Tests for Addiction (Chronic Intoxication) of Morphine Type

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A survey is presented of laboratory and clinical methods for the determination of addiction liability of substances with morphine-like effects. Since physical dependence is the outstanding pharmacological criterion of addiction of morphine type, the procedures for its qualitative and quantitative assessment are described in detail.

INTRODUCTION

In its seventh report, the WHO Expert Committee on Addiction-Producing Drugs (1957) defined addiction as follows:

"Drug addiction is a state of periodic or chronic intoxication produced by the repeated consumption of a drug (natural or synthetic). Its characteristics include:
(1) an overpowering desire or need (compulsion) to continue taking the drug and to obtain it by any means;
(2) a tendency to increase the dose;
(3) a psychic (psychological) and generally a physical dependence on the effects of the drug;
(4) detrimental effect on the individual and on society."

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The purpose of this definition was to aid in the characterization of substances which have been or should be subjected to international narcotics control. Some of the characteristics in the definition, the first and last particularly, are demonstrable only through prolonged experience and are, in part at least, based upon impressions rather than upon quantitative data: tolerance and physical dependence can be measured quantitatively.

Expressing themselves in more strictly pharmacological terms, Himmelsbach & Small (1937) said that addiction embraced three intimately related but distinct phenomena—tolerance, habituation and physical dependence. They were speaking of the opiates, morphine and morphine derivatives, but the statement applies to all synthetic substances with morphine-like effect. Tolerance, the gradual decrease in an effect developing during the repeated administration of a drug, is measurable to the extent...
that quantitative methods are available for investigating the effect in question. It can occur with a wide variety of substances, whether or not morphine-like. Habituation is a psychic dependence, adaptation and mental conditioning to the repetition of an effect manifested by craving for and efforts to bring about continuation of the drug's administration. Its possibility in animals has been claimed (Krueger, Eddy & Sumwalt, 1941b) and denied (Lindesmith, 1937). Currently efforts are being made to prove its development and measure it quantitatively. Physical dependence is an essential characteristic of opiate addiction. It is the distortion of physiological processes which results from prolonged administration of a drug and which requires the presence of an adequate amount of an addicting drug in the body for the maintenance of physical equilibrium. Physical dependence is demonstrated by the appearance of a characteristic syndrome of abstinence phenomena.

Until comparatively recently the only means of judging over-all addiction liability was the general impression from prolonged clinical experience, and under these circumstances years might elapse before a reasonably accurate appraisal was attained. The establishment of the Addiction Research Center at the Public Health Service Hospital for addicts at Lexington, Ky., USA, led to the development of at least semi-quantitative measurement of morphine-like properties as they related to addiction. Also the unequivocal demonstration of withdrawal phenomena in animals, proving the universality among species of physical dependence as a pharmacological consequence, stimulated efforts to measure it quantitatively. Therefore, there are now available tests applicable to animals and to man which permit an early estimate of the relative risk of abuse and of addiction to be expected under clinical conditions. In addition the production of nalorphine and other morphine antagonists and the discovery of their ability to precipitate an abstinence syndrome when physical dependence exists has made possible early detection of physical dependence and developing addiction under usual clinical conditions.

In this report we propose to describe these tests for addiction under four heads: appraisal of physical dependence in animals; determination of addiction (abuse) liability in former addicts; measurement of the development of tolerance and physical dependence under clinical conditions; and detection of drug use and recidivism. Our purpose is to assess the relative importance, reliability and interpretation of the tests and to stimulate their broader application.

TESTS FOR APPRAISAL OF PHYSICAL DEPENDENCE IN ANIMALS

Since the abstinence symptoms on which the assessment of physical dependence is based occur on a high level of physiological organization, the experimental object used is as a rule the whole animal. However, the occurrence of abstinence phenomena has also been shown in objects of a lower level of organization, such as tissue-cultures. Semura (1933), Sanjo (1934), Nakazawa (1937), and Sasaki (1938) observed the development of tolerance to the growth-inhibiting effects of morphine and certain of its derivatives in cultures of fibroblasts and iris epithelial tissue, and furthermore, as a consequence of the withdrawal of these drugs, either restoration of growth or damaging effects. The curative effect of morphine and its derivatives on the latter was also described and the more abrupt the withdrawal, the more pronounced were the abstinence signs (Kubo, 1939). However, these findings did not lead to the development of methods of evaluation (Heubner et al., 1952); nor has this been the case with certain reactions in isolated organs which might be interpreted as signs of abstinence on the basis of a physical dependence, such as the inhibitory effect of the withdrawal of morphine on the rabbit's heart (Wada, 1928) or the stimulation produced in the same way in preparations of intestines (Abe, 1930; Fujita, 1931; see also Paton, 1957). A more intimate analysis of these phenomena might disclose some parallelism between the physical dependence reactions of single cells, tissues, and isolated organs on the one hand and of the whole animal organism on the other.

For practical purposes there are at present available physical dependence tests in various animal species with a varying degree of reliability, that is, comparability to what happens in man.

Mice

After prolonged administration of morphine and analgesics with morphine-like effect mice do not appear to react to their abrupt withdrawal with symptoms which are sufficiently regular and distinct for an assessment of physical dependence. In the hope of finding a correlation between tolerance to the toxic effects of morphine and morphine-like substances and their addiction liability, it has been repeatedly examined whether mice can acquire a tolerance to the toxic (lethal) effects of such drugs by their chronic administration in increasing doses. From an extensive survey of the literature and from
her own experiments, Fichtenberg (1951) concluded that mice do not, or not nearly so easily as several other species, become tolerant to the toxic effects of morphine. Mercier and associates (1957) found that mice acquired no tolerance to the LD$_{50}$ of heroin, oxycodone, or pethidine, and only a partial and incomplete tolerance to that of morphine, methadone and levorphanol. However, in the latter cases the development of tolerance was not uniform and was difficult to compare because of different regimens of administration.

In view of the failure to establish a correlation between addiction liability and tolerance to the toxic effects, the relation between the tolerance of mice to the analgesic properties of the substance in question and its addicting properties has been investigated. Using a modification of Woolfe & MacDonald’s test (hot plate; licking response) Jacob and associates (1958) examined a benzodioxane derivative (3570 CT) which had, in mice, half the analgesic activity of morphine. When given in equi-analgesic doses tolerance developed to the analgesic effect of both substances. However, when tested in monkeys (for method, see page 148 of this report) 3570 CT did not produce evidence of physical dependence. Continuous administration by means of subcutaneous implantation of morphine (base) seemed to favour the development of tolerance to various morphine effects (such as sedation, analgesia, Straub reaction) and also the development of physical dependence, as shown by the unmasking action of nalorphine; but the symptoms of nalorphine-induced withdrawal were not uniform enough for an evaluation of physical dependence (Maggiolo & Huidobro, 1961).

Correlations have also been sought between the Straub tail-reaction in mice and addiction liability in man. While the low tendency of mice to develop tolerance to the effects of morphine refers also to the tail reaction (see Krueger, Eddy & Sumwalt, 1941a), Shemano & Wendel (1960; also personal communication, 1962) believe that the determination of a “Straub index” in mice might be useful for initial screening for potential addiction liability in man. They reported that, when drugs were administered intravenously, the wider the dosage separation between drug-induced Straub tail-reaction and death, the greater was the probability of high addiction liability. Compounds with a narrow dosage separation are likely to be minimally or mildly addicting. The degree of separation was expressed by the Straub index (LD$_{50}$/ED$_{50}$ Straub reaction). A statistically significant rank-order correlation (0.75 (P < 0.01)) was found between the Straub index and the “estimated” addiction liability in man in a series of drugs, including, inter alia, phenazocine, hydromorphone, heroin, morphine, methadone, pethidine, codeine, dextropropoxyphene and nalorphine. For most of the drugs tested, a similar correlation was noted between addiction liability and “analgesic index” in mice (LD$_{50}$/ED$_{50}$ analgesic effect), but a specific exception (apomorphine) throws doubt on the interchangeability of the indices.

Rats

Joël & Ettinger (1926) reported on the occurrence of withdrawal phenomena in rats and their relief by the re-administration of morphine. On the basis of Barlow’s (1932) observation that increased irritability was a measurable and rather constant response of rats to the sudden interruption of chronic morphine administration, Himmelsbach and associates (1935) developed a method for the assessment of physical dependence. The drugs tested in this way (morphine, codeine, heroin) were administered every 24 hours for five to six weeks and then abruptly withheld. Eddy & Himmelsbach (1936), applying in principle the same method, found that desomorphine had to be given at shorter intervals in order to produce a significant response with regard to physical dependence. According to Stanton (1936) the signs following abrupt withdrawal, after four weeks of morphine injections, reached a peak within two to four days of withdrawal. Fichtenberg (1951) reported that rats tolerant to 50 mg of morphine subcutaneously per 100 g body-weight became agitated and aggressive on the second and third days after discontinuation of morphine, with loss of weight, either temporary with recovery or continuing until death.

Motivated by the irregular results of withdrawal experiments with rats, Mercier & Sestier (1954) measured the development of tolerance and physical dependence by means of a discriminatory training test (choice between green and red drinking-water, with electrical punishment for the latter). The discriminatory performance was totally abolished by a single subcutaneous dose of 80 mg of morphine per kg and, as a result of tolerance, reappeared during continuing administration of increasing morphine doses of up to 120 mg/kg daily. Thirty-six to forty-eight hours after the abrupt withdrawal of morphine the discriminatory performance was seriously disturbed, but not completely abolished. Concomitant symptoms appearing after the same interval were increased.
motor activity, aggressiveness, squeaking, and hortipilation. All signs disappeared, generally within four days. With heroin, oxycodone, pethidine, levorphanol and methadone, also, the disturbance of the acquired behaviour could be demonstrated and so could its re-establishment as a sign of tolerance (Mercier & Mercier, 1957). After abrupt cessation of these drugs, impairment of the performance or other symptoms could, however, not be observed equally well in all cases (possibly because of considerable divergences in the dosages exceeding the equi-analgesic dose ratio).

In the course of experimentation in the Addiction Research Center, Lexington, on the conditioning of drug-seeking behaviour, the effects of sudden withdrawal were studied by Wikler & Martin (personal communication, 1962) in rats tolerant to large doses of morphine (200 mg/kg/day and 320 mg/kg/day, subcutaneously and intraperitoneally). Sudden withdrawal of morphine was followed by rapid subsidence of the locomotor hyperactivity, hyperthermia and elevated oxygen consumption rates characteristic of morphine-tolerant animals. These variables approached normal levels between the 8th and 12th hours of abstinence, but during this time the animals began to exhibit a marked increase in the frequency of spontaneously occurring episodes of repetitive shaking of the skin of the entire body ("wet dog" phenomenon). During the next 12-16 hours, these episodes increased in frequency, and the rats became more irritable, showed more grooming activity and diarrhoea, and began to lose weight; concomitantly, body temperature and oxygen consumption rate fell further towards normal or even slightly subnormal levels. These signs reached peak intensity between the 24th and 48th hours of abstinence and subsided thereafter. However, from the 4th day of abstinence onwards, for a period as yet undetermined, "wet dog" counts, body temperature, metabolic rate and total daily water intake were slightly higher in the formerly addicted rats than in the control animals.

In rats stabilized on a single dose of 200 mg/kg/day of morphine intraperitoneally, increased "wet dog" frequency and other signs of acute abstinence, similar to those described above, were noted before administration of the daily dose of morphine. If, however, the rats were permitted to drink an aqueous solution of etonitazene instead of water during the interval between two daily doses of morphine, the acute pre-injection abstinence syndrome was suppressed to a degree depending on the concentration of etonitazene in the solution. With concentrations of 20 and 40 μg/ml of etonitazene, all signs of morphine abstinence were suppressed but signs resembling those of chronic morphine intoxication (increased locomotor activity, hyperthermia and elevated oxygen consumption) were manifest.

Since the symptoms of spontaneous withdrawal in rats have not always been sufficiently uniform and regular to form the basis of a reliable test method, the nalorphine-precipitated withdrawal syndrome in rats has been examined, apparently with better results.

According to Hanna (1960) the demonstration of nalorphine-induced withdrawal signs in rats (of about 250 g in weight) required the previous administration, conveniently by the intraperitoneal route and at intervals not exceeding four hours, of very large doses of morphine, beginning with 90 mg/kg, with daily increases of 18 mg/kg until a dosage of 360 mg/kg every 4 hours was reached. This dosage, which caused weight loss and sometimes death, was maintained for 5 days. 10-20 mg of nalorphine per kg, given intraperitoneally 30 minutes after the last morphine injection, produced within a few minutes increased motor activity and hyperexcitability, with brief convulsions in some animals. The symptoms subsided after about two hours. As Hanna remarked, the requirement of very large doses of morphine "may or may not be of value in the evaluation of physical dependence liability of new compounds" in rats.

