaneously at the end of the fourth week but still had to lie down and rest soon after starting. At the end of the period of injection, no. 1 was still sleeping most of the time; it would get up and walk at intervals but only for short distances before becoming too weak to continue. No. 2 began to whine as if uncomfortable the latter part of the second week and moved about nervously with a markedly staggering gait, but was sleeping within an hour after injection. At the end of the period of administration, no. 2 still slept most of the time if undisturbed, and when forced to move showed marked weakness in the hind quarters. It was more easily roused than at first but promptly slumped back again. So far as general condition is concerned, then, both these dogs showed some tolerance, but this was very incomplete and much less than occurred in the morphinized dogs.

Both desomorphine dogs lost weight almost continuously throughout the period of administration of the drug—the first from 10.9 to 9.6 kilograms, the second from 5.5 to 4.2 kilograms. Both gained steadily during the withdrawal period—the first to 10.6 and the second to 5.0 kilograms at the end of the second week. This is a distinct difference from the sequence of weight changes during the prolonged administration of morphine. With the latter drug the animals lost weight rapidly at first but began to gain again as tolerance developed and again suffered a sharp loss in weight at the beginning of withdrawal.

After each dose of dihydrodesoxymorphine–D the rectal temperature fell about 1.5° C., the heart rate decreased about 30 beats per minute, and the respiratory rate was about 6 per minute less 1 hour after injection. In each of these respects there was no evidence of tolerance and no deviation from normal during withdrawal. Morphine produced the greater initial effect on temperature and respira-

tory rate, and a diminishing effect (tolerance) in respect to temperature and heart rate with repetition of the dose. Especially toward the end of the experiment, the Monday dose of morphine caused a greater fall in temperature than followed the administration of the drug on other days, indicating some loss of tolerance due to the omission of an injection on Sunday.

Neither of the first two dogs (given desomorphine) vomited at any time during the experiment, but both salivated slightly after the injection—no. 1 from the first day and no. 2 from the third day to the end of the experiment. Also both salivated moderately before injection from the tenth to the last day, the salivation beginning when the dogs were taken from their overnight pen for weighing. This preinjection salivation is especially interesting in view of the very slight direct emetic effect of the substance.

Both dogs (nos. 1 and 2) were quiet and drowsy during the first few days of withdrawal, becoming more active toward the end of the first week. No. 1 salivated during the period of observation on the first 3 days and no. 2 on the first 11 days of the withdrawal period. Aside from this the dogs showed no abstinence symptoms.

Summary.—The depressant effect of the initial dose of 2 or 5 milligrams per kilogram of desomorphine in the dog is greater than that of 10 milligrams and less, at least in duration of effect, than that of 50 milligrams per kilogram of morphine. Repeated administration of the same doses of desomorphine daily except Sunday for 2 months developed little tolerance, and abrupt withdrawal was followed by no definite abstinence phenomena.

EXPERIMENT 2

Four cats were started April 25, 1933, on daily intramuscular injections of dihydrodesoxymorphine-D, 0.2 milligram per kilogram. The injections continued for 2 months without change in dose. Frequent determinations were made of the response to pressure on the tail before and 1 hour after the daily injection for the detection of possible tolerance to the analgesic effect of the drug, and observations were made on the condition of the animals after injection in regard to restlessness and excitement.

Two of the cats remained in very good condition and gained weight slightly during the 2 months. A third remained well until June 9 (seventh week), then began to lose weight and died on June 27. The fourth cat lost weight slowly throughout and died July 11.

All four cats were excited by the first dose. By the end of the first week the excitement produced by the drug was very much less. It had very nearly disappeared in two animals at the end of the first month, and at that time had diminished to only slight and brief restlessness in the other two. On June 27, the dose for the three

surviving animals was increased to 0.5 milligram per kilogram. Marked excitement was produced by this new dose, but again this effect diminished rapidly so that at the end of 2 weeks the cats were only slightly restless for a brief period after injection.

The initial dose of 0.2 milligram per kilogram had a well-marked analgesic effect so that the pressure required to evoke a response at the end of an hour was at least double that used before injection. No diminution in this analgesic effect was noted during the experiment, although the animals seemed to become a little more sensitive to the pressure reaction before the daily dose was given. The averages for the group of the pressures required to evoke a response initially and 1 hour after injection were 6.0 and 12.0 kilograms, respectively, for the first 0.2-milligram dose, and 4.5 and 10.0 kilograms, respectively, for the last of these doses.

None of these cats vomited at any time during the experiment. Brief licking was noted on May 2 and 3 in cat no. 1 and on May 19 in cat no. 2. No. 4 salivated briefly after injection on April 20 and on May 8 and 18. It salivated more markedly daily after injection from May 29 to June 9, inclusive, and it salivated before injection daily from July 3 to July 10, which was the second week of administration of the larger dose.

For comparison with the above observations, four other cats were started April 25, 1933, on daily intramuscular injections of 2 milligrams per kilogram of morphine sulphate. Of these four animals, two (nos. 5 and 6) remained in good condition, maintained their weight, and were injected daily to July 11. The other two (nos. 7 and 8) lost weight rapidly, one dying on April 30 and the other on May 10. Two replacement animals (nos. 9 and 10) also lost weight rapidly and died, one after 11 and the other after 19 daily injections.

The morphinized cats showed definite excitement after the first dose, and again this diminished rapidly as with desomorphine. Exciting effect was completely absent during the second month in the two animals which remained in good condition.

The analgesic effect of the 2.0-milligram dose of morphine was in all respects comparable to that of the 0.2-milligram dose of desomorphine. It was of equal intensity after the first dose and showed no diminution during the experiment. Also, toward the end of the experiment the morphinized cats showed some increase in sensitivity to pressure applied to the tail before the giving of the daily dose. The average pressures used to evoke responses before and after injection were 7.0 and 15.0 kilograms, respectively, at the time of the first dose and 4.5 and 10.0 kilograms, respectively, at the time of the last dose of morphine.

Nos. 5 and 6 vomited at first very promptly after the morphine was injected—no. 5 daily for 9 days and no. 6 daily for 11 days. After

that, vomiting occurred only occasionally and was not seen at all in no. 5 after June 1 nor in no. 6 after June 8. Cat no. 8 also vomited daily for 8 days, showed nausea only on the next 2 days, and neither nausea nor vomiting on the next 5 days before its death.

Summary.—The analgesic effect in cats of 0.2 milligram per kilogram of desomorphine sulphate or 2.0 milligrams per kilogram of morphine sulphate did not diminish during 2 months of daily intramuscular injection. On the other hand, the exciting effect of both drugs promptly diminished and the emetic effect of morphine also disappeared during the first month of the experiment.

The third attempt to gain some knowledge of the tolerance and addiction potentialities of desomorphine in comparison with morphine consisted of an experiment, or series of experiments, on monkeys extending from November 13, 1933, to February 28, 1935. The experimental procedures and their attendant observations were conducted during four separate periods which, for convenience, will be described as experiments 3a, 3b, 3c, and 3d.

EXPERIMENT 3A

Two monkeys (nos. 5 and 6) *Macacus rhesus*, males, weighing 3.1 and 3.6 kilograms, respectively, were injected daily except Sunday with dihydrodesoxymorphine–D sulphate from November 13, 1933, to February 20, 1934, a period of 14 weeks. Two others, a male and a female, nos. 1 and 2, were injected simultaneously for the same period with morphine sulphate.

The monkeys were allowed to run loose in a small room about 16 feet square, except for a brief period of observation and injection each morning. About 8:30 a. m. the monkeys were caught, weighed, and injected subcutaneously. Daily at first and later twice a week, before and 1 hour after injection, records were made of rectal temperature and of pulse and respiratory rates. The monkeys were watched continuously during the first post-injection hour and notes were made on activity, degree of narcosis, etc. The monkeys were similarly observed during the first 10 days of withdrawal. The starting dose of desomorphine sulphate was 2 milligrams per kilogram. It was increased to 4 milligrams per kilogram in the third week and continued at that level to the end of the experiment. The starting dose of morphine sulphate was 10 milligrams per kilogram. It was increased to 20 milligrams on the second day, to 40 milligrams in the third week, and to 60 milligrams per kilogram in the twelfth week of the experiment.

