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Demerol : new substitute for morphine

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DEMEROL, NEW SUBSTITUTE FOR MORPHINE

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INTRODUCTION

A list of drugs used by the average physician of today would be revealing by the number, variety and duplications. But no Doctor would be willing to surrender opium in some form. No adequate substitute has been found to date, but probably the nearest approach was made when Demerol was placed at the disposal of the profession in 1939.

Since that time, numerous investigators, clinicians, and drug firms have tested the new drug both in the laboratory and on clinical patients. Although the drug is not in general use at the present time, more and more members of the profession are using it. From time to time more literature will be written on Demerol, which at present is still small in amount. Since most Demerol is going to the armed forces, it has become increasingly difficult to obtain, further hindering investigation.

The striking similarity of the action of Demerol to that of morphine on the central nervous system so far as analgesia and sedation are concerned, led us to the belief that the drug could be used in place of morphine. The increasing need

for morphine in the time of war and the present threat to our opium supply, make it important that appropriate consideration be given to this new analgesic, Demerol. This compound can be prepared synthetically from available chemicals, and according to its pioneer clinical investigators ranks "runner-up" to morphine in relieving pain. While morphine is dangerous both in toxicity and addition, Demerol is relatively safe.

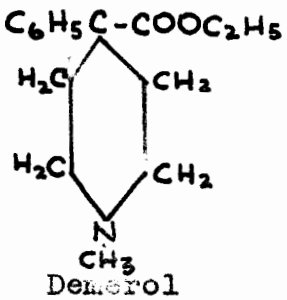
Demerol was originally intended as a safe analgesic for hopeless, bed-ridden sufferers of pain. Its rapid excretion and its non-accumulation in the tissues, however, render it ideal for ambulant patients with relatively constant pains. Demerol will prove a blessing to wounded soldiers, who no longer will need to"grin and bear it" lest relieving opiates lead to addiction.

Not having the opportunity to see Demerol in action on clinical patients, I shall attempt to review the available literature on Demerol and evaluate its effectiveness with especial reference to its, chemistry,pharmacology, clinical uses and safety. Comparisons with morphine will be made wherever possible.

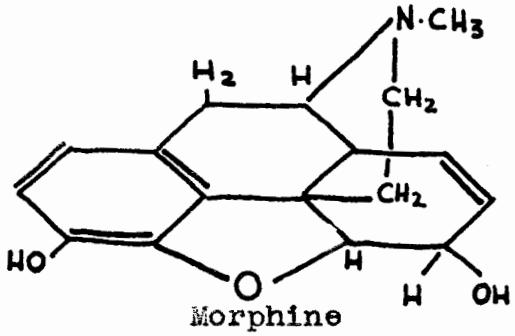
CHEMISTRY

In 1939, Eisleb and Schaumann introduced a new synthetic, phenylpiperidine derivative, Demerol, which was found to possess properties similar to those of atropine and morphine. It was discovered in the course of a search for compounds having spasmolytic properties of the atropine series of drugs. The patent rights were purchased by a United States drug manufacturer just before the outbreak of World War II.

Demerol is ethyl 1-methyl-4-phenylpiperidine-4-carboxylate and has the following structural formula:



Demerol



Morphine

Comparing its structural formula with that of morphine it is noted that little similarity exists between the two drugs. Upon rearrangement of the ethenamine chain of the morphine nucleus, a piperidine ring becomes evident. However, Demerol is lacking the phenolic and alcoholic hydroxyl

groups attached to the phenanthrene nucleus to which the properties of morphine have been attributed. However, its chemical similarity to morphine particularly the piperidine ring about which Demerol was built has been detected. It has been known for years that piperidine compounds were analgesic and that the esters of basic alcohols were spasmolytic.

In comparison with popular analgesics, such drugs as the salicylates, acetanilid, and amidopyrine may be dismissed. They are somewhat specific in the types of pains affected. Furthermore, their analgesic strength is but a fraction of that possessed by Demerol.

Of the opium alkaloids, codeines analgesic index ranks far below Demerol. Pantopon, dilaudid, and papaverine rank higher but are considerably less effective than Demerol. Morphine turns up as the only practical analgesic that rivals Demerol.

Demerol is not an opiate derivative. It is a white crystalline substance, slightly soluble in water and with a strong alkaline reaction. For medicinal purposes the hydrochloride is employed; this is also a colorless crystalline powder with

a melting point of from 185 to 187° C. It is readily soluble in water, has a neutral reaction and a slightly bitter taste. The solution is not decomposed by short periods of boiling.

PHARMACOLOGY

Demerol hydrochloride possesses not only a spasmolytic action common to the esters of basic alcohols, but also analgesic properties greater than ever before observed with synthetic compounds considered suitable for clinical use. It has a distinct spasmolytic (relaxing) action on the smooth muscle of the gut, the uterus, the bronchial tree and the urinary bladder. This action is due in part to a depression of the para-sympathetic endings, but is primarily the result of a direct depressant effect on the muscles, and although more effective is comparable in this respect to the action of papaverine.

R. V. Christie (9) states that Demerol will antagonize the effect of acetylcholine and of histamine on the gut. The effect of pilocarpine and physostigmine on the intestinal segment can be completely or temporarily abolished by the

addition of an adequate amount of Demerol hydrochloride. The effect of Demerol in this respect is less than that of atropine.

When the isolated frog heart is perfused in situ as described by Barlow and Sollmann (3), Demerol in dilutions of 1:200,000 or less produces a slight depression in amplitude and tone. Concentrations of 1:25,000 or more produce a heart block. With short perfusions the block is reversible. The depressant effects of high dilutions of Demerol are largely antagonized by atropine. In dilutions of from 1:5000 to 1:50,000, Demerol renders the cardiac vagus of the frog progressively less responsive and finally non-responsive to electric stimuli. The vagal threshold of the anesthetized dog is similarly affected by intravenous dosages of this compound.

The action of Demerol on the heart seems to be one of vagal depression superimposed on a primary muscular depression. The cardiac sympathetic is likewise depressed but this effect develops more slowly and recovery therefore occurs more rapidly than from the parasympathetic effect.

Bronchial spasm induced in guinea pigs by

exposing them to a mist of histamine in a closed chamber can be prevented if Demerol is injected prophylactically. Doses of 10 mg. per kg. of body weight subcutaneously become effective within five minutes or less and the effects persist for about an hour. With larger doses the effects last for from two to three hours.

Demerol hydrochloride injected subcutaneously in cats in a dose of 3 mg. per kg. of body weight produces a definite enlargement of the pupil. If applied directly to the eye in a 1 per cent solution, slight dilatation of the pupil is observed. Therapeutic doses in man administered either by mouth or parenterally cause little if any change in the size of the pupil.

Demerol hydrochloride in doses of 20 mg. per kg. injected subcutaneously in cats produces a marked diminution of salivary flow. However, this effect is considerably less than that which is produced by 0.1 mg. per kg. of atropine. The blood supply of the kidneys can be greatly decreased by the administration of epinephrine and related vasoconstrictors. The constriction of the renal vessels may be counteracted entirely by

appropriate doses of Demerol. Atropine in the same dosage is without effect.

