Demerol

HYDROCHLORIDE

Analgesic · Spasmolytic

Sedative

FOR ORAL AND
INTRAMUSCULAR
ADMINISTRATION

1

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DEMEROL

TRADEMARK REG. U.S. PAT. OFF. & CANADA

HYDROCHLORIDE

Brand of MEPERIDINE HYDROCHLORIDE

(Isonipecaine)

ANALGESIC • SPASMOLYTIC • SEDATIVE

For Oral and Intramuscular Administration

INTRODUCTION

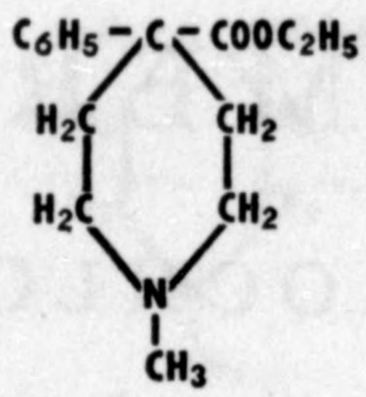
DEMEROL HYDROCHLORIDE is a synthetic compound which chemically and pharmacologically resembles both morphine and atropine. This unique combination of powerful analgesic action with spasmolytic and sedative effects accounts for its wide range of clinical application.

Demerol hydrochloride is indicated for the relief of severe pain regardless of etiology. However, since its analgesic effect is combined with spasmolytic action, it is particularly useful when pain is due to smooth muscle spasm.

The analgesic power of Demerol hydrochloride ranks between morphine and codeine, but carries with it considerably less risk of addiction than that inherent in morphine. The majority of patients do not acquire tolerance. The incidence of euphoria produced by Demerol hydrochloride, in the presence of pain, is about 10 per cent. Furthermore, respiratory depression from Demerol hydrochloride is uncommon, and the drug has no constipating effect.

CHEMISTRY

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



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 a short period of boiling.

Tests for the microchemical identification of Demerol hydrochloride have been described by Levine.[1] Demerol hydrochloride may be identified through formation of crystals with alkaloidal reagents. A doubly confirmatory test is available with a single reagent, in conjunction with scratching of test drops.

PHARMACOLOGY

ANALGESIC ACTION

Demerol hydrochloride possesses analgesic properties greater than ever before observed with synthetic compounds considered suitable for clinical use. This analgesic effect has been measured quantitatively in several experimental studies by a number of methods: in mice by the Von Killian technic; in rats by the tranquilizing technic of Barlow, by the potentiation of barbiturate hypnosis, and by the premedication effect in nitrous oxide anesthesia; in cats by the Eddy technic; in dogs and monkeys by observations on responses to stimulation; and in man by the Wolff-Hardy pain-threshold technic (Barlow,[2] Barlow, Climenko and Homburger,[3] Climenko[4]).

In a controlled study employing a modified Wolff-Hardy technic Barlow investigated the pain-threshold raising effect of Demerol hydrochloride on a group of individuals, and compared results with those obtained from morphine and codeine.

The percentage of elevation of the pain threshold after intramuscular administration of Demerol hydrochloride and after codeine medication is shown in Chart 1.

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1. Levine, J.: *Ind. & Eng. Chem.* (Anal. Ed.), 16:412, 1944; abstr. *Jour. Am. Pharm. Assn.* (Scient. Ed.), 34:90, Mar., 1945.
2. Barlow, O. W.: Unpublished data.
3. Barlow, O. W., Climenko, D. R., and Homburger, E.: *Proc. Soc. Exper. Biol. & Med.*, 49:11, Jan., 1942.
4. Climenko, D. R.: *Fed. Proc.*, 1:15, Mar. 16, 1942.

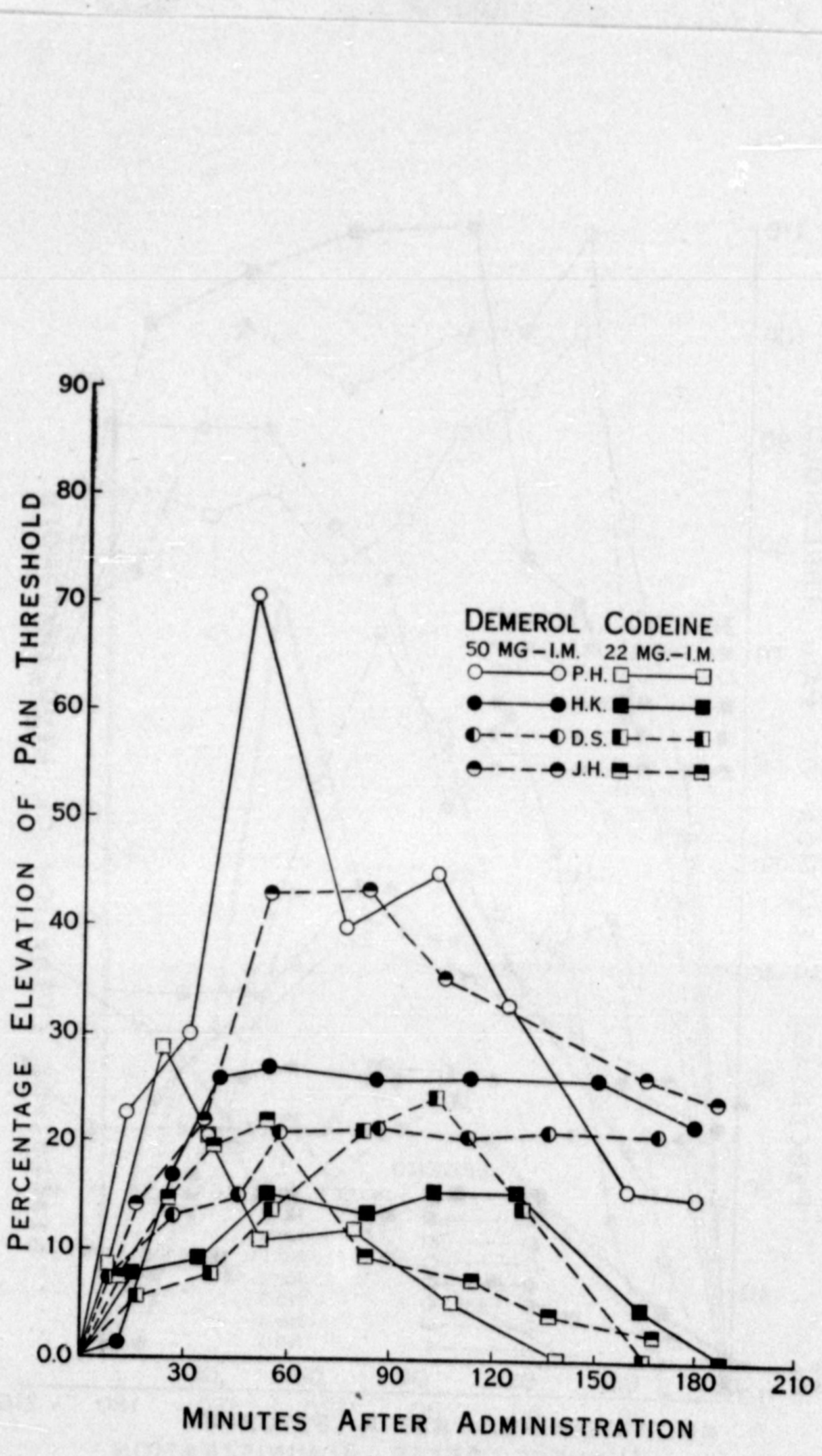

Chart 1. – Percentage of elevation of the pain threshold after intramuscular injection of Demerol hydrochloride and of codeine.

