MODIFICATION OF TOLERANCE TO NARCOTIC ANALGESICS BY THE PHENOTHIAZINE DERIVATIVES

by

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INTRODUCTION

In recent years scientists and physicians have worked indefatigably to ascertain the nature of pain and to improve the methods and drugs available for its alleviation. The chief disadvantages limiting the full employment of the analgetic drugs currently available to the physician are lack of potency, short duration of effectiveness, high incidence of untoward actions and the rapid development of tolerance and addiction with continued use. Much work has been done to find the ideal analgesic but morphine, as "God's gift to medicine", still stands supreme as the most effective and dependable drug for relieving all types of pain. Unfortunately, however, its analgetic effectiveness is offset by accompanying side effects and the propensity to develop tolerance.

Two lines of endeavor appear profitable in the search for more ideal analgetic agents than those now available. One approach is through the discovery of new drugs which retain the potency of morphine yet are unlikely to cause side effects or develop tolerance. Through chemical manipulation of the morphine molecule it was hoped to synthesize analgetic agents coming near to morphine in effectiveness yet lacking its disadvantages. An endeavor of this type was the organized study carried on between the years 1931-1940 in a number of universities in this country and sponsored by the National Research Council. The structure of the morphine molecule was torn apart and resynthesized in many variants. These reassembled compounds along with many new compounds were screened for toxicity and analgetic activity. While a great deal

was learned about the relationship of chemical structure to analgetic activity and other actions of morphine, only one new compound, methyldihydromorphinone (Metopon(R)) was found to be of value. This monumental investigation was described in 1940 in two volumes by Sumwalt, Eddy and Krueger (31). For some reason the study was concluded at this time, just before World War II and the discovery of meperidine.

Another method to provide better pain relief is by the use of combinations of analgesic drugs with other drugs. A number of drugs chemically and pharmacologically unrelated to morphine potentiate the analgetic action of morphine without enhancing its toxic effects (19). This is of great usefulness in the management of pain since it allows dosage reduction of the analgetic agent and, because of this, the incidence of side effects and tendency to develop tolerance and addiction are materially decreased.

Drug potentiation of analgesia is based on the premise that analgesia equivalent to that elicited by full dosages of the drug is obtained when only a fraction of this dosage is used in combination with a potentiating drug. Thus, with only part of the usual effective dosage being employed and, in many cases, being administered less frequently, there is less likelihood of undesirable side effects appearing. Since dosage and frequency of administration are decisive factors determining the rapidity and severity of the development of tolerance and addiction, any procedure which reduces dosage and/or prolongs duration of action should lessen tolerance development. Fortunately, drugs have been found which not only potentiate analgetic activity of narcotic agents but definitely decrease the incidence of untoward effects occurring with use of the latter drugs (25, 28, 29, 33, 48, 52).

Undoubtedly, the chief drawback to the full utilization of morphine and the other narcotic analgesics is the inexorable onset of tolerance and addiction. It is hoped that through the further study of drug combinations and the synthesis of new analgetic agents more effective and less dangerous ways will be found to conquer pain than those presently in the hands of the physician. The achievement of this goal requires the mutual efforts of the synthetic chemist to provide "made to order" analgesics, the pharmacologist to "screen" and evaluate these new drugs in the laboratory in order to select those of most promise, and the clinical investigator to carefully evaluate these analgetics as to safety and therapeutic effectiveness in the patient.

These, as yet, incompletely explored approaches to solving the problem of analgetic tolerance and addiction are a challenge to the investigator. This subject appears to be a promising field for further laboratory, as well as clinical, study. Hence, a laboratory study dealing with tolerance and addiction to morphine and similar analgesics was chosen as a field for endeavor by this writer. The purpose, then, of the research investigations done and reported in this thesis was to explore methods suitable to laboratory techniques for modifying or forestalling the development of tolerance (and addiction) which appears in man and animals with repeated use of all narcotic analgesics.

TOLERANCE AND ADDICTION TO MORPHINE

A. Analgetic Tolerance: In the case of morphine and related narcotic analgesics, tolerance develops readily to the analgetic action of the drug. Some of the other actions of morphine such as respiratory depression, diaphoretic action, and emetic action show tolerance less rapidly. Little or no tolerance is developed to morphine's miotic or constipating effects. Tolerance occurs with repeated administration of the drug and is a condition where larger and larger doses are required to provide the same degree of effect, in this case, pain relief equal to that initially obtained (19). As described below, the development of tolerance to analgetic drugs in man or animal progresses hand in hand with addiction.

B. Addiction: Numerous writers have attempted to define addiction since the problem was first recognized. Within recent years clinical and laboratory researchers, in general, have come closer to agreement. A cross section of modern views can be found in the work of Wolff (62), Himmelsbach and Small (24), Krueger, Eddy and Sumwalt (31), Vogel, Isbell and Chapman (57), Reichard (44) and Felix (15).

Himmelsbach and Small (24), writing in 1937, gave a very concise definition and explanation of what constitutes addiction in man or animal. Their treatise is a sound point of departure for any consideration of the nature of addiction; however, it is to be noted that these writers were thinking mainly of the opiate series of drugs (this was before the discovery of meperidine which differs chemically from the opiate alkaloids) and their definition should be considered with that

point in mind. They say:

"Addiction to opium and similar drugs embraces three intimately related but distinct phenomena: (1) tolerance; (2) physical dependence; and (3) habituation.

Tolerance is defined as a diminishing effect on repetition of the same dose of the drug, or, conversely, a necessity to increase the dose to obtain an effect equivalent to the original dose when the drug is administered repeatedly over a period of time. Physical dependence refers to an altered physiologic state, brought about by the repeated administration of the drug over a long period of time, which necessitates the continued use of the drug to prevent the characteristic illness which is termed abstinence syndrome. Habituation refers to emotional, psychologic, or psychical dependence on the drug--the substitution of the drug for other types of adaptive behavior. Habituation is closely related to the drug's euphoric effect, i.e., relief of pain or emotional discomfort."

To this description, a further requirement for addiction may be added. This is, as the fourth phenomenon, the appearance of the withdrawal syndrome upon abruptly stopping further administration of the narcotic in the addicted individual or animal (25).

A distinction should be made between the terms tolerance and addiction although it is realized that these two words are often used interchangeably in referring to narcotic "addiction". As mentioned, one condition implies, and occurs along with, the other.

True addiction is a condition where, by some process, the subject needs frequent use of the drug to experience its effects. In the case

of man, the drug is needed continually to satisfy conscious desires or to escape painful sensations or thoughts. In the continued use of morphine there readily develops some degree of tolerance to the depressant action, and without this feature, true addiction cannot be held to have occurred.

The factors causing tolerance and addiction are not well understood. Several theories, based on laboratory studies, have been advanced to explain the underlying mechanisms concerned in addiction and tolerance. Some of these are: that morphine is transformed to oxymorphine with resulting stimulation, causing the individual to seek further morphine to relieve this (46); anti-toxin formation to morphine occurs due to repeated exhibition to the effects of morphine. This leads to increased destruction or immobilization of morphine in the addicted animal or to a decreased rate of absorption (43). None of these theories are generally accepted due to lack of conclusive evidence (42, 43, 46, 55).

A theory of causation of addiction accepted by many pharmacologists is that of Tatum and Seever (55). The basis of their theory is that it can be readily demonstrated that morphine simultaneously produces both stimulation and depression of different parts of the central nervous system. The stimulatory action is shown by miosis, vagal slowing of the heart, and, as brought out in Tatum and Seever's article, there is an increase of excitability in certain parts of the central nervous system as a chronic manifestation of repeated administration of morphine. Recovery from the manifestations of depression is more rapid than recovery from the increased irritability. This leads to a condition where, with adequately repeated dosages of morphine, a higher level of

irritability results. Therefore, morphine given to an addicted animal (or man) depresses certain areas in the brain, possibly as much as in a normal animal, but having to overcome the excitability resulting from the preceding doses does not appear to depress as much as before. For a few hours depression from morphine predominates but this wears off more rapidly than the stimulation, with the result that the irritability of the excitable structures is increased. The exaggerated excitability requires more of the morphine to produce the same grade of depression equivalent to that produced in the normal; thus, the state of tolerance and addiction is reached.

DEVELOPMENT OF NARCOTIC ANALGESICS

In order to appreciate the problems involved in carrying on an experimental study dealing with narcotic addiction and analgesic potentiation, some background information on the history of narcotic drugs, analgesic potentiation and the phenothiazine derivative chlorpromazine is presented.

The knowledge of opium must go back many thousands of years since a description of its cultivation and preparation is included in the clay tablets left by the Sumerians dated some 7000 years B.C. (41). The Sumerians passed on their knowledge to the Egyptians and the latter then to the Greeks and Persians. The Arabs are thought to have taken opium into China by the 9th Century, although the extensive modern use of opium in China stemmed from India and did not become widespread until the 19th Century (37).

While opium was used and known in Europe as a medicant, at least since the time of Christ, the widespread use of it as a drug to satisfy

addiction did not develop until the East India Company imported it on a large scale. Opium was used widely for medicinal purposes in the American Colonies from the 18th Century on and apparently its promiscuous use often led to addiction.

It was not until 1805 that Sertuerner isolated morphine from opium in Germany. By 1832 the French had obtained codeine and numerous other alkaloids from opium. In 1898 Professor Heinrich Dreser of Germany reported a new chemical, a synthetic derivative of morphine, which was presented to and accepted by the medical profession as a miracle drug with all of the virtues of an opiate without any of the dangers thereof. This heroic drug was called heroin. Its dangers were not realized at first and heroin was used freely not only in Europe but in America also. Four years after its discovery it was finally recognized by the medical profession that the toxicity of heroin was greater than the toxicity of morphine. As an addicting drug, it exceeded all known substances at that time (51).

In 1852 Dr. Alexander Wood developed the use of the hypodermic needle to get morphine into the blood stream. The first needle addict to morphine was probably Mrs. Wood (37).

The Civil War in America provided the first opportunity for the widespread use of morphine administered hypodermically and resulted in multitudes of Civil War veterans becoming addicted to morphine or other opiates.

Since 1900 more refined injectable preparations of opium such as Omnopon (Pantopon$^{(R)}$) or synthetic compounds such as dihydromorphinone (Dilaudid$^{(R)}$) have been introduced only to be found just as addicting as their mother compound. In 1940 compounds of different chemical

structure than morphine, meperidine (Demerol(R)) and methadone (Dolophine(R)) were heralded as great new non-addicting analgesics only to be proven to be equal to or more so than morphine in their liability to addiction development.

Thus the search continues for new compounds which retain the pain relieving properties of the opiates while the undesirable side effects, especially addiction, are separated from the action of the molecule.

POTENTIATION OF ANALGESIA

A. Historical. Possibly the ancient Egyptians felt that wine and powdered opium gave an analgesic potentiating effect since they used this combination for trephining skulls (61). In the 16th Century Paracelsus introduced tincture of opium (Laudanum), a mixture of powdered opium in alcohol. Perhaps the alcohol facilitated absorption and produced an indirect type of potentiation in addition to providing a pleasant flavor and desirability as a beverage. With Sertuerner's isolation of the morphine molecule in the 19th Century, the physician now had a pure chemical and could use accurate doses and study the exact effects of these measured amounts of morphine. The later preparations of opium such as paregoric, Dover's Powder and Brown Mixture were not designed for the purpose of obtaining enhanced analgesia but rather they were an attempt to modify the unpleasant taste and offset the side effects of opium.