Demerol hydrochloride has little if any effect upon blood sugar. Following doses up to 10 mg. per kg. subcutaneously, the blood sugar level of fasting albino rabbits varies within normal limits, and doses of 20 mg. per kg. increase it but slightly.

The results by Gruber, Hart and Gruber (16) from experiments carried out in dogs are somewhat different from these cited above. They found that the effects of Demerol on smooth muscle (intestine, bronchus, uterus, and blood vessels) is unpredictable. If the muscle is relaxed, the drug usually causes some contraction, while if it is contracted, relaxation is often seen. On intact smooth muscle (stomach, pyloric sphincter, small intestine and urinary bladder) the drug shows no promise of value as a spasmolytic agent; contractions of the muscle occur. The value must be therefore, attributed to its analgesic potency. On intact and excised uteri, it was found that this chemical was of no value as a uterine sedative. The stimulant action, which is a most

common finding is much less potent than that of pituatrin.

Demerol hydrochloride is broken down very rapidly after oral or parenteral administration to the intact animal. The rapidity of the breakdown makes it difficult to trace the components of the drug. Only in extremely toxic doses is the presence of the drug demonstrated in the urine. It is thought to be broken down by the liver and to a much lessor extent by the tissues of the central nervous system. The rapidity of destruction of the drug in vivo may account for the relatively short period of analgesia, the small amounts of the drug detectable in the urine and the ability to administer the drug prolonged periods at intervals of three to four hours without cumulation of toxicity.

TOXICITY AND TOLERANCE

Demerol hydrochloride has been found to be relatively non-toxic. Eisleb and Schaumann (13) report the minimum lethal dose of Demerol for mice as 150 mg. per kg. subcutaneously and 60 mg. per kg. intravenously; for rabbits 30 mg. per kg. intravenously and 700 mg. per kg. orally. On the basis of his observations, Gruber (16) reported the lethal dose per kg. of Demerol to be as follows: For white mice, 147 mg. intraperitoneally and 221 mg. orally; for albino rats, 93 mg. intraperitoneally; and for rabbits weighing from 2.3 to 4.2 kg., 20 mg. intravenously.

The oral administration of Demerol to cats in doses up to 75 mg. per kg. produces a marked analgesic effect with little depression. Doses of 100 mg. per kg. or more produce excitement and clonic convulsions. Although there are a number of similarities between the action of Demerol and that of morphine, there is a striking difference between these drugs so far as their action on the cat is concerned. The wild or senseless random movements which characterize the action of morphine in cats are not seen following the adminis-

tration of Demerol. On the other hand, Demerol produces a quiet, mildly depressed analgesic state.

In dogs intravenous administration of doses of 5 mg. per kg. produce no significant effect. Larger doses produce excitement, and excessive doses may be associated with clonic convulsions. Following intramuscular administration of doses of 20 mg. per kg., dogs exhibit an increase in salivation and slight ataxia. With doses of from 30 to 50 mg. per kg., the ataxia is associated with marked spasticity, sluggish random movements and clonic convulsions.

Chronic administration of Demerol in a dose of 75 mg. per kg. to 8 adult dogs and 40 mg. per kg. a day to 24 monkeys was continued for a period of ten months. Although a slight degree of anorexia and a slight falling off in weight were observed, no deleterious effect was produced with respect to the hematopoietic system; upon necropsy no histologic changes in the liver, kidneys, spleen, gastric mucosa, or bone marrow were noted. In another experiment which consisted of daily intramuscular administrations of Demerol at eight hour

intervals for twenty-eight days in a similar dosage, there was no organic evidence of toxicity, but only apathy, spasticity and ataxia, hypersalivation and depression. The metabolism of these animals remained unaltered.

Gruber (16) studied the effect of excessive doses of Demerol on the hematopoietic system in dogs by administering the drug in doses of from 50 to 100 mg. per kg. per day for a period of seven weeks. At no time during the entire seven weeks was the blood picture of any animal significantly different from the control.

It has also been found the Demerol has no effect on the hematopoietic system or blood picture of the rabbit when given in doses up to 20 per cent of the M.L.D. daily (by intramuscular injection) over a period of thirty days whether to normal rabbits or to animals poisoned chronically with aminopyrine.

Batterman (5) found Demerol to be safe and with the exception of certain side effects is nontoxic in therapeutic doses. These side effects are usually insignificant, are of brief duration and do not as a rule inconvenience the patient to

any appreciable degree. Their occurrence is unpredictable, since they may appear after the first dose or only occasionally after several doses. The sex, age and weight of the patient, the diagnosis and the accompanying conditions do not have any relation to the type, frequency and severity of the side effects. After prolonged administration they occur with less frequency, may decrease in their intensity or may subside completely. It is not unusual for a rapid tolerance to the unpleasant reactions to develop and yet the patient may obtain an equal or even better relief of the pain. This tolerance varies for the individual subject.

Any discussion of tolerance must take into account the various effects that can be produced with Demerol. Repeated doses of morphine result in the development of tolerance to the depressant effects on the central nervous system, such as sedation, analgesia and respiratory depression. In the case of Demerol, tolerance to the skin pain threshold raising effect is usually manifest within two weeks and reaches a maximum at the end of eight weeks. In a group of 115 hospitalized patients receiving from 42 to 492 doses of Demerol

within periods of from four to twenty-eight weeks no appreciable tolerance to its general clinical analgesic effect occurred. Clinical analgesia is probably the result of one or more of the following effects: (1) a central action on the midbrain or the thalamic area blocking or reducing the transmission of pain sensation from the periphery to the cerebral cortex, (2) an altered reactivity of the patient to the pain, so that even if perceived the 'fear reaction' is not evoked and (3) an increased threshold to painful stimuli at the periphery. The latter factor, although of immense help in evaluating relative potency of analgesics, appears to be of minor importance as far as general analgesia is concerned.

One should avoid repeated large doses of either Demerol or morphine because of cumulative toxicity. In the case of Demerol, this may take the form of cerebral irritation or convulsions, while cerebral depression with marked respiratory difficulty is the rule with morphine. Convulsive seizures have occurred with Demerol if the dose exceeds 200 mg. every 2 hours. This has been particularly noted in previous opiate addicts who

abuse Demerol as a substitute drug. It has never been noted with therapeutic doses, although minimal signs such as tremors and uncoordinated muscular movements may occur in an occasional patient. This represents and indication for decreasing the dose or discontinuation of the drug.

With the exception of cerebral irritability with large doses, Demerol is relatively a safe drug. Prolonged use has not resulted in alteration of the hematopoietic system or produced disturbances in liver or kidney function. In contrast to morphine it may be used freely in patients with liver or kidney disease. To date no disease or other medication including the sulfonamide drugs has been found incompatible with Demerol.

R. C. Batterman (6) found significant side reactions in about 25 per cent of hospitalized or bedridden patients receiving the drug parenterally. These reactions are usually of minor importance and do not as a rule inconvenience the patient to any appreciable degree. The commonest reaction is dizziness which occurs in approximately 22 per cent of the patients. Unless associated with other reactions it is not very disturbing and with

repeated use of the drug may diminish or subside completely. Nausea and vomiting was noted in approximately 4 and 8 per cent respectively. These also subside promptly if the drug is continued. The incidence is much lower than that noted with morphine. Perspiration and dryness of the mouth may at times be marked.