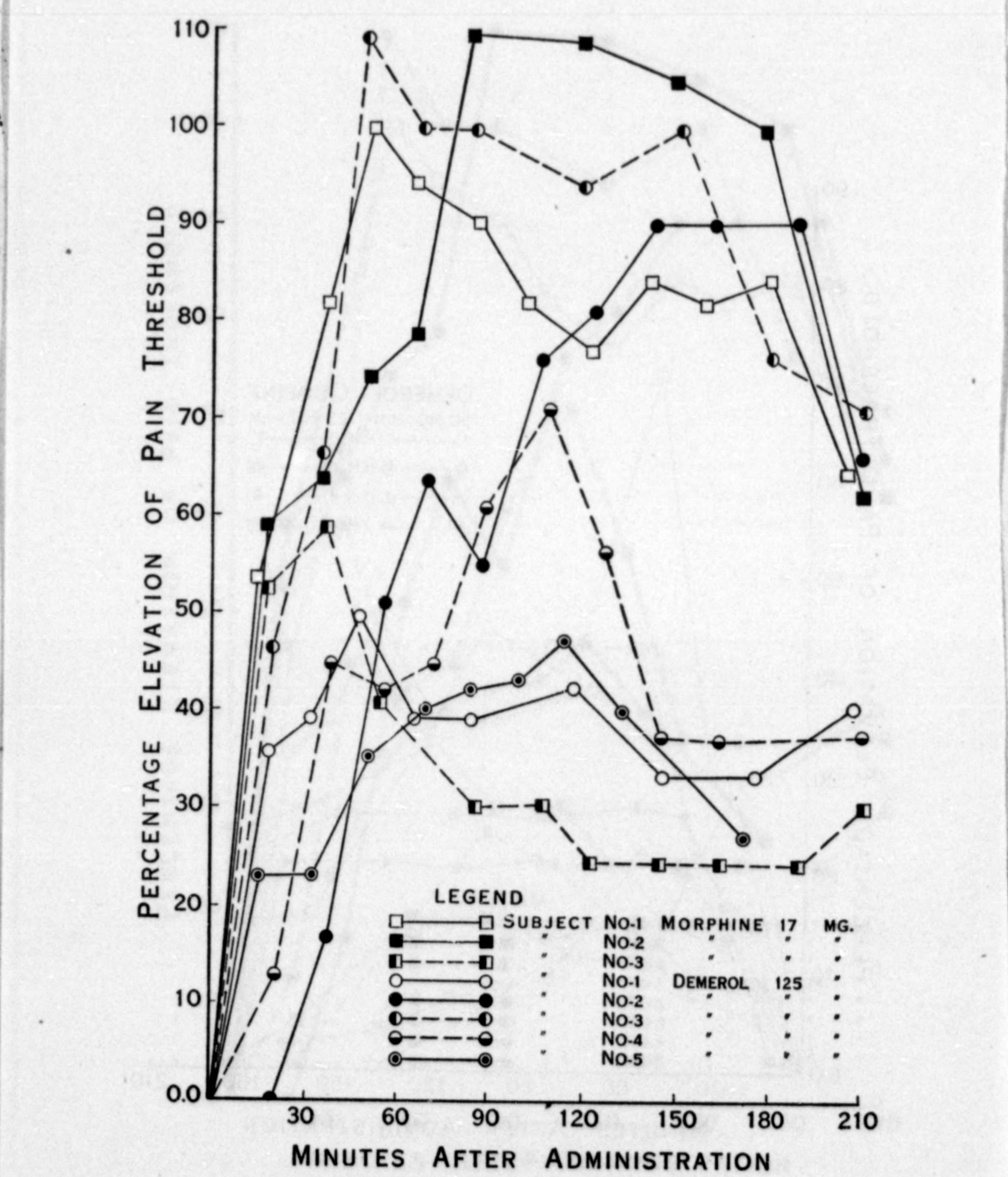

Chart 2. — Percentage of elevation of the pain threshold after intramuscular injection of Demerol hydrochloride and of morphine sulfate.

The percentage of elevation of the pain threshold after intramuscular administration of Demerol hydrochloride and of morphine sulfate is shown in Chart 2.

Woolfe and MacDonald,[5] using heat as pain stimulus in mice, found that Demerol hydrochloride can produce long lasting analgesia against mild pain stimuli, but is ineffective in mice against severe pain stimuli of the type used in their experiments.

While investigating the actions of Demerol hydrochloride, Way[6] noted pronounced corneal anesthesia when the compound was applied to the rabbit eye. The action obtained was essentially a local one, and was not due to the central actions of the drug. Subsequent studies on the local anesthetic properties of Demerol hydrochloride revealed that it possesses considerable specificity for nervous tissue when applied locally.

SPASMOLYTIC ACTION

Demerol hydrochloride 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 parasympathetic endings, but is primarily the result of a direct depressant effect on the muscles, and is comparable in this respect to the action of papaverine.

Intestine

The depressant action of Demerol hydrochloride has been demonstrated in a dilution of 1:10,000,000 on the isolated rabbit ileum using the Magnus preparation. The effect of pilocarpine and physostigmine on the intestinal segment was completely or temporarily abolished by the addition of an adequate amount of Demerol hydrochloride to the bath. The effect of Demerol hydrochloride in this respect was less than that of atropine. Histamine or barium chloride added to the drug-free or normal bath of the Magnus gut preparation produced a characteristic increase in motility and tone. These effects were promptly antagonized by Demerol hydrochloride, this antagonism being primarily due to a reversible direct muscular depression (Barlow,[2] Duguid and Heathcote[7]).

Yonkman, Noth and Hecht[8] reported balloon studies which they conducted twelve times in four trained, unanesthetized dogs with ileostomies or with Thiry-Vella loops of ileum. It was observed that the normal dog ileum was uniformly stimulated in tone, peristalsis and segmentation. These effects were evident even after atropine had rendered the intestine almost quiescent. However, if morphine had first been administered to activate the intestine, as was the case in six experiments, even to the point of vomiting, Demerol hydrochloride markedly depressed some phases of intestinal activity and especially segmentation.

The authors conducted similar studies in patients with ileostomies,

5. Woolfe, G., and MacDonald, A. D.: *Jour. Pharmacol. & Exper. Therap.*, 80:300, Mar., 1944.
6. Way, E. L.: *Science*, 101:566, June 1, 1945.
7. Duguid, A. M. E., and Heathcote, R. St. A.: *Quart. Jour. Pharm. & Pharmacol.*, 13:318, Oct.-Dec., 1940.
8. Yonkman, F. F., Noth, P. H., and Hecht, H. H.: *Ann. Int. Med.*, 21:7, July, 1944.

cecostomies, colostomies or with the indwelling Miller-Abbot tube at various levels of the gastro-intestinal tract. The results were opposite from those found in dogs inasmuch as Demerol hydrochloride failed to stimulate the human intestine but rather had a quiescent effect. Following administration of the drug normal peristaltic frequencies were aborted for almost forty minutes, after which morphine was capable of exerting its normal tone increasing or "splinting" effect upon the ileum. In contrast to morphine, cramp-like pain or colic was absent after Demerol hydrochloride injections.

There was no evidence of a lessened intestinal tone in any of the experiments conducted, save one, which developed gradually over a period of approximately one and one-half hours. The possibility of relaxation in the hyperactive or spastic human intestine was indicated by preliminary studies in three instances. Although previous experiments had demonstrated that Demerol hydrochloride exerted no spasmolytic effect on the pyloric sphincter of dogs, intubation studies in human subjects in various portions of the gastro-intestinal tract revealed an antispasmodic response.

In a subsequent publication Yonkman[9] pointed out that Demerol hydrochloride does not act as a "bowel splint" as does morphine. In the human gastro-intestinal tract it may either depress or arrest motility, and also exert a spasmolytic action on the tonic smooth muscle. Demerol hydrochloride may neutralize morphine spasms, but it does not prevent morphine's spasmogenic action. Demerol hydrochloride is similar to morphine in its central analgesic action although not quite as potent. It differs from morphine in producing a spasmolytic rather than a spasmogenic effect.

Bronchi

Barlow[2] found that bronchial spasm induced in guinea pigs by exposing them to a mist of histamine in a closed chamber can be prevented if Demerol hydrochloride is injected prophylactically. Doses of 10 mg. per kg. of body weight subcutaneously became effective within five minutes or less and the effects persisted for about an hour. With larger doses the effects lasted for from two to three hours. Bronchi of excised guinea pig lungs perfused according to the method described by Sollmann and Von Oettingen[10] were relaxed by Demerol hydrochloride.

Ureter

Climenko and Berg[11] studied the action of Demerol hydrochloride on the in situ perfused ureter of the dog and on the intact human ureter. Ureteral contractions were recorded by the method of Trattner which consists, in experimental animals, of the perfusion of the in situ ureter with normal Ringer-Locke solution and the recording of the ureteral contractions by means of a sensitive water membrane manometer. After recording the normal ureteral contractions of each day, histamine was administered and spasmodic contractions associated with a marked increase in tonus occurred. The intravenous administration of Demerol hydrochloride, 1 mg. per kg., after histamine stimulation resulted in the reestablishment of normal tonus

9. Yonkman, F. F.: *Anesth. & Analg.*, 23:207, Sept.-Oct., 1944.
10. Sollmann, T., and Von Oettingen, W. F.: *Proc. Soc. Exper. Biol. & Med.*, 25:692, May, 1928.
11. Climenko, R., and Berg, H.: *Jour. Urol.*, 49:255, Feb., 1943.

and inhibition of the amplitude of contractions. This phenomenon was observed repeatedly on 5 experimental animals.

Trattner's modification of this method for recording the contractions of the human intact ureter, with only the interference of an intra-ureteral catheter, was utilized in conjunction with a highly sensitive photo-electric recording device on a series of 14 patients who were subjected to cystoscopic examination for diagnostic purposes. Following the completion of the examination, the catheter was placed in the ureter with its tip immediately above the ureterovesical orifice. Normally occurring contractions were recorded for fifteen minutes, after which 75 mg. of Demerol hydrochloride were injected intramuscularly. Contractions were recorded as long after this as was deemed practicable. Results were consistent in all cases. Within ten minutes after the administration of Demerol, there was a 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 on the smooth muscle of the ureter was most marked in those cases in which the ureter was irritable initially or was in a state of heightened tonus; it was least marked in individuals showing an initial low tonus.