Kaymakcalan & Woods (1956) compared the symptoms of abrupt withdrawal from morphine with those produced by nalorphine in morphine-tolerant rats, that is, in animals which had received morphine sulfate twice daily, subcutaneously, in doses increasing from 20 mg/kg to 100 mg/kg and had been maintained on the latter dose for 12-25 days. In the course of the development of tolerance, morphine produced less sedation and, instead, more and more central stimulation. While the abrupt withdrawal of morphine generally resulted in mild sedation only, the nalorphine-induced withdrawal syndrome included a marked increase in intestinal activity with corresponding results appearing within a few minutes and followed, after about 30 minutes, by sedation that was distinctly greater than that after abrupt withdrawal. The dose of nalorphine (10 mg/kg) was administered 2 or 12 hours after the last dose of morphine; in the case of the longer interval the withdrawal symptoms were perhaps somewhat more pronounced.
To avoid the risks of local irritation and infection presented by frequent injections of the large quantities of drug necessary for the production and demonstration of physical dependence, Lister & Ettles (personal communication, 1961) have administered the test drug dissolved in drinking-water. Because of the usually unpleasant taste this is possible only with very low drug concentrations, that is, with highly potent substances. The authors employed a compound with 1500 times the analgesic potency of morphine in an estimated initial daily dose of 10 μg for rats weighing 35-45 g, and increased it within three weeks to 10 mg per rat per day. Then, a withdrawal syndrome was precipitated by administration of 3 mg of levallorphan per kg subcutaneously or intraperitoneally. The outstanding sign of withdrawal was stretching or writhing similar to that produced in rats and mice by the intraperitoneal administration of local irritants. The authors related this symptom to the gastro-intestinal withdrawal symptoms in man. By analogy with Himmelsbach’s system for scoring the abstinence syndrome (see Table 1, opposite), the authors established the following scale for scoring antagonist-precipitated (by levallorphan as well as by nalorphine) withdrawal symptoms in rats:

<table>
<thead>
<tr>
<th>Signs</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stretching</td>
<td>5</td>
</tr>
<tr>
<td>Squeal on touching</td>
<td>4</td>
</tr>
<tr>
<td>Teeth chattering</td>
<td>3</td>
</tr>
<tr>
<td>Hypersensitivity to noise</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>2</td>
</tr>
<tr>
<td>Sedation</td>
<td>2</td>
</tr>
<tr>
<td>Ptosis</td>
<td>1</td>
</tr>
<tr>
<td>Chewing</td>
<td>1</td>
</tr>
<tr>
<td>Pinna sensitivity</td>
<td>1</td>
</tr>
<tr>
<td>Ear twitch</td>
<td>1</td>
</tr>
<tr>
<td>Pilo-erection</td>
<td>1</td>
</tr>
<tr>
<td>Scratching</td>
<td>1</td>
</tr>
</tbody>
</table>

With suitable dosage of the addicting compound, physical dependence developed within one week, and the optimal dose of levallorphan for precipitation of abstinence signs was 2-3 mg/kg.

Lister & Ettles also demonstrated that the symptoms following precipitated withdrawal of their very potent compound could be suppressed, at least partially, by a moderate dose of the same compound or by the administration of morphine or another potent analgesic.

### Table 1

<table>
<thead>
<tr>
<th>Signs</th>
<th>(D^b) (by day)</th>
<th>(H^c) (by hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>points</td>
<td>limit</td>
</tr>
<tr>
<td>Yawning</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lacrimation</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Rhinorrhoea</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Perspiration</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Mydriasis</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Tremor</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Gooseflesh</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Anorexia (40% decrease in caloric intake)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Restlessness</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Emesis (each spell)</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Fever (for each 0.1°C rise over mean addiction level)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hyperpnoea (for each resp./min. rise over mean addiction level)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Rise in a.m. systolic BP (for each 2 mm Hg over mean addiction level)</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Weight loss (a.m.) (for each lb. from last day of addiction)</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

\(a\) The total abstinence syndrome intensity per day or per hour is the sum of the points scored in the "D" or "H" columns, respectively, with due attention to the limits.

\(b\) Kolb & Himmelsbach (1938).

\(c\) Himmelsbach (1939).

A nalorphine-precipitated abstinence syndrome has also been demonstrated in rats tolerant to codeine, a substance with a much lower addiction potential than morphine (Kuhn & Friebel, 1962). For eight weeks the animals received daily three subcutaneous doses of codeine phosphate, beginning with 10 mg/kg and rising, in three bi-weekly increases, to 22.2 mg/kg per dose. After eight weeks, the last codeine injection was followed, 30 minutes later, by the subcutaneous injection of 20 mg of nalorphine per kg. The ensuing abstinence syndrome, with its peak between 15 and 20 minutes after nalorphine administration, comprised practically the same symptoms as those observed by Lister & Ettles. These symptoms were classified by Kuhn & Friebel as follows:
Ptosis, sedation, and scratching—but not the more distinctive signs—occurred also in animals which were challenged with nalorphine after having received one single dose of codeine and, about half as frequently, in the controls. However, the difference in the total point score between these animals and those that had received codeine for eight weeks was significant.

**Rabbits**

In rabbits, which have been used far less for studies on morphine and its congeners than the other species included in this survey, morphine affects the carbohydrate metabolism in a typical way (see Krueger, Eddy & Sumwalt, 1941c). The animal develops tolerance to the hyperglycaemic effects of morphine and reacts to its withdrawal after chronic administration by a transitory hyperglycaemia. For racemic methadone and isomethadone as well as for their $l$-isomers, $a$-acetylmethadol, pethidine, alphaprodine, and levorphanol, the same changes were found to occur (see Phatak & David, 1953). These authors concluded that the withdrawal hyperglycaemia, being seemingly related to the rate of development of tolerance to the hyperglycaemic effect, might serve as an index of the addiction potential. However, since physical dependence has so far not been proven to be in immediate relation to tolerance, the usefulness of such a test would have to be examined by its application to a large series of substances with known physical dependence potency.

**Cats**

In cats, medium dosages of morphine and pharmacologically related substances produce a peculiar state of central excitation, marked by mydriasis, tachypnoea, and seemingly hallucinatory behaviour (see Schaumann, 1957; Wikler, 1944). This reaction is quite specific and has been utilized in the characterization of morphine-like analgesics (Eddy & Himmelsbach, 1936). Akad (1952) examined for morphine, heroin, hydromorphone, oxycodone, hydrocodone, codeine, dionine, methadone and pethidine the doses necessary to bring about the typical excitation in cats. Although he did not relate them to analgesic effects or otherwise, it would appear that some relation might exist between them and analgesic potency and, hence (see Eddy, Halbach & Braenden, 1956), physical dependence potency. Tavat & Akçasu (1956) extended Akad's investigations to ketobemidone, levorphanol, dextrophan, and levallorphan, using a simple device for recording motor activity. Relatively high doses of dextrophan and levallorphan were without effect—in parallel to lack of addiction liability. Levallorphan antagonized or prevented the exciting effects of morphine. Cullumbine & Konop (1959) examined a few more substances—addicting and non-addicting—in the same way with essentially the same results, including the demonstration of the preventive effect of the antagonists. They also noted exceptions to the parallelism between excitation in cats and addiction liability in men, for example, in the case of apomorphine. They confirmed the rapid development of tolerance to the excitatory effects of these substances (as already noted by Eddy & Himmelsbach, 1936) and concluded that the relation studied, although not strict, was "... sufficiently close to suggest that the cat injection test could be used to indicate the danger of inducing addiction..."

The value of the cat excitation method as a preliminary test would be improved by a check with specific morphine antagonists; the neutralizing effects of the latter in this respect have been described by the aforementioned authors and earlier by Unna (1943), Hart & McCawley (1944), Wikler & Carter (1952), and Winter et al. (1954).

**Dogs**

Abstinence symptoms in dogs addicted to morphine had already been observed and described by many workers (see review by Schaumann, 1957) when the introduction of pethidine and methadone into clinical practice stimulated new trials using this species for the evaluation of physical dependence to substances of morphine type.

**Intact dogs.** The morphine abstinence syndrome in dogs as described by Plant & Pierce (1928), Tatum, Seever & Collins (1929), Eddy & Reid (1934), and others includes muscular rigidity, tremor, convulsions, restlessness, yawning, salivation, lacrimation, rhinorrhea, singultus, vomiting, diarrhoea, tachypnoea, pulse irregularities, hyperpyrexia, hydro-

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**Table 1**

<table>
<thead>
<tr>
<th>Signs</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stretching</td>
<td>3</td>
</tr>
<tr>
<td>Chewing</td>
<td>2</td>
</tr>
<tr>
<td>Teeth chattering</td>
<td>2</td>
</tr>
<tr>
<td>Squeal on touching</td>
<td>2</td>
</tr>
<tr>
<td>Ptosis</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1</td>
</tr>
<tr>
<td>Sedation</td>
<td>1</td>
</tr>
<tr>
<td>Increased movements</td>
<td>1</td>
</tr>
<tr>
<td>Scratching</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>15</strong></td>
</tr>
</tbody>
</table>
philia, and loss of weight, with a peak 24-72 hours after abrupt withdrawal. The minimum dosages which the early authors considered necessary for the development of physical dependence signified by unmistakable abstinence symptoms were obviously sometimes too high; Wikler (1946, 1948) described the appearance of a “mild, but characteristic” abstinence syndrome in dogs when treated with two daily doses of 10 mg of morphine per kg during periods of 83-158 days. Under similar but not strictly comparable conditions as to dosage and duration of addiction, Wikler & Frank (1947) found that in dogs the “methadone abstinence syndrome appeared to be more rapid in onset, more severe and of shorter duration than that of morphine”, while Winter & Flataker (1950) found it somewhat less severe, but of similar duration. Two pethidine derivatives, piminodine and the closely related 1-(2-phenylaminoethyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester, were compared with morphine by means of the abrupt withdrawal method in dogs (Woods et al., 1961). The results would indicate that the relative sensitivities of the dog with respect to physical dependence on substances of the morphine and pethidine group resemble the situation in man, whereas, for example, monkeys are in this respect particularly sensitive to the pethidine group. This would speak in favour of using dogs for predicting addiction liability in man. Nevertheless, so far as is known, no systematic attempts have been made to determine the value of the abrupt withdrawal method in dogs for this purpose by extending the observations to a larger number of morphine-like substances with a known addiction potential.

By administration of nalorphine the demonstration of abstinence symptoms in dogs is made simpler and safer. After having ensured that nalorphine as such produced only mild sedation, Carter & Wikler (1954) demonstrated the precipitation of characteristic withdrawal signs by subcutaneous administration of 15 mg of nalorphine per kg in dogs addicted for 7 days or longer to morphine (5-10 mg/kg every 6 hours) or methadone (2-5 mg/kg every 6 hours). In its most complete form, the abstinence syndrome consisted of restlessness, lacrimation, rhinorrhoea, yawning, salivation, vomiting, urination, marked tremors, and persistent digging, gnawing and rooting in the earth or sand, but considerable individual variation, qualitative and quantitative, was observed. The symptoms appeared within 5-20 minutes and became more severe as the addiction proceeded and were more pronounced than those following the abrupt withdrawal of morphine or methadone after comparable periods of addiction. According to Kaymakcalan & Woods (1954), 1.5 mg of nalorphine per kg subcutaneously is sufficient to elicit the full abstinence syndrome in morphine-addicted dogs. Carter & Wikler concluded that “by use of N-allylnormorphine and a large number of dogs, a useful rapid screening method for testing addiction liability of analgesics with opiate-like actions may be developed”. This conclusion would not appear to be invalidated by their finding (Carter & Wikler, 1954, 1955) that neither spontaneous nor nalorphine-precipitated abstinence symptoms occurred after addiction to pethidine (possibly because of the limitations imposed on dosage and frequency of administration by the toxic effects of the drug). A “normal” sensitivity of the dog (in relation to what happens in man) to the physical dependence properties of piminodine and another pethidine derivative, as demonstrated by a typical abstinence syndrome following abrupt withdrawal, has also been found after nalorphine-induced withdrawal (Woods et al., 1961).

For the purpose of testing it would be advantageous if the period necessary for the development of physical dependence could be curtailed. In man (Wikler and associates, 1953; Fraser et al., 1961a) as well as in dogs (Wikler & Carter, 1953; Carter & Wikler, 1954), tolerance and physical dependence can indeed be produced and demonstrated, particularly when precipitated by specific morphine antagonists, in a measurable degree after a relatively short period of administration of morphine. Martin & Eades (1961) have shown that a single intravenous infusion of morphine brings about tolerance and physical dependence in a reproducible and measurable way. They considered that “the reproducibility and brevity of this method may recommend it for preliminary screening of analgesic agents to identify those that produce physical dependence”. The principle of this method is as follows.