With exception of perspiration, all these reactions occur with a higher incidence and severity in ambulatory patients. Thus dizziness is noted in 59 per cent of the patients, nausea in 26 per cent and vomiting in 12 per cent. Tolerance to the unpleasant reactions usually occurs with prolonged use but the majority of patients may experience mild side effects with each dose for several weeks or months. Of particular importance is the occurrence of weakness and syncope that are noted only in ambulatory patients. Since Demerol possesses vasodilating properties, the compensatory mechanisms necessary to maintain the circulation in the upright posture may be temporarily overcome. If the patient is advised to seek a recumbent position as soon as weakness is noted the reaction may be aborted or decreased in sever-

ity. Because of the higher incidence of reactions and the possibility of syncope, the drug should be used with caution in the ambulatory patient. It may be necessary to determine for each patient the optimum dose required for therapeutic effects and to reach this dose slowly as tolerance to the side effects develop. The drug should not be given intravenously or in a dose higher than 35 mg. hypodermically if the patient is ambulatory.

In contrast to morphine, urinary retention and respiratory depression occurred rarely with Demerol. Batterman (5) found the latter effect in 2 patients of 774 receiving the drug parenterally. In both instances the respiratory depression was of short duration and responded readily to the usual stimulants.

Batterman (5) also found that constipation, which occurs in practically every patient treated with opiates, never resulted from medication with Demerol.

THERAPEUTICS

In the realm of therapeutics, we find that Demerol possesses three main actions: analgesia, spasmolysis and sedation. The relative analgesic effect as compared with codeine and morphine can be demonstrated by the method of Hardy, Wolff and Goodell (17). The administration of 100 mg. of Demerol orally results in the elevation of the peripheral pain threshold within fifteen minutes, reaches a peak of approximately 50 per cent at the end of one hour and gradually subsides in about six hours. Intramuscularly the effect appears within ten minutes, reaches its peak in forty-five minutes and persists for several hours. By this method 50 mg. of Demerol intramuscularly was found to be approximately twice as potent as 22 mg. of codeine. Similarly, 125 mg. of Demerol approaches the effectiveness of 17 mg. of morphine but does not persist as long.

Demerol administered intramuscularly in a single dose of 100 mg. will allow the subject to experience approximately 80 per cent more pain than during the control period. This elevation of pain threshold approaches closely that obtain-

ed with 15 mg. of morphine but appears more quickly, usually reaches its peak within 45 minutes and subsides sooner. In actual use for the relief of pain, analgesia occurs within 15 minutes by the parenteral route, within 20 to 60 minutes by the oral route and usually subsides in the average patient within 2-4 hours. Analgesia does not persist as long as in the case of morphine, and for this reason, if the pain is severe or chronic, Demerol must be administered at more frequent intervals. In contrast, however, to morphine it possesses little danger of cumulation of undesirable effects such as respiratory depression, deep narcosis, urinary retention or constipation, and therefore may be used with a greater degree of freedom and safety. Moderately intense pain can be controlled with 50 to 100 mg. every 4 hours. With severe pain as much as 150 mg. may be given every 3 hours. It is rarely necessary to exceed this dose to achieve a satisfactory relief of pain. If the patient does not respond to this dose it is unlikely that a higher dose of Demerol or a comparable dose of morphine will be more effective. Occasionally a patient will stop re-

sponding to an analgetic not because of tolerance, but because the pain is so severe that any dose short of one resulting in marked cerebral depression would be ineffective. In such a case it is advisable to resort to other analgetic procedures such as nerve block or section.

The practical use of this effect in man has been applied to the relief of pain due to a large variety of conditions. The duration of analgesia is about three hours. Visceral pain such as that arising from the peritoneum, pleura or smooth muscle is relieved more effectively than pain arising from skeletal and neurologic structures.

Demerol administered parenterally is at least as effective as morphine in producing clinical analgesia. Comparative studies on the same patient would indicate that 100 mg. of Demerol parenterally in equivalent to 10 mg. of morphine. Oral administration of Demerol is less satisfactory than parenteral administration, perhaps because of variations in absorption. Nevertheless the oral route is useful and yields satisfactory results.

In connection with administration of the drug, Hoffman (22) concludes after fifteen months obser-

vation that the oral administration should be used to keep the pain threshold at a high level. But to relieve severe pain the injectable method should be used. The latter acts very promptly--much more rapidly than morphine.

The second important action of Demerol is its general spasmolytic effect in man. Intubation studies have demonstrated this action on the stomach, pylorus and small and large intestine of human subjects. The effect is due to an atropine-like action on the parasympathetic nerve endings and a papaverine-like direct depression of smooth muscle. In direct contrast to the action of opiates (morphine), the motility of the intestine is so influenced that the segmental contractions and tone are diminished or abolished, while propulsive action is unaltered. Clinically this action is manifested by the rapid and often dramatic relief of colicky pain. Prolonged use of the drug in therapeutic doses does not result in constipation. Hence, Demerol is of little value in the treatment of diarrhea and cannot replace opiates for this purpose. Thus it would appear that Demerol has definite spasmolytic action in

man.

In contrast to the effect of morphine, and antispasmodic response on the intact ureter by Demerol has been demonstrated in animals and man by Climenko and Berg (10). The relief to patients with renal and ureteral colic is thus explained by experimental evidence.

The third action of Demerol to be considered is sedation. This usually occurs with the larger parenteral doses, resulting in sleep from which the subject can be aroused easily. It usually subsides within two hours, but when the drug is given at night or to patients who have been sleepless because of pain the sleep may last longer. Patients note no after-reactions or mental confusion on awakening. Ambulatory patients may complain of drowsiness at first, but tolerance is developed to the sedative effect. In contrast to morphine, excitation is rarely if ever observed with Demerol.

Several of these properties attributed to Demerol caused attention to be focused upon its use in clinical anesthesia. Its hypnotic effect would serve to produce the psychic depression desirable for patients submitting to anesthesia. Its drying effect on secretions (atropine-like) would be of definite advantage. The analgesic effects would serve to eliminate pain preoperatively and diminish it postoperatively. The absence of appreciable respiratory depression would eliminate one of the most serious objections to morphine. The absence of untoward effects upon circulation and renal function would be welcome and the maintenance of normal pupillary reactions might aid in determining readily the degree of narcosis when inhalation agents were employed. Its reported negative effect upon metabolic rate might be considered as unfavorable. Preanesthetic medication serves one of its most useful purposes in reducing metabolic activity.

With this in mind Rovenstine and Batterman (26) observed the effects on a series of 12 dogs when Demerol was given prior to anesthesia. The

dogs were anesthetized by means of cyclopropane, ether and pentothal sodium. The results for each group of 4 dogs with a comparison of the findings with and without premedication were recorded. The results were similar to those noted when morphine was the preanestnetic agent. With Demerol, as in the case of morphine, the amount of inhalation agent required to secure a certain degree of anesthesia was reduced and the effectiveness of a given amount of pentothal sodium was prolonged.