Uterus

In a study reported by Yonkman, Noth and Hecht,[8] isolated strips from guinea pigs, virgin and nonvirgin, were suspended in tissue baths containing Locke's solution, pH 7.5 to 7.6 at 39° C, and contractions were recorded on the kymograph. Demerol hydrochloride, in over 55 experiments, usually relaxed the segment which had previously been activated either by epinephrine 1:1,000,000 to 1:250,000; pitocin 1:125,000 to 1:50,000; histamine 1:10,000,000 to 1:1,000,000; barium chloride 1:10,000, or physostigmine 1:20,000. The degree of relaxation or inhibition depended upon the dose of the stimulant as well as that of Demerol hydrochloride. The drug was an effective spasmolytic in a dose of 1:100,000 on a uterus under strong histamine stimulation. Frequently, but not consistently, Demerol hydrochloride activated the flaccid, previously untreated uterine strip. These results confirmed previous work showing that the flaccid uterus may be stimulated, whereas relaxation usually ensues in the tonic or active segment.

Solomons and Widdess[12] found that Demerol hydrochloride increases the tone and contraction of the rabbit and guinea pig uterine muscle in which spasm has been induced by pituitrin.

The effect of Demerol hydrochloride upon the pregnant uterus of human beings has been studied by Abreu and his associates.[13] In patients at three to eight months' gestation Demerol hydrochloride had no significant effect upon uterine tone or activity.

EFFECTS ON HEART, CIRCULATION AND RESPIRATION

The administration of Demerol hydrochloride in doses of 50 and 150 mg.

12. Solomons, E., and Widdess, J. D. H.: *Brit. Med. Jour.*, 1:643, May, 1943; *Irish Jour. Med. Sc.*, sixth series, Dec., 1943, p. 637.
13. Abreu, B. E., Woodbury, R. A., Fried, P. H., and Torpin, R.: *Fed. Proc.*, 2:73, Mar., 1943.

at three or four hour intervals, as it is used clinically in human beings, produces mild circulatory or respiratory effects only in occasional instances. Toxic doses, however, administered to experimental animals have a pronounced action on the heart, circulation and respiration.

When the isolated frog heart is perfused in situ as described by Barlow and Sollmann[14] Demerol hydrochloride 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. In dilutions of from 1:5000 to 1:50,000, Demerol hydrochloride 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 hydrochloride 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 therefrom occurs more rapidly than from the parasympathetic effect (Barlow[2]).

Duguid and Heathcote[7] demonstrated direct action of the drug on the cardiac musculature by means of a modification of Symes' perfusion method using isolated frogs' hearts. An atropine-like action on the vagus mechanism was confirmed by perfusion experiments with various concentrations of arecoline and Demerol hydrochloride and arecoline. Similar experiments were performed with rabbits using Gunn's method of perfusion, and a direct depressant action was also observed in this case. The amplitude was affected to a greater degree than was the rate of the beat, and the action of acetylcholine was abolished by the presence of Demerol hydrochloride. From the tests carried out it appeared that Demerol possesses the same twofold action on the mammalian as on the frog heart, namely, a direct depressant effect on the cardiac muscle itself and the power of antagonizing the effects of acetylcholine. In addition, Demerol was found to dilate the vessels of the coronary circulation, probably by direct action on the walls of the arterioles.

The effects of Demerol hydrochloride on heart rate, blood pressure and respiration were studied in anesthetized cats. Large doses, 5 mg. or more per kg., always produced an immediate and moderately prolonged fall of blood pressure, together with a reduction in the pulse rate. The blood pressure, though the initial fall might be large, returned in time to, or nearly to, its original level; this was succeeded by a second and much more gradual fall. The pulse rate, after its initial reduction, recovered its original frequency more rapidly than the blood pressure. Smaller doses, 1 to 2 mg. per kg., produced inconstant effects on the blood pressure and no change in the pulse rate. Repetition of these doses, however, proved cumulative, causing a gradual fall of blood pressure similar to the second reduction in the case of large doses. With a total dosage of 6 mg. per kg., whether given in one or in several doses, stimulation of the vagus failed to affect the blood pressure though a slight reduction of the pulse rate was still observed.

The respiration was invariably affected in any dosage greater than 1 mg. per kg. With smaller amounts the result was a slight, though prolonged slowing of the rate. With a single dose of 5 mg. per kg. the immediate effect was a

14. Barlow, O. W., and Sollmann, T.: *Jour. Pharmacol. & Exper. Therap.*, 28:325, Sept., 1926.

great reduction in both rate and amplitude of the chest movements, together with some degree of irregularity. With a single dose of 10 mg. per kg. the respiration was immediately and permanently arrested. When the total dosage had reached about 8 mg. per kg., the respirations, after becoming progressively slower, sometimes stopped altogether. While natural respiration was still continuing, the apnea resulting from vagus stimulation was not affected by injection of the drug. Epinephrine still retained, partially at least, its action on the blood pressure even after Demerol hydrochloride had been given to the extent of 30 mg. per kg.

Similar results were obtained by Gruber, Hart and Gruber[15] in dogs. Doses of Demerol hydrochloride as low as 0.25 mg. per kg. given intravenously to dogs usually produced a fall in blood pressure, due primarily to peripheral vasodilatation. The intensity of the effect was dependent upon the dose and the rate of injection of the drug. Respirations were temporarily decreased in depth and frequency. Repetition of small doses at intervals of about fifteen minutes ultimately led to death by respiratory failure. The spleen and intestines increased in volume while the extremities showed a decrease in size. This was due to powerful contractions of the intestinal smooth muscle. After a preliminary increase, the kidneys decreased in size, owing to the fall in blood pressure. Depression of the irritability of the cardiac vagus nerve was usually observable, the drug probably acting on the postganglionic vagal nerve endings.

EFFECTS ON THE CENTRAL NERVOUS SYSTEM

In clinical use Demerol hydrochloride has a marked analgesic and mild sedative effect. Toxic doses, however, produce central stimulation. This has been demonstrated in experimental animals as well as in human beings. Barlow[2] showed that the oral administration of Demerol hydrochloride 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 hydrochloride 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 administration of Demerol hydrochloride. On the other hand, Demerol hydrochloride 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.

Toxic doses administered subcutaneously to mice produce marked central stimulation. According to Duguid and Heathcote,[7] the excitement which is followed by clonic convulsions is apparently attributable to a stimulation of

15. Gruber, C. M., Hart, E. R., and Gruber, C. M., Jr.: *Jour. Pharmacol. & Exper. Therap.*, 73:319, Nov., 1941.

the cortex. The carriage of the tail resembles very closely the S-shaped position described in connection with morphine and similar drugs. The larger the dose, the more the tail is arched over the back. The respiratory rate was diminished from the commencement of the experiment, and death was due to failure of respiration. Thus, the effects of Demerol hydrochloride on the central nervous system of the mammal may be explained as the result of cortical stimulation followed by depression, together with a primary depression of the medulla. As the animals showed no symptoms of central depression until very late in the experiment, evidence of any narcotic action of the drug was lacking. Similarly, with nonfatal doses the only appearances were those of stimulation rather than of depression. It was observed that when painful stimuli were applied to the animals treated with Demerol hydrochloride the response was much less than that of untreated animals.

Rats given one-third of a minimal lethal dose subcutaneously daily for six days showed no lessening of the degree or duration of excitement produced by the last dose, as compared with the first dose.

Andrews[16] pointed out that Demerol hydrochloride has a profound effect on the human central nervous system when used in excessively large doses. The author studied the cortical effects of repeated doses of Demerol hydrochloride on 5 former addicts who had received no drugs for at least six months. Brain potentials were studied with a four-channel electro-encephalograph, recording on photographic paper. Tremors were recorded from the right index finger using the photo-electric recording method which permits free finger movements with no appreciable loading. Demerol hydrochloride was given in initial doses of 100 mg. Thereafter the men chose their dosages and intervals, limits of 300 mg. and one and one-half hour intervals being imposed. Many of them increased the dose to from 2000 to 3000 mg. daily after they had taken the drug for from fifty to seventy days. Electro-encephalograms (EEG) were taken each week and at fifteen day intervals following withdrawal until the records returned to prestudy types.

Each case showed grossly the same clinical picture, varying only in details. The common findings were constipation, exaggerated tremors, graduating into muscle twitches and finally gross jerking of the extremities, hallucination, increased sensitivity to sudden noise, and weakness in the extremities. The EEG's also followed the same course in each case. Slow waves were seen early in the study and became progressively slower and of greater amplitude, persisting for about forty-eight hours after withdrawal and slowly returning to normal. The tremor records showed some rhythms at frequencies not far from normal with large swings occurring at irregular intervals. It has been shown that in normal persons the frequency of finger tremors is almost identical with cortical frequencies, and that lesions below this level may result in an almost complete dissociation of these frequencies. The tremors recorded after Demerol administration show in general a component having a frequency not far from that of the cortical rhythms, but not corresponding as closely as in the normal. There is no cortical component corresponding to the large twitches regularly recorded from the finger. The complete dissociation of this component of the tremor suggests that the lower nerve centers are strongly involved, in fact may be the primary seat of drug action, for after

16. Andrews, H. L.: *Jour. Pharmacol. & Exper. Therap.*, 76:89, Sept., 1942.

withdrawal of the drug the cortical rhythms return to normal more quickly than does the tremor.