Probably the first purposeful use of drug combinations to potentiate analgesia was described by Meltzer and Auer (21), who used combinations of injectable magnesium sulfate and rectally instilled ether. The potentiation relationship was clinically proven by Gwathmey and Hooper in 1925 (21). These workers took one-half the hypnotic dose of magnesium

sulfate given intramuscularly along with approximately one-ninth the anesthetic dose of ether when rectally administered and produced full surgical anesthesia without any increase in toxicity. They claimed that the magnesium salt deepened or enhanced the effect of ether. While Meltzer and his associates did not work with morphine, Gwathmey (21) demonstrated potentiation of morphine by parenterally administered magnesium sulfate in 1925. He noted less respiratory depression and nausea and vomiting by the use of these drug combinations than when morphine alone was used in a dosage high enough to get equivalent analgesia.

In 1940 Slaughter and Gross (52) reported that the alkaloid physostigmine potentiated the action of morphine on the intact dog's intestine. In the light of these results, they extended their work to investigate the possibility that cholinergic drugs might increase the efficiency of morphine as an analgesic. They found that prostigmin potentiated the effect of morphine on pain.

Ivy and coworkers in 1944 found that dextroamphetamine enhanced the analgesic effect of morphine and tended to partly counteract and delay morphine depression. Nausea and vomiting, weakness, drowsiness and dizziness were decreased by the addition of dextroamphetamine to morphine (29). Further work by Ivy et al (28) in 1944 showed that ephedrine also potentiated morphine's analgesic action. Work by Gross et al (20) then demonstrated that epinephrine effectively increased morphine's analgesic action.

DeJongh and Knoppers (10) found it was possible to enhance, with more than additive effect, the intensity of the morphine analgesia by

simultaneous injection of quinine. Use of quinine also tended to prolong the action of morphine in some cases.

Previous studies in the pharmacology laboratory at the University of Oregon Medical School have shown that the dihydrogenated ergot mixture Hydergine(R) potentiated the analgesic effects of morphine and certain synthetic analgesics in rats (48).

B. Phenothiazine Derivatives as Analgesic Potentiators. Interest in the analgetic potentiating action of various drugs has recently been further stimulated by the discovery that some of the phenothiazine derivatives possess this quality. By the concommitant use of a phenothiazine derivative such as chlorpromazine and an opiate, it is possible not only to potentiate analgesia but to prolong the duration of analgesia (4). Clinically, with the use of chlorpromazine there are fewer side effects as well as reduced frequency of administration and, thereby, less cost to the patient both financially and emotionally (45). From this consideration of the advantageous properties of chlorpromazine when used with narcotics, it would seem that this drug, or another phenothiazine, may offer some hope in forestalling the development of tolerance and addiction to narcotic analgesics.

(1) Pharmacology of Chlorpromazine. In 1951 workers at the Rhone Poulenc-Specia Research Laboratories in France discovered the diverse properties of the phenothiazine derivative known generally as chlorpromazine. This agent was synthesized in the course of systemic search for a compound that would have a less powerful antihistaminic, and a more powerful central action than promethazine (Phenergan(R)). Phenothiazines already had been used as antihelminthics for livestock, as urinary antiseptics for man, and their antihistaminic activities were

also known. Studies in animals by Courvoisier and her associates (4) showed that this drug possessed a diversity of pharmacological properties that suggested a great number of clinical applications. Chlorpromazine was shown to be a depressor of metabolism, a circulatory depressant drug, was able to prevent apomorphine induced vomiting, had a mild but long-acting sedative action, a weak anti-convulsant and potentiated and prolonged the action of hypnotic and analgesic drugs.

(2) Chlorpromazine as a Potentiator of Hypnotic and Analgesic Drugs. Experimentally Courvoisier and associates demonstrated that chlorpromazine intensified and prolonged the action of narcotics, hypnotics, anesthetics and muscle relaxants. Clinically, these results were confirmed by many workers (16, 34). From the findings of these investigators the premise was made that one could expect that chlorpromazine, by augmenting the action of narcotics, might be useful for relieving pain in patients who no longer obtained adequate analgesia from large doses of narcotics. In 1954, Sadove et al (45) explored this premise and they reported that chlorpromazine given with narcotics significantly reduced narcotic requirements and provided equal or better analgesia than higher doses of narcotics alone. In further clinical research, Wallis (58) and Lehmann (35) both reported that chlorpromazine had a strong potentiating effect on analgesics and the combination was effective in treating the large majority of patients. Jackson and Smith (30) reported results that indicated that the addition of chlorpromazine to morphine sulfate and meperidine hydrochloride increased the analgesic properties of minimally effective doses of these narcotics. While David (7) in 1956 mentions the use of chlorpromazine to potentiate

analgesia and forestall tolerance in 9 clinical cases, he was unimpressed with its usefulness for these purposes.

This analgesic potentiating effect was investigated in the laboratory by Worth (64), Friebel and Reichle (17), and Murphy et al (39) and they substantiated the clinical impression that chlorpromazine significantly potentiated the analgesic action of narcotics.

LABORATORY METHODS FOR STUDYING ANALGESIA

The principal methods used for testing analgesia in animals can be divided into four groups. The first of these is mechanical which uses techniques of pinching the rat's tail (22) or adding weights to a cat's tail (12). The problems involved in employing this method are indefinite end points and causing a double stimulus (pressure and pain).

Siegmund et al (50) have recently proposed a method to test analgesia which relies on chemical stimulation by the injection of benzoquinone with a resulting syndrome which is antagonized by an analgesic. The major problems with this method are variation in the animals response to injection and end points which are very difficult to evaluate. The action of salicylates has been measured by studying their effect on chemically induced arthritis (32).

The method of electrical stimulation of teeth to provide objective analgesic information has been reviewed and supported by many workers (14, 18, 23).

The use of radiant heat as the painful stimulus has gained wide acceptance as an effective laboratory method for measuring analgesic response. Woolfe and MacDonald (63) proposed a method where mice were placed on a constant temperature surface (viz., a hot plate) and the

time interval was noted when they raised and licked their paws. Thermal stimulation of the skin of the back of a dog, with a muscle twitch response as an end point, has been suggested by Andrews and Workman (2). Davies and coworkers (9) placed a rat's tail near a hot wire and measured the time until it was jerked away.

Probably the most used method is the D'Amour-Smith technique (5) which measures the duration of a constant intensity heat stimulus required to produce a tail-flick response in the rat. However, this and other methods are most suitable for measuring compounds with a high degree of analgesia. The effects of mild analgesic agents, such as the salicylates, are usually not detectable by this means of testing (36).

In testing representative methods previously discussed for the present study, it was found that the end points of mechanical stimulation studies were difficult to evaluate. The constant temperature surface method of Woolfe and MacDonald (63) was discarded because it was impossible to train the mice sufficiently to arrive at a reproducable control value.

In the study reported on in this thesis a modification of the D'Amour and Smith method (5) was used to determine the pain threshold response in rats. This procedure was chosen because there was a relatively constant response to pain and reproducable control values were obtainable. By using small animals adequate numbers could be tested and still allow for individual variation. The intensity of stimulation does not have to be altered in this method to reach a "pain threshold" on each subject; rather, a fixed intensity stimulation is allowed to act until a response is elicited.

METHODS AND MATERIALS

1. Determination of Analgetic Activity in Rats.

Analgesic activity was determined by a modification of the radiant thermal stimulus method of D'Amour and Smith (5). Male Sprague-Dawley rats weighing from 100 to 150 gms., housed and fed under uniform conditions, were used in groups of 10 animals each. All tests were made in a quiet room kept at a uniform temperature of 24° to 26°C.

The method, as illustrated in Figure 1, requires focusing a beam of light of constant intensity on the rat's tail by means of a converging lens until the animal "flicks" its tail away. The pathway of the light beam was opened or closed manually with the simultaneous operation of the timer. An electrically operated shutter with coordinated timer, previously described in work from this laboratory (49), was not used since it was found that the heat source was causing significant sticking and slowing of opening and closure of the shutter.

The time between the beginning of the exposure and the tail-flick response is the "reaction time" (5). Only animals having an average control reaction time of 4 to 5.5 seconds were used. When analgesia, after drug administration, was great enough to prevent a tail flick at the end of 12 seconds, exposure was discontinued to avoid burning the tail and the animal was considered as having a reaction time of 12 seconds (5).

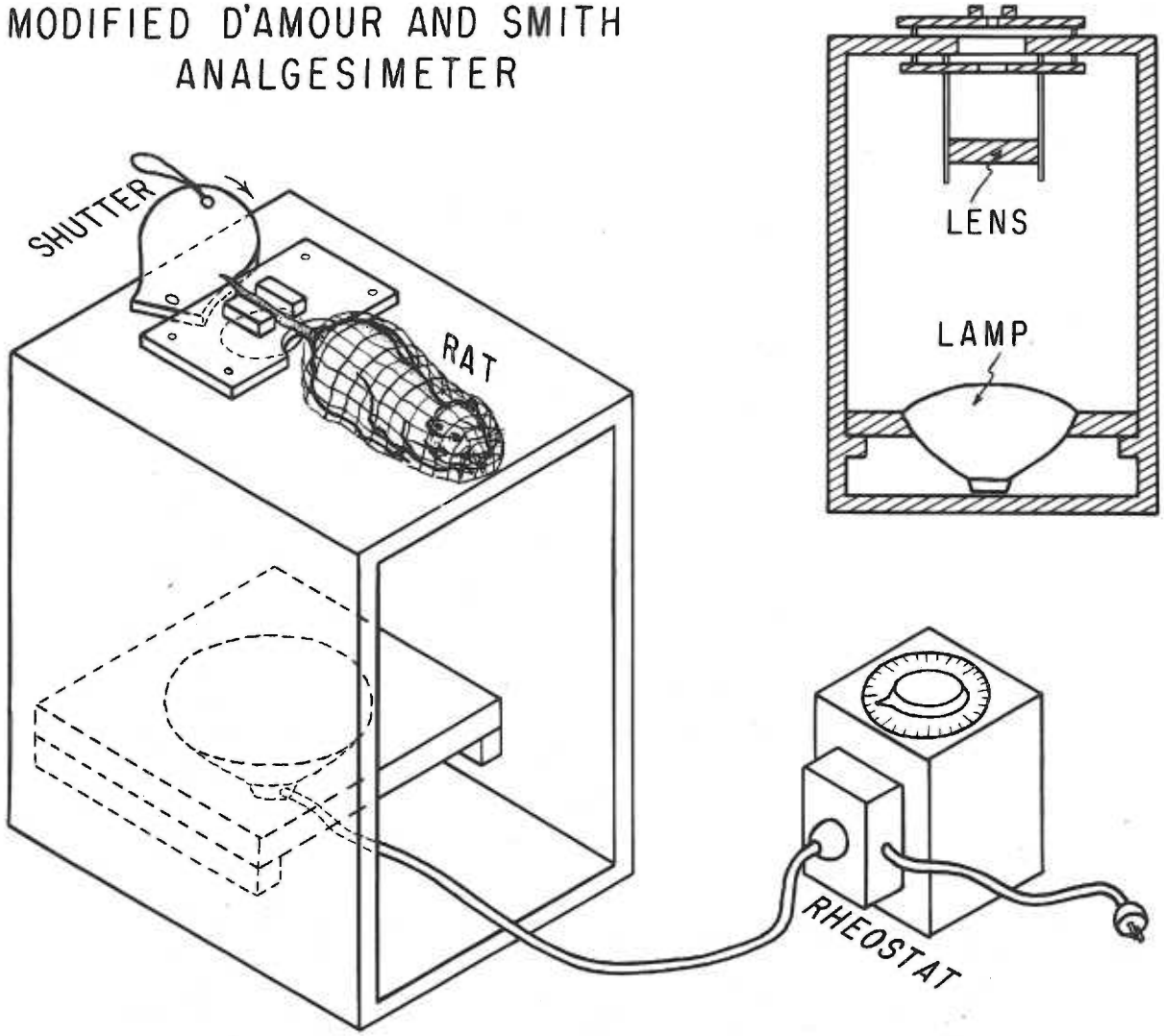
In preliminary studies the analgesic potency for the analgesic drug was first determined using several dose ranges for each drug. The dosages selected for the analgesics and the analgesic-phenothiazine combinations gave approximately an equivalent degree of analgesia when

Figure 1

Specifications of the Modified D'Amour and Smith Analgesimeter.