In beagle dogs (between 7 and 19 kg in weight) the following signs were measured every half-hour: pulse rate, respiratory rate, pupillary diameter, rectal temperature, skin-twitch reflex (on pinching the saddle area of the back), and hind-limb withdrawal reflex (following the roughly measurable squeezing of the left lateral digit). Nalorphine alone did not alter these signs significantly except for causing a slight miosis. The intravenous infusion of morphine
sulfate at the rate of 3 mg/kg hourly produced within one to two hours the known effects and changes in the 6 parameters. To 3 of them—namely, miosis and depression of the skin-twitch and withdrawal reflexes—as well as to the behavioural depression, the animals developed a partial tolerance after about three hours of infusion. Administration of nalorphine (20 mg/kg) after almost eight hours of morphine infusion produced, within five minutes, a striking reversal in the parameters measured, a reversal of the behavioural depression, and other symptoms of withdrawal.

La Barre (1959) and Desmarez (1960) have attempted to simplify the measurement of the state of physical dependence by singling out and recording those withdrawal symptoms which manifest themselves in changes of spontaneous motor activity. To this end the animal is kept in a spacious cage, fitted for automatic mobility recording, during the period of direct addiction or substitution and withdrawal of either morphine or a test substance. The period of building up tolerance and physical dependence to the addicting agent extends over several months, owing to the relatively low doses and their small increments. With morphine, for example, the daily dosages per dog (of 6-8 kg weight) were 10 mg subcutaneously for two months, 15 mg in the third month, 20 mg for the following three months, and then 40 or 50 mg (divided into two doses daily) to accentuate the withdrawal effect. With this scheme tolerance to the sedative effects of morphine develops within several days following each increase in dosage, but the sudden cessation of morphine during the first four to five months is not followed by a noteworthy increase in motor activity. This symptom appears clearly and with a statistical significance only when the withdrawal is effected after at least four months’ duration of this regimen.

With animals thus made physically dependent on morphine and using the recorded motor activity as the parameter for physical dependence, two types of tests can be carried out: (a) the suppression test, in which a single dose of the test substance is administered eight to ten hours after withdrawal of morphine, and (b) the substitution test, in which the last dose of morphine is replaced by the test substance. If the test drug suppresses the increase in motor activity in (a) or prevents it in (b) this is valued as a strong argument in favour of its morphine-like addicting character—on the basis of the experience that no substance is hitherto known which produces these effects of suppression or substitution without being itself capable of producing physical dependence, that is, addiction of morphine type (Eddy, Halbach & Braenden, 1956). In the view of the authors the results of these tests should be confirmed by a “direct addiction” test, that is, chronic administration of the test substance in increasing doses (as in the scheme described above for morphine) with abrupt withdrawal and relief of withdrawal symptoms by re-administration of the test drug, with recording of motor activity during all stages of the experiment.

As to the dosage of the test drug, La Barre (personal communication, 1961) recommends its establishment in relation to the LD100 (Knaff-Lenz method in guinea-pigs). The LD100 of the test substance is determined and a fraction of this is used versus the same fraction of the LD100 of morphine. To save their animals, the authors of this method prefer not to exceed one-fourth of the LD100.

Chordectomized (“spinal”) dogs. In the course of research on neurophysiological mechanisms of addiction, Wikler has developed a method using spinal dogs. With its distinct and readily reproducible effects this method could also be, and on a limited scale has already been, used to screen drugs for the presence and degree of physical dependence properties. Its relevant features, as described in detail by Wikler & Frank (1948), can be summarized as follows.

The experiments were made after recovery from chordectomy between D-10 and D-12 and return of the reflexes to a stable level. Single doses of morphine (2-100 mg/kg) produced marked and typical changes in certain mechanically elicited and graphically recorded hind-limb reflexes. Most prominent were the depression of the ipsilateral flexor and crossed extensor reflexes. During chronic administration of morphine, tolerance developed to its depressing action on these reflexes, as manifested by increased reflex responses between injections. Abrupt cessation of morphine was followed by their further increase; 30 hours after withdrawal, rhythmic movements of flexion and extension of the hind-limbs began and increased, and were accompanied later by the same withdrawal symptoms as seen in intact dogs, such as tachypnoea, tachycardia, rise in temperature, yawning, lacrimation, rhinorrhea, vomiting, and diarrhoea, reaching a peak at about the same time (72nd to 90th hour) as the “running” movements. With methadone the same effects appeared, but within a shorter sequence, and, as in the intact dog, the abstinence syndrome of either
drug could be suppressed by the other. Thus this preparation offers the elements essential for the demonstration of physical dependence and enables objective recording of specific symptoms.

While abstinence phenomena following abrupt withdrawal appear in the spinal dog only after a long period of addiction, they can be demonstrated by means of a single dose of nalorphine after two or three days of addiction (Wikler & Carter, 1953). The effect of nalorphine alone on the ipsilateral flexor and crossed extensor reflexes was qualitatively the same as that of morphine but quantitatively less. However, after pre-treatment with as little as 0.5 mg of morphine per kg every six hours for two or three days, 15 mg of nalorphine per kg precipitated a typical abstinence syndrome resembling closely that produced in spinal dogs by the abrupt withdrawal after weeks or months of addiction. Onset, intensity and duration of the nalorphine-induced withdrawal syndrome appeared to be related to the duration of addiction to morphine and the dose of nalorphine, that is, the longer the animal had been addicted to morphine the smaller was the dose of nalorphine necessary to produce a complete abstinence syndrome. This opens prospects for the quantitative testing of the physical dependence capacity of unknown substances. Relevant in this connexion appear the observations by Wikler & Carter that the nalorphine-induced withdrawal syndrome as measured by the reflex changes in spinal dogs was more intense than the abstinence syndrome seen in the same animals after abrupt withdrawal; and further that, after subsidence of the reflex hyperactivity following withdrawal of morphine, nalorphine had the same depressing effects on reflexes as before addiction to morphine. Interestingly, the impossibility of demonstrating in the intact dog either spontaneous or nalorphine-induced abstinence symptoms following addiction to pethidine (Carter & Wikler, 1954, 1955) was also encountered in the spinal dog (Carter & Wikler, 1955) and possibly for the same reason—namely, the limitations to dosage and frequency of application set by the toxic effects of pethidine.

Monkeys

Tatum, Seevers & Collins (1929) demonstrated the occurrence of abstinence phenomena when morphine was abruptly withheld from monkeys which had received the drug daily. The starting dose was only 2 mg/kg and was increased by about 2 mg each week. Kolb & DuMez, beginning their experiments in 1923 but not reporting them until 1931, made more extensive observations on attempted addiction experiments in monkeys, employing morphine, heroin and codeine. The drug was given in one daily dose for three months and twice daily thereafter, Sundays and holidays excepted. The dose of morphine was increased from 7 or 8 mg to 200 mg per animal per day in eight to ten months. By the seventh month the withdrawal symptoms were so severe after 40 hours of abstinence, that is, from the Saturday afternoon to the Monday morning dose, that an additional dose was given on Sunday morning. They said that morphine “caused marked dependence, shown by a crouching posture, facial distortion, hypersensitiveness, fall in temperature, and, in one case, death on withdrawal of the drug.” Monkeys made tolerant to large doses of morphine, heroin or codeine were tolerant to large doses of all three drugs; the dependence produced by morphine or heroin was satisfied by the other drug, but not by codeine.

This was the background situation when methadone came to general attention in 1946 and stimulated tremendous activity in the synthesis of compounds which might have morphine-like activity. Seevers and his associates tested many of these new compounds in the monkey and in 1950 he proposed a programme to determine the value of this animal for predicting addiction liability to the newer synthetic analgesics. The plan in the main was to carry out in the monkey all of the procedures employed in man at the Addiction Research Center in Lexington (single-dose administration, substitution for morphine and direct addiction) and to compare the results obtained with substances which were tested in both monkey and man. Seevers’ proposal was incorporated into the research programme of the Committee on Drug Addiction and Narcotics of the National Research Council (USA) and the work in this connexion of his laboratory at the University of Michigan still continues under the sponsorship and support of the Committee.

It was shown early that results in the monkey with many different chemical types were qualitatively like those obtained in man and that when strong morphine-like properties were manifested in the monkey this could be taken as a safe prediction of what would happen in man. From this earlier work there has been developed a screening programme in which more than 350 agents have been tested and which has proved of very great value to all those interested in the addiction liability, and hence the safety, of
potentially valuable medicinal agents. It is this screening programme which will be described here.1

It has been demonstrated in animal and man that any chemical substance capable of complete suppression of all of the specific signs of morphine abstinence is capable of creating physical dependence during chronic administration. Therefore, the primary and principal objective of the screening procedure is to ascertain whether or not the test drug is capable of complete suppression of all abstinence signs in the morphine-dependent monkey. If suppression is not complete the procedure determines the degree to which the total spectrum of signs is affected. The abstinence suppression potency is termed physical dependence capacity. Its determination is initially qualitative but serves a range-finding function for the subsequent quantitative study of potency relative to morphine.

Physical dependence capacity is characterized as:

High, when the drug produces complete suppression of all abstinence signs with doses which reveal no other overt pharmacological effect;

Intermediate, when complete suppression of all abstinence signs is obtainable, but only with doses which elicit other pharmacological actions, manifested by such signs as stupor, ataxia, tremors, etc.;

Low, when some suppression of abstinence signs is induced, but attempts to produce more or complete suppression with larger doses is prevented by the intervention of toxic effects such as coma, convulsions, etc.;

None, when the drug fails to produce any specific suppression of the morphine abstinence signs. Non-specific depressants may obscure individual signs.

A colony of 50 to 100 monkeys (Macaca mulatta) is maintained in a state of physical dependence by the subcutaneous administration of 3 mg/kg of morphine sulfate every six hours without interruption. After a stabilization period of 60 days these monkeys can be used for testing at weekly intervals.

For testing, regular morphine injections are withheld for 12-14 hours until abstinence signs of inter-

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1 We are indebted to Dr M. H. Severs, Professor of Pharmacology, and to Dr Gerald A. Deneau, Associate Professor of Pharmacology, University of Michigan Medical School, for permission to describe their methods. They are currently preparing for publication a series of reports on this programme. A great deal of credit is also due to Samuel Irwin, Duncan McCarthy and Richard Burns, who have been closely associated with the development of the procedures.
TIME-EFFECT CURVES, OBTAINED FROM THE SAME FIVE MONKEYS IN SINGLE-DOSAGE SUPPRESSION TESTS, FOR A TEST DRUG AT THREE DOSAGES ($\frac{3}{2}X$, $X$, AND $2X$), MORPHINE SULFATE (3 mg/kg) AND A PLACEBO $^a$

![Graph](image)

$^a$ In all cases the average pre-injection abstinence (withdrawal) severity was grade 3. The average maximum effect of each treatment is represented by the differences $P$ to $Q$ for $\frac{3}{2}X$, $P$ to $S$ for $X$, $P$ to $T$ for $2X$, and $P$ to $R$ for morphine, and is zero for the placebo.

After Deneau & Seevers (1961).

DOSE-RESPONSE CURVE OF THE TEST DRUG WHOSE TIME-EFFECT CURVES ARE SHOWN IN FIG. 1 $^a$

![Graph](image)

$^a$ The three points on the curve represent the effects $P$ to $Q$, $P$ to $S$ and $P$ to $T$ in Fig. 1. A dose of $Y$ is equivalent to 3 mg/kg of morphine sulfate.

After Deneau & Seevers (1961).

with respect to test drug versus morphine versus placebo and from the peaks of the average time-effect curves which are obtained for each treatment (see Fig. 1) a dose-effect curve (see Fig. 2) is established. The potency of the test agent relative to morphine is determined from this curve.

In some cases the physical dependence potential of a test drug is also investigated by chronic administration to monkeys which have not previously received narcotic analgesics. After the dose equivalent to 3 mg/kg of morphine has been determined by the single-dose suppression technique, this dose is administered for 31 days at intervals (usually two to six hours) which correspond to its duration of action so that the monkeys are continuously under the influence of the drug. If there is evidence of waning effect (tolerance) the individual dose is increased. The development of physical dependence is monitored on the 14th and 28th days of treatment by administering 2 mg/kg of nalorphine. As in man the administration of nalorphine precipitates an abstinence syndrome of one-half to four hours' duration, the severity of which corresponds to the degree of physical dependence which has developed. On the 31st day of treatment drug administration is terminated abruptly and the monkeys are observed for the following 7-14 days for signs of abstinence, graded according to the schema below.