EFFECT ON PUPIL, SALIVARY GLANDS AND BLOOD SUGAR

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 hydrochloride. 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 (Barlow[2]).

ACUTE TOXICITY

Demerol hydrochloride has been found to be relatively nontoxic. Eisleb and Schaumann[17] report the minimum lethal dose of Demerol hydrochloride 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 and his associates[15] reported the $L.D._{50}$ per kg. of Demerol hydrochloride 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. Duguid and Heathcote[7] state that the minimum lethal dose in frogs appears to be between 250 and 300 mg. per kg. on intralymphatic injection. In mice they found the minimum lethal dose to be 160 mg. per kg. on subcutaneous injection and 125 mg. per kg. on intraperitoneal injection.

Litter and Tornio[18] found the 50 per cent lethal dose of Demerol in mice to range between 42.5 and 50 mg. per kg. by Trevan's method and between 44.2 and 55.3 by Gaddum's method.

CHRONIC TOXICITY

Barlow[2] administered Demerol hydrochloride in a dose of 75 mg. per kg. to 8 adult dogs and 40 mg. per kg. a day to 24 monkeys 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 liver, kidneys, spleen,

17. Eisleb, O., and Schaumann, O.: *Deutsche med. Wchnschr.*, 65:967, June 16, 1939.
18. Litter, M., and Tornio, A.: *Semana méd.*, 50:615, 1943; abstr., *Jour. Am. Pharm. Assn.* (Scient. Ed.), 33:202, July, 1944.

gastric mucosa, or bone marrow were noted. In another experiment which consisted of daily intramuscular administrations of Demerol hydrochloride 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, Hart and Gruber[15] studied the effect of excessive doses of Demerol hydrochloride 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.

Demerol hydrochloride had 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 (Barlow[2]).

The lack of chronic toxicity has been pointed out also by a number of clinical investigators. Batterman[19] found that prolonged use of Demerol hydrochloride (over one month) resulted in no alteration of the hematopoietic system or impairment of kidney function. In his series of 1119 hospitalized patients there was no alteration in the electrocardiogram and basal metabolic rate, and the blood pressure and ventricular rates were unaffected.

Hecht, Noth and Yonkman,[20] who administered Demerol over periods up to 211 consecutive days, state that regular urinalyses, blood counts, electrocardiograms and liver function tests showed no alteration attributable to the drug. Hoffman[21] also mentions that Demerol hydrochloride does not affect blood pressure, hemoglobin, red cells, white cells or differential counts.

ABSORPTION AND EXCRETION

Demerol hydrochloride is absorbed rapidly when administered intramuscularly or orally. This is evident from its clinical effectiveness (within fifteen and twenty or thirty minutes, respectively) as well as from laboratory studies. The drug is very speedily absorbed when administered intralymphatically to frogs, the effect becoming visible within a few minutes after administration (Duguid and Heathcote[7]).

Barlow[2] believes that Demerol hydrochloride is destroyed very rapidly by the liver and to a lesser extent by other tissues such as muscles and the central nervous system. He suggests as a possible metabolic mechanism a deesterification of the molecule on hydrolysis of the ethyl ester. This hydrolysis occurs readily in vitro and may conceivably occur under in vivo conditions.

The urinary excretion of Demerol hydrochloride has been studied by Lehman and Aitken[22] and by Oberst.[23] These authors described a method of

19. Batterman, R. C.: *Fed. Proc.*, 1:143, Mar. 16, 1942; *Tr. Am. Therap. Soc.*, 42:133, 1942; *Arch. Int. Med.*, 71:345, Mar., 1943.
20. Hecht, H., Noth, P. H., and Yonkman, F. F.: *J.A.M.A.*, 121:1307, Apr. 17, 1943.
21. Hoffman, R.: *Jour. Indiana Med. Assn.*, 36:135, Mar., 1943; *Anesth. & Analg.*, 22:336, Nov.-Dec., 1943.
22. Lehman, R. A., and Aitken, T.: *Jour. Lab. & Clin. Med.*, 28:787, Mar., 1943.
23. Oberst, P. W.: *Jour. Pharmacol. & Exper. Therap.*, 79:10, Sept., 1943.

determining the drug in the urine. The method depends upon the formation of a benzene soluble compound between the free base of Demerol hydrochloride and bromthymol blue (dibromthymolsulfonphthalein), in an equimolar ratio.

The percentage excretion of Demerol in 10 post-addicts not requiring an analgesic varied, as determined by this method, between 2.2 and 21.2 per cent when doses of from 300 to 800 mg. were administered daily. The average for 273 analyses was 9.1 per cent. Tolerance was not a factor influencing Demerol excretion. The excretion of Demerol after single doses of 100 mg. was, after twenty-four hours, about the same as in patients receiving daily multiple doses varying from 300 to 800 mg. About 72 per cent of the total amount of detectable Demerol in urine was excreted within seven hours after a dose (Oberst[23]).

Oberst's method for the determination of Demerol hydrochloride in urine is a modification of that described by Lehman and Aitken and consists of the following steps:

Urine must be fresh or preserved with mercuric chloride (0.5 Gm. per 24 hour sample) and kept cold. The pH of the mixture of urine and phosphate buffer must be adjusted to approximately 7.5 by the addition of sufficient amounts of alkali. To determine the amount of alkali to be used 5 cc. of urine (or an aliquot portion diluted with water to 5 cc.) are placed in a test tube with 5 cc. phosphate buffer (pH 7.5) and 2 drops of stock bromthymol blue solution. The color of the resulting solution should be greenish blue to blue. If it is yellow or yellowish green, 0.5 N NaOH is added from a pipette until the desired color is obtained. After determining the amount of alkali needed for the preliminary test, the same amounts of urine, water, phosphate buffer and alkali (but no indicator) followed by 20 cc. of benzene are placed in a 50 cc. separatory funnel. This mixture is agitated gently for three minutes and then allowed to stand until the benzene separates from the aqueous layer. Then 10 cc. of the benzene extract are decanted into a 10 cc. graduate cylinder and transferred to a 25 cc. separatory funnel containing 5 cc. of the buffered bromthymol blue solution. This mixture is also agitated for three minutes and then allowed to stand until the benzene separates from the blue aqueous solution, which is drained off and discarded. The benzene solution, which is light yellow in color, is poured from the top of the funnel into a special test tube used for reading in the Evelyn photoelectric colorimeter. After standing several hours or over night in the stoppered tubes for clearing of any moisture held in suspension, the color intensity is read in the colorimeter, using a filter having a mean wave length of 420 millimicrons of the transmitted band. The center setting for the apparatus is obtained by adjusting the galvanometer to 100 with a benzene extract made of the reagents in the absence of Demerol. The galvanometer reading (per cent transmission of light through the solution) is converted into milligrams of Demerol by means of a graph.

TOLERANCE AND HABITUATION LIABILITY

With any drug producing morphine-like action on the central nervous system, consideration must be given to the possibility of psychic dependence or habituation, and physical dependence or addiction. In the pain-free normal

subject, the effect of Demerol hydrochloride is dependent upon the psychologic make-up 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. These sensations are neither consistent nor predictable.

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 resulting from the bona fide use of Demerol hydrochloride has not yet been encountered in normal persons.

Clinical investigation in a number of prominent and exceptionally well controlled clinics, comprising many thousands of patients (some of whom received Demerol hydrochloride for from several months to a year), has demonstrated no physical dependence upon withdrawal, nor has tolerance to parenteral administration of the drug been manifest.

Batterman[19] reported that in a group of 115 hospitalized patients treated at Bellevue Hospital for a period of from four to twenty-eight weeks, who received from 42 to 492 doses of Demerol hydrochloride, there was no evidence suggesting tolerance to general clinical analgesia. Further, in patients receiving Demerol hydrochloride for as long as three months, withdrawal symptoms did not occur. In a few instances, however, because of the analgesic and sedative effect, or the occurrence of euphoria, a desire for the drug was expressed. It was felt that physical dependence is not likely to occur if the therapeutic requirement is not exceeded. In a subsequent publication,[24] based on 4000 patients, Batterman concludes that Demerol hydrochloride possesses a lesser liability for the development of physical dependence than any opiate.

Hoffman[21] doubts that Demerol hydrochloride could become habit forming except in rare instances. He has never encountered a patient who had any difficulty in stopping the use of Demerol hydrochloride at any time. Hoffman also states that with careful management tolerance may be avoided or effectively deferred.

Christie[25] did not observe addiction in any of his 335 cases. Noth, Hecht and Yonkman,[26] however, observed withdrawal symptoms in 9 of 21 patients who had received Demerol hydrochloride for varying periods of time. The withdrawal of the drug and the substitution of one of the opiates were followed by certain undesirable symptoms suggesting the possibility of addiction to Demerol hydrochloride. Reactions on withdrawal of Demerol hydrochloride consisted of nausea, vomiting, perspiration, jerking and tremor of muscles, nervousness, irritation, depression and itching of the skin. The authors conclude that the drug may possess addictive properties but these are apparently not as marked as those of some of the opiates, morphine and its derivatives.