Other observations during these studies revealed that (1) the animals exhibited mild excitement characterized by restlessness, hyperpnea and tachycardia twenty to thirty seconds after the intravenous injection of Demerol. This excitement stage resembled that seen in dogs after morphine is injected intravenously, but was less severe and not as persistent, usually subsiding within one minute. (2) It was possible to insert an endotracheal airway within two to four minutes in animals given Demerol. On the other hand, in the same animals without premedication, intubation could not be carried out conveniently in less than five to eleven minutes. (3) These untrained

animals exhibited no excitement during induction of anesthesia after Demerol was given. (4) Mucous secretions were not increased when anesthesia was induced after the dogs had received Demerol. (5) Although the pupils became pinpoint after administration of Demerol, the movements of the eyeball remained active. (6) The respiratory rate returned to normal following the short period of hyperpnea in the initial excitement stage.

From these few observations, favorable for the use of Demerol as a preanesthetic agent in dogs, its use in man for this purpose appeared warranted.

In a group of 338 unselected consecutive patients, both male and female, ranging in age from 15 to 89 years of age, Demerol was used for preanesthetic medication. Demerol was given in doses of 50, 75 and 100 mg., and when combined with scopolamine the amounts of the latter were 0.4, 0.5, and 0.6 mg. respectively. A dose of 100 mg. of Demerol was used whenever it was decided that the patient would require 0.016 Gm. (1/4 grain) of morphine. Similarly, 75 mgm. of Demerol was used in place of 0.011 Gm. (1/6 grain) of morphine. This ratio of the doses of the two drugs

was not altered for any patient.

For the Demerol-scopolamine combination regardless of the anesthetic used a satisfactory response was obtained with 100 mg. of Demerol hypodermically in 76 per cent of the 166 patients treated, and undue depression was noted in 3 per cent. An equivalent amount of morphine (0.016 Gm.) given to a corresponding number of patients resulted in a satisfactory response in 81 per cent and in deep depression in 9 per cent. Demerol, given in doses smaller than 100 mg., produced less favorable results except in the patients in the age group over 60 years. A satisfactory preanesthetic state was recorded in 83 per cent of the older patients receiving 75 mg., but this dose was insufficient for 60 per cent of the patients in the 20 to 60 age group. Three of the 56 patients receiving 75 mg. were too depressed. One of these was 62 years of age. The dose of 50 mg. was likewise unsatisfactory. This was definitely true in those under 60 years. No individual receiving this amount was thought to be 'too depressed.' In 4 patients, aged 63 to 69, the results were satisfactory but more than half of

those between 15 and 60 years of age were apprehensive or the drug appeared to have little or no effect.

The optimal time that should elapse after Demerol and scopolamine are administered before anesthesia is begun was found to be between forty-five and ninety minutes. A satisfactory preanesthetic state was recorded in approximately 89 per cent of the patients when this period of time was allowed to elapse. On the other hand, if this interval was twenty to forty-five minutes, and when the period was more than ninety minutes, the response was satisfactory in only 5 per cent. All of the group recorded as 'too depressed' had received the drug more than forty-five minutes previously.

Those patients with satisfactory preanesthetic medication were usually breathing quietly at a rate varying from 18 to 24 per minute. The blood pressure recorded during anesthesia compared with that taken during the physical examination was not significantly different in 70 per cent of the patients. It was increased in 20 per cent and decreased in 10 per cent. No extreme changes were

noted. The changes in pulse rate were not significant although it was usually increased slightly.

Demerol was given as the only preanesthetic drug in a group of patients with results similar to those observed when the drug was combined with scopolamine. The effects on respiratory rate were not significantly different. Mucous secretions were definitely less when Demerol was used than when morphine alone was given for preanesthetic medication.

Demerol's ability to dry secretions is more effective than morphine. In a group of patients a majority complained of thirst or dryness of the mouth after administration of Demerol and scopolamine. This makes Demerol particularly valuable in surgery of the mouth and throat in which analgesia and control of the salivary flow are desired. In addition it is of interest to note that in man Demerol has little if any sedative effect on cough, although because of its atropine-like action an occasional patient may be benefited by its decreasing the bronchial secretions.

Of particular advantage in the use of Demerol hydrochloride as a preanesthetic analgesic agent

is the fact that unlike morphine the size of the pupil remains unchanged and the pupillary reflexes are easily elicited. However, the corneal reflex and sensitivity of the cornea are abolished in about 80 per cent of the patients.

Inhalation anesthesia was induced with nitrous oxide-oxygen, nitrous oxide-oxygen-ether; ether; vinethene and cyclopropane. In the group adjudged to have a satisfactory effect the induction was recorded as entirely uneventful in 50 per cent of those receiving nitrous oxide-oxygen or nitrous oxide-oxygen-ether, while in 35 per cent there was some excitement (15 per cent slight, 14 per cent moderate, 5 per cent severe) and in 17 per cent laryngospasm occurred (none severe). In those receiving vinethene the results were approximately the same. When cyclopropane was used induction was uneventful in 82 per cent, and of those having excitement none was severe and in only one was laryngospasm recorded. Mucous secretions did not interfere with the induction in any of these patients.

For comparison another group of patients were given morphine and scopolamine for preanesthetic

medication and were anesthetized with nitrous oxide-oxygen-ether. Induction of anesthesia was entirely uneventful in 64 per cent, there was excitement in 26 per cent (8.5 per cent moderate, 7 per cent severe) and in 19 per cent laryngospasm occurred (2 per cent severe). Nausea was observed in 3 per cent. The induction of cyclopropane anesthesia after morphine anesthesia after morphine scopolamine premedication in 100 patients chosen for comparison was uneventful in 84 per cent.

Demerol and scopolamine were given a group of 25 patients who received spinal anesthesia. The effect was satisfactory for 21, one was apprehensive and 3 were not sufficiently depressed. Regional anesthesia was employed for 16 patients who received similar premedication, with good results in 13 and apprehension recorded in 3.

Recovery from anesthesia was similar in Demerol and morphine. Such complications as hemorrhage, shock, and abnormal reflex activity during operation after Demerol had been given were no different than would be anticipated if morphine had been used as far as the reaction of the patient and

response to treatment was concerned.

THE USE OF DEMEROL FOLLOWING SURGERY

In evaluating the effectiveness of Demerol in surgery and medicine several factors were taken into consideration. It must be emphasized that one is dealing with a symptomatic measure and not a specific cure. An analgesic agent offers only a means of controlling the pain, thus making the patient comfortable while the specific cause of his complaints is discovered and eradicated. This aspect is often overlooked, and when assessing an analgesic drug one finds, particularly if the medication is given only occasionally, that the patient may continue to have pain. On close questioning, however, one may discover that there was complete relief of pain for the duration of the drug's action, but when the effect is dissipated, the patient considers himself unrelieved.

According to some investigators Demerol has its greatest usefulness in the postoperative relief of pain. Regardless of the severity of the condition, the underlying disease, the ultimate prognosis or the type of operation performed, the

administration of 75 to 100 mg. every 3 to 4 hours during the immediate postoperative period will be sufficient to make the patient comfortable, reduce any restlessness and facilitate the usual postoperative procedures. For this purpose Demerol is superior to morphine because it rarely results in deep narcosis, respiratory depression or urinary retention. The cough reflex is unaltered so that expectoration is not interfered with as in the case of morphine, thus elimination an important contributing factor for pulmonary complications.