The source of radiation is a prefocused narrow spot lamp of 300 watts and 120 volts. The biconvex lens, with a diameter of 10.2 cms. and a focal distance of 15.5 cms., concentrates the beam of light on the 1.5 cm. circular opening in the center of the asbestos platform.

MODIFIED D'AMOUR AND SMITH
ANALGESIMETER



tested by the D'Amour-Smith method.

Before testing, the animals were placed in individual conical cages made of wire mesh in order to prevent much movement. Readings were taken at 15 minute intervals for 2 hours. By thus subjecting the animals to a preliminary conditioning period, it was found that the individual variations among rats of a group decreased. This observation has been previously reported by Irwin et al (27) and Bonneycastle and Leonard (3).

2. Method for Studying the Development of Analgetic Tolerance to Narcotic Drugs in Rats.

In order to demonstrate tolerance development, groups of 10 rats each were used. The rats were given daily subcutaneous injections of the analgesic drug either alone or in combination with a phenothiazine. When the drugs were used in combination, the phenothiazine compound would be injected first, followed in 20 minutes by injection of the analgesic. Saline was substituted for the phenothiazine compound in the groups in which the analgesic alone was being tested. Injections were continued over a period of nine weeks. All solutions were made in such concentration that each animal would receive one cubic milliliter per kilogram of body weight (ml./kg.) so that all injections would be of the same volume.

On days when tests were done, following a 1 hour conditioning period, two control reaction times were obtained for each rat at 15 minute intervals. These readings served as a control basis for later changes in the reaction time. Reaction times were tested at 15 minute intervals during the first hour after the injection of the analgesic

or phenothiazine-analgesic combination and the maximum reaction time was used as the peak analgesic response.

During the nine week injection period the maximum thermostimulus response was measured the first day and at the end of the first, third, fifth, seventh and ninth week to provide the per cent change in the mean reaction time. During withdrawal, the mean reaction time was determined on the third, seventh and fourteenth day using the same pre-withdrawal drug dosages. Dosage increments were not used nor were the drugs injected more than once daily.

3. Analgesic Drugs Studied.

Morphine sulfate, phenazocine, meperidine and raceoramide (SKF 5137) were the analgesic drugs studied. They are further described below.

Morphine sulfate, because of its frequent use and its general acceptance as a model example of a narcotic analgesic, was used as the control drug in these experiments to establish the base values for making comparisons. Structurally, most organic chemists agree that the morphine molecule consists of the phenanthrene nucleus, an oxide bridge, a tertiary amine attached to the phenanthrene ring, and two hydroxyl groups, each attached to opposite poles of the phenanthrene ring. The commonly accepted structural formula for morphine is shown in Figure 2.

Raceoramide (SKF 5137) is a relatively new synthetic analgesic. It had just recently been made available for clinical and laboratory study in 1956 when this study was undertaken. Raceoramide was selected in order to compare its tolerance liability, if any, with that of morphine. As can be seen in Figure 2-A, raceoramide is an amidone-like compound somewhat similar in chemical structure to alpha-acetylmethadol.

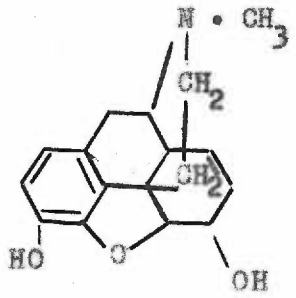
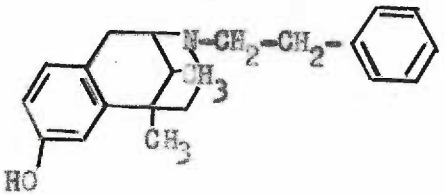
It has been reported to have a rapid onset of action similar to that of meperidine and to be more effective on a milligram per kilogram basis than morphine (6).

Meperidine is known to have a rapid onset of action and, compared to morphine, a shorter duration of action. It was thought that it would be of interest to test this drug, as well as racemoramide, to see if the method used in this research would accurately compare the effects of those analgesics having a rapid onset and short duration of action with those having a slower onset and longer action such as morphine and phenazocine. The formula for meperidine is shown in Figure 2-A.

Phenazocine (Prinadol(R), SKF 6574-C) is a new analgesic recently synthesized by May and associates (38). It is derived from a class of compounds designated as benzomorphanes which are structurally related to, but simpler than, the morphine molecule. Tedeschi et al (56) found phenazocine to be 15 to 35 times as potent as morphine as an analgesic in rats. Wendel and his associates (59) suggest that a cross-over tolerance between phenazocine and morphine does not exist to a great degree and, therefore, phenazocine may be a better analgesic than morphine and other narcotics. A communication from Smith, Kline and French Laboratories (54) states that "studies in both animals and human subjects suggest that tolerance to the analgesic effects of phenazocine develop very slowly and that the addiction liability is lower than that of morphine and possibly even lower than that of codeine". With only limited clinical studies (8, 13) to date on this active new drug, it was felt it would be of special value to include it in this study. The formula for phenazocine is shown in Figure 2.

Figure 2

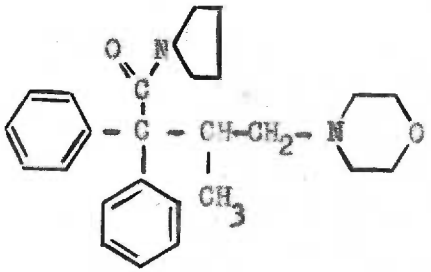
Chemical Structures of Morphine and Phenazocine.

STRUCTURAL FORMULA	GENERIC NAME	TRADE NAME
	Morphine	None
	Phenazocine	Prinadol(R) (SKF 6574)

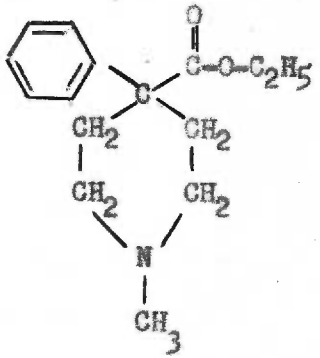
(1,2,3,4,5,6-hexahydro-8-hydroxy-6,
11-dimethyl-3-phenethyl-2, 6-methano-3-benzazocine).

Figure 2-A

Chemical Structures of Racemoramide and Meperidine.

STRUCTURAL FORMULA	GENERIC NAME	TRADE NAME
	Racemoramide	SKF #5137 (no Trade Name assigned)

dl-N- [2:2-diphenyl-3-methyl-4-(N-morpholino)-butryl] -pyrrolidine (base).

	Meperidine	Demerol(R)

N-Methyl-4-phenyl-4-carbethethoxypiperidine.

4. Phenothiazine Derivatives Used as Potentiators of Analgesia.

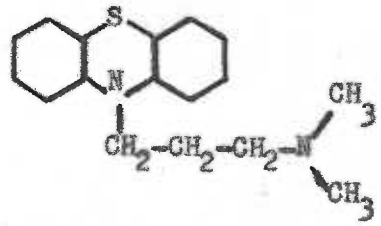
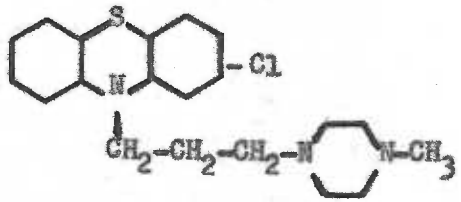
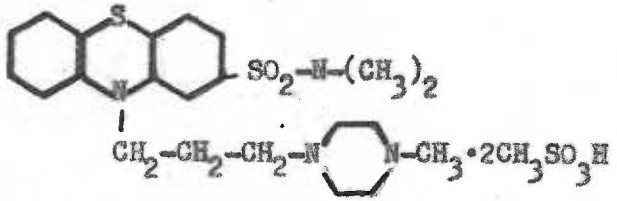
The phenothiazine derivatives studied as possible potentiators of the analgesic drugs were chlorpromazine, prochlorperazine and thioperazine (Vontil(R), SKF 5883).

One of the striking actions of chlorpromazine, as previously discussed, is its ability to potentiate the effects of analgesics and anesthetic preparations, although, in itself, it has little or no analgesic action (17). This potentiating action is accomplished usually without change in the toxicity of the primary drug (53). Chlorpromazine's chemical formula is shown in Figure 3.

Prochlorperazine, like chlorpromazine, was developed by the Rhone Poulenc-Specia Research Laboratories in cooperation with Smith, Kline and French Laboratories. The actions of prochlorperazine are similar to those of chlorpromazine with the various pharmacologic and therapeutic effects being attributed to the changes in the side chain of prochlorperazine, as illustrated in Figure 3. Prochlorperazine is reported to be a very safe drug and more potent than chlorpromazine as an antiemetic, antipsychotic and as a tranquilizer in that it is effective at lower doses. It does not seem to have the sedative effect that chlorpromazine has (53). It is believed that chlorpromazine exerts its potentiating effect through its ability to alter the patient's reaction to pain and resulting in a more relaxed and cheerful patient (26, 40). Therefore, it seemed of interest to test this similar compound which, as stated, lacks the sedative action of chlorpromazine. Prochlorperazine is reported to be less active than chlorpromazine in prolonging and enhancing morphine effects in mice (53).

Figure 3

Chemical Structures of Chlorpromazine, Prochlorperazine, and Thioperazine.

STRUCTURAL FORMULA	GENERIC NAME	TRADE NAME
	Chlorpromazine	Thorazine(R)
10-(y - dimethylaminopropyl) - 2 - chlorphenothiazine.		
	Prochlorperazine	Compazine(R)
2-chloro-10- [3-(1-methyl-4-piperazinyl)-propyl] -phenothiazine.		
	Thioperazine	Vontil(R) (SKF 5883)
[N,N-dimethyl-10- [3-(1-methyl-4-piperazinyl) propyl] -2-phenothiazinesulfonamide dimethansulfonate] .		