The first dose of 2 milligrams of desomorphine produced a marked narcosis in both animals. No. 6 was more affected than no. 5, and on the first day the former was almost unconscious. Both animals were prone and sound asleep a few minutes after the injection. When

aroused from this sleep they showed marked muscular weakness. Only very slowly did the degree of depression decrease. Very gradually they became more easily aroused to activity and moved about more of their own accord. However, marked muscular weakness and drowsiness continued as soon as they became inactive. The increase in the dose to 4 milligrams per kilogram in the third week caused a return of the deep sleep after injection in both animals. Again tolerance developed very slowly so that at the end of the period of administration, although they could be aroused more easily, both monkeys were still made very sleepy by the daily dose of 4 milligrams per kilogram.

No. 5 did not lose weight during the period of administration of the drug. No. 6 lost about 10 percent of his weight after the dose had been increased. Neither lost weight upon withdrawal; rather they gained steadily during the 10 days of observation. The rectal temperature fell as a rule 0.6° to 0.8° C. within the first hour after injection, and the pulse and respiratory rates were usually slowed; but in none of these respects was there any evidence of tolerance, unless the fact that there was no greater effect when the dose was increased can be so construed, and there was no deviation from the normal on withdrawal.

Neither on Monday mornings during the experiment, the monkeys not having been injected on Sunday, nor during the withdrawal period did either of the animals show any sign of hyper-irritability. On the other hand, they seemed slightly quieter than normal on the first 2 days of the withdrawal period. No. 6, especially, sat almost continuously hunched up as if cold.

Contrast these effects of desomorphine in the monkey with the results of the morphine administration which have already been described (*7*). The principal differences are these: The first 20-milligram dose of morphine sulphate caused less depression and less muscular weakness than the 2-milligram dose of desomorphine. Tolerance to morphine developed more rapidly and more completely and was evident not only in the narcotic effect but also in the effect on temperature and pulse and respiratory rates. Morphine caused a different sequence of weight changes—a greater fall in weight, which in one animal at least began to be recovered while the administration continued, and a sharp fall at the beginning of withdrawal, followed by a rapid gain. During withdrawal from morphine administration, definite abstinence phenomena were noted. These consisted of hyperirritability, nausea, loss of appetite and loss of weight, shivering, and a fall in rectal temperature. One especially interesting difference was the change in the behavior of the morphinized monkeys on Monday mornings as compared with their behavior of the preceding week, no drug having been given on Sunday. On Monday before

injection these animals were cross, harder to catch, harder to handle, scolded a great deal and were often trembling or shivering. These symptoms of irritability were first apparent at the beginning of the third week of injection; they were observed on each succeeding Monday morning, and in fact showed a definite increase in severity as the experiment progressed.

Summary.—Desomorphine in the monkey had more than 10 times the depressant effect of morphine, developed tolerance less rapidly and less completely, and did not lead to the appearance of abstinence symptoms during withdrawal.

EXPERIMENT 3B

It seemed possible that the development of tolerance or the appearance of withdrawal phenomena after desomorphine administration might be facilitated if the dose could be pushed to a higher level as had been done with morphine. Accordingly, readministration of the drug, 2 milligrams per kilogram, to monkeys no. 5 and no. 6 and another male, no. 7, was begun on March 26, 1934, 5 weeks after the beginning of the last withdrawal period. On April 25 the dose was increased to 4 milligrams, on May 15 to 6 milligrams, on May 22 to 8 milligrams, on June 5 to 10 milligrams, and on June 12 to 12 milligrams per kilogram, respectively. The last dose was given on July 4, 1934, and the animals then passed through another period of acute withdrawal. Again the drug was given in the form of the sulphate and injected subcutaneously, daily except Sunday. Observations on weight, temperature, etc., were made as before.

Morphine sulphate was readministered simultaneously to nos. 1 and 2, the dose this time starting and remaining throughout at 10 milligrams per kilogram.

The first dose of desomorphine, on March 26, produced an effect practically identical with that seen at the outset of the preceding experiment; the animals went into a deep sleep, and when aroused, they walked with a very drunken gait. Toward the end of the first month the monkeys were still very sleepy after the daily injection and showed moderate muscular weakness, but were able to sit up most of the time. The first dose of 4 milligrams per kilogram undoubtedly had a greater effect in respect to both drowsiness and muscular weakness than did the preceding 2-milligram doses but not as great an effect as was first produced by the 2-milligram dose. The increment of increase in effect with the first dose at each new level seemed to become less until when the shift was made to 12 milligrams no difference could be detected from the effect seen on the previous day when 10 milligrams per kilogram were given. It should be remembered of course that, although each step up in the dose was 2 milligrams per kilogram, in the first instance this increase amounted

to 100 percent of the previous dose while on the occasion of the last 2 milligram increase this was only 20 percent of the dose to which the animal was becoming accustomed. At the end of the administration the monkeys were still quite sleepy, especially when inactive for a short time, and still showed moderate muscular weakness, but the effect was not nearly as great as after the first 2-milligram dose of this series.

No. 5 lost weight sharply during the first 2 weeks of administration, from 3.4 to 3.15 kilograms, and then maintained its weight with a slight gain near the end of the period. During the first 10 days of withdrawal it gained to 3.45 kilograms without initial loss. No. 6 also lost sharply at first, from 3.25 to 3.0 kilograms, and then gained steadily to 3.3 kilograms at the end of administration. It also did not lose upon withdrawal, but continued to gain to 3.6 kilograms on the tenth day. No. 7 neither gained nor lost significantly during administration or withdrawal.

The preinjection rectal temperature of each of the three monkeys showed a slight gradual decline during the course of the experiment amounting to about 0.4° C. on the average. Probably due to this, for the post-injection temperatures were practically the same at the end as at the beginning of the experiment, the post-injection fall became less, in spite of the sixfold increase in the dose being administered. During the first week of withdrawal the temperature of no. 5 showed no further decline, that of no. 6 fell off slightly, and that of no. 7 fell about 0.5° C. At the end of the second week of withdrawal the temperature of all three animals was rising toward the level at the beginning of administration of the drug.

On the first day of withdrawal the monkeys were very quiet, sitting hunched up most of the time. On the second day no. 6 became noisy and belligerent, and continued so for 2 days. Aside from this no deviation from normal behavior was observed in these animals, in spite of the much greater increase in the dose over that used in experiment 3a.

As was to be expected, the effect of the 10-milligram dose of morphine in monkeys no. 1 and no. 2 was slight. Tolerance to its depressant action developed rapidly, but signs of irritability did not appear on Monday mornings. Abstinence manifestations upon withdrawal were definite but less severe than in experiment 3a, when these monkeys had received much larger doses.

Summary.—Rapid increase in desomorphine dosage caused a more rapid development of tolerance in monkeys than was previously observed. This was, however, less complete than occurred with morphine when its dose was similarly increased over the same period of time. Some slight changes upon withdrawal of desomorphine in this experiment were observed, but these were not at all comparable to those seen after similar administration of morphine.

EXPERIMENT 3C

The evidence thus far was against the occurrence of significant abstinence symptoms in animals after prolonged administration of dihydrodesoxymorphine–D. However, a new experiment was undertaken in the fall of 1934 to overcome certain deficiencies existing in the previous work; namely, in respect to the intermittent character of the administration of the drug and the incompleteness of the observation for withdrawal symptoms. The procedure was suggested by the work of Seevers (*8*).

At a time when the monkeys had been free from any drug for a long enough time to insure normal behavior, they were continuously observed for 24 hours. Each observer watched the monkeys for a 3-hour period, noting the behavior of the animals, their habits of activity, eating, sleeping, etc., and then he was relieved by another member of the staff. With this observation as a basis, the administration of the drug was begun with the intention of similar observation of the monkeys during the first 48 hours of withdrawal.

Five monkeys were used in this experiment—nos. 1 and 2, the animals which had received morphine in the previous experiments; nos. 3 and 4, which had passed through two periods of dilaudid administration; and no. 5, one of the desomorphine monkeys of experiments 3a and 3b. They were allowed to run free in the room as before, and during the time of continuous observation, as well as for several days and nights previously, the room was continuously illuminated to avoid the sudden addition at the time of observation of this possibly disturbing factor. The drug was injected subcutaneously about 8:30 a. m. daily, including Sundays; and daily, except Sunday, the behavior of the animals was watched throughout the remainder of the forenoon. They were fed at 9 a. m., after receiving the daily injection, and again at 3 p. m. The starting dose was 3 milligrams per kilogram. This was continued for 1 week and then increased 1 milligram per kilogram per day until the dose reached 26 milligrams per kilogram. The first dose was given on October 20 and the last dose on November 21, 1934.