The immediate relief of restlessness, the rapidity with which the patient becomes comfortable and the minimal distress produced by the usual postoperative therapeutic procedures are all striking objective evidence for the effectiveness of Demerol under such circumstances. If pain or discomfort persists for more than 48 hours, satisfactory relief can subsequently be obtained with the orally administered preparation.

The effectiveness of Demerol immediately becomes apparent when its ability to control postoperative pain is observed. In a group of 164

patients, reported by Batterman and Mulholland (7), receiving the drug parenterally during the postoperative period after laparotomy 95.5 per cent of the 182 trials resulted to complete, satisfactory relief of the pain, discomfort and restlessness. After procedures other than laparotomy Demerol is only slightly less effective. Thus in 91.5 per cent of 271 trials in 252 cases, postoperative pain was completely controlled. An additional 5.2 per cent experienced a moderate effect, or relief for approximately three hours.

Batterman (5) reported that the postoperative course following surgical procedures such as laparotomy, thyroidectomy, mastectomy and herniorrhaphy is very well controlled with a minimum of untoward reaction. The immediate relief of restlessness, the rapid establishment of the patient's comfort, and the minimal distress produced by the unusual postoperative therapeutic procedures are all striking objective evidence of the effectiveness of Demerol hydrochloride in such cases.

It is well known that after-effects of rectal operations are notoriously painful, occasionally necessitating the use of large doses of opiates.

In a group of patients there was failure to give a satisfactory response to Demerol in only 4 instances out of 45 trials, and even in the 4 patients who failed to respond in one trial the subsequent administration of a larger dose resulted in alleviation of the pain. However, postoperative control of pain was hitherto achieved only by the use of morphine or one of its derivatives.

In the postoperative phase of treatment Demerol was found to be a safe drug, rarely causing untoward reactions. The subjective responses of dizziness and nausea occurred rarely. Here again the anesthetic may have influenced the incidence of untoward reactions. The incidence of vomiting was no higher than one would expect after major operations. Since Demerol has been in use in surgery there has been no instance of respiratory depression in a postoperative patient. Here obviously is a distinct advantage over morphine, for respiratory depression resulting from frequent and repeated use of morphine is a cause for grave concern. With several patients who had received morphine and in whom respiratory depression had developed, it was possible to continue the administration of Demerol

for the control of pain without producing this serious side effect.

Of postoperative complications, urinary retention may be most troublesome. Catherization, especially if repeated at frequent intervals, may result in cystitis or pyelonephritis. The incidence of catheterization among consecutive postoperative patients receiving morphine was determined for a period of ten months. During this period 160 operations were performed; 20 patients, an incidence of 12.5 per cent, required catheterization within twenty-four to forty-eight hours postoperatively. Another group in the following eleven months, in which Demerol was used exclusively, there were 178 consecutive postoperative patients, of whom 14, or 7.8 per cent, required catheterization. There is no doubt that the type of surgical procedure plays a significant role in the development of urinary retention and must be considered in an evaluation of the results just cited. The majority of the patients who were catheterized, whether they received morphine or Demerol, had had a rectal operation, a herniorrhaphy or an operation on the lower part of the abdomen.

Although the number of postoperative patients is too small and the difference in incidence of urinary retention between patients given morphine and those given Demerol may not be statistically significant, Batterman and Mulholland believe that Demerol is less likely to produce this undesirable complication.

The only disadvantage of Demerol as far as postoperative use is concerned is its short action. This, however, is rarely apparent in the first postoperative day. For patients with a protracted and 'stormy' course the average dose may be sufficient for only two hours. This may be overcome either by administering the same dose more frequently or by increasing the dose. There is no particular danger of causing undue depression in such cases.

DEMEROL IN MINOR AND NON-OPERABLE CONDITIONS

Minor surgical procedures such as dressings, application of casts, small incisions and drainages, thoracentesis, paracentesis and bladder irrigations may be performed with greater ease and with less pain if 75 to 100 mg. of Demerol are given intramuscularly one-half hour previously. According to Hoffman (21) thoracentesis was relatively painless in three cases, without employment of local anesthesia. The same was true in seven spinal punctures.

Following the administration of Demerol, cystoscopic examinations and bladder irrigations may be accomplished with greater ease and less discomfort to the patient. A group of 14 patients were subjected to a cystoscopic examination and had a catheter placed in the ureter with its tip immediately above the ureterovesical orifice. Employing the procedure described by Trattner in conjuction with highly sensitive photoelectric recording device normally occurring contractions were recorded for a period of fifteen minutes, after which 75 mg. of Demerol were injected intramuscularly. Within from 2 to 20 minutes there was

diminution in tonus associated with a marked decrease in the amplitude of contractions. In most instances the rate at which contractions occurred was not seriously affected, but the intensity was markedly diminished. This spasmolytic action of Demerol hydrochloride on the ureter is most marked in those instances where the ureter is in a state of heightened tonus.

In the treatment of non-operative surgical conditions the parenteral use of Demerol was found to be effective for skeletal pain associated with fractures and metastatic malignant growths, arterial occlusions, impending gangrene, thrombophlebitis, pleuritic pain of fractured ribs, cellulitis, abscesses, carbuncles, burns, and non-specific pain associated with various malignant growths. The severe pain of malignancies or chronic hopeless diseases has always been a problem for analgesia. With Demerol several disadvantages of morphine are circumvented. Demerol may be used relatively freely with little if any occurrence of general tolerance to the analgetic effects.

DEMEROL IN MEDICINE

Demerol relaxes effectively the smooth muscle of the gastrointestinal tract, urinary bladder, uterus and bronchi, thus resembling both atropine and papaverine. Its action upon the gut is unique. It inhibits segmental peristalsis, but actually seems to activate propulsive peristalsis. Patients on regular daily dosage frequently are awakened in the morning by sensations denoting the necessity of immediate bowel evacuation. Instead of diarrhea following, there is likely to be no bowel evacuation until the following morning, when the propulsive action recurs. Demerol was used in a small number of cases of colicky enteritis, stopping the incessant cramps out the bowel emptied effectively daily. Hoffman (22) reports that in four cases of suspected appendicitis and one of ruptured duodenal ulcer Demerol relieved pain, but in no manner masked diagnostic signs.

Hoffman (22) also has found the drug quite effective in relieving angina pectoris. However, on account of its action on the vagus nerve it seems wise to employ it cautiously in degenerative

heart disorders.