Thioperazine (Vontil(R), SKF 5883) is a new phenothiazine derivative recently made available for clinical and laboratory study by Smith, Kline and French Laboratories. Since it has been reported that SKF 5883 has a mild side effect of sedation (60) it seemed of interest to compare this new phenothiazine derivative with chlorpromazine and prochlorperazine as an analgetic potentiator. Thioperazine's chemical formula is shown in Figure 3.

5. Reliability of Method.

The response of untreated and saline treated rats to pain was quite uniform with the method used. The reaction time for all control animals studied, before injection, was a mean of 4.84 seconds with a standard deviation of individual animals of ± 0.51. However, individual variation in the response to the action of analgesics was great, as shown in Table 1, with some animals showing almost no analgesic effect, others the maximum degree. Tests on individuals are therefore of little value and the unit employed is the mean of a group consisting of 10 animals. The variability of this 10 animal mean is thus reduced to $\frac{S}{\sqrt{10}}$, giving a considerably increased stability and preciseness to the estimate of response.

To determine if the response to the agent injected was significant, the comparison used was the peak mean response compared pairwise to the control value. This is estimated with 95% confidence to lie in the interval:

$$\overline{X_e - X_c} \pm t \frac{s_{x_e - x_c}}{\sqrt{N}}$$

The hypothesis being tested is that this difference is zero. If the 95 per cent interval includes zero, the hypothesis of no difference is accepted. If it does not include zero, the conclusion is that the difference is real.

To compare two different groups of animals to determine if a significant difference exists between their respective responses to analgesics, the difference between the two independent means is estimated with 95 per cent confidence as lying in the interval:

$$\bar{X}_1 - \bar{X}_2 \pm t_{sp} \sqrt{\frac{1}{N_1} + \frac{1}{N_2}}$$

The hypothesis being tested is that the two means are equal. If the 95 per cent interval includes zero, the hypothesis that the two means are equal is accepted. If it does not include zero, the conclusion is that the means are not equal and the difference is real (11).

RESULTS

The per cent increase of the peak mean reaction time following drug injection is interpreted as the index of analgesic activity. This was calculated as per cent change by taking the peak mean reaction time (seconds) after injection and subtracting the mean control response time (seconds) and dividing by the mean control response time and then multiplying the result by 100. A portion of a typical protocol, which illustrates this, is presented in Table 1.

A curve of the analgesic response over an eleven week period can be constructed by plotting as ordinate the per cent change from the control threshold (index of analgesic activity) and as abscissa, the period of time injections were given, in weeks, for the drug or drugs studied (Figure 1). The decrease in the analgesic response occurring over the nine week period was used as a measure of the development of tolerance.

1. Controls.

In the control studies single injections of chlorpromazine, prochlorperazine, thioperazine and saline showed no significant analgetic activity nor was there any evidence of analgetic tolerance when these drugs were given in repeated daily doses (Table 2).

2. Morphine.

Figure 4 shows that tolerance developed rapidly, and to a great degree, with 2 mg./kg. of morphine sulfate. When the initial dose of a phenothiazine preceded morphine the greatest potentiation of analgetic response was observed with chlorpromazine, next with thioperazine

Table 1

PROTOCOL FOR MEASUREMENT OF PER CENT CHANGE IN MEAN REACTION TIME (ANALGESIC RESPONSE*) IN RATS GIVEN 2 MG./KG. MORPHINE.

Rat No.	Wt. Gms.	Control Pre-Injection 15 min.	30 min.	Ave.	(Morphine, 2 mg./kg.) Post-Injection 15 min.	30 min.	45 min.	60 min.
1	105	5.2	4.6	4.9	6.4	6.3	6.0	5.3
2	115	5.3	5.3	5.3	11.8	11.7	10.9	9.8
3	115	4.9	5.4	5.2	6.6	5.9	5.5	4.3
4	115	5.4	5.6	5.5	12.0	11.6	11.0	10.8
5	100	5.0	5.1	5.0	7.8	7.6	6.0	5.4
6	110	4.5	5.3	4.9	5.9	6.2	6.5	5.2
7	115	5.5	5.5	5.5	12.0	12.0	11.2	9.7
8	110	4.8	4.6	4.7	9.2	5.7	5.1	4.6
9	130	3.8	4.6	4.2	6.9	7.0	8.0	8.9
10	120	4.3	4.1	4.1	5.9	5.1	6.3	4.8
			Ave.	4.9	8.5			

*Control Response Time = 4.9 Seconds; Peak Response Time = 8.5 Seconds.

% Change from the control threshold equals $\frac{8.5 - 4.9}{4.9} = 72\%$.

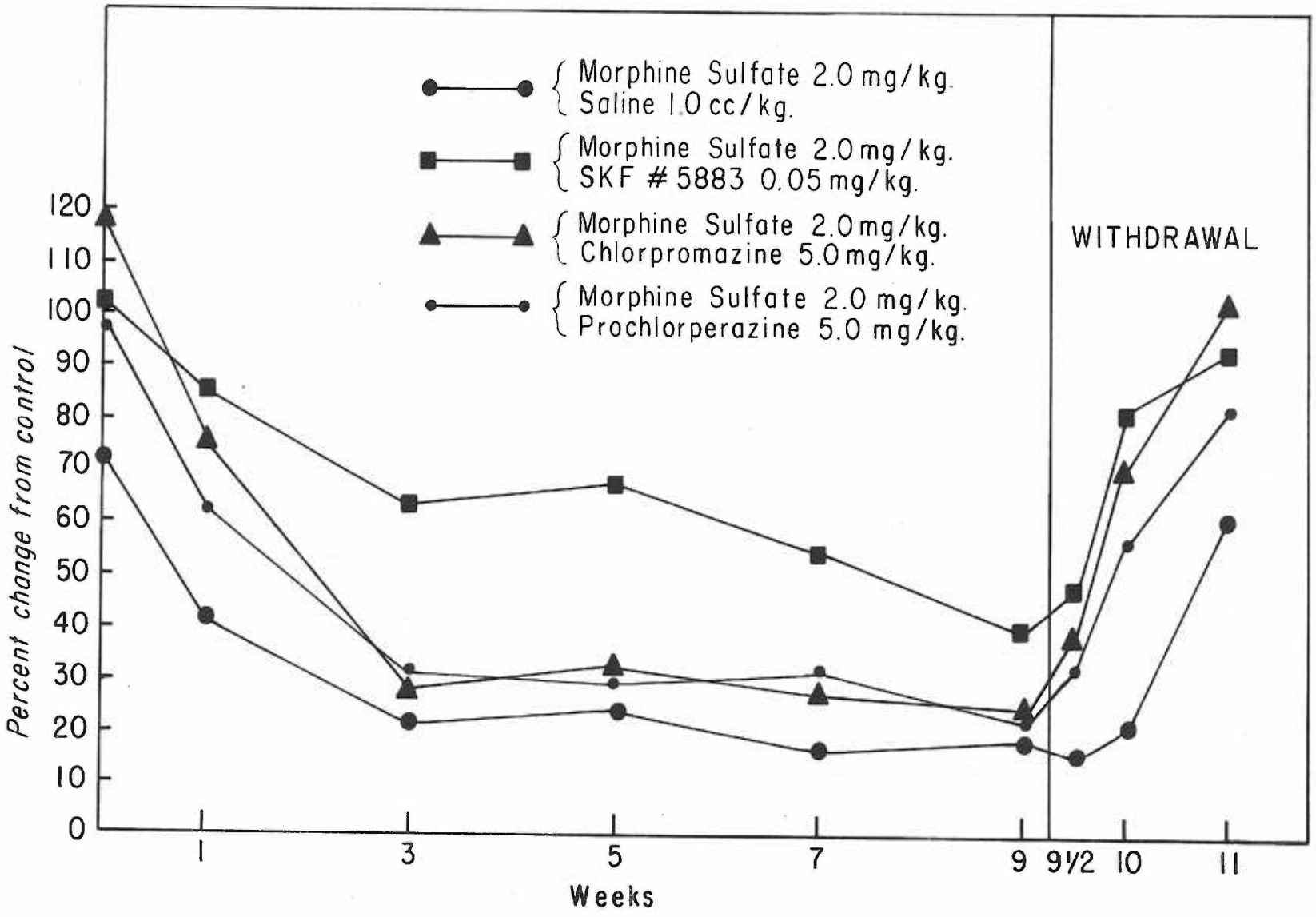
Table 2

The Per Cent Change in Mean Reaction Time (Analgesic Response) in Groups of Rats Injected Daily For Nine Weeks With Saline and Phenothiazines.

Drug and Dosage	Per Cent Change in Analgesic Response								
	Injection Period						Withdrawal		
	Initial	1 wk.	3 wks.	5 wks.	7 wks.	9 wks.	3 days	1 wk.	2 wks.
	%	%	%	%	%	%			
Saline 1 ml./kg.	-2	-2	4	-4	7	4	5	-2	7
Chlorpromazine 5 mg./kg.	4	0	0	-9	2	5	-4	-2	6
Prochlorperazine 5 mg./kg.	-11	0	-9	-7	-2	-6	-7	-11	-6
Thioperazine 0.05 mg./kg.	6	-4	-2	4	0	-2	5	0	-4

Figure 4

Comparison of the mean response curves of rats to a radiant thermal stimulus during a nine week period of injection and two week withdrawal period. Subcutaneous injections of saline, chlorpromazine, prochlorperazine, and thioperazine (SKF #5883) followed in fifteen minutes by morphine sulfate were used.


Morphine Sulfate 2.0 mg/kg.
Saline 1.0 cc/kg.
Morphine Sulfate 2.0 mg/kg.
SKF # 5883 0.05 mg/kg.
Morphine Sulfate 2.0 mg/kg.
Chlorpromazine 5.0 mg/kg.
Morphine Sulfate 2.0 mg/kg.
Prochlorperazine 5.0 mg/kg.
WITHDRAWAL
Percent change from control
120
110
100
90
80
70
60
50
40
30
20
10
0
1
3
5
7
9
9½
10
11
Weeks

(SKF 5883) and least with prochlorperazine. This generally held true for all of the analgesics tested.

By the third week of the study, when injections of chlorpromazine or prochlorperazine preceded morphine (Figure 4) there was no significant difference in the curves for the percentage decreases in the mean reaction time from that noted for morphine alone. But when thioperazine (SKF 5883) preceded injections of morphine, the degree of tolerance development throughout the nine week period was significantly less than that seen with morphine alone.

Figure 5 demonstrates little tolerance development to a lower dosage of morphine (1 mg./kg.). When injections of chlorpromazine or thioperazine preceded morphine there was not a significant difference in the degree of analgesic activity between the various groups over the nine week period.

3. Meperidine.

When meperidine (Figure 6) was studied and compared using the same methods there was significant but less rapid or marked development of tolerance than that observed for morphine. The pre-administration of phenothiazines, with the exception of thioperazine (SKF 5883) which was effective through the fifth week, did not further decrease the rate and degree of analgetic tolerance to meperidine.