Twenty-four hours after the last dose, the period of continuous observation for possible abstinence symptoms began. Each observer served the same period of the day as during the previous watch, and an attempt was made to record approximately periods of activity, quiet or sleep, eating, noise, and signs of irritability, as well as any unusual symptoms. Subsequently the notes were collated according to the period of the day and the individual animal, for both the control and the withdrawal periods, and were studied not only by the observers themselves but also by other members of the staff who had not participated in the watch.

In this connection we wish heartily to acknowledge the willing cooperation of the whole staff in the experiment, particularly Drs. Edmunds, Sacks, Krueger, and Wright and Mr. Barbour and Mr. Sheldon.

After the first dose, of course, the monkeys were very sleepy and showed marked muscular weakness and a staggering gait. At the end of a week the depression was not noticeably less, nor did it seem to be deepened by the increase in dose. At the end of the month, when the daily dose had been increased more than eightfold, the animals were still very sleepy but probably less so than after the first dose of 2 milligrams, and certainly showed less muscular weakness.

The monkeys lost weight during the first week, an average amount of 200 grams per animal, but for the remainder of the experiment the additional loss was only 50 grams per animal. During the first 2 days of withdrawal the average weight fell slightly, from 3.39 to 3.32 kilograms; then all gained so that on the fifth day the average weight was 3.51 kilograms. At the beginning of the experiment the weights of the five monkeys averaged 3.64 kilograms.

Rectal temperatures were taken only during the last week of administration of the drug and during withdrawal. The average preinjection temperature for the group on November 15 was 39.6° C., and on November 21, when the last dose was given, it was 39.4°. The daily morning temperatures thereafter for the days of withdrawal, group averages, were 39.2°, 39.1°, 38.7°, 38.9°, 38.8°, 39.4°, and 39.4° C. on December 2, so that during the withdrawal there was a sharp decline in body temperature similar in character but less in degree than was seen upon withdrawal of morphine.

As to the behavior of the animals during the continuous observation of the first 48 hours of withdrawal, the consensus of opinion of all observers was that there was scarcely any difference from the behavior of the same animals in the control period. The following were the only exceptions to this conclusion noted: During the first 12 hours of the observation period all of the animals were probably a little more quiet and less attentive to outside disturbances, such as noise and visitors, than normally. No. 1 vomited once at 3:40 p. m., November 22. From 12 midnight to 3 a. m., November 24, this animal was a little more noisy and a little more restless than normally. At 1:55 a. m. this note was made: "Complaining. Looks as if he were having muscular cramps." No. 2 slept less continuously than usual during the second night of observation. No. 3 was reported to be slightly irritable and briefly quarrelsome during the evening of November 23. Concerning no. 4, a note at 11:05, November 23, stated, "Irritable", but this note did not occur again. The note for No. 5, at 12 midnight, November 23, was, "Irritable; has

eaten little." Again this note was not repeated, and this animal was normally the most irritable of the group.

Summary.—The intensive administration of desomorphine, with rapid increase in dose, resulted in a high degree of tolerance; but even under these circumstances only slight deviations from normal, which were possibly low-grade abstinence phenomena, were observed during withdrawal.

It has been suggested that one means of testing the addiction potentiality of a new substance of the morphine group would be to substitute it for morphine in an individual addicted to the latter drug, subsequently to withdraw the new substance abruptly, and to evaluate the abstinence phenomena, if any, in comparison with those to be expected after abrupt withdrawal of morphine itself. The suggestion assumed that if the new substance satisfied the preformed addiction—that is, prevented the occurrence of abstinence manifestations and if its later withdrawal was followed by the appearance of these symptoms—one should conclude the presence of addiction potentiality in the new substance. The suggestion and the conclusion are valid only if the previous administration of morphine does not affect the ability of the new substance to cause abstinence phenomena and only if abstinence symptoms after acute withdrawal of the new substance were the same in character and degree whether or not there had been previous morphine administration and addiction in the individual under observation, or, in other words, only if it can be shown that a substance which will maintain preformed addiction is essentially addictive in itself.

The fourth part of our experiment on monkeys was designed to test the assumptions underlying the suggestion just referred to.

EXPERIMENT 3D

To the same five monkeys that were used in experiment 3c (nos. 1 to 5) and to four others (nos. 7 to 10 [3]) morphine sulphate was administered intensively, then dihydrodesoxymorphine–D sulphate was substituted for it, and later the substituted drug was abruptly withdrawn. The procedure was made as nearly as possible like that of experiment 3c in regard to graduation of dosage, time and mode of injection, and nature and time of observation. The administration of morphine sulphate was begun on January 7, 1935, the starting dose being 15 milligrams per kilogram. On January 15 the dose was increased to 20 milligrams per kilogram, and it was increased thereafter 5 milligrams per kilogram per day. On February 4, when the dose of morphine for the other monkeys was 120 milligrams per kilogram, no. 1 was given, instead, dihydrodesoxymorphine–D. Not knowing the extent of cross tolerance present, if any, 10 milligrams

[3] No. 7 was the no. 7 of experiment 3b; nos. 8, 9, and 10 were new monkeys, not previously subjected to narcotic administration.

per kilogram of the substitute were given at the regular injection time. There was no apparent depression following this dose and another 10 milligrams per kilogram were given an hour later. The next morning and each succeeding morning of the experiment this monkey was irritable, objecting to being handled and scolding markedly, whereas previously he had been quiet and uniformly docile. On February 5 no. 1 was given 20 milligrams per kilogram of desomorphine sulphate in one dose; on February 6 he was given 25 milligrams, and on February 7 and each succeeding morning, 26 milligrams per kilogram. On February 12, when all of the other monkeys had been receiving 130 milligrams per kilogram of morphine sulphate daily for several days, nos. 2, 3, 4, and 5 were each given 26 milligrams per kilogram of dihydrodesoxymorphine–D sulphate. The administration of morphine to nos. 7 to 10 was continued without further change in the dose. Each of the animals received its last dose of the drug on February 17, and on February 18 a 48-hour period of continuous observation was begun by the same persons and in the same way as at the end of experiment 3c.

The first dose of 15 milligrams per kilogram of morphine on January 7 produced nearly as much depression as had been observed previously after 3 milligrams per kilogram of desomorphine. The dose was well borne, and tolerance developed rapidly in all except no. 3. This animal was very markedly depressed at first, refused food for several days, and in some way injured its forearm. (*Cf.* increased susceptibility to dicodide (*7*) and increased sensitivity of monkeys to morphine under similar conditions described by Kolb and DuMez (*9*).) Its daily dose of morphine was omitted on the third day of the experiment, and thereafter it was held at a low level longer than with the others. However, no. 3 also had reached the 130-milligram-dose level before the substitution of desomorphine was made.

The weight of the animals decreased from an average of 3.40 to 3.19 kilograms during the first week of morphine administration and to 3.08 kilograms during the second week. At the end of the third week their average weight was 3.12, and on the last day that the whole group was given morphine it was 3.09 kilograms. The first five monkeys lost slightly during the first 48 hours of the substitution period, an average of 50 grams per animal. The others maintained their weight during this time.

In the substitution group, nos. 1 to 5, the immediate effect of the daily dose of 26 milligrams per kilogram of desomorphine was definitely greater depression than had been produced in the same animals by 130 milligrams per kilogram of morphine; yet, the next morning after the substitution was effected, each of the animals showed signs of irritability. These did not, however, appear to change in intensity from day to day during the period of substitution.

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Another interesting observation was that the rectal temperature fell sharply at the beginning of the substitution period, recovered slightly during this period, and fell off again when the drug was completely withdrawn. The temperature of the monkeys kept on morphine was maintained to the end of the period of administration, when there was a sharp decline, with gradual recovery during the abstinence period. The average temperatures for the two groups were as follows: (1) Substitution group—February 11, last dose of morphine, 39.9° C.; February 13, 24 hours after the first dose of desomorphine, 38.9° C.; February 17, last dose of desomorphine, 39.2° C.; February 19, 38.9° C.; February 20, 39.0° C.; February 23, 39.4° C.; March 2, 39.8° C. (2) Morphine group—February 11, 39.9° C.; February 13, 39.9° C.; February 17, last dose of morphine, 39.7° C.; February 19, 38.7° C.; February 20, 38.5° C.; February 23, 39.3° C.; March 2, 40.0° C.