In the single-dose suppression technique, effective doses of test drugs reduce the intensity of abstinence signs more or less completely, or, having brought about complete suppression, may then produce typical signs of narcotic depression. In all of the tests described abstinence signs are graded, two grades for each classification, according to Seevers’ classification of abstinence signs (Deneau & Seevers, 1961) and narcotic depression is graded (again two grades for each classification) according to Irwin’s classification of the effects of narcotic analgesics in the monkey (Irwin, 1954). These classifications are as follows:

For abstinence signs:

Mild (may be considered as of no significance by the untrained observer): Apprehension, continual yawning, rhinorrhea, lacrimation, hiccup, shivering, perspiration on face, chattering, quarrelling and fighting;

Intermediate: Intention tremor, anorexia, pilomotor activity, muscle twitching, rigidity and holding the abdomen (cramps);

Severe: Extreme restlessness, assumption of peculiar attitudes, vomiting, severe diarrhoea, erection and
continued masturbation, inflammation of the eyelids and conjunctiva (insomnia), continual calling and crying, lying on the side with eyes closed, and marked spasticity;

Very severe: Docility in the normally excitable animal, dyspnœa, pallor, strabismus, dehydration, weight loss, prostration, circulatory collapse, and occasionally death.

It will be noted that these signs fall into four categories of hyper-irritability: sympathetic, parasympathetic, psychic (behavioural) and somatic (neurormuscular). Whereas morphine will suppress all signs of the syndrome evenly to an extent dependent upon the dose, many narcotic analgesics fail to suppress one or another category of signs to the same extent as the remainder of the syndrome. For this reason grades of abstinence intensity during the suppression test are assigned according to the behavioural signs and not on the basis of the entire abstinence syndrome.

For narcotic depression. The central nervous system depression which is produced by narcotic analgesics in the monkey is a combination of two factors, referred to collectively as stupor: a decreased awareness of, and diminished responsiveness to environmental stimuli, and a decrease in the degree of apprehension, as indicated by alteration in behaviour, once his attention has been gained. The classification of stupor is:

Mild: Inattentive to ordinary movements and actions of other monkeys within the cage and of the observer outside the cage;

Intermediate: Attention gained by other monkeys within the cage only by strong threatening gestures and attentive to the observer only when extraordinarily loud noises are made or the latch on the cage door is opened (a strong conditioned stimulus);

Severe: Responds only to such exteroceptive stimuli as shouting or clapping the hands loudly near its ear, or to being touched by other monkeys or the observer;

Very severe: Comatose and cannot be roused by any stimuli.

In the actual operation of the screening procedure a request for testing is made by the interested party to the Executive Secretary of the Committee on Drug Addiction and Narcotics of the National Research Council (USA). A sample of the drug is submitted to him, together with information as to its chemical identity, such pharmacological data as are available and the reason for interest in the compound. He codes the compound and forwards it to the pharmacology laboratory of the University of Michigan Medical School under code number, suggesting a starting dose based upon the pharmacological data. When the tests have been completed the results are reported to the Executive Secretary, who transmits a copy to the producer and upon mutual agreement reveals the nature of the agent to the investigators. The results may be the determining factor either in the abandonment of interest in the compound, should its physical dependence capacity be high without compensating advantages, or in the decision to subject it to further laboratory and clinical testing, including addiction liability testing in man. In some unequivocal cases the tests in the monkey may also be the basis for a recommendation for narcotics control.

**TESTS FOR ADDICTION (ABUSE) LIABILITY IN FORMER ADDICTS**

Given a new substance whose morphine-like properties and addiction liability are to be determined, the investigators at the Addiction Research Center at Lexington must assume responsibility with respect to the risks involved in carrying out tests in man. Accordingly, they have indicated that, prior to the initiation of tests, they wish to be supplied with information upon the general pharmacology of the compound, including its toxicity and relative potency, evidence that it has been administered to man and that it may be a useful therapeutic agent, its relative potency in man and some indication of the side-effects which it may produce. They request that the data on the general pharmacology of the compound include information on acute and chronic toxicity, on relative potency with respect to analgesic, antitussive and/or constipating action, on whether or not the actions of the drug are antagonized by one of the specific antagonists such as nalorphine, on the rate and extent of dosage increase in chronic administration in attempted determination of tolerance, on whether or not tolerance develops and cross-tolerance to morphine for example, and on physical dependence capacity in monkeys and acute tolerance and physical dependence development in dogs. All such information is pertinent to the establishment of dosage schedules and to the safety of investigation of the agent in man.

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1 We are indebted to Dr Harris Isbell, Director, to Dr H. F. Fraser, Associate Director, and to their associates at the Addiction Research Center for permission to describe their methods, of which not all details have been published previously.
The subjects in the studies at Lexington are former opiate addicts, male, coloured or white, in good physical condition, who are serving a sentence for violation of the narcotic laws and who have volunteered for the experiment.

**Single-dose administration for the determination of morphine-like (euphoricogenic) effects**

Starting with small doses—their actual size is based upon previous experience with the drug—a new agent is administered by various routes, depending upon its solubility and other physical properties. The dose is then increased, two or three men being given the drug at each dose level, until a definite effect is obtained or signs indicative of impending toxicity are seen. Up to this point administration is on a single-blind basis, the nature of the drug being unknown only to the patient, who is, however, allowed to express his feelings about it in comparison with his previous drug experience. An idea of relative potency thus having been arrived at, the next step is administration on a double-blind basis, identity of drug and dose being unknown to both patient and immediate observers. Two dose levels of the new agent are given at weekly intervals in random order with two comparable doses of a standard of similar potency and a placebo as controls to a group of eight to twelve individuals. Administrations are continued until each individual in the group has received each of the medications. Certain objective measurements may be made before and at intervals after each dose, such as pupil size, respiratory rate and minute volume, blood pressure and body temperature, and both the patient and the observer are required to fill out a "Single-dose attitude questionnaire" (see Annexes 1 and 2). It will be noted that both the subject and the observer are asked to check whether the agent seems to be an opiate ("dope") or is like some other drug, the degree of the patient's liking for the drug and the frequency of opiate-like symptoms. The mean of the group for all observations with each medication is determined and plotted for comparison with the standard and the placebo. The results obtained in a typical experiment are illustrated in Fig. 3. Both patients and observers agreed very well in their evaluation of the drugs and the frequency of opiate-like symptoms paralleled changes in pupillary diameter.

**Substitution for morphine**

Formerly a single dose of the agent under investigation was given to individuals stabilized on morphine, approximately 240 mg per day. The dose was given 30 hours after abrupt discontinuance of morphine, when the withdrawal syndrome was reaching its peak. The subsequent course of abstinence intensity was compared with that to be expected in otherwise untreated individuals. A more adequate procedure has since been devised—a procedure that can be repeated on the same individual at weekly intervals because the abstinence syndrome is never allowed to reach a seriously disturbing intensity. Thus double-blind cross-over observations can be made comparing, in the same individual, one or more dose levels of one or more experimental agents, a placebo and a standard dose of morphine (Fraser & Isbell, 1960a, 1960b).

A group of 5-12 individuals is given morphine subcutaneously regularly, the dose being built up rapidly to 240 mg per day and stabilized at that level for not less than 30 days. Beginning with the evening dose (10 p.m.) and continuing through 24 hours a coded substance (experimental drug, placebo or standard morphine dose given as an unknown) is administered in place of the regular morphine doses. Beginning the next morning, 14 hours after the last regular dose of morphine, observations are made at regular intervals, recorded and evaluated according to the Himmelsbach (1939) hourly score for abstinence phenomena (Table I). The substitution procedure is repeated at weekly intervals until each individual has received in random order at least one dose level of the experimental drug, a saline injection as a placebo, the regular stabilization dose of morphine and perhaps one or more dose levels of one or more other agents. The mean hourly Himmelsbach score for all patients for each agent is plotted and a comparison is made between the experimental agent and morphine or placebo. If the drug is ineffective as a morphine substitute, the graph of abstinence phenomena intensity will coincide with that obtained after the administration of a placebo. If it is morphine-like in some degree, the graph of abstinence phenomena observed will approximate to that obtained after continuation of morphine as an unknown during the substitution period or will fall between the placebo and morphine graphs, depending upon the effectiveness of the dose used as a morphine substitute (see Fig. 4). A more direct and perhaps simpler comparison is obtained by summing for each agent for each individual the hourly point scores and calculating the mean total abstinence score for 24 hours (TAS-24). This score
RESULTS OF SINGLE-DOSE ATTITUDE QUESTIONNAIRES, FILLED OUT BY PATIENTS AND OBSERVERS, AND DECREASE IN PUPILLARY DIAMETER AFTER SINGLE DOSES OF DIPHENOXYLATE (70 mg), CODEINE (140 mg) AND A PLACEBO

**FIG. 3**

- **IDENTIFICATION AS "DOPE"**
  - DIPHENOXYLATE TRS = 2.4 ± 1.13
  - CODEINE TRS = 1.9 ± 1.23
  - PLACEBO TRS = 0.0

- **POSITIVE ATTITUDE SCORE**
  - DIPHENOXYLATE TRS = 10.2 ± 6.2
  - CODEINE TRS = 10.5 ± 2.5
  - PLACEBO TRS = 1.0 ± 0.27

- **OPIATE SYMPTOMS**
  - DIPHENOXYLATE TRS = 13.6 ± 3.61
  - CODEINE TRS = 15.2 ± 3.28
  - PLACEBO TRS = 1.1 ± 0.30

- **DECREASE IN PUPILLARY DIAMETER**
  - DIPHENOXYLATE TRS = 23.4 ± 4.26
  - CODEINE TRS = 18.9 ± 3.32
  - PLACEBO TRS = 7.7 ± 3.04

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*A The maximum number of positive answers hourly for identification as "dope" = 1.0; for positive attitude (liking) score = 4.0; and for frequency of opiate symptoms = 7.0. Each point on each curve represents the average of data obtained on 8 men, each of whom had diphenoxylate and codeine three times and the placebo once. The TRS values (total response scores for 14 hours) represent the mean of the areas under the curves ± standard errors.

After Fraser & Isbell (1960c).

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will be high (150 or more) for placebo substitution and low (50 or less) for morphine continuation.

In many instances, especially if the 24-hour substitution does not completely suppress the appearance of abstinence phenomena, substitution may be continued for 10 days. Individuals are stabilized on morphine and substitution is begun as in the 24-hour experiment. An attempt is made to substitute the new drug at such a dose and interval of administration as to maintain the addiction; that is, to prevent completely the appearance of abstinence phenomena which would have occurred as a result of the cessation of morphine administration. Whether or not this is attained, one gets an impres-
sion of the individual’s satisfaction with the substitute. At the end of 10 days the substituted drug is replaced by placebo, the change not being revealed to either patient or observer. Throughout the 10 days of substitution and for a week of withdrawal (placebo administration), observations are made daily for signs of abstinence and evaluated according to the Kolb & Himmelsbach (1938) daily point score (Table 1). The score during the withdrawal period is compared with the abstinence syndrome after abrupt withdrawal of morphine, affording a qualitative and quantitative appraisal of the withdrawal symptoms after the substituted drug.

It is possible to re-stabilize the individual on morphine and subsequently to withdraw him abruptly for a comparative appraisal of his morphine abstinence intensity; or, after re-stabilization, a second 10-day substitution with another agent can be carried out if a direct comparison of two new agents in the same individual is desired.

Direct addiction

If previous experience has shown a compound to be significantly more or less effective than morphine, if it is a new chemical type, and particularly if its introduction into clinical practice is contemplated, a direct addiction experiment may be undertaken. Individuals previously addicted to morphine or a related drug and free of drugs for some months are given the new agent regularly at an interval and dose and by a route deemed appropriate according to previous experience. The dose is increased as rapidly as possible, avoiding, of course, cumulative effects and toxic reactions. The objective is to increase the dose, if possible, by a schedule paralleling that leading to stabilization on morphine in the experiments already described. The direct addiction attempt may be continued for 30, 60, or 90 days or longer, and is followed by abrupt withdrawal; a comparison is then made with similar periods of administration and withdrawal of morphine. During the latter part of such direct addictions, a few days before withdrawal, patients are challenged by administration of a small dose (3, 5 or 10 mg) of nalorphine. If signs of abstinence are precipitated by nalorphine, these are compared with the withdrawal syndrome observed subsequently.

Recently a modification of the above procedure has been tried, shortening the addiction period and affording cross-over data on the same individuals (Fraser & Isbell, 1960b; Fraser et al., 1961b). Eight drug-free former addicts were selected and to each was assigned in random order a coded medication to be administered on a double-blind basis in ascending dosage for a period of 18 or 19 days. The medications were placebo capsules, morphine capsules, codeine capsules, morphine for subcutaneous injection and four experimental drugs, one in capsule form, the others for subcutaneous administration. The initial dosage (except of the placebo, of course) was usually that judged to be equivalent in effectiveness to morphine on the basis of 24-hour substitution; it was, however, sometimes less than the equivalent in order to avoid toxic reactions (Fraser et al., 1961b, p. 378, footnote 1). Since no difficulty is experienced usually in increasing morphine dosage in former addicts to 240 mg a day in 18 days, such a regimen of administration of morphine was employed and a schedule of increasing dosage for
all other drugs was arranged which would parallel that for morphine. Since tolerance to new agents may or may not develop as rapidly as tolerance to morphine, patients were watched for depth of sedation and toxic reactions and the increasing dosage schedule was halted or modified as necessary.