4. Racemoramide.

With racemoramide (SKF 5137) (Figure 7) given alone, tolerance developed slowly and to a mild degree; this was even less marked when chlorpromazine or thioperazine (SKF 5883) injections preceded this analgesic.

Figure 5

The mean response curves of rats to a radiant thermal stimulus during a nine week period of injection and two week withdrawal period. Effect of saline, thioperazine (SKF #5883), and chlorpromazine followed in fifteen minutes by morphine sulfate 1.0 mg./kg. as compared to saline followed by morphine sulfate 2.0 mg./kg.

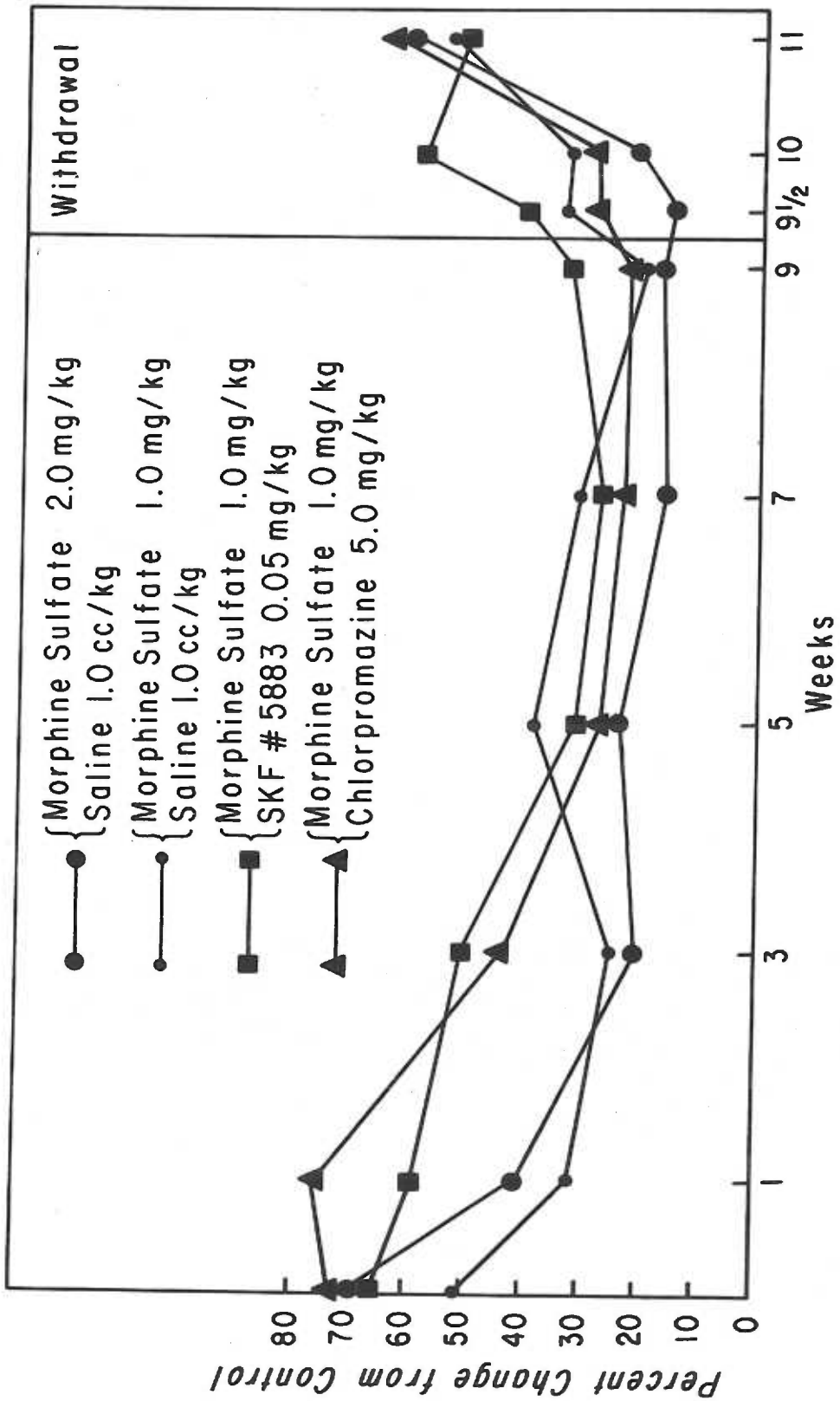

Withdrawal
Morphine Sulfate 2.0 mg/kg
Saline 1.0 cc/kg
Morphine Sulfate 1.0 mg/kg
Saline 1.0 cc/kg
Morphine Sulfate 1.0 mg/kg
SKF # 5883 0.05 mg/kg
Morphine Sulfate 1.0 mg/kg
Chlorpromazine 5.0 mg/kg
Percent Change from Control
0
10
20
30
40
50
60
70
80
1
3
5
7
9
9½
10
11
Weeks

Figure 6

Comparison of the mean response curves of rats to a radiant thermal stimulus during a nine week period of injection and two week withdrawal period. Subcutaneous injections of saline, chlorpromazine, prochlorperazine, and thioperazine (SKF #5883) followed in fifteen minutes by meperidine were used.

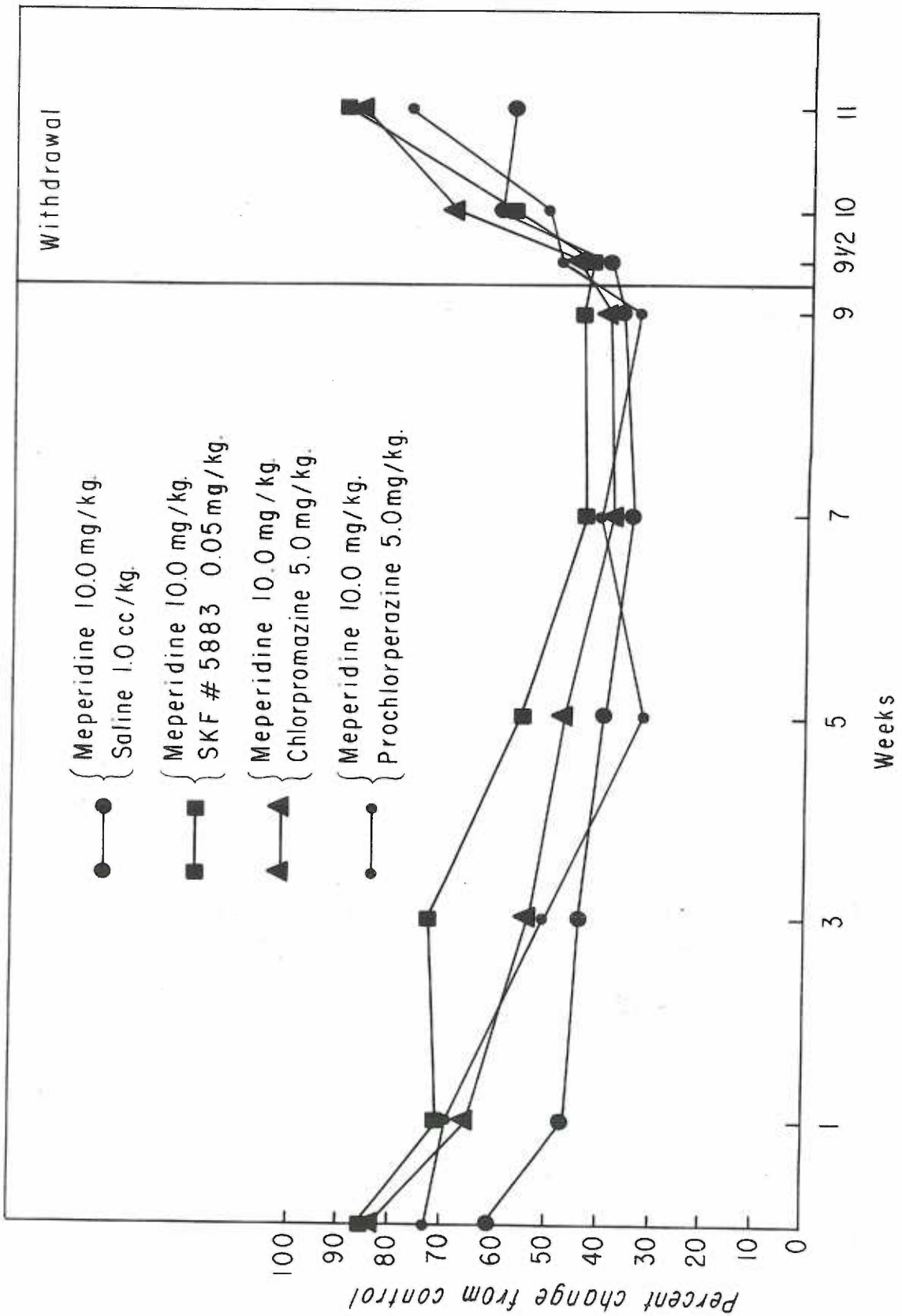
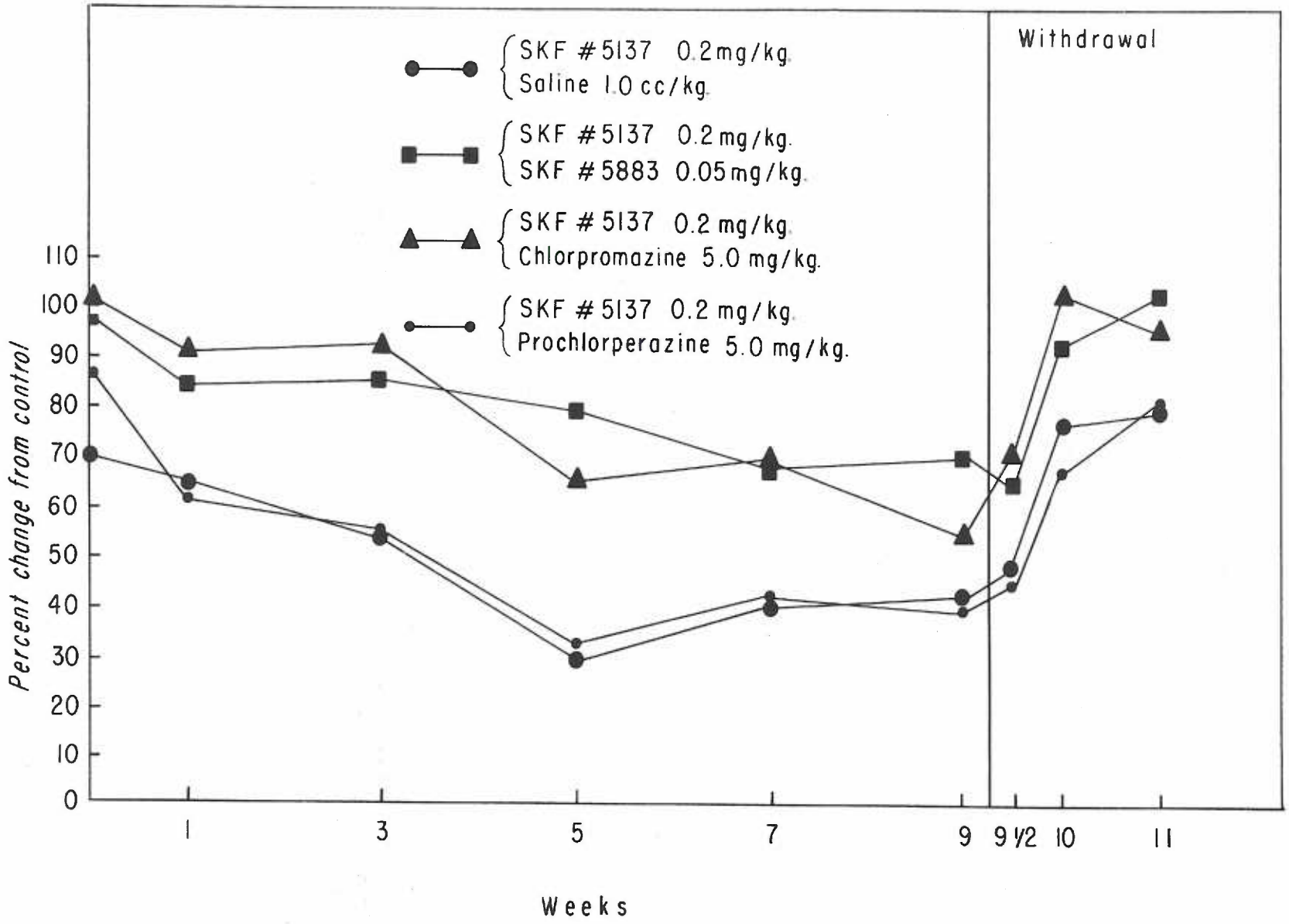