The greater depression observed upon the substitution of desomorphine for morphine suggests, on the one hand, incomplete cross tolerance of the morphinized monkeys for the substituted drug, and the temperature changes described suggest, on the other hand, incomplete satisfaction of the morphinized monkeys; that is, incomplete suppression for 24 hours of the abstinence phenomena by dihydrodesoxymorphine–D.

All of the monkeys were observed continuously during the first 48 hours of withdrawal, and the notes were subsequently collated according to the period of the day and the individual, as in experiment 3c. Also these notes have been studied by various members of the staff as were those for experiment 3c, and there is complete agreement in regard to the conclusions to be drawn from them. Both groups of monkeys showed frank abstinence symptoms. These consisted of irritability, manifested by scolding, quarreling, and restless activity, shivering, and vomiting. The only difference between the two groups that could be detected was the greater incidence of vomiting in the animals which had received morphine only.

The conclusion is definite that the previous administration of morphine affected in some way the results when its administration was substituted by dihydrodesoxymorphine–D. The abrupt withdrawal of dihydrodesoxymorphine–D, the administration of which was superimposed upon a previous morphine addiction, resulted in the appearance of abstinence manifestations not significantly distinguishable from those appearing after abrupt withdrawal of morphine alone, and in marked contrast to the very slight modifications of behavior which occurred upon abrupt withdrawal of dihydrodesoxymorphine–D when it was the only drug used. This contrast is very clearly illustrated in the following excerpt from the notes in regard to monkey no. 5 for the same 3-hour period of the day under

normal conditions, after withdrawal of desomorphine alone, and after withdrawal of desomorphine superimposed upon a morphine addiction. The period selected is 12 midnight to 3 a. m.

CONTROL PERIOD

12 midnight: Active; eating.
12:15 a. m.: Quiet, huddled with other monkeys.
1:40 a. m.: Same. Has screamed twice, probably pinched by one of the others.
2:20 a. m.: Still quiet; not disturbed by visitor.
2:30 a. m.: Quiet until now; moves away from huddle and again becomes quiet.
3:00 a. m.: Quiet.

NOVEMBER 23, DURING FIRST 24 HOURS OF WITHDRAWAL FROM DIHYDRODESOXYMORPHINE–D ALONE

12 midnight: Irritable, guttural noise; has eaten little; huddled most of time.
12:05 a. m.: Quiet; huddled with other monkeys.
1:10 a. m.: Still quiet in huddle.
1:11 a. m.: Leaves huddle and goes down to floor to eat; takes drink.
1:20 a. m.: Eating.
1:25 a. m.: Goes back to huddle, but not sleeping.
2:05 a. m.: Being defleaed and making noise like hiccup.
2:45 a. m.: In huddle with others; mostly quiet.
3:00 a. m.: Same.

NOVEMBER 24, DURING SECOND 24 HOURS OF WITHDRAWAL FROM DIHYDRODESOXYMORPHINE–D ALONE

12 midnight: Quiet.
12:10 a. m.: Eating.
12:30 a. m.: Still moving about.
12:50 a. m.: Quiet, in huddle with other monkeys.
1:30 a. m.: Still quiet.
1:35 a. m.: Briefly active.
1:45 a. m. Back in huddle; quiet.
1:50 a. m.: Briefly active.
2:00 a. m.: Back in huddle; quiet.
2:30 a. m.: Same.
2:55 a.m.: Active.
3:00 a.m.: Eating.

FEBRUARY 19, DURING FIRST 24 HOURS OF WITHDRAWAL FROM DIHYDRODESOXYMORPHINE–D, SUPERIMPOSED UPON MORPHINE ADDICTION

12 midnight: Mainly quiet.
12:10 a. m.: Screaming.
12:30 a. m.: Restless.
12:45 a. m.: In group with other monkeys, but restless.
1:00 a. m.: Still restless.
1:17 a. m.: Very restless. Looks very uncomfortable, retching.
1:45 a. m.: A little quieter.
2:00 a. m.: Quiet.
2:10 a. m.: Retching.

2:30 a. m.: Again restless.
2:50 a. m.: Briefly quiet.
3:00 a. m.: Restless and chattering.

FEBRUARY 20, DURING SECOND 24 HOURS OF WITHDRAWAL OF DIHYDRODESOXYMORPHINE–D, SUPERIMPOSED UPON MORPHINE ADDICTION

12 midnight: Mainly quiet.
12:20 a. m.: Sleeping by himself.
12:25 a. m.: Moves into huddle with others, chattering.
12:35 a. m.: Very noisy.
12:40 a. m.: Moving about.
1:00 a. m.: Constant chattering.
1:25 a. m.: Briefly quiet.
1:30 a. m.: Moving about, screaming.
1:45 a. m.: Quarreling with no. 10.
1:50 a. m.: Fighting with no. 3.
1:55 a. m.: Briefly quiet.
2:00 a. m.: Again quarreling with anyone near.
2:10 a. m.: Still quarrelsome.
2:15 a. m.: Very noisy.
2:25 a. m.: Again quarreling.
2:45 a. m.: Moving about.
3:00 a. m.: Chattering, retching.

EXPERIMENT 4

The fourth attack upon the problem of the addiction potentiality of desomorphine was based upon the work of Himmelsbach (*10*), who reported that repeated administration of morphine to rats caused the development of preinjection hyperirritability. This manifested itself by increased struggling of the rats, tied down by the Barlow method (*11*) before the giving of the daily dose. Himmelsbach believed this hyperirritability to be a sign of addiction in the rat, since hyperirritability is definitely a part of the abstinence syndrome in man and other animals. We have, in the main, been able to confirm his observation in regard to the effect of the administration of morphine. Although we found greater individual variations, greater variation in the struggling of the same rat from week to week, and a smaller increase in the number of struggles than did Himmelsbach, there was undoubtedly an upward trend in the rate of struggling per unit of time. We injected 22 rats, 8 males and 14 females, daily for 18 weeks with morphine sulphate in increasing dose from 20 to 200 milligrams per kilogram. The struggles per rat per minute increased during the experiment from 6.5, control days before the injections started, to 13.7, when the dose reached the 200 milligram level. Some rats react to being tied down by crying repeatedly with little body movement; some react by violent body movements; and some react in both ways. In addition, there is a wide variation in the amplitude of movement communicated to the recording lever by respiratory

activity when the lever is attached, as in the Barlow method (*11*), to the hair over the lower end of the sternum. Consequently, very close surveillance is required to count the struggles of the rat per unit of time, and in our hands at least, great difficulty was encountered subsequently in checking the count from the record.

These considerations and difficulties have led us to employ a different method of recording the struggles. The rat is supported on a balanced beam, the ends of which rest on air cushions. The movements of the animal then change the pressure conditions in the air

APPARATUS FOR RECORDING RAT STRUGGLES

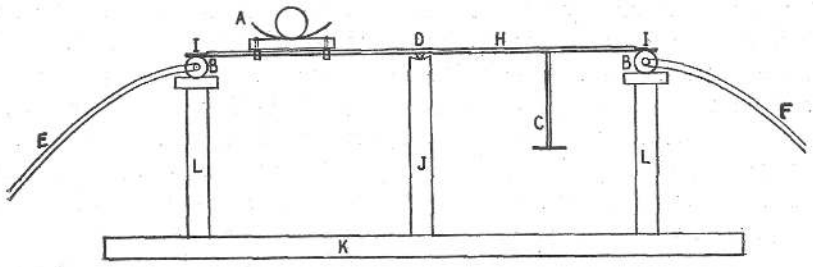

FIG. 1. SIDE VIEW SCALE 1"

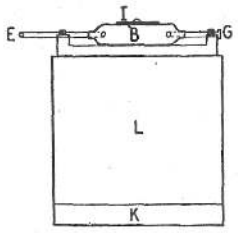

FIG. 2 END VIEW

A RAT BOARD
B BALLOON
C COUNTERWEIGHT
D PIVOT
E TUBING TO RECORDING TAMBOUR
F RUBBER DAMPENINGTUBE
G SEALED GLASS TUBE
H METAL CROSS BEAM
I FLAT METAL PLATE
J METAL SUPPORT
K WOODEN BASE
L WOODEN UPRIGHT

cushion and these changes are transmitted to a recording tambour. The method requires practically no attention once the record is started, is sensitive enough to record all body movements, but is not noticeably affected by respiratory activity. The record is sharp and presents no difficulty in counting the struggles per unit of time except for the proper evaluation of grouped movements, a difficulty which is obviated by the establishment of a uniform criterion for evaluation based upon experience with records of this type. The device is illustrated in figures 1 and 2.