24. Batterman, Robert C.: *Connecticut Med. Jour.*, 8:13, Jan., 1944.
25. Christie, R. V.: *Lancet*, 1:294, Mar. 9, 1943.
26. Noth, P. H., Hecht, H. H., and Yonkman, F. F.: *Ann. Int. Med.*, 21:17, July, 1944.

Addiction and tolerance have been produced experimentally in morphine or other opiate addicts who were permitted to use Demerol hydrochloride indiscriminately in huge doses.

Himmelsbach[27] of the United States Public Health Service reported on 13 morphine addicts who received Demerol hydrochloride instead of morphine for a period of ten days. The results indicated that Demerol hydrochloride 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 liked the effects and considered the substitute a "good treatment" for withdrawal. In another experiment Demerol hydrochloride 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 two and one-quarter 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 or 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 hydrochloride; also, because of the brief duration of dependence on Demerol hydrochloride and its lesser potency than morphine in this regard, the experimental production of physical dependence on Demerol hydrochloride 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.

From this and a subsequent study Himmelsbach[28] concluded that Demerol hydrochloride possesses a lower order of addiction liability than morphine. He pointed out that even though the extent of the difference in addiction liability of the drugs given in equally effective clinical doses for the control of pain has not yet been estimated, it appears that Demerol hydrochloride would be the safer of the two drugs.

Andrews[29] studied the development of tolerance to Demerol hydrochloride administered in repeated doses at the United States Public Health Service Hospital at Lexington, Ky. Subjects for the experiment were 4 patients who had been addicted to opiates but who had received no drugs for at least nine months. The Hardy-Wolff pain threshold method was used.

The effect of an initial dose of 100 mg. of Demerol hydrochloride on the pain threshold was determined. Thereafter, the men were allowed to determine the dosage and frequency of administration, with limits of 300 mg. per dose and at minimum intervals of one and one-half hours. All of them took

27. Himmelsbach, C. K.: *Fed. Proc.*, 1:153, Mar. 16, 1942.
28. Himmelsbach, C. K.: *Jour. Pharmacol. & Exper. Therap.*, 79:5, Sept., 1943.
29. Andrews, H. L.: *Jour. Pharmacol. & Exper. Therap.*, 75:338, Aug., 1942.

the drug at fairly regular intervals in gradually increasing doses. A pain threshold determination was made each week on three of the patients and at less regular intervals on the fourth.

The magnitude of the pain-threshold-raising effect of the initial dose of 100 mg. was different in each case. However, there was always a marked reduction in the effect as the study progressed. Tolerance to the drug developed rapidly and at the end of eight weeks there was a reduced response from a dose considerably greater than that originally used. As tolerance developed, the time at which the threshold-raising effect reached a maximum decreased progressively. Since this time depends to some extent upon the relation between the rate of absorption and the rate of removal of the drug, it appears that tolerance is accompanied by or is the result of changes in the rate of drug utilization. Tolerance had nearly reached a maximum at the end of eight weeks. The most striking result was the failure of a single test dose (100 mg.) to produce a threshold-raising effect for at least thirty days after withdrawal.

After forty-five days of abstinence, one patient continued to show no effect, two showed a small irregular effect, and one gave a response almost equal to that obtained from the first dose. The tolerance developed to Demerol hydrochloride appeared to be less permanent than that developed to morphine.

WARNING: MAY BE HABIT FORMING

Inasmuch as a euphoric reaction occasionally follows the use of Demerol hydrochloride, 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 than any opiate for the development of physical dependence. The following additional cautionary statement would therefore seem to be in order:

Clinical research on Demerol hydrochloride 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 compound 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 two months).

CLINICAL USE

Demerol hydrochloride possesses three main properties — analgesic, antispasmodic and sedative actions. The analgesic action approaches that of morphine in effectiveness. The antispasmodic action of Demerol hydrochloride offers a definite advantage over the opiates; it not only contributes to the rapid and often dramatic relief of colicky pain, but also obviates the undesirable constipation commonly seen after opiate therapy. The sedative action is definite but not marked. Restlessness is generally effectively relieved and in the majority of patients sleep is induced following parenteral administration.

In a study on the clinical effectiveness and safety of Demerol hydrochloride, Batterman[19] reported on the use of this drug in more than 1000 patients, comprising over 10,000 injections and a similar number of oral doses. For the average patient 100 mg. of Demerol hydrochloride proved satisfactory and resulted in a good analgesic effect in 88 per cent of the trials following parenteral administration, and in 66 per cent following oral administration. The drug was used in the treatment of pain due to surgical conditions in 824 patients and due to medical conditions in 406 patients. The majority of the patients received the drug for less than a week, but in 60 patients it was possible to study the effect for over a period of one month.

The results showed that following oral administration of Demerol hydrochloride an analgesic effect is apparent within from twenty to sixty minutes, and after parenteral administration within fifteen minutes and lasts from two to six hours with an average duration of three hours. In either case the analgesia lasts for from one to several hours with an average duration of three hours. Pain of visceral origin is relieved for longer periods of time than pain arising from skeletal or neural structures.

MEDICINE

Demerol hydrochloride has been employed successfully for the relief of severe pain and as a spasmolytic in a large variety of conditions. These include biliary colic, renal colic, gastro-intestinal colic, bronchial asthma, pleuritic pain of various etiologies, cardiovascular pain such as severe anginal syndrome and distress of congestive heart failure, hypertensive headache, arthritic pain, and various painful neurologic conditions such as sciatica, tabes dorsalis and radiculitis.

Visceral, Cardiovascular, Neuromuscular and Arthritic Pain

Batterman[19] found Demerol hydrochloride very effective for the control of pleuritic pain of all etiologies; sciatica, tabes dorsalis and radiculitis; cardiovascular pain, such as severe anginal syndrome and distress of congestive heart failure; and visceral or colicky pain of biliary, renal and gastro-intestinal origin. For the latter type of pain the drug appeared to be an ideal one since it combines an analgesic effect with an antispasmodic action. It was possible to demonstrate this effect in 23 of 27 human subjects by means of direct intubation studies with balloons in various portions of the gastro-intestinal tract. With from 50 to 100 mg. intramuscularly complete cessation or diminution of motility occurred usually within ten minutes and at times lasted from fifteen to ninety minutes. This effect is exactly the reverse of the one noted with morphine. It did not appear to be as great as after atropine but possessed the same gradient on stomach, ileum and colon in the order named.

For the average patient 100 mg. of Demerol hydrochloride proved a satisfactory dose resulting in a good effect in 88 per cent of the trials following parenteral administration and 66 per cent following oral administration (equivalent to an effect obtained with 50 mg. intramuscularly). In many instances where an opportunity presented itself for a comparison with morphine, it was apparent that 100 mg. of Demerol given intramuscularly equaled the effect of 10 mg. of morphine but the duration of action was shorter.

In a subsequent publication based on 4000 cases Batterman[24] pointed out that Demerol hydrochloride — in contrast to morphine — may be used relatively freely for the relief of the severe pain of malignancies or chronic hopeless diseases with little if any occurrence of general tolerance to the analgesic effects. For the relief of pain arising from spasms of smooth muscle, as in renal and biliary colic, Batterman found Demerol hydrochloride at least or even more effective than morphine, since in contrast to morphine, Demerol hydrochloride is a potent antispasmodic drug. Relaxation of smooth muscle spasm whether gastro-intestinal, biliary or renal can be achieved within ten minutes after administration of 100 mg. intramuscularly. In addition to this spasmolysis, the central analgesic effects and sedative action contribute to the excellent relief of such pain.

Chronic nerve pain 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 Batterman found that Demerol hydrochloride is superior to morphine. In many instances, where appropriate doses of Demerol hydrochloride were administered at regular intervals of three hours, the pain often abated to such a degree that the question arose whether further medication was necessary or whether the patient was psychoneurotic and magnified his complaints.

For chronic chest conditions where the use of codeine or morphine is undesirable because of depression of the cough reflex, Demerol hydrochloride has proved itself to be more than satisfactory.

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

Demerol hydrochloride 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 an arsenoxide-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.

Heldt, Dallis and O'Connell[30] described the use of Demerol hydrochloride in 22 cases receiving a total of 165 artificial fever treatments in the Kettering hypertherm. The youngest patient was 17 years and the oldest was 65 years of age. Treatments were usually given at weekly intervals with the temperature maintained between 105° and 107° F for three to five hours. Most of the patients had syphilis of the central nervous system.