Withdrawal
Meperidine 10.0 mg/kg.
Saline 1.0 cc/kg.
Meperidine 10.0 mg/kg.
SKF # 5883 0.05 mg/kg.
Meperidine 10.0 mg/kg.
Chlorpromazine 5.0 mg/kg.
Meperidine 10.0 mg/kg.
Prochlorperazine 5.0 mg/kg.
Percent change from control
100
90
80
70
60
50
40
30
20
10
0
1
3
5
7
9
9½
10
11
Weeks

Figure 7

Comparison of the mean response curves of rats to a radiant thermal stimulus during a nine week period of injection and two week withdrawal period. Subcutaneous injections of saline, chlorpromazine, prochlorperazine, and thioperazine (SKF #5883) followed in fifteen minutes by racecoramide (SKF #5137) were used.


SKF #5137 0.2mg/kg.
Saline 1.0 cc/kg.
SKF #5137 0.2 mg/kg.
SKF #5883 0.05mg/kg.
SKF #5137 0.2 mg/kg.
Chlorpromazine 5.0 mg/kg.
SKF #5137 0.2 mg/kg.
Prochlorperazine 5.0 mg/kg.
Withdrawal
Percent change from control
110
100
90
80
70
60
50
40
30
20
10
0
1
3
5
7
9
9 1/2
10
11
Weeks

5. Phenazocine.

Phenazocine 0.1 mg./kg. (SKF 6574-C) (Figure 8) showed the least tendency to cause the development of tolerance of the four analgesics studied. Probably this is why pre-injection of chlorpromazine and thioperazine (SKF 5883) (prochlorperazine was not tested) did not materially further delay analgetic tolerance development, although a significantly higher degree of analgesia was maintained with the pre-administration of these two drugs than in the group which received only phenazocine.

Figure 9 demonstrates that no significant tolerance develops to phenazocine (SKF 6574-C) 0.05 mg./kg. and the pre-injection of chlorpromazine did not significantly increase the analgetic response after the third week.

6. Withdrawal.

The other observations used to measure and compare the degree of analgetic tolerance reached by the end of the injection period were those made during withdrawal. On the basis that the tolerance developed to morphine is more slowly dissipated than that seen with less addicting analgesics (1), the analgetic response was again measured on the third, seventh and fourteenth day after drug withdrawal. In the withdrawal period percentage increases in the mean reaction time demonstrate the disappearance of tolerance.

For morphine (Figure 4) 2 mg./kg. only slight loss of tolerance had occurred by the seventh day and by the fourteenth day, the analgetic response was still below the value recorded at the start of the injection period. On the other hand, meperidine, racemoramide and phenazocine all showed some loss of tolerance by the third day and, as evidence that

Figure 8

Comparison of the mean response curves of rats to a radiant thermal stimulus during a nine week period of injection and two week withdrawal period. Subcutaneous injections of saline, chlorpromazine, and thioperazine (SKF #5883) followed in fifteen minutes by phenazocine (SKF #6574-C) were used.

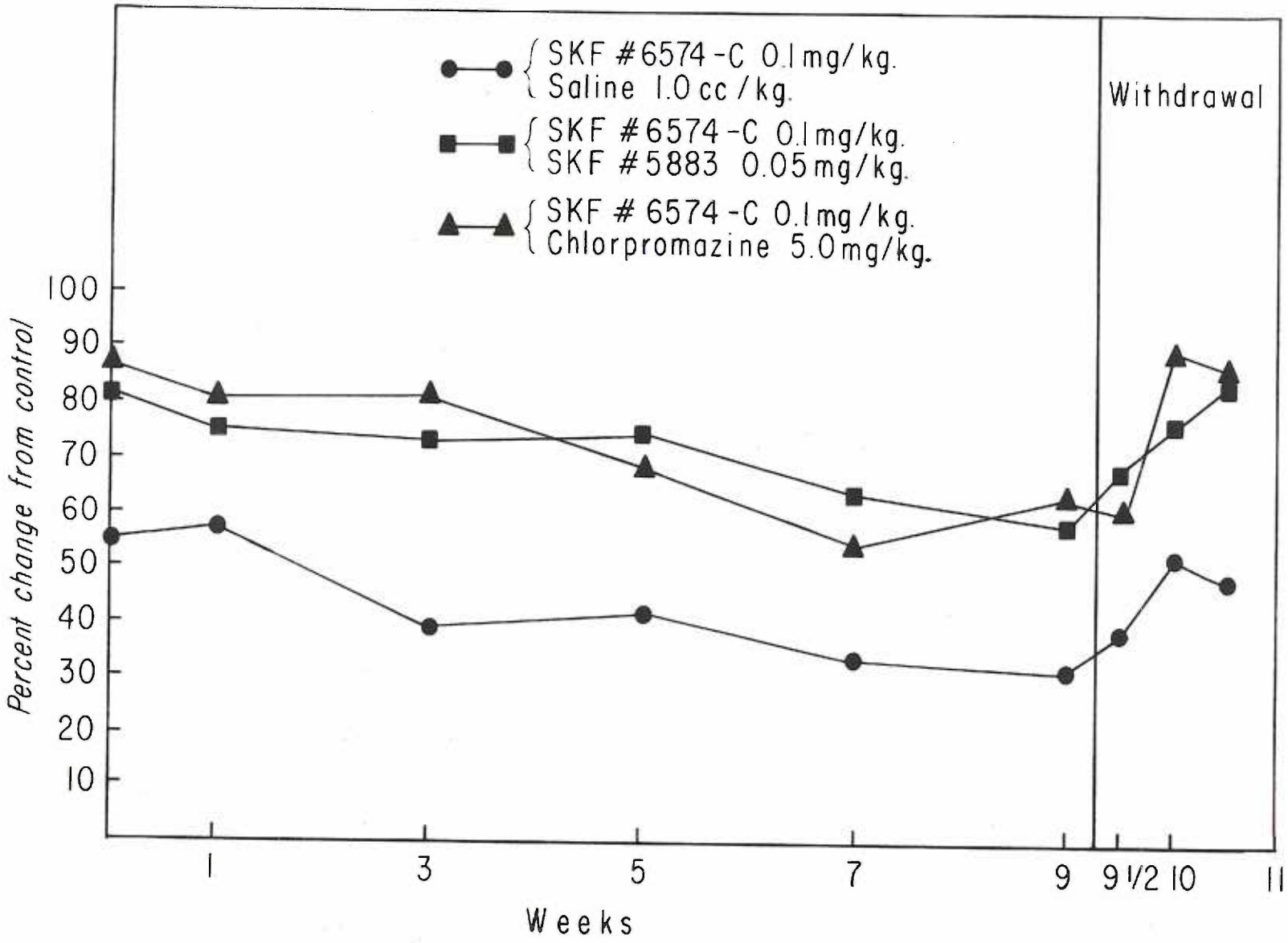
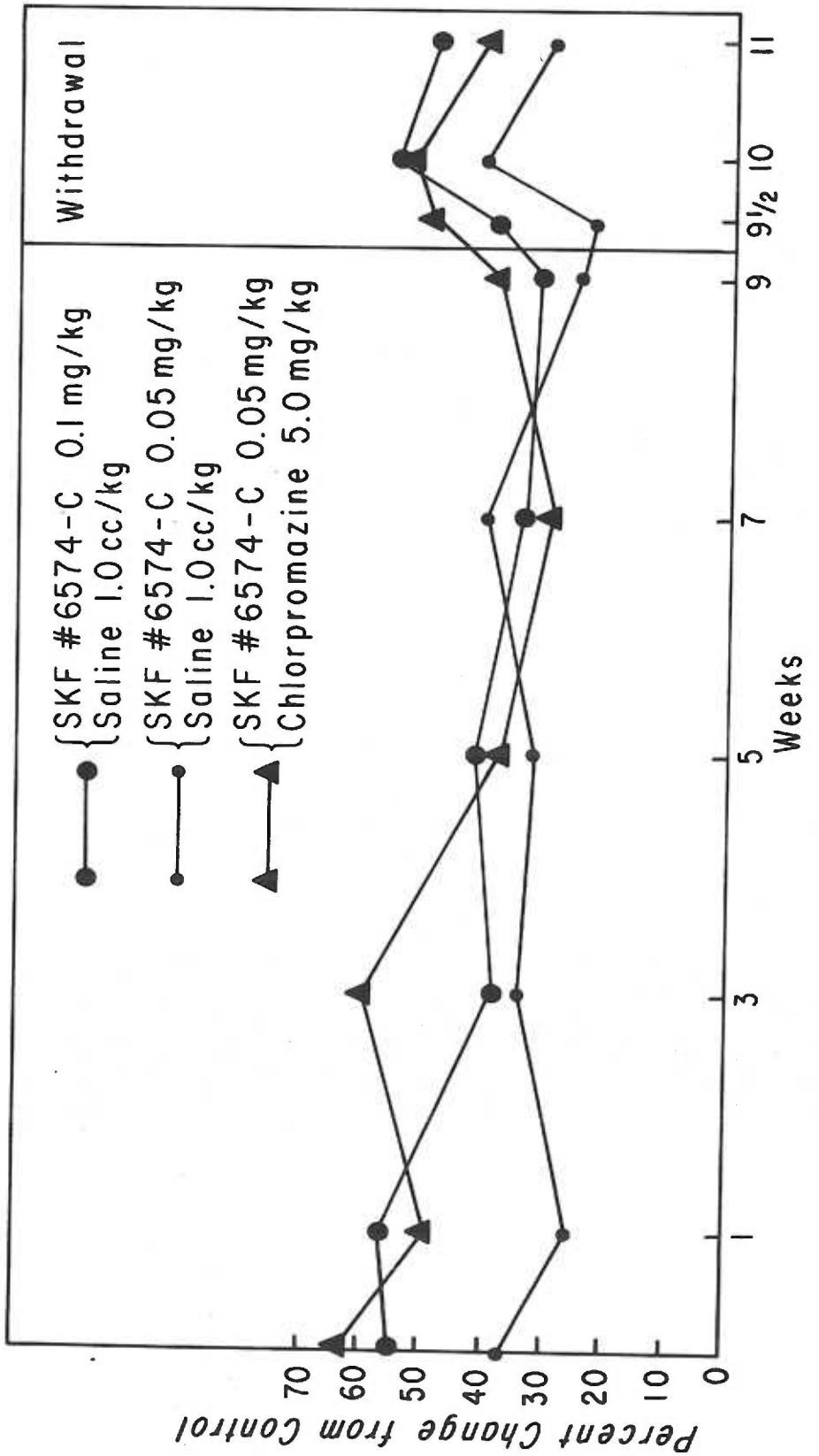