It consists of a brass beam (H) with a cross-member at right angles to it at its center. Each end of the cross-member terminates in a knife edge resting in a V-bearing (D) at the top of a central upright (J). Each end of the beam is fitted with a thin smooth flat plate (I)

which rests on a balloon (B). The balloon nearer the rat board (A) is connected to a recording tambour through tube E and a three-way stopcock. The system is air-filled and the stopcock serves to adjust it to atmospheric pressure. The other balloon is connected to a 3-foot length of rubber tubing (F) of 6-millimeter bore. The end of this tube is left open. This second balloon and the restricted column of air in its connecting tubing damps the movements of the beam. The balloons used are the same as those described by Krueger (*12*) in another connection, except for the omission of the central perforated tube. The supports (L, L) are of such a height that when the beam is horizontal the end plates slightly flatten the balloons.

To make a record of the rat's struggles, the animal is tied to a board of the Barlow type and this is bolted in position on the beam. Then the rat is carefully balanced by adding weights at C. The tambour system is adjusted to atmospheric pressure and 20 grams are removed from the counterbalance (C). This degree of unbalance with the accompanying slight rise in pressure in the tambour system gives the latter an optimum degree of sensitivity to movements of the beam. Now all body movements of the rat move the beam, and these movements are transmitted to the tambour and recorded on a smoked surface. On the other hand, cries and respiratory activity unaccompanied by body movement do not record.

On March 26, 1935, the daily administration of dihydrodesoxymorphine-D sulphate, 1 milligram per kilogram intraperitoneally, to each of 12 male albino rats was begun. The administration, with changes in dosage as will be described, was continued until July 28, 1935, to determine the extent to which tolerance and preinjection hyperirritability might develop under the influence of this drug. For 13 weeks the daily dose was given between 8:30 and 9 a. m. Beginning on July 1 (14th week) each rat was given two doses daily, one at 8:30 a. m. and one at 4:30 p. m., and from July 18 to July 28 each animal was given three doses daily, one at 8:30 a. m., one at 4:30 p. m., and one at 11 p. m. Throughout, the individual dose continued to be 1 milligram per kilogram. One animal was found dead on the third morning of the experiment; another developed an intercurrent infection and was discarded. The other 10 satisfactorily withstood the 13 weeks of daily injection. Their average weight decreased from 351 grams on the first day to 317 grams on the 8th day, remained at about the latter level during the second and third weeks, and then began to increase slowly. The average weight of the group reached the preinjection level at the beginning of the 12th week and was 358 grams on July 1 when we began to give two doses a day.

The animals withstood the two doses a day less well and reacted to the regime of three intraperitoneal injections in 24 hours very poorly.

During the three-dose period several of the animals died—one on July 22, one on July 24, one on July 27, and one on July 29; so that only six rats are considered to have passed through the latter part of the experiment at all satisfactorily.

The average weight of these six rats was 361 grams on July 1, 347 grams on July 18 (the first three-dose day), 327 grams on July 28, the last day of injection, and 306 grams on August 1, 4 days after the injections were stopped.

Before any injection was given, each animal was tied down on two occasions, March 23 and March 26, and their struggles were recorded for a 10-minute period as previously described. One week after the first dose was given and once a week thereafter struggles were recorded before injection. On each of these occasions, 30 minutes after injection, each animal was released and its righting time was noted as described elsewhere (*13*) in connection with the measurement of depressant action. These observations on righting time were used as a criterion of tolerance to the drug. Table 1 summarizes the results in this connection. Obviously, tolerance developed, this being more apparent in the average righting time than in the percentage of the group righting immediately, but this tolerance is less rapid in its development and less complete than would be expected from daily administration of an equally depressant, constant dose of morphine.

Table 2 summarizes the results in regard to preinjection struggling or the evidence for preinjection hyperirritability. In preparing the table, the figures for only the six rats which completed the experiment were used.

While the administration was held at one dose per day of 1 milligram per kilogram, very little change in the average number of struggles per unit of time was noted. However, when two doses per day were given, and more particularly when three doses were given, there was a definite increase in the preinjection struggling. Whether or not this is evidence of addiction in the rat is still an open question and work in this connection is being continued. However, the short duration of the effect of desomorphine has already been referred to (*3*), and it is apparent from the table that some change in the rats occurred when the doses were given at less than a 24-hour interval, which did not appear when only one dose of the drug per day was given.

Summary.—Rats injected daily with a constant dose of desomorphine developed tolerance slowly to the depressant effect of the drug. Increased preinjection struggling, described by Himmelsbach as an addiction phenomenon in the rat, did not develop to a significant degree until the drug was administered at intervals of less than 24 hours. The rats withstood poorly the injections given at such short intervals.

TABLE 1.—*Righting time 30 minutes after injection of rats repeatedly injected with desomorphine*

Date	Average righting time	Percent of group righting immediately	Remarks
	Seconds		
Mar. 23	0	100.0	Control.
Mar. 26	202+	0.0	After first dose.
Apr. 2	233+	0.0	
Apr. 9	153+	10.0	
Apr. 16	166+	10.0	
Apr. 23	142+	0.0	
Apr. 30	125+	30.0	
May 7	123+	40.0	
May 14	97+	50.0	
May 21	147+	50.0	
May 28	115+	0.0	
June 4	120+	40.0	
June 25	131+	20.0	
July 2	83+	33.3	Second day of 2 doses per day.
July 9	54	33.3	
July 16	107	16.6	
July 23	16	33.3	Fifth day of 3 doses per day.
July 29	0	100.0	12 hours after last dose.

TABLE 2.—*Preinjection hyperirritability, struggles per minute, of rats tied down during repeated administration of desomorphine*

Date	Average struggles per rat per 10 minutes preceding injection	Remarks	Date	Average struggles per rat per 10 minutes preceding injection	Remarks
Mar. 23-26	52.0	Control.	June 25	79.4	
Apr. 2	63.7	After 1 week of daily injection.	July 2	82.0	Second day on which 2 doses were given.
Apr. 9	55.3		July 9	86.1	
Apr. 16	53.4		July 16	97.6	
Apr. 23	73.5		July 23	125.7	Fifth day of 3 doses per day.
Apr. 30	52.6				
May 7	40.5		July 29	110.1	12 hours after last dose.
May 14	48.0		July 30	81.7	36 hours after last dose.
May 21	45.9		July 31	76.4	60 hours after last dose.
May 28	54.5		Aug. 1	68.0	84 hours after last dose.
June 4	68.0		Aug. 5	88.0	1 week after last dose.

III. Clinical Observations

EXPERIMENT 5

The clinical approach to the problem of the addiction potentiality of desomorphine started with the substitution of the drug for morphine in active cases of human addiction. The method employed in this part of the study has been described previously (*14, 15*) and referred to earlier in this paper. (See discussion preceding experiment 3d.)

Five male addicts with active morphine "habits" were accepted as study subjects. Their addiction was supported by the subcutaneous administration of morphine, four doses per day, for a day or two, and then desomorphine was completely substituted for morphine in 1 day. No more morphine was given and the subjects were not informed that

a substitution had been made. An attempt was made to maintain stability by adjusting the size of the four doses per day of the substituted drug so that they would equal morphine in effectiveness. After 8 to 21 days desomorphine was abruptly and completely withdrawn. No measures directed toward therapeutic relief of "abstinence" were undertaken during the first 72 hours after withdrawal.

Complete physi al isolation, together with thorough observa ion and supervision for 24 hours daily, insured the uniformity and control of all conditions. Weight and blood pressure determinations were made each morning before breakfast, and all physical examinations were made after the subject had been at rest in bed for at least 5 minutes. Observations for evidence of "abstinence" were made three times daily throughout the course of the study.

In order to facilitate the evaluation of the degree of "abstinence", the syndrome of abstinence phenomena has been divided into four groups of signs as follows, the division being based so far as possible upon the apparent severity of the suffering of the individual when the various signs are present:

Signs grouped by degree of "abstinence"

Mild (+)	Moderate (++)	Marked (+++)	Severe (++++)
Yawning.	Goose flesh.	Air hunger.	Emesis.
Lacrimation.	Muscle tremor.	Restlessness.	Defecation.
Rhinorrhea.	Dilation of pupils.	Insomnia.	Weight loss (5 pounds or more in 24 hours).
Perspiration.	Anorexia.	Elevation of blood pressure.	