An initial dose of 100 mg. of Demerol hydrochloride was given intramuscularly as the patient was placed in the Kettering hypertherm. Blood pressure readings were recorded before the patient entered the cabinet and at half hour intervals thereafter. Temperature, pulse and respirations were recorded at fifteen minute intervals throughout the entire procedure. None of

30. Heldt, T. J., Dallis, N. P., and O'Connell, W. J.: *Amer. Jour. Psychiat.*, 101:789, May, 1945.

these recordings showed any significant change as a result of the injection of Demerol hydrochloride. A second dose of 100 mg. was again given parenterally between two and three hours after the first dose. Most patients were able to be carried comfortably throughout each treatment without the need for an additional amount. A third injection of 50 or 100 mg. was required at another two to three hour interval on an average of one of every seven treatments. Objective and subjective improvement in the general comfort of the patient was noted approximately fifteen minutes following each injection of Demerol hydrochloride. The usual apprehension so often seen in the hyperpyrexia patient was noticeably allayed by Demerol hydrochloride. In addition, there was little tendency to delirium, with its resulting confusion. The fact that the sleep induced by Demerol hydrochloride was not deep made management of the patient less difficult. The patient could be easily awakened to take liquids and to follow whatever instructions were necessary in his care. In 5 cases Demerol hydrochloride was compared with the use of barbiturates. In all such clinical comparisons Demerol hydrochloride was found to be superior from a standpoint of management, safety and comfort of the patient.

Hoffman[21] used Demerol hydrochloride for a small group of cases of widely varying types of pain. Six patients (with arthritis, myositis or neuritis), all of whom had been forced to stop working from time to time, were enabled to remain regularly at work for three months (to the date of writing of the paper) with an average of 2 tablets of Demerol hydrochloride daily by mouth, and 0.5 cc. intramuscularly about twice weekly. Salicylates were added after a successful trial of three weeks on Demerol hydrochloride alone. Five patients with "slipped" intervertebral discs were able to resume their work for about two weeks until arrangements were made for surgery. Two patients with unrelieved, intense, localized pain along the spine, following spinal fusion performed in the hope of relief, were kept sufficiently free from pain for five months to permit regular employment. Five patients with coronary sclerosis, 2 of whom had experienced previous myocardial infarctions, were given 0.6 cc. of Demerol hydrochloride intramuscularly one-half hour prior to dental extractions and drilling, and none experienced enough pain during the dental procedures to constitute shock. Thoracentesis was performed relatively painlessly in 3 cases using Demerol hydrochloride but no local anesthesia. Spinal puncture was also performed with relatively little pain in 7 of 8 patients who received only Demerol hydrochloride as an analgesic. Root pains in 2 patients with tabes dorsalis were greatly relieved by Demerol hydrochloride. One patient, a truck driver who had been unable to keep a steady job because of unpredictable intense pains, has been able to keep at continuous employment by reporting for injection of Demerol hydrochloride as soon as the pain appeared. Demerol hydrochloride was used over a period of four months in 4 cases of nonoperable carcinoma and relief was second only to that produced by morphine; 3 of the patients were satisfied with Demerol hydrochloride alone, using but slightly increased dosage, and the fourth required morphine from time to time.

In his second evaluation of Demerol hydrochloride, Hoffman points out that the drug's low sedative ratio and high analgesic index characterize it as a favored analgesic for ambulatory patients. The author found that Demerol hydrochloride relaxes effectively the smooth muscle of the gastro-intestinal 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 hydrochloride was utilized in 5 cases of colicky enteritis, in 4 cases of suspected appendicitis and in 1 case of ruptured duodenal ulcer. The combined analgesia and spasmolysis were found valuable in asthma and other respiratory tract pains, especially pleuritis, in biliary and ureteral tract spasms, for controlling labor pains and for relieving angina pectoris. It also proved equally effective in pain from faulty skeletal structure, especially of the spine. Forty-eight "backs" were treated, including old vertebral body fractures, ruptured intervertebral discs, spondylolisthesis, spinal fusions with complications, and hypertrophic spondylitis.

Fifteen months of observation led to the conclusion that oral administration of the drug should be used to keep the pain threshold at a high level, but in cases of severe pain the injection method should be applied. Demerol hydrochloride can be given every four hours, 2 tablets per dose. As there is no cumulative action, the dosage of 400 mg. (8 tablets) per day should suffice. If not, the injectable form is used, commencing with 25 mg. every four hours or until relief occurs. More severe pains may require a gradually doubled dosage.

Fitzgerald and McArdle[31] reported on 12 patients suffering from severe pain arising from diverse types of neurologic conditions who were selected for treatment with Demerol hydrochloride. The different types of pain were classified into the following groups: (1) pain of peripheral origin, 5 cases; (2) pain of central origin, 3 cases, and (3) pain during and after operation, 3 cases.

In 10 of the 12 cases Demerol hydrochloride was given intravenously; in 8, 100 mg. were given; in 1, 66 mg., and in another, 50 mg. One patient also received, on a separate occasion, 150 mg. of Demerol hydrochloride intravenously. Four patients were given the drug subcutaneously; the dose in 3 of these was 100 mg. and in one 50 mg. Four patients received the drug orally, in doses of 50 mg. in 3 cases and of 100 mg. in 1 case. Whenever the drug was used intravenously, the injection was given slowly, taking from two to four minutes. In all but one case, by whatever route Demerol hydrochloride was given, some degree of relief from pain resulted. The shortest duration of relief followed an intravenous injection of 100 mg.; relief lasted only thirty-six minutes. Relief for thirty hours followed a subcutaneous injection of 100 mg. The average duration of relief was between six and eight hours and was often accompanied by sleep.

The pain response to Demerol hydrochloride was excellent in 8 of the 12 cases. In 3 cases relief was considerable, although pain was not entirely abolished and the duration of relief was not beyond four hours. The only patient who did not obtain relief was a highly emotional subject who had been accustomed to considerable amounts of opium and rather resented receiving a different drug.

31. Fitzgerald, G., and McArdle, B.: *Lancet*, 1:296, Mar. 6, 1943.

The authors compared the relief after Demerol hydrochloride with that following ¼ grain of morphine in 7 cases. With morphine, all the patients received considerable relief, but it was less definite and of shorter duration than that following Demerol hydrochloride. Codeine tablets and other similar analgesics gave much the same relief as Demerol hydrochloride given orally in 50 mg. doses, but the period of relief was shorter than with Demerol hydrochloride.

Branwood[32] administered Demerol hydrochloride for the relief of pain in a series of 23 cases. The drug was given orally, subcutaneously, intramuscularly and intravenously, the usual dosage being 50 mg. Pain due to muscular spasm was invariably relieved by Demerol hydrochloride, as shown in cases of hypertensive headache, post-concussional headache, renal colic, Dietl's crisis, intestinal colic, biliary colic and Buerger's disease. Pain was not relieved to any extent in cases of lymphadenomatous bone deposits, acute purulent cholecystitis, sciatica, hepatico-lenticular degeneration, and spondylitis ankylopoietica. The intravenous route appeared to offer no advantages since the drug acted with sufficient rapidity after subcutaneous and intramuscular administration.

Batterman and Himmelsbach[33] conclude from their own extensive experience with Demerol hydrochloride and the reports published up to the beginning of 1943 that with the exception of the negative results in relief of cough and diarrhea, Demerol hydrochloride is a satisfactory therapeutic substitute for morphine. It appears to possess the following advantages over morphine: (1) Its spasmolytic action makes it ideal for the relief of pain due to smooth muscle spasm, in which morphine is pharmacologically contraindicated. (2) Its rapid dissipation tends to offset undesirable cumulative effects, such as respiratory depression and urinary retention. (3) Although prolonged use may lead to habituation, it appears to possess a lesser liability than morphine for the development of physical dependence. In order to avoid the dangers of habituation, physical dependence and undue cerebral irritability, the authors recommend that doses greater than 150 mg. every three hours should not be given. If this amount does not meet the clinical need, increasing the dose and shortening the interval not only may not have any additional therapeutic value, but may result in serious consequences.

Hecht, Noth and Yonkman[20, 26] recorded their observations on a series of 146 patients, 118 of whom were suffering from various diseases in which pain was severe enough to justify the use of one of the opiates. Included was a group of 26 patients with persistent severe pain of weeks' or months' duration. Six of these patients had been taking morphine, 13 codeine, and 2 dilaudid for considerable periods of time. These 26 patients were given Demerol hydrochloride at regular intervals for as long as 211 consecutive days; the average duration of therapy was 51.4 days, and the average total dose 32.6 Gm. Most of the other 118 patients suffered from more acute illnesses and received an average total dose of 1 Gm. during an average period of six days.

As a rule Demerol hydrochloride was given in a dose of 100 mg. orally or intramuscularly from one to eight times daily. Because of a more prompt and therefore more easily evaluated response the intramuscular route was used

32. Branwood, A. W.: *Edinburgh Med. Jour.*, 50:177, Mar., 1943.
33. Batterman, R. C., and Himmelsbach, C. K.: *J.A.M.A.*, 122:222, May 22, 1943.

about twice as frequently as the oral route. In the chronic cases in which Demerol hydrochloride was substituted for morphine or dilaudid, it was often necessary to shorten the usual four hour interval between doses to three hours.

The analgesic effect of Demerol hydrochloride upon 118 patients with various diseases giving rise to the types of pain listed is summarized in the following table.