Because of the antispasmodic action of Demerol it is of definite value for the treatment of acute and chronic asthmatic conditions. It is a well known fact that morphine is contraindicated for such patients. Twenty-five or 35 mg. subcutaneously, a dose much lower than that required for either analgesia or sedation, will relieve the average patient with an acute asthmatic attack within 10 minutes. Where sedation is also desired as much as 100 mg. may be given every 3 hours. There is little danger of respiratory depression. The rapidity and duration of action as well as the degree of reaction is not as great as with epinephrine. The oral route is not very effective for the acute attack because of the delayed response, but it is of undoubted value in chronic asthmatic conditions, particularly those associated with bronchitis. With an appropriate dose, individually determined for each patient, administered several times daily and before retiring, it is possible to decrease the number and severity of the attacks. Demerol is purely a symptomatic measure and does not alter in any way the course of the

disease. With acute respiratory infections, the asthma may become so severe that only epinephrine or aminophylline (parenteral) is effective. However, when the acute phase subsides Demerol is again helpful. Many patients prefer it to ephedrine since it is taken constantly for several months. An occasional patient is not benefited because the atropine-like effect of drying the secretions may temporarily aggravate the condition.

Ambulatory asthmatic patients have fewer and less severe attacks when Demerol is administered every four hours. An acute attack of asthma can be relieved within 10 minutes by the subcutaneous injection of 35 mg., a dose far below that required to produce analgesia or sedation. The bronchial relaxation is less than that achieved with epinephrine. Nevertheless Demerol probably has a theoretical advantage as an antiasthamatic agent, since it would tend to reduce the autonomic reactions usually associated with a severe attack. Epinephrine would heighten the fear component even though the asthma was relieved. Good results have been obtained with a mixture consisting of 35 mg.

of Demerol and half the usual amount of epinephrine.

Demerol also affords good relief in pleuritic and arthritic pain regardless of causation. For the severe pain of myocardial infarction, it may be necessary to repeat the dose within one hour. As in the case of morphine a patient in severe pain may tolerate very large doses. The dangers of overdosage, however, are much less with Demerol.

Hoffman (21) reported six cases of the general arthritic group, who had been compelled to lay off work from time to time. After taking an average of two tablets daily, by mouth, and 0.5 cc. of Demerol intramuscularly about twice weekly they have now remained at work regularly for three months. Salicylates were added after each had had a successful trial of three weeks on Demerol alone.

Pruritus, a symptom closely related to pain, may be successfully alleviated with Demerol. This is in contrast to morphine which commonly produces pruritus and is therefore contraindicated for most skin diseases. Patients with chronic eczema in particular are made more comfortable with Demerol so that the decreased scratching contributes to the quicker response of appropriate ointments.

Demerol has been used successfully in alleviating the reactions to fever therapy, particularly those associated with the rapid method of antisyphilitic therapy. If 150 mg. are administered shortly before or simultaneously with the mapharsen-typhoid injection and repeated at the height of the fever, the patient will be relatively free of the more severe reactions and usually will remain asleep throughout the period of therapy.

DEMEROL IN NEUROLOGICAL CASES

Chronic nerve pains such as neuritis, radiculitis, the shooting pains of tabes dorsalis, intercostal neuralgias following thoracoplasty, have been always difficult to treat and are not satisfactorily relieved with the opiates. For such cases Demerol is superior to morphine.

Satisfactory results were also obtained in treatment of pain in neurologic conditions such as sciatica, cardiovascular pain, such as severe anginal syndrome and distress of congestive failure; and visceral or colicky pain of biliary, renal and gastrointestinal origin.

A small group of patients with 'slipped'

intervertebral discs, complicated by sciatic neuralgia, were able to resume their work for about two weeks, until arrangements were made for surgical removal of the discs. They had an average of 1.5 cc. Demerol injected daily (given morning and evening) while at work.

Two cases of unrelieved intense localized pain along the spine have been reported by Hoffman (21), following classical spinal fusions performed in the hope of relief, were kept sufficiently free from pain for five months to permit their regular employment. Neither was wholly freed of pain, but pain previously unbearable was diminished enough to prepare each for additional surgery.

Demerol proved to be effective as a reliever of pain from faulty skeletal structure, especially of the spine. A group of 'backs' were treated including old vertebral body, body fractures, ruptured intervertebral discs, spondylolisthesis, spinal fusions with complications, and hypertrophic spondylitis. Many of these had 'trigger spots' of excruciating pain. Slightly less than half of the latter, when their muscle spasms were held in check for a fortnight by Demerol, required no

correctional treatment by braces or by operation. Such temporary improvement is not cited as a 'cure'.

Root pains, resulting from tabes dorsails, have been greatly relieved by the administration of Demerol. One man who had been unable to keep a steady job during the previous year due to unpredictable 'lightning' pains, enjoyed three months of continuous employment by reporting for injection as soon as the pain appeared. On six different occasions he was able to return to his work within a half hour following the injection. The need for getting patients back to their jobs quickly calls for the rapidly effective injected drug rather than orally administered.

Fitzgerald and McArdle (14) reported a series of 12 neurological cases in which Demerol was found to have effects comparable with, and in some cases superior to, morphine. With morphine all received considerable relief, but it was less definite and of a shorter duration than that following Demerol. The group of patients included; radial neuritis with fibrosis, brachial neuritis, supraorbital neuralgia, trigeminal neuralgia,

sciatica, thalamic syndrome, tabetic crisis, Gasserian gangalion injection for tic douloureux, lumbar puncture headache, and encephalographic headache. When the drug was given intravenously it occasionally produced objectionable side-effects ranging from transient giddiness lasting a few minutes to giddiness, pallor, syncope, sweating, and nausea persisting for about one-half hour.

DEMEROL IN OBSTETRICS

It is felt by several investigators that Demerol is fast becoming a safe and effective means of medicating full-term patients during labor, while the absence of serious respiratory depression in the newborn makes this type of analgesia particularly suitable in obstetrics. According to Stander (28) morphine is not an ideal analgesic in labor and its use will eventually be restricted to a small group of neurotic patients upon whom it is desirable to exert a psychic effect. In addition, several serious objections are inherent to this form of analgesia. In the first place, it results in a definite prolongation of the second stage, necessitating more frequent instrumental interference, with its addi-

tional danger of infection. In the second place, it is attended by a definite, but slight, increase in the fetal mortality, estimated at between 1 and 2 per cent, which is apparently due to direct poisoning of the fetus. A large proportion of the children are born in a apneic condition: a smaller number are deeply asphyxiated, but can be resuscitated without great difficulty; while occasionally the asphyxia is so deep that resuscitation is impossible.

Demerol is being used for analgesia in obstetrics in many institutions with uniformly good results. Once labor is well established, the administration of 150 mg. intramuscularly immediately alleviates the restlessness and the severe pain without interfering with the course of labor. If anything, the first stage appears to be accelerated. The mother usually rests well between contractions, can easily be aroused for questioning or given supportive therapy without difficulty. A second dose of 100 to 150 mg. may be given within three hours, but it should not be repeated if delivery is expected shortly thereafter. The majority of patients require no more than 2 doses. If

labor is prolonged, however, 100 mg. may be given every 3 hours. Although Demerol may be used in conjection with scopolamine or barbiturates, their use is not absolutely necessary. The fetus is usually born in good condition and the incidence of depression is not greater than what one would expect from the course of the labor, complication and the general anesthetic used during the second stage. Blood loss is not excessive and the fundus contracts down properly with oxytocics.