The degree and duration of "abstinence" exhibited following withdrawal presumably gives a rough measure of the degree of addiction which had been present. The extent or degree of addiction is modified by the nature and potency of the drug employed, and probably by the duration of the drug's action, by the size of the doses, by the rhythmicity of administration, by the duration of the period of administration, and by the type of individual taking the drug.

A summary of the drug administration to the five subjects of this study is given in table 3, and a summary of the observations made is presented in tables 4 to 8.

TABLE 3.—*Summary of drug administration*

Case no.	Stabilization dose of morphine	Dose of desomorphine substitution	Duration of substitution
	Milligrams per day	*Milligrams per day*	*Days*
1	400	80 increasing to 180	10
2	400	80 increasing to 180	10
3	200	70 increasing to 180	8
4	400	160 increasing to 220	21
5	400	160 increasing to 210	20

Legend for tables 4 to 8.—Dosage given in milligrams of the salts; m=morphine sulphate and d=dihydrodesoxymorphine–D sulphate; *=presence of manifestation during the specified 24 hours. Values for respiratory rate are the averages of 3 daily determinations at 6 a. m., 12 m., and 5 p. m. D=dilated pupils. Appetite: F=fair, P=poor, and 0=none. Appearance and behavior: N=nervous, R=restless, and W=weak. Weight is given in pounds, stripped; sleep in hours, observed; and blood pressure in mm of Hg. Defecation and emesis are given in whole numbers covering the 24-hour periods.

TABLE 4.—*Case no. 1: Dihydrodesoxymorphine–D substitution*

	April 1934																
	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Doses—6 a. m.	100m	100m	20d	20d	25d	30d	40d	40d	40d	40d	40d	50d					
Doses—12 m.	100m	100m	20d	25d	30d	40d	40d	40d	40d	40d	40d	40d					
Doses—5 p. m.	100m	100m	20d	25d	30d	40d	40d	40d	40d	40d	40d	40d					
Doses—10 p. m.	100m	100m	20d	25d	30d	40d	40d	40d	40d	40d	50d	50d					
Yawning				*		*	*				*		*	*	*	*	
Lacrimation			*	*		*	*			*	*	*	*	*	*	*	
Rhinorrhea			*	*		*	*			*	*		*	*	*	*	
Perspiration				*		*					*		*	*		*	
Goose-flesh														*	*		
Muscle tremor													*	*	*	*	
Size of pupils	C	C	C		C								D				
Respiratory rate	15	13	15	16	15	17	17	14	16	18	18	17	27	24	25	23	25
Appetite													P	F			
Emesis													2				
Defecation		2	2	2	1	3		2	3	2	2	2	6	11	2	2	2
Appearance and behavior				N									N/R	N/R	N/R	N/R	
Weight	139	141	138	134	137	138	138	139	140	139	140	141	141	135	136	137	137
Sleep	6	8	5½	6½	7½	7½	7½	7½	7½	7½	7½	6½	7	½	1½	2	6½
Blood pressure {	160	132	128	130	108	120	130	132	130	150	160	144	154	146	148	142	132
Blood pressure {	102	94	88	100	74	94	98	100	100	98	108	100	100	100	100	100	98
Degree of abstinence	0	0	+	+	0	+	+	0	0	+	+	0	++++	++++	+++	+++	0

TABLE 5.—*Case no. 2: Dihydrodesoxymorphine–D substitution*

	April 1934															
	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Doses—6 a. m.	100m	100m	20d	20d	25d	30d	40d	40d	40d	40d	40d	50d				
Doses—12 m.	100m	100m	20d	25d	30d	40d	40d	40d	40d	40d	40d	40d				
Doses—5 p. m.	100m	100m	20d	25d	30d	40d	40d	40d	40d	40d	40d	40d				
Doses—10 p. m.	100m	100m	20d	25d	30d	40d	40d	40d	40d	40d	50d	50d				
Yawning				*		*							*	*	*	
Lacrimation					*	*	*	*		*	*		*	*	*	*
Rhinorrhea				*		*	*	*		*			*	*	*	*
Perspiration					*									*		
Goose-flesh						*	*						*	*	*	*
Muscle tremor													*	*		
Size of pupils				D									D			
Respiratory rate	15	13	16	14	13	18	17	16	16	18	18	18	20	25	26	24
Appetite						F							P	F		
Emesis													1	3		
Defecation	1		3	4		2	4	3			2		6	8	5	4
Appearance and behavior				N/R									N/R	N/R	W/R	
Weight	116	119	119	116	116	115	115	116	116	117	116	117	117	113	115	117
Sleep	6	7½	6	5½	6	7	6	7	7	6½	6½	5½	6½	2½	2	2½
Blood pressure	156	132	138	116	138	136	148	130	124	132	140	150	144	126	128	158
	98	98	104	94	92	98	108	98	94	100	100	102	96	90	100	108
Degree of abstinence	0	0	0	++	+	++	+	+	0	+	0	0	++++	++++	+++	+

TABLE 6.—*Case no. 3: Dihydrodesoxymorphine–D substitution*

	April 1934													
	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Doses—6 a. m.	50m	10d	20d	40d	40d	40d	40d	40d	50d					
Doses—12 m.	50m	20d	40d	40d	40d	40d	40d	40d	40d					
Doses—5 p. m.	50m	20d	40d	40d	40d	40d	40d	40d	40d					
Doses—10 p. m.	50m	20d	40d	40d	40d	40d	40d	50d	50d					
Yawning		*	*			*	*	*	*	*	*	*	*	
Lacrimation		*	*	*	*	*	*	*	*	*	*	*	*	*
Rhinorrhea		*	*	*	*			*		*	*	*	*	
Perspiration		*						*		*	*	*		
Goose-flesh			*	*				*	*	*	*	*		
Muscle tremor										*	*	*	*	
Size of pupils														
Respiratory rate	16	18	19	18	18	18	18	18	18	24	27	21	24	23
Appetite			F							0	0	0	P	P
Emesis			2							2	9	3	3	2
Defecation	1		2	2		1	1	4	1	12	13	6	4	4
Appearance and behavior			N							N/R	W/R	W/	W/	W/
Weight	140	137	135	135	134	134	134	133	132	133	126	125	126	126
Sleep	7	7	4	6½	7	7½	6	6	6	6	0	3½	2½	4
Blood pressure	136	144	128	120	120	110	122	110	112	120	130	130	126	122
	102	92	78	74	78	78	80	78	70	80	82	86	82	78
Degree of abstinence	0	+	++++	++	+	+	+	++	+	++++	++++	++++	++++	++++

TABLE 7.—*Case no. 4: Dihydrodesoxymorphine–D substitution*

	June 1934									July 1934															
	22	23	24	25	26	27	28	29	30	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Doses—6 a. m.	100m	20d	40d	40d	40d	40d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	60d	60d	60d	60d			
Doses—12 m.	100m	40d	40d	40d	40d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d			
Doses—5 p. m.	100m	40d	40d	40d	40d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d			
Doses—10 p. m.	100m	40d	40d	40d	40d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d			
Yawning		*	*			*	*	*			*	*	*	*	*	*		*	*	*	*	*	*	*	
Lacrimation						*		*	*		*	*	*		*	*	*	*	*	*	*	*	*	*	*
Rhinorrhea	*		*						*														*		
Perspiration		*	*				*	*															*	*	
Goose flesh			*																				*	*	
Muscle tremor		*																					*	*	*
Size of pupils		D																					D	D	D
Respiratory rate	15	15	16	19	18	18	21	21	20	20	19	20	23	18	18	19	20	19	18	18	21	20	19	27	24
Appetite																							0	P	F
Emesis																							3	5	
Defecation	1		1	1		1	1		1	2	1	1		1	1	1			3	1	1	2	3	3	2
Appearance and behavior																							N/R	N/R	W/R
Weight	131	132	133	134	134	133	133	134	134	134	133	133	133	133	134	134	133	132	132	133	133	132	133	127	125
Sleep	7	5	7	7	7½	5	5	5	5	6	5½	5½	5½	5½	5	5½	5	4½	6	5	5	4½	4½	0	3
Blood pressure	130	110	124	128	120	126	126	134	126	142	132	132	126	132	128	130	126	122	120	124	126	122	120	136	124
	76	60	78	78	78	80	80	80	74	78	80	78	82	78	72	78	76	74	76	78	74	76	76	66	76
Degree of abstinence	0	++	+	0	0	+	+	+	+	0	+	+	+	0	+	+	0	+	+	+	+	+	++++	++++	++