SKF #6574-C 0.1mg/kg.
Saline 1.0cc/kg.
SKF #6574-C 0.1mg/kg.
SKF #5883 0.05mg/kg.
SKF #6574-C 0.1mg/kg.
Chlorpromazine 5.0mg/kg.
Withdrawal
Percent change from control
100
90
80
70
60
50
40
30
20
10
1
3
5
7
9
9 1/2
10
11
Weeks

Figure 9

The mean response curves of rats to a radiant thermal stimulus during a nine week period of injection and two week withdrawal period. Effect of saline and chlorpromazine followed in fifteen minutes by phenazocine (SKF #6574-C) 0.05 mg./kg. as compared to saline followed by phenazocine (SKF #6574-C) 0.1 mg./kg.


Withdrawal
SKF #6574-C 0.1 mg/kg
Saline 1.0 cc/kg
SKF #6574-C 0.05 mg/kg
Saline 1.0 cc/kg
SKF #6574-C 0.05 mg/kg
Chlorpromazine 5.0 mg/kg
Percent Change from Control
0
10
20
30
40
50
60
70
1
3
5
7
9
9½
10
11
Weeks

tolerance had completely disappeared, all three drugs showed a return to the original analgetic response values by the seventh day. In general, loss of tolerance occurred more rapidly when phenothiazines had been given with the analgetics.

DISCUSSION

When repeated daily injections of morphine, racemoramide, meperidine and phenazocine are given to rats, analgetic tolerance develops. While the dosages used were selected because they all produced about the same degree of analgesia initially, the severity of the tolerance differed in degree and in the time it reached its peak. Morphine rapidly developed marked tolerance but that resulting from meperidine, even when given in five times the dosage of morphine, was barely significant.

An explanation for this difference in tolerance development between morphine and meperidine may be provided by Tatum and Seever's theory of narcotic tolerance and addiction (55). They point out that morphine has a double action on the brain, the more prominent and important depressant (and analgesic) action being of short duration is followed by emergence of an excitatory effect which lasts for a considerable period of time. In addition to causing symptoms such as nausea or emesis, the stimulation may intensify pain and apprehension in the sick or agitate the otherwise normal person. If another dose of the analgesic be given at this time, the depressant effects are again exhibited for a short time only to be followed by a somewhat severer period of excitation. Thus, as dose follows dose of the narcotic drug, tolerance develops to the depressant effects, but not to the excitatory effects. Because of the development of tolerance each subsequent dose, unless increased, is unable to suppress the stimulatory effects for more than a short while. Actually, following each dose the subject suffers withdrawal symptoms during the longer-lasting excitatory phase. Consequently, when a drug possessing a short duration of depressant and analgesic

action such as meperidine is used in the management of severe pain, or is taken by an addict, larger and larger doses are required at more frequent intervals. Probably when meperidine was first tested in the laboratory for the development of tolerance and addiction only single daily doses were used in the same manner as the experiments reported here; hence, it was heralded as a non-addicting drug in comparison with morphine!

The present investigations were not patterned according to the recommendations recently suggested for demonstrating tolerance development when short-acting analgesics are studied (47). While the present studies showed that tolerance to meperidine did develop, had meperidine been administered several times daily in the same dosage, the results may have been more dramatic.

On the other hand, the small degree of tolerance developed to phenazocine cannot be explained on the basis that the drug has a short duration of analgesic action. From other observations (13) and clinical studies done at this school (67), the duration of analgetic action of phenazocine was found to be similar to that for morphine. Thus, in comparison with morphine, the results suggest that phenazocine is less likely to cause addiction than morphine.

Lower doses of morphine (1 mg./kg.) and phenazocine (0.05 mg./kg.) were used in order to determine if phenothiazine potentiation produced significant analgesia, comparable to higher doses of the narcotic used alone. Initially this proved to be so but by the third week of the trial, there was no significant difference in the analgesia derived from the lower dosage of narcotic plus the phenothiazine as compared to the higher dose of narcotic drug used alone.

The modification of the development of tolerance to narcotics by the phenothiazines may also be explained on the basis of Tatum and Seever's theory. Not only did the combination of the phenothiazine with the analgetic serve to potentiate the analgetic effect but the continued, longer-lasting depressant action of the phenothiazine probably suppressed the excitatory effects of the narcotics. While the phenothiazines did not particularly delay the rate at which tolerance developed, they did lessen its severity.

It may appear from inspection of the graphed data that combination of the phenothiazine with the analgetic simply allowed measurements of the mean reaction time for analgetic responses to begin at higher levels. With the rate of tolerance development (decrease in mean reaction time) being the same for either the narcotic or the phenothiazine-analgesic combination, it would seem that, actually, there was no difference in the results. However, the fact remains that the degree of severity of the tolerance reached was, with one or two exceptions, not as great for the combination as the single analgesic.

In each instance the combination of chlorpromazine with the analgetic showed decreased tolerance development. It is of interest that thioperazine, which is a potent antiemetic agent (71), was found to be nearly as effective as chloropromazine both in potentiating analgesia and in lessening analgesic tolerance development. Prochlorperazine, while fairly effective in potentiating narcotic analgesia, in the dosages used in this study, proved to have little effect in modifying the development of tolerance.

In the withdrawal periods it was noted that loss of tolerance occurred more rapidly if phenothiazines had been given with the analgesic drugs. The groups of rats given chlorpromazine, prochlorperazine or thioperazine with morphine showed some increase in the mean reaction time on the third withdrawal day. By the seventh withdrawal day there was a marked decrease in analgetic tolerance and by the fourteenth day, the analgetic responses had almost all returned to the original values.

Loss of tolerance in the groups given phenothiazine-meperidine combinations occurred less rapidly during the first week of withdrawal than for meperidine alone. However, by the fourteenth day the analgetic responses for all three groups had returned to original values.

With the group given racemoramide and pre-injections of chlorpromazine or thioperazine, there was complete loss of tolerance in one week. However, the group given racemoramide-prochlorperazine lost tolerance slowly. This group had shown but little difference in tolerance development from the group given only racemoramide.

Phenazocine developed the smallest degree of tolerance observed for the four analgesics tested. It would be expected, then, that combination of this drug with a phenothiazine would not only further lessen tolerance development but would materially decrease the severity and duration of the withdrawal period. This was demonstrated when thioperazine or chlorpromazine was used with phenazocine; by the seventh day of withdrawal, both groups showed complete loss of tolerance.

It is to be remembered that laboratory procedures are most effective in classifying compounds with a high degree of analgesia, such as morphine. The study of analgetics in animals is least satisfactory when compounds of a low order of activity are assayed (36). Also, these

laboratory techniques are complex, time consuming, and unsatisfactory in many ways, yet they do provide a rough screening process and more important, they set the foundation for eventual trial in man. While animal experimentation can suggest, but not accurately predict, the effects of a drug in man, such studies are a necessary prerequisite to human experimentation.

We, therefore, are well aware that even the best methods leave unsolved many fundamental problems of analgesic research and that results obtained in the laboratory must be applied in the clinic with the utmost care. Because of these difficulties which are inherent to analgesic research, the following point is made: the results reported in such studies as this investigation are necessarily limited to the influence of drugs on the reaction thresholds in the animals tested toward thermal stimuli. Whether these results can be interpreted as analgesic actions comparable with those to be found in the human being is not within our present knowledge.

SUMMARY AND CONCLUSIONS

The purpose of the work described in this thesis was to explore the effectiveness and practicability of the use of a new group of drugs, the phenothiazine tranquilizers, as potentiators of the analgesic drugs such as morphine and meperidine (Demerol(R)) and, when so used together with analgesic drugs, to determine their effectiveness in forestalling the development of tolerance and addiction to the narcotic drugs. In addition to studying these effects using standard analgesics such as morphine and meperidine, it was thought of interest to study two new, recently introduced analgesic drugs, racemoramide (SKF 5137) and phenazocine (Prinadol(R)) which are claimed to be potent analgesics having a low order of addictive propensity. Also, a new phenothiazine derivative, thioperazine (Vontil(R)), which is a potent antiemetic agent, was studied in comparison with the clinically established phenothiazines, chlorpromazine (Thorazine(R)) and prochlorperazine (Compazine(R)).

The technique of D'Amour and Smith was used for measuring the changes in the analgesic activity produced by the narcotic analgesics when used alone or in combination with the phenothiazines. Tolerance to analgesia developed most rapidly with morphine, next with the new analgesic racemoramide, less with meperidine, and least with phenazocine. When lower dosages of morphine and phenazocine were used, only mild analgesia was produced and, consequently, tolerance development was not demonstrated.

When used in single doses, chlorpromazine was the most effective phenothiazine potentiator of morphine analgesia. Thioperazine was nearly as effective as chlorpromazine, while prochlorperazine was the

weakest potentiator. Thioperazine was the most effective in forestalling the development of tolerance.

Used alone in single experiments or when given over a long period of time, phenazocine proved to be a potent analgesic with a low tolerance liability compared to morphine. Phenazocine, given with thioperazine, was found to be the most effective combination for forestalling the development of tolerance in the rat.

From these results, it would appear that the combined use of a phenothiazine derivative with an improved narcotic analgesic, such as phenazocine, should provide effective analgesia with suitable duration of effect, minimal untoward effects and less rapid development of tolerance and addiction than is now achieved clinically when morphine or meperidine, alone, are used to provide pain relief.

BIBLIOGRAPHY

1. A.M.A. Council on pharmacy and chemistry. What to do with a drug addict. J.A.M.A., 1952, 149, 1220-1223.

2. Andrews, H.L., & Workman, W. Pain threshold measurements in the dog. J. Pharmacol. & Exper. Therap., 1941, 73, 99-103.

3. Bonneycastle, D.D., & Leonard, C.S. An estimation of the activity of analgesic materials. J. Pharmacol. & Exper. Therap., 1950, 100, 141-145.