Roby and Schumann (25) studied the effect of Demerol with scopolamine in labor. Preliminary trials indicated that oral administration was ineffective in the parturient patient. Consequently, when the patient began to complain of her pains, regardless of the state of dilatation of the cervix, she received 100 mg. of Demerol intramuscularly and scopolamine gr. 1/100 subcutaneously followed by scopolamine gr. 1/200 in one hour. This was sufficient to maintain the multiparous patient throughout the balance of her labor, while primiparas required additional medication in the form of scopolamine gr. 1/200 every one to five hours.

Satisfactory amnesia was obtained in 95 of

112 patients. The possibility of prolonging labor by the use of Demerol and scopolamine was not apparent. The condition of the patients, receiving the medication was, in general, favorable. The incidence of vomiting of other undesirable effects was no greater than when other types of medications were used. A few patients complained of dizziness but attending euphoria was not present. The majority of the patients were conscious enough to be cooperative and restlessness was kept at a minimum by infrequent administration of scopolamine.

Demerol and scopolamine were used in a series of 1,000 cases by Schauman (27) for the purpose of studying the maternal and fetal effects of this combination when used as an obstetrical analgesic. Demerol was used to obtain psychic sedation through its analgesic effect, thereby securing a favorable background for the action of scopolamine, reducing the excitement, and enhancing amnesia. A routine of medication was adopted using initially Demerol 100 mg. and scopolamine gr. 1/100 intramuscularly. Subsequently, Demerol 100 mg. and scopolamine 1/200 was given intraven-

ously every 4 hours. New admissions, expected to deliver within 2 hours, were given Demerol 50 mg. and scopolamine 1/200 by slow intravenous injection, using a minimum of 2 minutes for 2 cc. (100 mg.).

Satisfactory amnesia was obtained in 70.5 per cent of 847 cases. The remaining patients who had analgesia but no amnesia or failure of analgesia and amnesia, may have received the medication too late to benefit materially from its effects, while a few had not been medicated as frequently as called for in the routine. If the fault in these cases be thought to lie in the administration rather than the drug itself, then 9.6 per cent of the entire group may be discredited. The average primiparous labor in this series was 12.4 hours, the average multiparous labor, 7.6 hours. This is a reduction in the length of labor of approximately 15 per cent as compared with a group of patients who received barbiturate analgesia. The only maternal untoward effects in the series were seen in the intravenous group. With the exception of transient nausea in one-fourth of the cases, no further side effects were seen when the drug was

administered slowly.

The newborn infant breathed spontaneously in 82 per cent of the cases. In another 12 per cent, the infant respired within 2 minutes upon administration of oxygen; all babies were eventually discharged as normal.

Realizing that any depressant action of obstetrical analgesia on the newborn would be maximal in the premature group, an analysis was made of the premature infants in a series of cases. It was observed that not only were 91.0 per cent of the prematures in satisfactory condition on leaving the delivery room but also that there is no correlation between the weight of the baby and the degree of respiratory depression. There is little to suggest a respiratory depressant effect in this group. Demerol exerts no demonstrable depressant effect on either full-term or premature infants, whether administered by the intramuscular or the intravenous route.

In view of the satisfactory amnesia, the absence of pulmonary complications, and the freedom from depressant effect on the fetus, it is the opinion of Schauman (27) that Demerol in conjunc-

tion with scopolamine is superior as an obstetrical analgesic to other analgesics in common use.

Gilbert and Dixon (15) studied the use of Demerol as an obstetric analgesic in 150 women. In 70 cases, Demerol was used alone and in 80 cases in combination with other drugs. Intramuscular injections were given the majority of the patients because of greater uniformity and rapidity of effect when so given.

In 54 primipara patients an average dose of 294 mg. of Demerol was administered; the average total length of labor was eleven hours and eighteen minutes. When seconal was combined with Demerol the results were substantially the same. In 16 multipara patients, receiving Demerol alone, the average length of labor was nine hours and four minutes and in 10 cases receiving Demerol and seconal the average length of labor was six hours and six minutes. It seems likely that in analgesia of multipara patients Demerol alone may prove to be particularly suitable, since often the institution of a major amnesic regime to carry such cases through and ease labor seems scarcely warranted.

With experience limited to only 150 cases, conclusion as to the effect on length of labor must be tentative, but it appears that shortening of labor occurs when Demerol is given. This may be result of the drug's spasmolytic effect acting upon the cervix, or may simply result because the patient bears down more vigorously when the pain threshold is raised. Doses of 100 mg. of Demerol even when given at onset with the cervix not effaced, will not stop labor or diminish the effectiveness of mild contractions.

Of the 70 patients receiving Demerol alone, adequate analgesia without amnesia was found in 72 per cent. Of the 72 patients receiving Demerol and seconal, 61 per cent of the patients obtained satisfactory amnesia. The poor statistical results was due to inadequate doses of seconal ($1\frac{1}{2}$ to 3 gr.). While an occasional case would obtain satisfactory amnesia with this low hypnotic dosage, particularly after fairly large amounts of Demerol had been given, less than $4\frac{1}{2}$ gr. of seconal were uncertain. Demerol does potentiate the action of seconal enough to reduce significantly the amount of this hypnotic necessary to obtain amnesia in

the labor patient. With proper utilization of seconal in a patient adequately prepared with Demerol, amnesia can be obtained consistently with smaller doses of the barbiturate than can be used successfully alone.

With large doses of Demerol (300 to 500 mg.) a moderate sedative effect was noticed and women would frequently sleep between pains. This was never so pronounced that the patient would not awaken when spoken to in an ordinary conversational tone. No excitement, disorientation, or irrationality because of the drug was noticed in patients under Demerol alone. Complaint of dizziness and light-headedness was occasionally noted but was not prominent. Complaint of thrist and dryness of the mouth was frequent. With patients delivered under inhalation anesthesia, this depressed secretory activity in the nasopharynx had an obvious advantage. No post-partum depression, confusion, or 'hangover' as a result of Demerol medication occurred. No effect on the third stage was seen. Bleeding was not increased.

Of the 70 babies born to mothers when Demerol alone was used, 66 breathed spontaneously. No

babies showed any persistent cyanosis, evidence of narcosis, or otherwise merited the term 'sleepy baby' where this is meant to describe drug effects. Of the 80 babies born to mothers when Demerol in combination with other drugs was used, 69 breathed spontaneously and 10 breathed only after insufflation.

In the presence of apnea at birth, it is the usual practice to allow ordinary methods of cutaneous stimulation only a brief trial, usually not more than one minute, before resorting to insufflation to relieve anoxemia. It cannot be denied that the addition of barbiturates to Demerol analgesia has a slight to moderate depressant effect on the baby, but in the dosages recommended it is rarely of disturbing degree. Fetal narcosis was not a major factor in the apnea presented by these babies. All breathed and progressed normally after a brief period of artificial oxygenation.

The use of Demerol as recommended permits an elastic type of obstetric care during labor. Conduct of each case may be individualized in accord with the character and rapidity of labor; the de-

cision to institute amnesic therapy, with its additional nursing responsibility and possible risk to mother and baby, may be made relatively late, depending upon the reaction of each patient to the stress of labor.