TABLE 8.—*Case no. 5: Dihydrodesoxymorphine–D substitution*

	June 1934								July 1934															
	23	24	25	26	27	28	29	30	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Doses 6 a. m.	-----	100m	40d	40d	40d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	60d	60d	60d	60d	-----	-----	----
Doses 12 m	100m	40d	40d	40d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	-----	-----	----
Doses 5 p. m.	100m	40d	40d	40d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	-----	-----	----
Doses 10 p. m.	100m	40d	40d	40d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	-----	-----	----
Yawning	-----	-----	-----	-----	*	*	*	*	-----	*	*	*	*	*	*	*	*	*	*	*	*	*	*	----
Lacrimation	-----	*	-----	-----	*	*	*	*	*	*	*	*	-----	-----	*	*	*	*	-----	-----	*	*	*	*
Rhinorrhea	-----	*	*	-----	-----	-----	*	*	-----	*	*	-----	-----	-----	*	-----	-----	*	-----	-----	*	*	*	*
Perspiration	-----	-----	-----	-----	-----	*	*	-----	*	-----	-----	-----	-----	-----	-----	-----	-----	-----	*	-----	*	*	-----	----
Goose flesh	-----	*	-----	-----	-----	-----	*	-----	-----	-----	-----	*	-----	-----	-----	-----	-----	-----	*	-----	-----	*	*	----
Muscle tremor	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	*	*	*
Size of pupils	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	D	-----	----
Respiratory rate	20	20	22	22	19	19	18	20	21	19	19	19	17	20	18	16	18	16	21	17	20	20	28	24
Appetite	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0	0	P
Emesis	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	4	----
Defecation	-----	1	1	1	1	1	1	1	1	-----	1	2	1	1	1	1	1	2	2	1	1	1	1	1
Appearance and behavior																						/R	N/R	W/
Weight	128	128	126	128	126	126	127	127	128	127	127	126	126	126	127	126	126	126	125	125	127	127	122	121
Sleep	7	7½	7	7¼	5½	4½	5	5	5	5	6	5½	5	6	5½	4	5	6	4½	5	5	4½	4	P-8
Blood pressure	126	106	124	118	130	118	128	126	114	120	116	116	116	114	114	118	116	116	112	118	120	118	118	114
	68	74	72	70	78	70	78	88	76	78	76	74	76	76	78	74	78	76	74	76	76	78	76	70
Degree of abstinence	0	+	0	0	+	+	+	+	+	+	+	+	0	0	+	+	+	+	+	0	+	+++	++++	++

Figure 3 shows the abstinence manifestations during stabilization on morphine alone and following its withdrawal. Compare with this

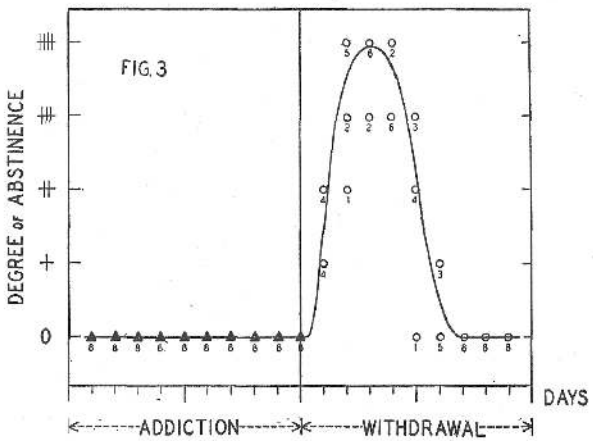

FIGURE 3.—Addiction to and withdrawal of morphine alone—8 cases. Each point with the figure beneath it indicates the case observations at that point: ▲, on days of morphine stabilization; O, on days without drug. The curve is the estimated mean of all the observations.

figure 4, which shows the degree of abstinence observed during the substitution of desomorphine for morphine and following the withdrawal of desomorphine.

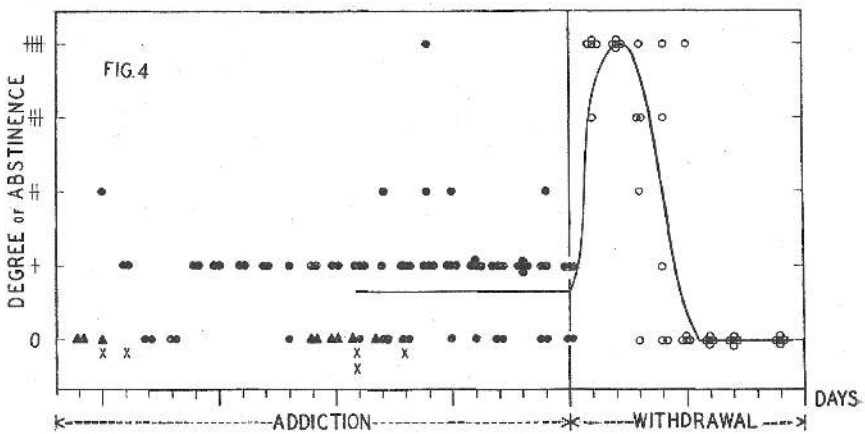

FIGURE 4.—Substitution of desomorphine for morphine in addiction to latter drug and withdrawal of desomorphine—5 cases. Each point represents the day's observation on a single case: ▲, on days of morphine stabilization; ●, on days of desomorphine substitution; O, on days without drug; ×, transition from morphine to desomorphine. The curve is the estimated mean of all the observations.

Upon transition from morphine to desomorphine all of the subjects exhibited mild or moderate abstinence and one individual became severely abstinent the day after the change was made. It is apparent that, although there are a few observations of an individual

being free from abstinence symptoms for a single day, the group was never completely stable—that is, normal in feeling and appearance—during the substitution period. Following withdrawal of desomorphine, severe abstinence set in quite promptly in all cases, but the total course of "abstinence" was somewhat less than is usually seen following abrupt morphine deprivation.

The duration of the action of desomorphine is briefer than that of morphine, and it is probable that this was an important factor in the failure to maintain the stability of the subjects with the former drug when administration was at the same interval, namely, four times a day. Abstinence consistently appeared within 4 hours after each injection of desomorphine, and this difficulty was not circumvented by major increases in the amounts of the individual doses It is possible that, had the frequency rather than the size of the injections been increased, stability would have been maintained satisfactorily. Although the attempt to compensate for the brief duration of action of desomorphine by increased dosage makes any comparison of doses or side actions with those of morphine unsound, it should not affect the significance of the addiction study.

The total course of abstinence is somewhat shorter after desomorphine than following abrupt morphine deprivation, but the duration of intense manifestations is about the same after each drug; the chief difference is in the abrupt onset of abstinence subsequent to desomorphine withdrawal. In this respect desomorphine is quite similar to dilaudid (*15*). If one might give the different degrees of abstinence a numerical value, and from this derive a mean figure for the abstinence phenomena per case after morphine and after desomorphine, this figure would be for the former drug 14.8 and for the latter 12.5. In other words, the total abstinence phenomena after morphine exceeded slightly the total after desomorphine withdrawal.

Summary.—According to this substitution method, then, desomorphine is able to replace morphine in cases of active addiction, although incompletely so at the interval of administration employed. Its subsequent abrupt withdrawal results in the occurrence of typical abstinence phenomena, and it is, therefore, of no value in the treatment of drug addiction.

EXPERIMENT 6

As already discussed, the validity of conclusions drawn from the substitution method might be questioned; and, besides, it does not seem possible to evaluate by that method the degree of addiction liability. Therefore, it was decided to determine whether or not addiction would result from the clinical administration of desomorphine for the control of pain of a chronic nature due to incurable

cancer. In cooperation with the Department of Public Health of the Commonwealth of Massachusetts, certain cases at the Pondville Hospital were selected for treatment with this derivative. In making this selection, there were accepted only hopelessly incurable patients who had had no previous opiate experience and whose pain required treatment. Cases 1, 3, and 5 were given desomorphine, while cases 2, 4, and 6 were treated with morphine.

Previous experience at the Pondville Hospital indicated that small doses of opiates at frequent intervals control pain more satisfactorily than large doses at less frequent intervals. Hence, these patients were given small doses of the drugs at intervals sufficiently frequent to control pain almost continuously. The spacing of the injections was established by the duration of action of the drugs as indicated by post-injection subjective analgesia. The initial doses were 1 milligram of desomorphine sulphate and 10 milligrams of morphine sulphate (total doses).