4. Courvoisier, S., Fournel, J., Ducrot, R., Kolsky, M. & Koetschet, P. Propriete pharmacodynamiques du chlorhydrate de chloro-3 (dimethyl-amino-3' propyl)-10 phenothiazine (4560 RP), etude experimentale d'un nouveau corpsutilise dans l'anesthesie potentialisee et dans l'hibernation artificielle. Arch. internat. de pharmacodyn. et de therap., 1952-1953, 92, 305-361.

5. D'Amour, F.E., & Smith, D.L. A method for determining loss of pain sensation. J. Pharmacol. & Exper. Therap., 1941, 72, 74-79.

6. David, N.A., Progress in the search for morphine substitutes. Portland Clinic Bulletin, 1957, 1, 33-42.

7. David, N.A., Semler, H.J., & Burgner, P.R. Control of chronic pain by Dl-alpha acetylmethadol. J.A.M.A., 1956, 161, 599-603.

8. David, N.A., & Porter, C.A. Phenazocine (Prinadol, SKF 6574): Oral use in chronic pain. Clinical Research, 1960, 8, 117. (Abstract)

9. Davies, O.L., Raventos, J., & Walpole, A.E. A method for the evaluation of analgesic activity using rats. Brit. J. Pharmacol., 1946, 1, 255-264.

10. DeJongh, D.K., & Knoppers, A.T. Action of quinine hydrochloride on pain thresholds in animals. I. Experiments on Guinea Pigs. Arch. internat. pharmacodyn., 1952, 90, 449-461.

11. Dixon, W.J., & Massey, F.J., Jr. Introduction to statistical analysis. (2nd Ed.) New York: McGraw-Hill Book Co., Inc., 1957.

12. Eagle, E., & Carlson, A.J. Toxicity, antipyretic and analgesic studies on 39 Compounds including aspirin, phenacetin, and 27 derivatives of carbazole and tetrahydrocarbazole. J. Pharmacol. & Exper. Therap., 1950, 99, 450-457.

13. Eckenhoff, J.E. Phenazocine, a new benzomorphan narcotic analgesic. Anesthesiology, 1959, 20, 355-358.

14. Everett, Frank G. The local anesthetic properties of amidone (Dolophine). Anesthesiology, 1948, 9, 115-120.

15. Felix, R.H. An appraisal of the personality types of the addict. Am. J. Psychiat., 1944, 100, 462-467.

16. Forster, S., Forster, E., Maier, A., & Blum, H. Potentialized anesthesia in thoracic surgery. Anesth. & Analg., 1952, 9, 250-260.

17. Friebel, H., & Reichle, C. Analgesic and analgesia-potentiating effect of chlorpromazine (Megaphen). Arch. exper. Path. u. Pharmakol., 1955, 226, 551-557.

18. Goetzl, F.R., Burrill, D.Y., & Ivy, A.C. A critical analysis of analgesimetric methods with suggestions for a useful procedure. Quart. Bull., Northwestern Univ. M. Sch., 1943, 17, 280-291.

19. Goodman, L.S., & Gilman, A. The pharmacological basis for therapeutics: (2nd Ed.) New York: The Macmillan Co., 1955.

20. Gross, E.G., Holland, H., Carter, H.R., & Christensen, E.M. The role of epinephrine in analgesia. Anesthesiology, 1948, 9, 459-471.

21. Gwathmey, J.T. Synergism of magnesium sulphate and morphine and magnesium sulphate and ether. J.A.M.A., 1925, 85, 1482-1485.

22. Haffner, F. Experimentelle prnfung schmerzstellender mittel. Deutsche med. wchnschr., 1929, 55, 731-733.

23. Harris, S.F., & Blockers, L.E. The reliability and validity of tooth pulp algesimetry. J. Pharmacol. & Exper. Therap., 1952, 104, 135-148.

24. Himmelsbach, C.K., & Small, L.F. Clinical studies of drug addiction. II. "Rossium" treatment of drug addiction. Pub. Health Rep. Suppl. 125, 1937.

25. Himmelsbach, C.K., & Andrews, H.L. Studies on modification of the morphine abstinence syndrome by drugs. J. Pharmacol. & Exper. Therap., 1943, 77, 17-23.

26. Hunter, A.R. Chlorpromazine. Brit. J. Clin. Pract., 1956, 10, 217-221.

27. Irwin, S., Howde, R.W., Bennett, D.R., Hendershot, L.C., & Seevers, M.H. The effects of morphine, methadone and meperidine on some reflex responses of spinal animals to nociceptive stimulation. J. Pharmacol. & Exper. Therap., 1951, 101, 132-143.

28. Ivy, A.C., Goetzl, F.R., Harris, S.C., & Burrill, D.Y. The analgesic effect of intracarotid and intravenous injection of epinephrine in dogs and subcutaneous injection in man. Quart. Bull., Northwestern Univ. M. School, 1944, 18, 298-306.

29. Ivy, A.C., Goetzl, F.R., & Burrill, D.Y. Morphine-dextroamphetamine analgesia. The analgesic effects of morphine sulfate alone and in combination with dextroamphetamine sulfate in normal human subjects. War Med., 1944, 6, 67-71.

30. Jackson, G.L., & Smith, D.A. Analgesic properties of mixtures of chlorpromazine with morphine and meperidine. Ann. Int. Med., 1956, 45, 640-652.

31. Krueger, H., Eddy, N.B., & Sumwalt, M. The pharmacology of the opium alkaloids. Pub. Health Rep. Suppl. 165, 1941.

32. LaBelle, A., & Tornaben, J.A. Effects of various analgesics on inflammatory edema resulting from silver nitrate injection. Science, 1957, 114, 187-188.

33. Laborit, H. Narcotic potentiation in artificial hibernation. Arch. Exper. Path. u. Pharmakol., 1954, 222, 41-58.

34. Laborit, H., Jaulmes, C., & BeniHe, A. Certain experimental aspects of artificial hibernation. Anesth. & Analg., 1952, 9, 232-239.

35. Lehmann, H.E. Neurophysiologic activity of chlorpromazine in clinical use. J. Clin. & Exper. Psychopath., 1956, 17, 129-141.

36. Manske, R.H.F. The alkaloids, Volume V. Pharmacology. New York: Academic Press Inc., 1955.

37. Maurer, D.W., & Voegl, V.H. Narcotics and narcotics addiction. Springfield, Illinois: Charles C. Thomas, 1954.

38. May, E.L., & Eddy, N.B. A new potent synthetic analgesic. J. Org. Chem., 1959, 24, 294-295.

39. Murphy, E., Griffith, W.B., Carter, P.B., & David, N.A. SKF 5137 (dl-N-[2:2-diphenyl-3-methyl-4-(N-morpholino)-butyrl] - pyrrolidine HCL), an analgetic: potentiation of various effects in rats by chlorpromazine and prochlorperazine. J. Pharmacol. & Exper. Therapy, 1957, 119, 172-173. (Abstract)

40. Nance, M.R. Chlorpromazine. Am. J. Nursing, 1956, 56, 609-612.

41. Neligan, A.R. The opium question, with special reference to Persia. London, 1927. Quoted in: Terry, C.E., & Pellens, M. The opium problem. Camden, N.J.: The Haddon Craftsmen, 1928.

42. Pellini, E.G., & Greenfield, A.D. Narcotic drug addiction. The formation of protective substance against morphine. Arch. Int. Med., 1920, 26, 279-292.

43. Pierce, I.H., & Plant, O.H. Excretion of morphine in dogs made tolerant by long continued administration of moderate doses. J.P.E.T., 1930, 39, 265-266.

44. Reichard, J.D. Narcotic drug addiction, a symptom of human maladjustment. Dis. Nerv. System, 1943, 4, 275-281.

45. Sadove, M.S., Levin, M.J., Rose, R.F., Schwartz, L., & Witt, F.W. Chlorpromazine and narcotics in the management of pain of malignant lesions. J.A.M.A., 1943, 155, 626-628.

46. Schmidt, C.F., & Livingston, A.E. A note concerning actions of pseudomorphine. J.P.E.T., 1933, 47, 473.

47. Seevers, M.H. Termination of drug action by tolerance development. Fed. Proc., 1958, 17, 1175-81.

48. Semler, H.J., & David, N.A. Potentiation of morphine and l-isomethadone analgesia by dihydrogenated ergot alkaloids. Am. J. Med., 1952, 13, 99-100.

49. Semler, H.J. Effects of dihydroergocornine, CCK #179 (Hydergine), N,N-dibenzyl-beta-chloroethylamine (Dibenamine), and benzyl midazoline (Priscoline) on the analgesic activity of morphine sulfate and levo-isomethadone. Unpublished master's dissertation, Univ. of Oregon Medical School, 1953.

50. Siegmund, E., Cadmus, R., & Lu, G. A method for evaluating both non-narcotic and narcotic analgesics. Proc. Soc. Exper. Biol. & Med., 1957, 95, 729-731.

51. Silverman, M.M. Magic in a bottle. (2nd Ed.) New York: Macmillan Co., 1948.

52. Slaughter, D.H., & Gross, E.G. Some new aspects of morphine action. J. Pharmacol. & Exper. Therap., 1940, 68, 96-103.

53. Smith, Kline and French Laboratories. Thorazine, a review of the pharmacology; Compazine, a review of the pharmacology. Science information dept., research and development div., unpublished information. Revised August, 1956.

54. Smith, Kline and French Laboratories. Prinadol, a review of the pharmacology. Science information dept., research and development div., unpublished information. Revised March, 1959.

55. Tatum, A.E., Seevers, M.H., & Collins, K.H. Morphine addiction and its physiological interpretation based on experimental evidences. J.P.E.T., 1929, 36, 447-475.

56. Tedeschi, D.H., Tedeschi, R.E., & Fellows, E.J. Observations on the neuropharmacologic effects of Phenazocine, a new analgesic agent. The Pharmacologist, 1959, Fall, 78. (Abstract)

57. Vogel, V.H., Isbell, H., & Chapman, K.W. Present status of narcotic addiction. With particular reference to medical indications and comparative addiction liability of the newer and older analgesic drugs. J.A.M.A., 1948, 138, 1019-1026.

58. Wallis, R. Potentiation of hypnotics and analgesics. New York J. Med., 1955, 55, 243-244.

59. Wendel, H., Shemans, I., & Ross, S.D. Phenazocine (N.I.H. 7519, 'Prinadol') as a narcotic analgesic. The Pharmacologist, 1959, Fall, 78. (Abstract)

60. Wilson, W.L., Shane, L.L., & Moyer, J.H. The use of thioperazine as an antiemetic, Antibiotic M., 1959, 6, 421-425.

61. Winter, L. A textbook of exodontia, oral surgery, and anesthesia. St. Louis: The C.V. Mosby Co., 1937.

62. Wolff, P.O. The treatment of drug addicts. A critical survey. Bull. Health Organ., League of Nations, 1945-46, 12, 455-470.

63. Woolfe, G., & MacDonald, A.D. The evaluation of the analgesic action of pethidine hydrochloride (Demerol). J. Pharmacol. & Exper. Therap., 1944, 80, 300-307.

64. Worth, W. Attempts to combine action of Megaphen with strong acting analgesics. Arch. exper. Path. u. Pharmakol., 1954, 222, 75-76.