Type of pain	No. of cases	Complete relief	Partial relief	No relief
Arthritic	9	6	2	1
Gastro-intestinal	22	15	6	1
Biliary tract	5	3	1	1
Renal	6	6		1
Neural and thalamic	18	11	6	
Osseous	8	3	2	1
Headache	18	13	2	3
Pleural	12	8	2	3
Cardiac	10	5	4	2
Miscellaneous	15	9	4	2
Total	123*	79 (64.2%)	29 (23.6%)	15 (12.2%)

*Five patients had 2 types of pain.

When pain was graded according to severity, the percentage of failures was higher in the groups with what was considered to be more severe pain, but even in the severest degrees of pain complete relief was obtained in nearly 60 per cent of instances. The groups with partial or no relief included 4 patients who had been addicted to morphine or dilaudid and who resisted the attempted substitution of Demerol hydrochloride for these drugs. Whenever codeine had been administered, Demerol hydrochloride could be substituted without any difficulty and was always claimed to be superior in its analgesic effect. In the group with micellaneous pain 8 of the 15 patients suffered from carcinoma of the bladder or of the female genital tract; 2 suffered from dysmenorrhea, 2 from extensive dermatitis, and 1 each from burns, posthemorrhoidectomy pain, and muscular pains associated with sickle-cell anemia. The results in the patients with carcinoma were variable but generally good. One patient with dysmenorrhea was completely relieved, but failure was recorded in the other. Both the pain and intense pruritus present in the cases with dermatitis were completely relieved. The patient with extensive second and third degree burns obtained only slight relief.

The onset of relief was from five to twenty minutes following intramuscular injection, and from twenty to thirty minutes following oral administration. Its duration varied between one and six hours, but was usually three or four hours. Relief was more often complete following intramuscular injection. The analgesic potency of Demerol hydrochloride in the dose employed was greater than that of 1 grain or more of codeine, or combinations of codeine and aspirin. It was usually less than that of morphine in 1/4 or 1/6 grain doses.

The sedative effects of Demerol hydrochloride were studied in two groups of patients, one in which pain was present and the other, a smaller group of 24 patients, in which pain was absent. The group of patients with pain received, as a rule, only a few doses. Administration of Demerol hydrochloride was followed by sleep in about 50 per cent, by mild sedation in about 30 per

cent, and by no noticeable sedative effect in about 20 per cent of instances. The hypnotic or sedative effects following repeated administration were not profound, a fact which was of advantage in the treatment of patients with chronic painful diseases. It is believed possible that the sedative effects in these patients were due in part to the relief from pain combined with a state of physical exhaustion incident to the illness rather than to a purely sedative action. Of the 24 patients without pain most suffered from cardiac disease with congestive failure. Demerol hydrochloride seemed useful in 2 patients who were restless and disoriented during the terminal phase of uremia; they were not as deeply sedated as with morphine or barbiturates, but were quiet and slightly euphoric. Two patients with toxic delirium went to sleep promptly after intramuscular injection, and 2 other patients who experienced episodes of acute apprehension were similarly affected. Of the entire group, sleep was induced in 11, a sedative effect without sleep in 4, no effect in 3, a variable effect in 3, and an indeterminate effect in 3 patients.

Batterman[34] treated with Demerol hydrochloride 183 patients with arthritis who required hospitalization and 73 ambulatory arthritics. Demerol hydrochloride was given both orally and parenterally. Regardless of diagnosis, severity of pain or dose, Demerol hydrochloride administered parenterally resulted in satisfactory analgesia in approximately 83 per cent of the trials, and an additional 13 per cent had moderate relief of pain. In spite of prolonged administration in many instances for weeks and months, the same result was achieved as long as the medication was given at regular intervals. Excellent results were obtained in alleviating the pain of the sciatic syndrome regardless of causation. Similar effects were noted in patients with myositis, acute bursitis, advanced osteoarthritis, rheumatoid, gonococcus and nonspecific infectious arthritis. Particularly striking was the relief of secondary muscle spasm and increased mobility of the joint following prolonged administration of Demerol hydrochloride.

The treatment of the ambulatory patient was complicated by the fact that a high percentage of such patients experienced unpleasant side reactions. Since these may take the form of dizziness, nausea, vomiting and, rarely, syncope, it is very difficult in certain individuals to obtain a satisfactory response. However, tolerance to the side reactions develops very quickly, thus allowing the analgesic effects to become manifest. Many patients gradually obtain greater and more prolonged relief of their pain even though they may have experienced some reactions at the onset of therapy. For this reason it is advisable when initiating the use of Demerol hydrochloride for ambulatory patients to start with a small dose, usually 25 mg., for the first few days until the tendency to untoward reactions subsides. No attempt should be made to achieve analgesia during this phase of therapy, but as soon as possible the dose should be increased to 50 or 100 mg. every four hours. This regime invariably gives satisfactory results regardless of the type of arthritis or severity of the pain.

Batterman concludes that, although insufficient cases are available for a statistical survey of the effectiveness of Demerol hydrochloride in any specific arthritic condition, it is apparent that the drug is of definite value in the treatment of chronic pain associated with arthritis. Hospitalized patients

34. Batterman, Robert C.: *Ann. Int. Med.*, 22:382, Mar., 1945.

respond to a degree comparable to the effects expected with morphine. However, the dangers of addiction are minimal and the incidence of side reactions is much lower. Ambulatory patients can also be treated satisfactorily if the dose is determined individually for each patient and time is allowed for untoward reactions, if any, to subside.

Bronchial Asthma

Although Demerol hydrochloride has been shown to be of decided effectiveness in status asthmaticus, it is not recommended for long continued and frequent medication of chronic bronchial asthma, but as a possible aid in bringing under control those attacks which do not respond to the usual therapeutic measures. Acute attacks of asthma can be quickly relieved by doses far below those required to produce analgesia or sedation. The bronchial relaxation is less than that achieved with epinephrine, but there is less autonomic reaction usually associated with severe attacks. Good results have been obtained with a subcutaneous injection of a mixture of 35 mg. of Demerol hydrochloride and half the usual amount of epinephrine.

Batterman[24] found that acute asthmatic attacks may be relieved within ten minutes by as little as 25 or 35 mg. when injected subcutaneously. The oral route is not recommended for these attacks because of delayed response, but chronic asthmatic conditions, particularly those associated with bronchitis, may be benefited with an appropriate oral dose, individually determined for each patient. When taken several times a day and before retiring, the number and severity of attacks may be reduced. Even if employed constantly for several months, Demerol hydrochloride continued to afford relief.

Barach[35] administered Demerol hydrochloride in 100 mg. doses by mouth or by injection to patients with intractable bronchial asthma. He found this drug of unquestionable value in reducing psychic tension and promoting bronchial relaxation.

Noth, Hecht and Yonkman[26] reported on 3 patients suffering from bronchial asthma who obtained no relief from epinephrine or aminophylline but were benefited by Demerol hydrochloride. A fourth patient, however, with only moderately severe asthma was not relieved.

Douthwaite[36] states that Demerol hydrochloride, 100 mg. subcutaneously, should be tried if other measures fail in severe asthmatic attacks. The drug has none of the alarming effects of morphine, which is most dangerous in asthma. Status asthmaticus is promptly terminated by Demerol hydrochloride when continuous epinephrine treatment has failed.

Hobbs[37] warns against unsupervised use of Demerol hydrochloride which he believes may easily occur in patients with asthma. He cites as example the case of a woman with persistent urticaria and asthma for whom the treatment was recommended. It gave her so much relief that she gave herself three injections of 50 mg. daily for several months, when she became completely irrational and disoriented. Although the drug was stopped, the patient remained in the same state for a week and then gradually recovered.

35. Barach, Alvan L.: *Bull. New York Acad. Med.*, 20:538, Oct., 1944.
36. Douthwaite, A. H.: *Brit. Med. Jour.*, 2:200, Aug. 5, 1944.
37. Hobbs, F.B.: *Brit. Med. Jour.*, 2:328, Sept. 2, 1944.

Hepburn,[38] who suffers from bronchial asthma, has treated himself with Demerol hydrochloride for seven months. He started with 25 mg. by injection at night but increased it soon to 50 mg. which he did mainly to secure a night's sleep. He found that small doses of 25 or 35 mg. act promptly and efficaciously in the morning, and the effects – sedative and antispasmodic – last usually for from four to five hours. Thereafter, a dose of 35 or 50 mg. was necessary at more frequent intervals to procure the same results. Hepburn finally used an average daily amount of 300 mg.

SURGERY

Demerol hydrochloride has been used extensively for the relief of pain and apprehension preoperatively and postoperatively, as well as in fractures and other injuries.

Preoperative Use

Demerol hydrochloride administered from twenty minutes to an hour preoperatively has a desirable sedative effect upon the patient and relieves much of the apprehension of the surgical ordeal. It does not interfere with the cough reflex or the size and reflexes of the pupil. Corneal sensitivity, however, is often abolished.