As already pointed out in experiment 5, the duration of action of desomorphine is brief, and this could not be prolonged by increasing the dose. The attempt to do so caused an early increase in the dose; and once this had occurred, it was not feasible to reduce it again. Although this error may have crept into experiment 6, insofar as it was possible to ascertain by the patients' subjective reactions, the per dose and per day pain requirements were not exceeded. The significant data on dosage are presented in table 9.

TABLE 9.—*Summary of drug administration*

Case no.	Drug	Amount injected, milligrams per day			Number of injections per day			Duration of administration, in days
		Minimum	Mean	Maximum	Minimum	Mean	Maximum	
1	Desomorphine sulphate	5	50	60	5	10	12	57
3	do	5	33	36	5	11	12	68
5	do	6	14	20	6	7	10	32
2	Morphine sulphate	40	60	80	4	6	8	73
4	do	70	160	200	7	8	10	55+
6	do	50	70	80	5	7	8	42

The immediate effect of the drugs in terms of the patients' sensations was noted in each case. In addition the acute (post-injection) and chronic (preinjection) effects on blood pressure, oral temperature, pulse rate, and respiratory rate were determined several times weekly throughout the period of study. These determinations were made at 15-minute intervals for the first hour after the administration of one of the usual doses of the drug. The following is from one of the protocols and is a typical story of the immediate effect of an initial dose of desomorphine. The words in quotations are the patient's expressions at the times noted.

Case 3.—A. P., white, female, 42 years of age; inoperable carcinoma of the rectum; complaining of severe pain in the rectum.

February 7, 1935:

9:30 a. m.: Severe pain. Temperature, 99.4° F.; pulse, 108; respiration 12; blood pressure, 116/80.
9:32 a. m.: 1 milligram desomorphine sulphate injected subcutaneously.
9:37 a. m.: "This medicine makes me dizzy."
9:40 a. m.: "The pain is going away."
9:41 a. m.: "I feel nice now."
9:45 a. m.: "The pain is gone; it feels nice." Temperature, 99.0° F.; pulse, 108; respiration, 13; blood pressure, 116/80.
9:50 a. m.: "I feel like I could get up and walk again."
10:00 a. m.: Temperature, 99.0° F.; pulse, 104; respiration, 11; blood pressure, 116/80.
10:15 a. m.: Temperature, 98.7° F.; pulse, 100; respiration, 10; blood pressure, 114/80.
10:30 a. m.: Temperature, 98.4° F.; pulse, 96; respiration, 10; blood pressure, 112/80.

The prompt and complete relief of pain is very striking. The patient became very talkative, so that it was possible, after the above observations had been made, for the resident physician to obtain a much more complete history than he had been able to get on the previous afternoon. Pain recurred to a degree which required repetition of the dose of desomorphine at 1:30 p. m.

In each of the six cases the drug was withheld for 6 to 12 hours at about 10-day intervals throughout the course of the study, at which times observations for specific evidence of "abstinence" were made. The same method of evaluation of the degree of "abstinence" was employed as in experiment 5. In figure 5 the data on the degree of abstinence shown during these periods of temporary withdrawal is presented graphically.

Evidently addiction to desomorphine began to develop within 10 days, but no addiction to morphine was observed. After the third week, definite evidence of "abstinence" appeared if desomorphine was withheld for only 4 hours, and the manifestations became severe if the period of temporary withdrawal was extended to 6 hours.

After a certain dose level was reached, significant increases in dose of either drug were not necessary. The analgesic effect of morphine lasted from 3 to 4 hours, while that of desomorphine lasted only 2 or 3 hours and sometimes less.

The acute effect of each drug on blood pressure was mainly depressant, but sometimes there resulted no change or a slight elevation. No tolerance to this effect of desomorphine developed, but slight tolerance to morphine did appear. Neither drug had any chronic effect on the preinjection blood pressure level.

The acute effect of both drugs on the pulse rate was always a slowing, and no tolerance to this effect developed. All six cases showed

a progressive lowering of the preinjection pulse rate. The respiratory rate was mainly decreased after the administration of these drugs. Desomorphine constantly in two cases slowed the respiration more than did morphine. In the third case the respiratory rate often increased slightly. Tolerance to the respiratory depressant effect of morphine was seen, but none resulted from the chronic administration of desomorphine. Neither drug had any effect on the preinjection level of respiratory rate.

It was observed that there usually occurred a slight rise in oral temperature immediately after the giving of either drug, although occasionally there was a biphasic change, a decrease, or no change at all. Again, no tolerance in respect to the initial rise in temperature

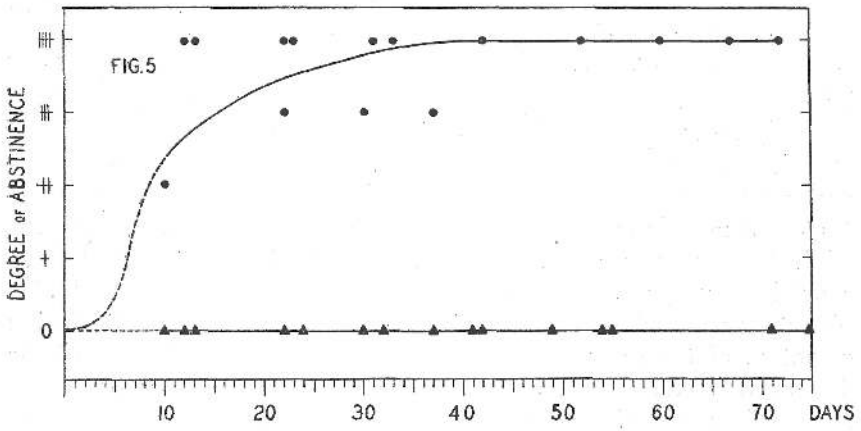

FIGURE 5.—Development of addiction from clinical use of dihydrodesoxymorphine-D in comparison with morphine. Points represent observations during temporary withdrawal: ●, during desomorphine administration; ▲, during morphine administration. The curves are the estimated means of all the observations.

was seen. The rise was the same with either drug and also the same irrespective of the preinjection level. The chronic effect of both drugs was progressively to lower the preinjection level of oral temperature.

So far no attempt has been made to determine the mechanism of the acute and chronic effects of these drugs on temperature, respiration, and circulation.

Summary.—Dihydrodesoxymorphine-D appears to be an adequate substitute for morphine in symptomatic treatment. It possesses relatively brief but powerful narcotic and anaglesic actions. It has also a relatively powerful respiratory depressant effect to which no tolerance developed during the period of this study.

In the doses given for the continuous relief of pain, it produced addiction rapidly. In respect to the last statement probably the best criterion available at present for judging the degree of addiction

potentiality is the rapidity of onset of dependence. The more addictive agent of two applied in about equally effective amounts to a clinically homologous pair will produce addiction more rapidly than the less addictive agent. But, there is probably a relationship between addiction liability and the size of the starting dose; that is, addiction will probably develop more rapidly if the causative agent is given in excess of the amount required to relieve the symptom (pain) for which it is used. It is possible that the starting doses of desomorphine in the clinical cases were larger than were absolutely necessary to control pain, a possibility to be taken into account in drawing conclusions from these cases.

IV. Conclusions

Clinical observations confirm laboratory experiments in regard to the tremendous analgesic power of dihydrodesoxymorphine–D (desomorphine); its effect comes on with striking rapidity but is of brief duration.

In regard to the addiction property, the laboratory and the clinical experiences are not in complete accord. From the laboratory experience alone, where administration was once daily, one would conclude that desomorphine exhibited little addiction liability. From the clinical experience alone, where administration was repeated at short intervals, one would conclude that desomorphine exhibited a high degree of addiction liability. It is possible that the brief duration of action of the drug and the differences in the relative size of the doses employed and in the intervals of administrations may be factors in this discrepancy.

NOTE.—Under date of November 30, 1935, the Committee on Drug Addiction of the National Research Council formally unanimously expressed the opinion that in the interest of the public it is not desirable to license the production of dihydrodesoxymorphine-D at this time.

The Surgeon General of the Public Health Service, under date of April 8, 1936, recommended to the Secretary of the Treasury that the United States Government prohibit the importation, manufacture, sale, or distribution of this drug in the United States.

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