On the 19th or 20th day, the exact time being known to the person preparing the drugs, but not to the patient or the observer, a placebo (capsule or injection according to which the patient had been receiving) was substituted and continued on the same schedule for 10 days. Then each individual was started on another of the series of medications, again assigned in random order, and the whole procedure was repeated until each individual had received each of the eight preparations.

Throughout drug administration and placebo substitution, the following observations were made three times daily; rectal temperature, respiratory rate, pulse rate, blood pressure and the usual observations for abstinence signs according to the Kolb & Himmelsbach scoring system. Caloric intake was measured daily; body-weight was recorded each morning, and hours of sleep, hours of inactivity (lying horizontally on bed, whether or not asleep) and hours of initiative activity (off the ward in various voluntary pursuits) were recorded at half-hour intervals daily. For each withdrawal period a total abstinence score for 10 days (TAS-10) was calculated. These scores for all drugs individually and as means for all patients were compared with the scores for placebo and all other drugs were compared similarly with morphine and with each other.

At 7 p.m. on each day of the experiment each patient completed a questionnaire dealing with the subjective effects of the drug he was receiving, and concurrently a separate questionnaire dealing with the behavioural changes was completed by the observer (see Annexes 3 and 4). These recorded such things as recognition of the drug as an opiate, the patient's liking for it and inclination towards continuation of its use, and judgement of its strength.

The results of this experiment as revealed by the chronic dosage attitude questionnaires are shown in Fig. 5. All ratings of patients and observers were tabulated, but the figure is restricted to the parameters: identified as "dope", estimate of "strength," and "would like to take drug daily". The data were analysed for statistical differences between drugs by the paired "t" test, using total responses for the first 18 days on each drug and a placebo.

An alternative short direct addiction test has been employed by Fraser and his associates which is especially applicable to the evaluation of intravenously administered drugs (Fraser et al., 1961a). A typical experiment employing this technique is described as follows: In a single-blind study six subjects received drugs intravenously and one subcutaneously because all of his superficial veins were sclerosed. A "sample" of a high dose of each drug was given at 3-day intervals—180 mg of I-K-1 (1-(p-chlorophenethyl-6,7-dimethoxy 2-methyl-1,2,3,4-tetrahydroisoquinoline), 180 mg of d-propoxyphene, 120 mg of codeine and 30 mg of morphine—in randomized order. Each patient rated each of these drugs on the single-dose attitude questionnaire (see Annex 1) and after each had received all four sample doses he was asked to review his response to each on the questionnaire and to rate them in order of preference, 1 to 4. In this preferential ballot morphine ranked first, d-propoxyphene second, and codeine and I-K-1 equal and last.

It was explained to each subject that he would then receive, in randomized order, all the sample drugs which he elected to take in increasing doses for seven days, with a withdrawal period of three days between each drug phase. However, after his rating of the single doses, a subject could elect not to take any of them during the seven-day phase, to take one or more of them, or after starting any particular drug to stop at any time during the seven days, go on to the next drug or discontinue entirely without penalty. At the end each subject was asked again to rate the drugs in order of preference.

The daily amounts of the drugs were as follows: for I-K-1 and d-propoxyphene, 360 mg (divided into three equal doses) on the first and second days and 480, 600, 600, 720 and 720 mg (divided into four equal doses) on the third to seventh days; for morphine, 60, 60, 80, 100, 100, 120 and 120 mg (divided into four equal doses); and for codeine, 240, 240, 320, 400, 400, 480 and 480 mg (divided into four equal doses). All drugs were administered intravenously (with the one exception noted above) slowly over a 2-minute interval. Nalorphine (3 mg) or a placebo, on a randomized double-blind basis, was injected subcutaneously at 9 a.m., that is, three hours after the last dose of an experimental drug, on the sixth or seventh day of the test. Observations for abstinence signs were made also on the three days between drug administrations.

Morphine was definitely the preferred drug in this series; it was taken by all the subjects, one dis-
continuing it, however, on the second day because of nausea. *d*-Propoxyphene was taken by all the subjects and by two of them for the whole period of seven days; the average duration of administration for all subjects was 5.3 days. Even though five men identified the drug as "dope", five discontinued *d*-propoxyphene for such reasons as pain at the site of injection, nausea, loss of appetite, dizziness and nervousness. One patient took *d*-propoxyphene intravenously for seven days, but his veins became progressively occluded; successive injections of the higher doses had to be given in different veins and as much as 45 minutes was spent locating a suitable vein. As to codeine, two patients elected not to start the 7-day course of addiction and only three completed the course. Those taking codeine intravenously complained that all they felt was a temporary pins-and-needles sensation. Although all the subjects elected to take I-K-I for the seven days, it was feasible to administer it to only two subjects (for 2.5 and 6.3 days, respectively) because it induced severe phlebitis and venous thrombosis. All patients complained that with I-K-I morphine-like effects were absent or very weak and there was pain at the site of injection.

This short-term direct addiction technique has the following advantages: The programme is less rigid in design than in the original long-term technique.
and permits the former addicts to make elections among drugs and on how long they wish to take an agent before trying another. Furthermore, as indicated above, it brings out rapidly differences among drugs respecting the quality of the subjective effects and characteristics of a drug which determine its suitability for intravenous administration—for example, its solubility and its local irritant and/or thrombotic properties. The primary deficiency of the method is that it does not evaluate adequately the degree of physical dependence. It does, however, give valuable information on the subject's immediate like or dislike of a drug by his usually preferred route of administration and, hence, on whether or not he would be inclined to use it thus if it were available to him.

TESTS FOR THE DEVELOPMENT OF TOLERANCE AND PHYSICAL DEPENDENCE UNDER CLINICAL CONDITIONS

A direct attack upon the question of addiction liability in clinical practice was initiated about 25 years ago under the auspices of the Committee on Drug Addiction of the National Research Council (USA). Selected subjects with chronic pain were given morphine or another comparable analgesic in an amount and at an interval just sufficient to control their pain. At 2- or 3-week intervals the analgesic was withheld for a period up to 24 hours and careful hour-by-hour observations were made for the appearance of abstinence phenomena. Recurrence of pain was the major difficulty and often made the period of withdrawal so short that no signs of abstinence could be expected (Eddy & Himmelsbach, 1936; Lee, 1942).

The production of morphine antagonists, as mentioned earlier, has made possible a new line of attack. Wikler, Fraser & Isbell (1953) showed that nalorphine would precipitate abstinence phenomena in subjects who had received 15-30 mg of morphine four times daily for 3-7 days, or 10 mg of methadone four times daily for 2-5 days, or 15 mg of heroin four times daily for 2 days. Later, in the addiction period with any one of these drugs, the same dose of nalorphine precipitated a more intense abstinence syndrome. Indeed, later during continued methadone administration, nalorphine precipitated abstinence signs which exceeded in severity those which ensued after abrupt withdrawal of morphine following long periods of addiction to high doses of that drug. These observations implied that physical dependence on morphine-like substances began to develop very early, perhaps even with the first dose, and increased in intensity with continued administration. However, the results with methadone indicated that the intensity of abstinence signs precipitated by nalorphine was not necessarily a basis for the prediction of the intensity of abstinence which would follow abrupt withdrawal, since withdrawal of methadone was followed by a slowly developing and relatively mild abstinence syndrome (Isbell et al., 1947). Nevertheless, if morphine or another morphine-like analgesic were given for chronic pain and if nalorphine (or another specific antagonist) were given periodically during such administration in fixed amount and in fixed relation to the last dose of the analgesic, followed by observation for characteristic abstinence symptoms, the appearance and intensity of such symptoms could be a measure of the time required for, or the rate of development of, physical dependence. The procedure should be applicable to any form of chronic administration.

Parenteral administration of potentially addicting agents

From a population of patients with inoperable cancer individuals are selected who have persistent pain of an intensity to warrant the application of an opiate. Their histories are scanned to select those with little previous narcotic experience and each patient is screened by an initial "allyl test" to rule out already existing detectable physical dependence. A suitable patient is started on subcutaneous administration of the medication, coded to provide double-blind conditions. The patient remains on that medication throughout the study, other analgesics being avoided entirely and, so far as possible, other sedatives. The initial dose is that determined previously to be equivalent to 10 mg of morphine per 60 kg of body-weight, but it is adjusted if necessary by 10% increments within the first few days to provide adequate relief in the individual patient. Repetition of the dose is based on the demand of the patient because of the return of pain. The dose is increased only as necessary to maintain adequate relief. As a check on the adequacy of pain relief, with the first dose of coded medication and with a single dose at weekly intervals, a careful record is kept of the degree of pain before and at hourly intervals after medication. (See Eddy & Lee, 1959.)

While the coded medication is continued, a record is kept of the individual dose and the total amount of narcotic administered per day. From this record and the weekly pain-relief scores a judgement is
made regarding the development of tolerance to the analgesic effect of the drug. One must bear in mind that advancing disease in these mainly terminal cases may cause some increase in pain, and in consequence some increase in narcotic consumption independently of tolerance development.

Estimation of the development of physical dependence is based upon the periodic administration of nalorphine, the "allyl test". This test is performed before coded medication is started and every two weeks thereafter. In the alternate weeks a "placebo test" is carried out in like manner, saline solution being injected in place of nalorphine. In each instance the test is begun two hours after a dose of narcotic. Blood pressure, rectal temperature, respiratory rate and pupil size are determined and immediately afterwards 1.0 mg of nalorphine hydrochloride (or 0.5 ml of saline solution for the placebo test) is injected subcutaneously. At 5-minute intervals up to 20 minutes blood pressure, temperature, respiratory rate and pupil size are re-determined and simultaneously the patient is observed for other characteristic abstinence signs. Unless the symptoms observed are strikingly characteristic or severely disturbing to the patient, 2.0 mg of nalorphine hydrochloride is injected 25 minutes after the first dose and the observations are continued for at least another 20 minutes. Alternatively, each allyl test may be performed with the administration of a single dose of 3.0 mg of nalorphine hydrochloride. The decision to employ one or two doses of nalorphine should be made initially and the procedure remain the same for all patients of a study group.

The signs looked for in each test and the numerical values assigned to them, both modified slightly from the Himmelsbach hourly scoring system, are shown in Table 2. A limit of 10 points is set for changes in systolic blood pressure but no limit for an increase in respiration or rise in temperature. The difference scored for blood pressure, respiration and temperature is the maximum observed after a dose of nalorphine compared with the value before any nalorphine is given. The pupil size may be determined by comparison with a series of dots differing one from another by 0.5 mm in diameter or, preferably, by photographing the pupil. A score of 15 (the sum of the values for all signs observed) is judged to be significantly indicative of the presence of physical dependence, provided that the score is contributed to by some sign in addition to changes in blood pressure and respiratory rate. This condition or restriction is necessary because lability of blood pressure and respiration may occasionally, under the conditions of the unusual procedure of the allyl test, produce wide non-specific fluctuations. In all cases a positive allyl test should be confirmed by another test giving the same or a greater score, two weeks or more later, before a definite conclusion of physical dependence is reached.

Eddy, Lee & Harris (1959) have reported on the application of the procedures just described to a study of addiction under clinical conditions. They have, by this method, compared oxymorphone and anileridine with morphine and currently some other old and new drugs are being compared in the same way.

Schrappe and his associates (1959), believing that the Himmelsbach scoring system did not give an adequate quantitative representation of abstinence phenomena, have devised an alternative classification. They separate the abstinence signs into two groups, specific and non-specific, as shown in the tabulation below:

<table>
<thead>
<tr>
<th>Abstinence signs</th>
<th>Symbol</th>
<th>Numerical value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>BP</td>
<td>1 point for each 2 mm Hg maximal rise, total not to exceed 10 points</td>
</tr>
<tr>
<td>Rectal temperature</td>
<td>T</td>
<td>1 point for each 0.1°C rise</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>R</td>
<td>1 point for each resp./min. increase</td>
</tr>
<tr>
<td>Yawning</td>
<td>Y</td>
<td>1 point</td>
</tr>
<tr>
<td>Lacrimation</td>
<td>La</td>
<td>1 point</td>
</tr>
<tr>
<td>Rhinorrhoea</td>
<td>Rh</td>
<td>1 point</td>
</tr>
<tr>
<td>Sweating</td>
<td>S</td>
<td>1 point</td>
</tr>
<tr>
<td>Gooseflesh</td>
<td>G</td>
<td>3 points</td>
</tr>
<tr>
<td>Mydriasis</td>
<td>My</td>
<td>3 points</td>
</tr>
<tr>
<td>Tremor</td>
<td>Tr</td>
<td>3 points</td>
</tr>
<tr>
<td>Restlessness</td>
<td>Re</td>
<td>5 points</td>
</tr>
<tr>
<td>Abdominal or other cramps</td>
<td>C</td>
<td>5 points</td>
</tr>
<tr>
<td>Urge to defaecate</td>
<td>D</td>
<td>5 points</td>
</tr>
<tr>
<td>Nausea</td>
<td>Na</td>
<td>3 points</td>
</tr>
<tr>
<td>Emesis</td>
<td>V</td>
<td>5 points for each act of emesis</td>
</tr>
</tbody>
</table>

After Eddy, Lee & Harris (1959).
Abstinence symptoms of the first order (specific)

1. Shivering, feeling of cold, gooseflesh.
2. Yawning, sneezing, cough, hiccup.
4. Rhinorrhea, lacrimation, salivation.
5. Diarrhoea.
6. Colic, increased peristalsis, borborygmus, urge to defaecate.
7. Retching and vomiting.
8. Extreme mydriasis (widening of the pupil by 3 mm or more).
10. Muscular discomfort and pain.