ADDICTION AND HABITUATION

With any drug possessing morphine-like action on the central nervous system, serious consideration must be given to questions concerning the possibility of addiction. In the pain free, normal subject, the effects of Demerol are described variously, depending perhaps on the underlying psychologic makeup of the individual. In some the effect is pleasant, a sense of well-being or euphoria; in others, there is a disagreeable sense of insecurity or the occurrence of unpleasant dreams. Some subjects like the effect and want to repeat it, while in others the converse attitude occurs. Since this may involve the 'nitritoid' reaction, the position of the patient may influence the effect and subsequent use of the drug. The implications of the experience and the personality makeup of the individual are obvious.

Drug addiction is a condition in which a person has lost the power of self control relative to a drug. When a regularly pleasant effect leads to a strong desire for frequent repetition, psychic dependence or habituation is likely to result. An extension of such frequent and regular repetition of a drug as regards both dosage and interval of administration may lead to the development of physical dependence.

Physical dependence, a serious consequence of morphine abuse, is perhaps related to overcompensation by the autonomic nervous system in order to maintain homeostasis of certain vital functions disturbed by the drug. On discontinuation of the drug an abstinence syndrome consisting of characteristic signs and symptoms occurs. While physical dependence on Demerol has not yet been encountered in 'normal' persons, it has been produced in former addicts. However, because of the brief duration of the physical dependence action of Demerol and its lesser potency than morphine in this regard, the experimental production of physical dependence on Demerol is not easy even of such patients. For example, habituation but not

significant physical dependence resulted from the administration of 75 mg. of Demerol four times a day for a period of three months. Nor did clinically significant physical dependence develop when the drug was administered in amounts of 75 to 100 mg. eight times a day for four weeks to former addicts who had never before received Demerol. However, those who had had previous experience with Demerol developed definite physical dependence to the latter dosage after two weeks of readministration. On the other hand, when Demerol was clinically readministered to patients who were not former addicts, abstinence phenomena were not encountered on its subsequent discontinuation. While the implication of these results is not yet clear, they suggest that a somewhat different mechanism may be involved than that entailed in the development of physical dependence to morphine.

Demerol may produce physical dependence, however, physical dependence is not likely to result if the therapeutic requirement is not exceeded. On the other hand, it is not uncommon to note the development of physical dependence on morphine by patients requiring its use for a chronic ailment.

Such patients are not usually considered addicts in the sense that abuse of the drug is not an outstanding feature. Nevertheless, it is often difficult to distinguish between the actual necessity for morphine to alleviate the condition or satisfy the physical dependence. This experience agrees with the theoretical relationship to the development of physical dependence of the relative potencies and the durations of action of morphine and of Demerol, the latter being weaker and shorter in its physical dependence action.

If Demerol is abused by a former morphine addict, physical dependence is apt to result. This raises the question of whether or not the drug is of any value in the treatment of the morphine abstinence syndrome. Although it is conceded that the best drug for this purpose is morphine itself, Demerol also definitely modifies the syndrome and can be used satisfactorily in place of morphine for this purpose. Its ameliorative action is considerably briefer than that of morphine, and this must be taken into account in prescribing a rapid reduction treatment with the drug. Large frequent

doses are required when patients are being treated who have shown a strong dependence on morphine. For such patients Demerol is less satisfactory than morphine. Demerol is a satisfactory but it must be emphasized, however, that if Demerol is continued in the treatment of such patients, physical dependence may be shifted from morphine to this drug. Hence it is necessary to reduce the dose progressively. Furthermore, 'breaking the habit' in an individual case while under observation does not constitute a 'cure', since the psychiatric make-up of the patient remains unaltered and, unless corrected, drugs are resorted to again on discharge.

Himmelsbach (19,20) of the United States Public Health Service reported on thirteen morphine addicts who received Demerol instead of morphine for a period of ten days. The results indicated that Demerol only partially satisfied the physical dependence established to morphine. The abstinence syndrome following withdrawal not only was less severe by objective criteria than that of morphine or codeine, but the subjective complaints were markedly reduced. Some patients remarked that

the effect of medication was similar to atropine or hyoscine; the majority like the effects and considered the substitute a "good treatment" for withdrawal. In another experiment Demerol was administered to 4 former addicts in progressively increasing amounts. An average dose of 173 mg. was administered hypodermically at a mean interval of approximately 2¼ hours throughout each twenty-four hours for a total of ten or eleven weeks. On withholding the drug for twenty-two hours after one month of administration, mild signs of abstinence appeared. Nevertheless, the patients complained of no appreciable subjective discomfort. Following ten of eleven weeks of administration the drug was abruptly discontinued and there occurred withdrawal symptoms, less severe than those of morphine but of essentially the same order as those of codeine. It should be emphasized that the subjects in this study received daily as much as ten times the therapeutic dose of Demerol; also, because of the brief duration of dependence on Demerol and its lesser potency than morphine in this regard, the experimental production of physical dependence on

Demerol is not easy even for such patients. While the implication of these findings is not yet clear, they suggest that a somewhat different mechanism than that entailed in the development of physical dependence to morphine may be involved.

Inasmuch as a euphoric reaction occasionally follows the use of Demerol, it is logical to conclude that prolonged use in some individuals may lead to the development of psychic dependence or habituation. The drug appears to possess a lesser liability that morphine for the development of physical dependence. Clinical research on Demerol indicates that when it is administered for relief of pain in amounts not in excess of 150 mg. every three hours, habituation and physical dependence on the drug are not likely to occur. However, the medication should be used with caution inasmuch as in the absence of pain, physical dependence has been produced experimentally in former or active morphine addicts when daily amounts in excess of therapeutic dosages were administered for prolonged periods of time (upwards of 2 months).

DEMEROL UNDER THE NARCOTIC LAW

Demerol was brought within the purview of the federal narcotic laws by a law enacted by Congress and approved by the President, July 1, 1944. All manufacturers, wholesalers, retailers, and practitioners procuring, prescribing, or dispensing Demerol, if not already registered, must register in an appropriate class under the federal narcotic law. An inventory on appropriate forms of all Demerol on hand before July 1, 1944 must be submitted to the collector of internal revenue before September 1, 1944. Manufacturers must tax stamp each package before sale or removal. The effect of this law is to subject the use of Demerol to the same restrictions imposed on the use of narcotic drugs.

CONCLUSIONS

With the exception of cough and diarrhea, Demerol has been found to be a satisfactory therapeutic substitute for morphine. It appears to possess the following clinical advantages over morphine:

1. Its spasmolytic action makes it ideal for the relief of conditions due to smooth muscle spasem, in which morphine is pharmacologically contraindicated.
2. Its rapid dissipation tends to offset undesirable cumulative effects such as respiratory depression and urinary retention.
3. Prolonged use of Demerol may lead to the development of habituation, but it appears to possess a lesser liability than morphine for the development of physical dependence.
4. It may be used without fear in patients with severe anemia, disease of the liver or kidneys or bronchial asthma.
5. Demerol has proven to be a satisfactory obstetrical analgesic. There is an absence of pulmonary complications and freedom from depressant effect on the fetus. Satisfactory amnesia is ob-

tained and labor may be shortened by its use.

6. As a pre-anesthetic analgesic, Demerol presents the following advantages: Has fewer unfavorable side effects such as nausea, vertigo; will not depress respirations or other vital functions; and is more effective in drying secretions than morphine.

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