Abstinence symptoms of the second order (non-specific)

1. Increase in body temperature of 0.3°C or more.
2. Increase in respiratory frequency of three per minute or more.
3. Mydriasis (widening of the pupil by only 1 or 2 mm).
4. Increase of systolic blood pressure of 10 mm or more.
5. Anxiety, inner unrest.
7. Headache, heart pain, palpitation, faintness.

Each of the non-specific signs is given a value of one point; the specific signs are given a cumulative value based on 10 for the first to be observed. The emphasis on the various abstinence phenomena differs in the Schrappe and Himmelsbach systems and the former does not use a simple summation to arrive at the total abstinence score. Schrappe and his associates used successive doses of nalorphine to precipitate abstinence signs during continuing narcotic administration and compared the syndromes thus produced with those occurring spontaneously after abrupt withdrawal of morphine or methadone.

Oral administration of analgesic mixtures

Himmelsbach et al. (1940) showed that codeine administered either subcutaneously or orally supported previously established physical dependence to morphine. Himmelsbach reviewed the literature on addiction to codeine, cases of which continue to appear occasionally. Even the oral preparations of codeine of relatively low concentration are subject to some abuse, and abuse of dihydrocodeinone oral preparations is comparatively common (United States Bureau of Narcotics—personal communication, 1960). However, specific information on the degree and rate of development of physical dependence with oral administration of analgesic mixtures is only now being sought by a technique adapted from that described above for parenteral administration of analgesics. For the first report on this work, see Cass and associates (1961). The following is a description of the procedure as modified for a continuation of the study of this problem.

Hospitalized patients are selected for the study who have persistent mild to moderate pain of a degree that warrants and is generally relieved by an oral analgesic mixture such as codeine plus APC (codeine phosphate 32.5 mg, aspirin 227.5 mg, acetophenetidin 162.5 mg, caffeine 32.5 mg) or its equivalent. Background information is entered on a special record sheet (see Annex 5) and the patient begins a control period of eight days, during which his analgesic medication, whatever it was previously, is changed to five grains of aspirin three cr four times a day. A record sheet (see Annex 6) is filled out for each of the control days to provide a baseline for the degree of relief afforded by aspirin, the patient’s daily complaints, etc. Also during this period a screening allyl test is carried out and, if this test is negative, the patient is assigned to a drug group. The assignment is based on the background information and the data obtained on the control days and is intended to make the several drug groups as homogeneous as possible, since a number of drug mixtures will be compared. The objective will be drug groups each comprising about 25 persons, half males and half females. The medication is supplied in capsules, under code number, of course, to make the study double-blind, and is administered on a routine four-times-a-day schedule to those patients who get adequate pain relief on such a schedule and on a patient demand (p.r.n.) schedule to all others. In the latter group, the number of capsules per dose, the interval between doses and the total number of capsules per day are adjusted to the patient’s need or demand, thus further simulating usual clinical conditions and allowing psychic dependence and tolerance, if they develop, to play their roles in total drug consumption. The medication for a particular patient remains the same, but the code is changed with the consumption of each 100 dosage units. A record is kept for each patient each day (see Annex 7), showing total medication (number and time of administration of dose units taken), whether pain was present or absent at three interviews during the day, and patient’s complaints (side-effects), if any.
To check for the development of physical dependence an allyl test (nalorphine hydrochloride, 3 mg subcutaneously) will be carried out once a month, also on a double-blind basis. To effect this, nalorphine and saline solution are provided in identically appearing ampoules, each ampoule carrying a different code number, and tests are carried out on successive days using two coded ampoules, one of which contains nalorphine and the other saline. The tests are carried out as described in the section on parenteral administration and the data are recorded (see Annex 8) and evaluated by the modified Himmelsbach score (Table 2).

The daily record sheets and the allyl or placebo test results are reviewed by a person not directly associated with the patients, so that the narcotic medication can be stopped and a withdrawal period instituted, by substitution of APC capsules under code number for the specific analgesic mixture, as soon as a significant degree of physical dependence is demonstrated. During this withdrawal period observations will be made three times a day for the first three days and then daily through ten days for the spontaneous appearance of withdrawal signs, according to the Kolb & Himmelsbach daily scoring system (Table 1).

In the initial study by Cass and his associates, results were reported on 63 patients who received their medication on a rigid four-times-a-day schedule. The drugs employed were codeine plus APC, ethoheptazine plus aspirin, oxycodone plus a modified APC, and dextropropoxyphene. The experiment was terminated in each case after not more than 90 days of specific medication followed by a 10-day withdrawal period. The authors said:

"On periodic administration of Nalline (nalorphine), some signs of addiction were demonstrated with all products, but these symptoms were not consistent, progressive or clear-cut. Upon withdrawal, some symptoms suggestive at least of physical dependence were observed with all drugs except ethoheptazine. All four drugs demonstrated analgesic effectiveness."

In the current continuation of the study the medications are APC alone, codeine phosphate plus APC, methadone hydrochloride plus APC, and levorphanol tartrate plus APC. These were deliberately selected on the basis of previous experience to provide a range in the development of physical dependence as a background for inclusion in the study later of new substances, concerning which nothing is known of their addictiveness when administered orally under clinical conditions.

Tests for detection of drug use and recidivism

The diagnosis of addiction or of return to drugs by an individual who has undergone treatment or incarceration for violation of the narcotic laws is not easy in the absence of definite signs of abstinence. This problem has been discussed at length in a report, entitled "What to do with a drug addict?", by Isbell (1952) to the Council on Pharmacy and Chemistry of the American Medical Association. The report points out that there are no pathognomonic physical signs of addiction and comments on various aspects of the situation and devices employed by addicts that need to be borne in mind if one is not to be misled. Since complete or partial tolerance to many of the effects of morphine and allied drugs develops during the course of addiction, addicts will not show the same effects as might be expected in persons not addicted. Constriction of the pupil and signs of sedation are not likely to appear unless a dose of the addicting drug has been received recently. Superficially tolerant addicts will appear to be physically and mentally normal unless they have been without drugs for some time and signs of abstinence are beginning to appear. The most important findings are the presence of old and recent needle marks. These should be sought over the veins in the antecubital spaces, the deltoid region, the abdomen, the anterior surfaces of the thighs and along the veins of the legs and hands. Long scars or tattooing over superficial veins is extremely suggestive, especially if fresh needle marks are present. Also suggestive are multiple abscesses or old abscess scars. Addicts using either pethidine or methadone are likely to have induration and inflammation of large areas of the skin, particularly over the deltoid region and the anterior surface of the thigh. An important feature may be that no physical findings are present which satisfactorily explain the serious symptoms detailed by the patient. A complete physical examination as part of the diagnostic procedure is imperative.

A definitive diagnosis of addiction to morphine or similar drugs depends upon the demonstration of the characteristic signs of abstinence following complete and abrupt withdrawal of drugs. To prove the presence of physical dependence, the addict must be isolated in an environment so well controlled that there is no possibility of his obtaining any narcotic drugs other than those prescribed. If such an environment is available, isolation of the addict and withholding of all narcotics will prove the presence or absence of dependence on these drugs. Detection
requires, of course, familiarity with the signs of abstinence and at best the procedure is prolonged and difficult for patient, physician and attendants. The precipitation of an abstinence syndrome by nalorphine or another specific opiate antagonist and the utility of such a procedure in experimental clinical designs have been described above. As early as the report to the Council that has been quoted above, the possibility of the use of nalorphine for diagnosis was suggested and a little later its use for this purpose was described more explicitly (Isbell, 1953). As mentioned later, however, there are certain basic requirements for the safety and interpretation of this test.

When these requirements have been met, a 3-mg dose of nalorphine is given subcutaneously. If signs of abstinence have not appeared in 20 minutes, an additional 5-mg dose is given and, if a definite abstinence syndrome does not appear after 20 more minutes, a final dose of 8 mg is administered. If abstinence has not become evident within 20 minutes after the final injection, the patient is not addicted and can be released after the direct effects of nalorphine have worn off, usually in less than six hours. If signs of abstinence appear after any of the doses of nalorphine the individual has been taking morphine or an allied drug at sufficiently short intervals and in sufficient amounts to produce physical dependence, and therefore is addicted. Obviously this method of diagnosing addiction requires familiarity with the signs and symptoms of nalorphine-induced abstinence. Within two or three minutes after the administration of nalorphine an addicted person experiences a sensation of heat in the back or abdomen spreading over the body. There follow abdominal cramps and frequently defaecation. The patient becomes apprehensive and restless, perspires profusely and yawns frequently. Lacrimation and rhinorrhea appear and increase in degree. The patient complains of chilly sensations and recurring waves of gooseflesh are observed. Vomiting is likely to occur. The patient may become quite hostile and antagonistic. Respiratory rate and minute volume increase and the blood pressure is sharply elevated. The pupils are dilated. These symptoms constitute a full-blown abstinence syndrome, which may begin in five minutes, reach peak intensity in 20, start to decline in 60 minutes and disappear after three hours. The symptoms are relieved, but not easily, by the administration of morphine.

A negative nalorphine test does not exclude the possibility that the person has been taking occasional doses of narcotics, nor does it prove that he was not actively addicted a week before the test was done. A positive test, as just described, can have but one meaning. However, efforts have been made to use a much milder reaction, even dilatation of the pupil alone, as presumptive evidence of the use of narcotics and this aspect of the procedure requires further discussion.

Terry & Braumolller (1956) reported upon the use of nalorphine for the detection of addiction, relying upon changes in pupil size for a definitive result. They mentioned other withdrawal symptoms, but said:

"The observation of gross withdrawal symptoms should not be depended upon for a diagnosis but should be avoided if possible. To some degree patients themselves can control withdrawal symptoms. The pupillary response alone is an accurate, sufficient, and sensitive index of narcotic addiction or of occasional use, or of the absence of narcotics."

The authors reported upon the use of the nalorphine test in 454 patients suspected of taking an opiate. They used a single dose of 3 mg. A card with black dots was used to measure the size of the pupil, the authors believing this to be accurate to 0.5 mm of diameter. According to the authors' interpretation,

"If the person tested has not been using opiates the diameter of the pupil is reduced by 0.5 mm. In a person who has been using opiates occasionally but who is not addicted, the pupils will remain unchanged in size. In a person who is addicted the diameter of the pupils will increase by from 0.5 to 2 mm, the amount of increase depending upon the degree of addiction."

Other localities in the USA have been employing the nalorphine test for the detection of addiction and in some it has been made a condition of probation that the individual report periodically for such a test to determine whether or not there has been a return to drugs. It is now generally believed that the dose of nalorphine in these tests should not exceed 3 mg, but there is not general agreement on the reliance to be placed on pupillary changes alone or on the desirability or necessity for other evidence. There is a strong feeling that a positive finding—definite pupillary dilatation—could be used as a presumptive basis for holding an individual, but that confirmation of such results should be sought by immediate urinalysis. Urinalysis should be done in the cases showing equivocal results (slight dilatation or no change in pupil size) after nalorphine. Such analysis is cumbersome and time-consuming.
and attention is being given to simplification. Cochin & Daly (1962), for example, have described a method employing thin-layer chromatography that is rapid and accurate in its differentiation of opiates in the urine and attention is being given to the application of gas chromatography to this problem.

The proponents of the nalorphine test for detecting drug addiction and relapse are strongly of the opinion that it is a deterrent to relapse where it has been used as a condition of probation. The test has value and merits wider application, but it needs to be carried out under better conditions and with precautions which have not always been observed. Isbell (personal communication, 1961) has outlined the requisite conditions for the nalorphine test as follows: It should always be performed by a physician who has studied the technique, is aware of the observations to be made, the precautions to be followed and the interpretation of the reaction. Before the test is done the patient should be given a complete physical and mental examination, which will yield information on the history of addiction, the presence or absence of needle marks, miosis, etc., the presence or absence of serious organic disease and the patient’s competence to sign a consent form. The test is contra-indicated in any person who has serious organic disease, whatever the nature of that disease may be. The consent of the patient should be obtained in writing, after the test and its purpose have been explained to him. This explanation should include the possibility of severe reactions, their hazards and possible medico-legal implications. If the patient is under legal age or is mentally incompetent, consent must be obtained from a parent or legal guardian. The test should be done in a clinic or hospital where there are adequate facilities for care of the patient in the case of a severe reaction and it should not be done unless there are facilities for putting the patient to bed before, during and after the test and resuscitative equipment is at hand, including epinephrine and/or other stimulants, infusion sets with normal saline and plasma expanders, mechanical respirators and aspirators and injectable forms of morphine and barbiturates. The dose of nalorphine should not exceed 3 mg initially and additional doses should not be given except by persons with considerable experience. There should always be present two professional observers—two physicians or a physician and a nurse—each of whom will make observations independently.

Isbell’s recommendations have been in large part accepted by the State of California Department of Public Health, which has published a guide explaining the purpose and application of the test, the manner in which it is to be carried out and the criteria for determining that the test is positive (State of California Department of Public Health, 1961). This guide says with respect to the test:

“The procedure recommended here is intended to serve only as a guide to physicians performing the synthetic opiate-antagonist test as an adjunct to the diagnosis of opiate usage. The procedure is not recommended as an aid in detection of obvious addiction to opiates. As in any clinical circumstance, the results of a single test or procedure do not constitute a diagnosis.”

This is a statement worthy of emphasis, because often the impression has been given that the nalorphine test or even a small degree of pupilary dilatation occurring in the test is all that is needed for a positive diagnosis, whereas the test may give some false positives and false negatives when checked by urinalysis and other evidence. Mason & Shepherd (1962) have reviewed tests performed on 154 cases in Illinois, USA, one of the States that authorizes the use of the nalorphine test as a check on return to drug use of individuals on probation. They reported that in 59.1% of the cases the result of the test was unequivocal, 37.0% negative and 22.1% positive. In 28.6% the test was equivocal, 11.7% negative and 16.9% positive according to further analysis. There were 15 (9.6%) false positives and 4 (2.6%) false negatives. All of the nalorphine tests were checked by urinalyses, but in these only morphine (by indirection heroin and codeine also) was looked for. Very probably this raised the number of apparent false positives, since the nalorphine test is strongly positive when methadone is the drug used and may be positive when the individual has been taking pethidine or a related addicting substance.

DISCUSSION AND SUMMARY

The many procedures which have been described, both laboratory and clinical, have been devised partly to learn more about the phenomena of tolerance and physical dependence and partly as attempts at predicting the risks or relative safety for clinical practice of new agents possessing in some degree one or more of morphine’s clinically useful properties. Undoubtedly much has been and can be learned by these methods that is pertinent to their first purpose. Some comments are in order with respect to the degree of attainment of the second objective.

What happens in man is, of course, our real concern, but human material for abuse and addic-
tion liability testing is not readily available. The Addiction Research Center at Lexington is the only place in the world where tests of this nature are going on and very few studies (to our knowledge less than half a dozen) of the development of tolerance and physical dependence in man under carefully controlled conditions are in progress. An animal method, therefore, which could be relied upon not to give false positive results would be very valuable. Negative results in animal experiments may be encouraging but are at present not conclusive and are not likely to be.

The method of Shemano & Wendel for predicting the probability of addiction on the basis of a relationship between the dose producing a Straub tail-reaction and the dose with a lethal effect in the mouse is simple and economical of time and material, particularly since it does not require any period of repeated administration. However, a Straub tail-reaction has been described in the action of substances which are not at all morphine-like and are known not to produce tolerance or physical dependence. The authors report the highest Straub index for apomorphine, though they point out that its ability to produce physical dependence has never been tested. The practicability and reliability of the method with respect to other false positives, if the apomorphine result is a false positive, will need confirmation through extension to a much wider series of compounds to establish confidence in its predictive value as a screening procedure.

The several procedures which have been developed in experiments on the rat have demonstrated that this animal can become physically dependent on morphine and related substances. Also an abstinence syndrome, not unrelated to that seen in man, can appear after abrupt withdrawal of chronically administered morphine and, more particularly and more characteristically, following administration of nalorphine or another opiate antagonist during chronic morphinization. Attempts have been made to quantify the components of the nalorphine-precipitated syndrome. Confirmation and refinement of this quantitative evaluation may yield a preliminary screening test for substances with physical dependence liability of morphine type, at least for positive results. Again negative results cannot be considered more than suggestive. Also it should be borne in mind that continuity of administration, seven days a week without interruption, at an around-the-clock interval consonant with the duration of action of the drug, is essential for the full development of physical dependence and quantitative comparisons, whatever the experimental subject, small or large animal (Seevers, 1958).

The investigators at the Addiction Research Center in Lexington have pointed out similarities in the behaviour of dog and man during chronic administration and withdrawal of morphine, and particularly the comparability of results with similar administration and withdrawal of pethidine and its derivatives. They have reported that the demonstration of physical dependence can be made more rapidly and definitely by the use of nalorphine to precipitate abstinence signs and Martin & Eades (1961) claimed very recently that a single intravenous infusion of morphine brought about, in a matter of hours, reproducible and measurable tolerance and physical dependence. Spinal dogs, too, have been shown to exhibit characteristic and reproducible withdrawal signs spontaneously and after the use of nalorphine. However, these various procedures as applied to the dog have not yet been investigated systematically by extending the observations to a large number of morphine-like substances of known addiction potential in man to determine their predictive value in screening. In addition, maintenance of spinal dogs in good physical condition is beset by major technical difficulties.

La Barre’s method of measuring motor activity in the dog during addiction to morphine or a test substance and withdrawal or substitution of a potentially addicting agent is relatively simple and objective. The limited number of substances studied so far by this method does not allow extensive comparison to be made with the results obtained by other methods and in other species, including man. Also the limitation that has been imposed on dosage in direct addictions and in substitutions may increase very greatly the likelihood of false negatives in comparison with tests in the monkey or man. In both of these species the tendency has been to push dosages upward until the appearance of signs of toxicity, unless positive results have been obtained at lower dose levels. It should be advantageous to include in La Barre’s method the nalorphine abstinence precipitation technique and to attempt determination of dosage equivalence in terms of intensity of withdrawal phenomena and completeness of substitution of one agent for another, as well as to remove the limitation on dosage increase.

Seevers and his associates have demonstrated repeatedly the qualitative similarity in the results
obtained in suppression of the morphine abstinence syndrome in the monkey and in man and have warned of the hazard of quantitative predictions. In the single-dose abstinence suppression tests the monkey is more sensitive than man to pethidine derivatives and less sensitive than man to benzomorphan derivatives (substances related to phena-zocine). Nevertheless, observations in the monkey have now been extended to the largest series of compounds of related and diverse structure and the results are subject to the greatest number of comparisons with the results in man. The single-dose abstinence suppression technique in the monkey is proving of practical value in that it discourages the continuation of work with new compounds which show high physical dependence capacity and encourages the development of compounds which have low physical dependence capacity, and demonstrates the presence or absence of morphine-like properties in new agents not yet sufficiently well known for trial in man.

From the work in monkeys and the study of addiction liability in man no substance has yet been found which will significantly suppress (to the extent that codeine does, for example) morphine abstinence phenomena, or which will substitute for morphine in an established addiction, maintaining the addiction and preventing the appearance of abstinence symptoms, which will not itself produce addiction (physical dependence). Therefore, ability to substitute for morphine, suppressing the abstinence syndrome and sustaining the addiction, defines a compound as addicting just as certainly as producing an addiction.

All of the observations at the Addiction Research Center in Lexington are made on individuals who have been or are currently addicted to an opiate, and the question must arise of the validity for clinical practice of conclusions and predictions based on work with such a population. All of the procedures at Lexington are designed to push the dosage if necessary to the limits of safety, to determine the subjective and objective reactions of the subjects to the agent tested in comparison with their reactions to known drugs given to the same subject in a cross-over design, and to determine the likelihood of these individuals using the drug if it were available to them. In other words, these tests determine the patient’s ability to identify the compound tested as “dope” (morphine- or heroin-like) or as being like some other agent of his experience, the subject’s liking for or attitude towards the new drug, and, if a direct addiction experiment is done, the rate and degree of development of tolerance and physical dependence, again in comparison with morphine and perhaps other known agents. The tests at least provide direct evidence on the likelihood of abuse, one of the criteria for narcotics control, and may measure directly addiction liability. It is significant that predictions made as a result of work at Lexington have been confirmed whenever the agent in question has entered into extensive clinical use.

The more recent additions to the series of tests devised at the Addiction Research Center merit a final word. Reference is made particularly to (a) the 24-hour substitution procedure, which reduces the discomfort to which the subject may be exposed and permits extensive cross-over observations with positive and negative controls; (b) the short-term, 20-day, direct addiction experiment, which is time-saving and again permits cross-over observations; and (c) the very short, 7-day, intravenous drug administration, which gives an opportunity for the patient to express his likes or dislikes and his preference for one drug over another.

The final test in which the physician is likely to have the most confidence is the experience of clinical practice. Before nalorphine, this was so time-consuming and impressionistic as to be of no immediate value. The working out of techniques for monitoring, by periodic nalorphine injection, narcotic analgesic medication for chronic pain without seriously disturbing the patient, makes possible the accumulation of data on tolerance and physical dependence and comparison of one agent with another in the same environment. The method requires painstaking and long-continued observation, but where groups of suitable patients are available results of practical importance for the physician’s guidance can be obtained.

RÉSUMÉ

Pendant longtemps, seules des observations de cas réels de toxicomanie permettaient de se rendre compte des effets toxicomanogènes des opiacés ainsi que des substances analgésiques à effet morphinique. Actuellement, des méthodes ont été élaborées, applicables à l'animal et à l'homme, permettant d'estimer le risque de toxicomanie qu'implique l'emploi de ces substances.

Le critère sur lequel sont fondés les tests est la dépendance physique (toxicomanie). Les animaux de choix, pour ces épreuves, par ordre croissant d'analogie avec les
réactions de l'homme, sont le rat, le chien et surtout le singe. Les auteurs évaluent les divers tests et esquissent certains développements ou perfectionnements possibles.

Mais pour établir de façon certaine le pouvoir toxicomanogène de produits inconnus, l'observation sur l'homme reste indispensable. On trouve dans cet article le détail des modalités d'observation, et des tentatives d'évaluation quantitative approximative de l'effet des substances à l'étude.

La mise au point d'antagonistes spécifiques de la morphine (du type de la nalorphine) grâce auxquels le syndrome d'abstinence peut être précocement décelé a contribué pour une large part à la précision des tests permettant de mettre en évidence le pouvoir toxicomanogène, et a beaucoup accéléré l'obtention des résultats. L'utilisation de ces antagonistes, en particulier, a permis l'observation clinique de l'apparition de l'effet toxicomanogène, et de la tolérance, au cours de traitements prolongés par des substances morphinomimétiques.

Les travaux sur les singes, de même que les observations sur l'homme, ont montré qu'une substance qui supprime le syndrome d'abstinence dû au retrait de la morphine, ou qui, substituée à la morphine, entretient la toxicomanie, est elle-même toxicomanogène. C'est pourquoi, la capacité d'une substance de remplacer la morphine en supprimant le syndrome d'abstinence ou d'entretien la toxicomanie, permet de la qualifier de toxicomanogène.

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Annex I

SINGLE-DOSE ATTITUDE QUESTIONNAIRE (PATIENTS' RATINGS)

Name: .................................................. No. ........................................ Date: ..................................................
Medication: .................................................. Dose: ............................. Time: ..................................................

Questions to be answered by you about the effects of this drug. In answering all questions check only sensations which you have experienced since your last examination by the aide. If the words listed are not satisfactory for describing your feelings, please write in other words or make comments.

<table>
<thead>
<tr>
<th>Hour:</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you feel the medicine?</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>2. This drug is most like what drug listed below (check one)?</td>
<td>(a) A blank (water)</td>
<td>(d) Marihuana (reefer)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) &quot;Dope&quot; (opiates)</td>
<td>(e) &quot;Goof balls&quot; (barbiturate-like)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(c) Cocaine</td>
<td>(f) Benzedrine (&quot;Benny&quot;)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(g) Other (please name)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. Check each sensation which you feel:
   (a) Normal (no change) .......................................................... (g) "Pleasant sick"
   (b) "Turning of stomach" ..........................................................
   (c) Skin itchy ..........................................................................
   (d) Relaxed .............................................................................
   (e) "Coasting" ........................................................................
   (f) "Soap-box" (loquacious; tendency to brag) ..........................
   (i) Sleepy ..............................................................................
   (j) Nervous ...........................................................................
   (k) Drunken ...........................................................................
   (l) Other (please describe) ....................................................

4. Your liking for this drug is most nearly described by which of the following?
   (a) Not at all ...........................................................................
   (b) Slight ..............................................................................
   (c) Moderate ...........................................................................
   (d) A lot ................................................................................
   (e) An awful lot .....................................................................
   (f) Other (please describe) ....................................................

5. Comments: ............................................................................
Annex 2

SINGLE-DOSE ATTITUDE QUESTIONNAIRE (OBSERVERS' RATINGS)

Name: .............................................................................. No. .................................................. Date: ..................................................

Medication: ........................................................................ Dose: .................................................. Time: ..................................................

In answering all questions check only the items of behaviour observed since your last examination. If the words listed are not satisfactory, please insert others which you consider more appropriate or make comments.

<table>
<thead>
<tr>
<th>Hour:</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Any evidence of drug effects?</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

2. Behaviour is most like that seen after (check one):
   (a) A blank .................................................................
   (b) "Dope" (opiates or potent synthetic analgesics) .................................................................
   (c) Cocaine .............................................................
   (d) Marihuana (reefer) .................................................
   (e) "Goof balls" (barbiturates) ....................................................
   (f) Benzedrine ("Benny") ..................................................
   (g) Other (please name) ..................................................

3. Check each item which you think the patient shows:
   (a) Normal (no change) ..................................................
   (b) Scratching ............................................................
   (c) Red eyes ..............................................................
   (d) Relaxed ...............................................................
   (e) "Coasting" ...........................................................
   (f) "Soap-box" (loquacious; tendency to brag) .................................................................
   (g) Vomiting .............................................................
   (h) "Nodding" ............................................................
   (i) Sleepy ...............................................................
   (j) Nervous .............................................................
   (k) Drunken .............................................................
   (l) Other (please describe) ..................................................

4. How much do you think the patient liked the effects of this drug during the past hour?
   (a) Not at all .............................................................
   (b) Slightly .............................................................
   (c) Moderately ...........................................................
   (d) A lot ...............................................................
   (e) An awful lot ........................................................
   (f) Other (please describe) ..................................................

5. Pupils: ..........................................................................

6. Comments: ..................................................................

Initials of aide: ......................................................
Annex 3

CHRONIC DOSAGE ATTITUDE QUESTIONNAIRE FOR OPIATES (PATIENTS’ RATINGS)

Name of patient: .......................................................... Date: ...........................................
Answer all questions according to how this drug is affecting you today.

1. Has this drug produced any effect on you?  Yes ...................... No ......................

2. Does this drug feel like an opiate ("dope")?  Yes ...................... No ......................
   If so, which of the drugs given below is this drug most nearly like, and how strong do you think it is?
   It is most nearly like (check one):
   (a) Heroin .................................................................
   (b) Morphine .................................................................
   (c) Codeine .................................................................
   (d) Other "dope"-like drug (please name) ......................................
I think the strength of this drug is (check one):
   (a) No effect .................................................................
   (b) Very weak .................................................................
   (c) Weak .................................................................
   (d) Average .................................................................
   (e) Strong .................................................................
   (f) Very strong .................................................................
   (g) Overdose .................................................................

3. Is the feeling from this drug like that from one of the drugs given below?  Yes ...................... No ......................
   It is most nearly like (check one):
   (a) A blank (water) .................................................................
   (b) Marihuana (reefer) .................................................................
   (c) Cocaine .................................................................
   (d) "Goof balls" (barbiturate-like) .................................................................
   (e) Alcohol (whiskey or beer) .................................................................
   (f) Benzedrine ("Benny") .................................................................
   (g) Other (please name) .................................................................
I think the strength of this drug is (check one):
   (a) No effect .................................................................
   (b) Very weak .................................................................
   (c) Weak .................................................................
   (d) Average .................................................................
   (e) Strong .................................................................
   (f) Very strong .................................................................
   (g) Overdose .................................................................

4. Would you like to take this drug every day?  Yes ...................... No ...................... Don’t care ..............

5. Does this drug make you feel bad?  Yes ...................... No ......................
   If so, does it make you feel so badly that you would stop taking it if you were not on a test?  Yes ...................... No ......................

6. Describe briefly the most important effects of this drug on you: .................................................................

7 Are you "kicking a habit"?  Yes ...................... No ......................
**Annex 4**

**CHRONIC DOSAGE ATTITUDE QUESTIONNAIRE FOR OPIATES (OBSERVERS’ RATINGS)**

Name of patient ................................................................................................................. Date ..............................................

Answer all questions according to how this drug is affecting this patient today.

1. Is this drug affecting the behaviour of this patient in any way?  
   Yes ................................................. No .................................................................

2. Does this patient show behaviour resembling that seen after opiates?  
   Yes ................................................. No .................................................................
   If so, indicate from your observations of the patient’s behaviour the drug listed below which induces behaviour most nearly resembling that of the patient. Also describe the potency of this drug in inducing opiate-like behaviour.
   Behaviour is most nearly like that seen after (check one):
   (a) Heroin ...................................................... (c) Codeine ......................................................
   (b) Morphine ...................................................... (d) Other opiate (please name) ......................................

   The potency of this drug in inducing behavioural changes is (check one):
   (a) No effect ...................................................... (d) “Goof balls” (barbiturates) ......................................
   (b) Very weak ...................................................... (e) Alcohol ......................................................
   (c) Weak ...................................................... (f) Benzedrine (“Benny”) ......................................
   (g) Overdose ......................................................

3. Is the behaviour after this drug like that after one of the drugs listed below?  
   Yes ................................................. No .................................................................
   Behaviour is most nearly like that seen after (check one):
   (a) A blank ...................................................... (d) “Goof balls” (barbiturates) ......................................
   (b) Marihuana (reefer) ...................................................... (e) Alcohol ......................................................
   (c) Cocaine ...................................................... (f) Benzedrine (“Benny”) ......................................
   (g) Other (please name) .................................................................

   The potency of this drug in inducing behavioural changes is (check one):
   (a) No effect ...................................................... (d) Average ......................................................
   (b) Very weak ...................................................... (e) Strong ......................................................
   (c) Weak ...................................................... (f) Very strong ......................................................
   (g) Overdose ......................................................

4. Do you think this patient would like to take this drug every day?  
   Yes ................................................. No ................................................................. Doesn’t care ..............................................

5. Do you think this drug makes this patient uncomfortable?  
   Yes ................................................. No .................................................................
   If the answer is “yes” to this question, do you think he dislikes it sufficiently to voluntarily stop taking it if he were not on an experimental test?
   Yes ................................................. No .................................................................

6. Describe briefly the most important effects of this drug in this patient: ..............................................

7. Is this patient “kicking a habit”?  
   Yes ................................................. No .................................................................
   Initials of aide: ..............................................
## Annex 5

**PATIENT'S INITIAL DATA SHEET**

<table>
<thead>
<tr>
<th>Field</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name:</td>
<td></td>
</tr>
<tr>
<td>Hosp. No.</td>
<td></td>
</tr>
<tr>
<td>Date:</td>
<td></td>
</tr>
<tr>
<td>Patient No.</td>
<td></td>
</tr>
<tr>
<td>Age:</td>
<td></td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
</tr>
<tr>
<td>Weight:</td>
<td></td>
</tr>
<tr>
<td>Diagnosis and general condition:</td>
<td></td>
</tr>
<tr>
<td>Mental state:</td>
<td></td>
</tr>
<tr>
<td>Nature or origin of pain:</td>
<td></td>
</tr>
<tr>
<td>Current treatment for pain:</td>
<td></td>
</tr>
<tr>
<td>Kind:</td>
<td></td>
</tr>
<tr>
<td>Dose:</td>
<td></td>
</tr>
<tr>
<td>Frequency:</td>
<td></td>
</tr>
<tr>
<td>Has codeine or other narcotic analgesic been used for this patient within three months?</td>
<td>Yes</td>
</tr>
<tr>
<td>If yes, give details:</td>
<td></td>
</tr>
<tr>
<td>Does this patient require laxative medication?</td>
<td>Yes</td>
</tr>
<tr>
<td>If yes, give details:</td>
<td></td>
</tr>
<tr>
<td>Does this patient require any other regular medication?</td>
<td>Yes</td>
</tr>
<tr>
<td>If yes, give details:</td>
<td></td>
</tr>
</tbody>
</table>
Annex 6

DAILY RECORD: CONTROL PERIOD

<table>
<thead>
<tr>
<th>Name:</th>
<th>Date:</th>
<th>Patient No.</th>
<th>Control day:</th>
</tr>
</thead>
</table>

Analgesic medication:

<table>
<thead>
<tr>
<th>Analgesic</th>
<th>Dose: 5 grains</th>
<th>Time:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pain relief *(circle figure which applies)*:

<table>
<thead>
<tr>
<th></th>
<th>8 a.m.</th>
<th>12 noon</th>
<th>4 p.m.</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning: 8 a.m.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Afternoon: 12 noon</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Evening: 4 p.m.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Side-effects (complaints) *(circle figure which applies)*:

<table>
<thead>
<tr>
<th></th>
<th>8 a.m.</th>
<th>12 noon</th>
<th>4 p.m.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Nervousness</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Mental dullness</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Lightheadedness, faintness</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Unsteadiness</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Euphoria</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Other (explain)</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Bowel movement</td>
<td>0</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Laxative required</td>
<td>0</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

1. 0 = moderately severe pain; patient claims no relief from medication.
   1 = very little relief from medication.
   2 = slight to moderate pain; moderate relief attributed to medication.
   3 = very little pain.
   4 = no pain; comfortable in this respect, whether or not on account of medication.

2. 0 = not present; 1 = slight; 2 = moderate; 3 = severe.
### Annex 7

**DAILY RECORD: STUDY PERIOD**

<table>
<thead>
<tr>
<th>Name:</th>
<th>Date:</th>
<th>Coded med. No.</th>
<th>Patient No.</th>
<th>Study day:</th>
</tr>
</thead>
</table>

#### Analgesic medication:

<table>
<thead>
<tr>
<th>Units:</th>
<th>Time:</th>
<th>Units:</th>
<th>Time:</th>
</tr>
</thead>
</table>

#### Pain relief *(circle figure which applies):*

| Morning: 8 a.m. | 0 | 1 | 2 | 3 | 4 |
| Afternoon: 12 noon | 0 | 1 | 2 | 3 | 4 |
| Evening: 4 p.m. | 0 | 1 | 2 | 3 | 4 |

Average ....................................

#### Side-effects (complaints) *(circle figure which applies):*

<table>
<thead>
<tr>
<th>8 a.m.</th>
<th>12 noon</th>
<th>4 p.m.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Nervousness</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Mental dullness</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Lightheadedness, faintness</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Unsteadiness</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Euphoria</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Other (explain)</td>
<td>0 1 2 3</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Constipation</td>
<td>0 +</td>
<td>0 +</td>
</tr>
<tr>
<td>Bowel movement</td>
<td>0 +</td>
<td>0 +</td>
</tr>
<tr>
<td>Laxative required</td>
<td>0 +</td>
<td>0 +</td>
</tr>
</tbody>
</table>

* 0 = moderately severe pain; patient claims no relief from medication.
  1 = very little relief from medication.
  2 = slight to moderate pain; moderate relief attributed to medication.
  3 = very little pain.
  4 = no pain; comfortable in this respect, whether or not on account of medication.

* 0 = not present; 1 = slight; 2 = moderate; 3 = severe.
### Annex 8

#### ALLYL OR PLACEBO TEST RECORD SHEET

<table>
<thead>
<tr>
<th>Name:</th>
<th>Date:</th>
<th>Code No. of solution injected:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Study day:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test No.</th>
<th>Time:</th>
<th>Time of last preceding coded drug given:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Blood pressure:

<table>
<thead>
<tr>
<th>Control</th>
<th>10 min.</th>
<th>20 min.</th>
<th>30 min.</th>
<th>40 min.</th>
<th>Points</th>
</tr>
</thead>
</table>

#### Pupil size:

<table>
<thead>
<tr>
<th>Control</th>
<th>10 min.</th>
<th>20 min.</th>
<th>30 min.</th>
<th>40 min.</th>
<th>Points</th>
</tr>
</thead>
</table>

#### Respiratory rate:

<table>
<thead>
<tr>
<th>Control</th>
<th>10 min.</th>
<th>20 min.</th>
<th>30 min.</th>
<th>40 min.</th>
<th>Points</th>
</tr>
</thead>
</table>

#### Rectal temperature:

<table>
<thead>
<tr>
<th>Control</th>
<th>10 min.</th>
<th>20 min.</th>
<th>30 min.</th>
<th>40 min.</th>
<th>Points</th>
</tr>
</thead>
</table>

#### Other signs (circle as observed):

- Yawning: 0 +
- Lacrimation: 0 +
- Rhinorrhea: 0 +
- Sweating: 0 +
- Gooseflesh: 0 +
- Tremor: 0 +
- Restlessness: 0 +
- Abdominal or other cramps: 0 +
- Urge to defeacate: 0 +
- Nausea: 0 +
- Emesis: 0 +

**Total score:**

**Remarks:**