Rovenstine and Batterman[39] made an extensive study of the use of Demerol hydrochloride for preanesthetic medication. Demerol hydrochloride was used in combination with scopolamine on the New York University Service at Bellevue Hospital in place of morphine in 286 patients, and as the only preanesthetic agent in an additional 52 patients (all 338 individuals were unselected consecutive patients, both male and female, ranging in age from 15 to 89 years). The dose given varied from 100 mg. (assumed to correspond to 0.016 Gm. morphine) to 75 and 50 mg., and, when used in combination with scopolamine, the amounts of the latter were 0.6, 0.5 and 0.4 mg., respectively. A satisfactory response was obtained with 100 mg. hypodermically in 76 per cent of the 166 patients treated and undue depression amounted to 3 per cent. With doses smaller than 100 mg., less favorable results were obtained (except in patients in the age group of over 60 years).

It was found that the optimal time that should elapse after Demerol hydrochloride and scopolamine are administered, before anesthesia is begun, was between forty-five and ninety minutes. Approximately 80 per cent of the patients responded satisfactorily when this time was allowed.

The results obtained when Demerol hydrochloride was administered as the only preanesthetic drug were found to be strikingly similar to those observed with a combination of Demerol hydrochloride and scopolamine, but it appeared that patients receiving Demerol hydrochloride alone were less drowsy and more alert.

Observations during the maintenance and after recovery of anesthesia were recorded, reviewing for comparison the records of 200 unselected patients who had received morphine and scopolamine as the preanesthetic medication.

38. Hepburn, J.: *Brit. Med. Jour.*, 1:174, Feb. 3, 1945.
39. Rovenstine, E. A., and Batterman, R. C.: *Anesthesiology*, 4:126, Mar., 1943.

Although more extended studies are required for accurate evaluation, the authors gained the impression that Demerol hydrochloride (1) will provide psychic sedation not surpassed by morphine; (2) will not depress respiration or other vital functions to the same degree as will comparable amounts of morphine; (3) will facilitate induction of anesthesia as does morphine; (4) will be more effective in drying secretions than morphine; (5) will cause fewer unfavorable side effects, such as nausea and vertigo, than morphine, and (6) will reduce the amount of anesthetic agent required to produce the optimal degree of narcosis to the extent that can be obtained with morphine.

Weinstein[40] found Demerol hydrochloride to be ideal as a preanesthetic medication and particularly valuable in surgery of the mouth and throat in which analgesia and control of the salivary flow are desirable. A dosage of 100 mg. was found sufficient for the average adult, and in many cases 50 mg. were ample. Injections of 50 or 100 mg. usually produced an effect within fifteen minutes; oral doses of 100 mg. produced analgesia within from twenty to sixty minutes.

In about 50 cases in which White[41] used Demerol hydrochloride as part of the preanesthetic preparation, the drug seemed to relax the patient but did not produce narcosis to any degree. When combined with one of the barbiturates, it was a most satisfactory substitute for morphine and atropine. It can be relied on to eliminate the excitation and nausea that sometimes follow the initial dose of morphine. The impression was gained that a dose of 100 mg. of Demerol hydrochloride is equivalent to about 1/6 grain of morphine and 1/100 grain of atropine combined.

Hori and Gold[42] used Demerol hydrochloride in combination with scopolamine or the barbiturates in the majority of cases. For the average patient receiving a general anesthetic, 100 mg. of Demerol hydrochloride with 1/100 to 1/150 grain of scopolamine were given intramuscularly an hour before the operation. For patients receiving a spinal anesthetic, 100 mg. of Demerol hydrochloride with 1/100 grain of scopolamine one and one-half hours before the operation and another 100 mg. of the drug one-half hour before the operation were given. When the sedation was not sufficient with this scheme, another 50 mg. was given in the operating room during the course of the operation. Demerol hydrochloride, 100 to 150 mg. parenterally, was used in combination with 1½ to 3 grains of nembutal orally, particularly for patients receiving a spinal anesthetic. Demerol hydrochloride, from 100 to 150 mg., has been given alone especially for the patients receiving a general anesthetic, since it was found to decrease bronchial and salivary secretion even with ether anesthesia.

The sedative effect of Demerol hydrochloride with or without scopolamine began to appear in from fifteen to twenty minutes after intramuscular injections, as determined by the signs of apprehension being relieved, the patient becoming calmer and drowsy. However, even after 200 mg. were given, a patient who had his eyes closed and was seemingly asleep with sonorous respiration responded readily when spoken to. The sedative effect seemed to

40. Weinstein, M. L.: *Am. Jour. Surg.*, 60:267, May, 1943.
41. White, C. S.: *Med. Ann. District of Columbia*, 12:388, Oct., 1943; *Virginia Med. Monthly*, 71:351, July, 1944.
42. Hori, C. G., and Gold, S.: *Canad. Med. Assn. Jour.*, 51:509, Dec., 1944.

last only one to two hours on the average. Often during the course of the operation under a spinal anesthetic that lasted over an hour, the patient became apprehensive and restless and it was necessary to give more sedative; 1 to 2 cc. of Demerol hydrochloride solution given slowly intravenously quieted the patient within a few minutes and usually induced sleep, although the latter effect lasted only from thirty to forty-five minutes at times.

Although no quantitative study had been undertaken to determine the effect of Demerol hydrochloride on the quantity of inhalation anesthetics required, it has been Hori and Gold's experience that a less amount of the anesthetic agent is required for the induction and the maintenance of anesthesia, that the induction is smoother and easier, and that the excitement and delirium of the second stage are greatly diminished. Nevertheless, these sedative effects were less than those of morphine. The analgesic effect appeared about the same as the hypnotic effect but it seemed to last longer than the sedative effect. The duration of the analgesic effect of Demerol hydrochloride was from three to four hours, while that of morphine is from four to six hours. The analgesic effect of Demerol hydrochloride was much more prominent than its hynotic effect. This has been noted particularly in 7 cases of thyroidectomy where premedication consisted of Demerol hydrochloride and a basal anesthetic dose of Avertin rectally. Although cyclopropane was given in these cases the amount used was so small that it almost could have been omitted.

In those patients who were given only Demerol hydrochloride, Hori and Gold observed no appreciable change in blood pressure nor in pulse rate that could be ascribed to the drug. Furthermore, no untoward respiratory depression attributable to Demerol hydrochloride has been observed.

In doses of 100 and 150 mg. Demerol hydrochloride appeared to suppress the bronchial and salivary secretions even with ether anesthesia; but with smaller doses it did not seem to have much effect. Of the 40 patients who had only Demerol hydrochloride (100 to 150 mg.) premedication, 10 had a small amount of secretion under cyclopropane but not sufficient to cause any annoyance. In only three was there such an amount of secretion in the pharynx that the administration of the anesthetic had to be interrupted in order to suction out the secretion. With Demerol hydrochloride and scopolamine in combination, the secretion was markedly decreased, with resulting dry mouth, coated tongue and parched lips. However, compared with atropine, its effect was much weaker in this respect. It did not seem to have any effect on lacrimal secretion which is often stimulated by cyclopropane anesthesia. Unlike morphine, Demerol hydrochloride did not cause any change in the size of the pupil.

Preparation for gastroscopy with Demerol hydrochloride has been described by Hufford.[43] Thirty-eight patients with various types of gastro-intestinal lesions were prepared for gastroscopic examination with from 75 to 150 mg. of Demerol hydrochloride. The best method proved to be intramuscular administration of a single dose, the amount depending upon the weight and nervousness of the patient. In addition, all patients received 1 or 2 sprayings or swabbings of the oral cavity, pharynx and upper esophagus with 2 per cent

43. Hufford, A. R.: *Rev. Gastro-enterol.*, 11:328, Sept. Oct., 1944.

Pontocaine solution. The adult of average size is well relaxed by 100 mg. of Demerol hydrochloride given intramuscularly about twenty minutes before insertion of the gastroscope. This amount of drug replaces the routine preparation with codeine 1/2 grain and atropine 1/100 grain. Five patients complained of slight dizziness after the examination and were slightly nauseous, but the symptoms disappeared while the patients remained at rest for about half an hour. It was found that with Demerol hydrochloride the patients cooperate and relax better, and the gastroscope is more easily passed. During the examination the patients were not as restless and tense as with the codeine-atropine preparation and gagging was seldom encountered.

Postoperative Use

In his evaluation of Demerol hydrochloride, based on over 4000 cases, Batterman[24] states that as an analgesic agent the drug 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 three to four hours during the immediate postoperative period will be sufficient to make the patient comfortable, reduce any restlessness and facilitate the usual post-operative procedures. For this purpose Demerol hydrochloride 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 eliminating an important contributing factor for pulmonary complications. If pain or discomfort persists for more than forty-eight hours, satisfactory relief can subsequently be obtained with the orally administered preparation.

Batterman and Mulholland[44] analyzed in detail the use of Demerol hydrochloride in 488 postoperative patients, 165 of whom had had abdominal section. The dose varied between 50 and 150 mg., orally or parenterally, in a single dose or in repeated doses several times daily.

Regardless of the severity of the condition, the duration of the operation, the age of the patient and the ultimate prognosis, with rare exceptions the administration of 75 to 100 mg. parenterally every three to four hours, if necessary, was sufficient to make the patient comfortable and facilitate the usual therapeutic procedures.

The effectiveness of Demerol hydrochloride immediately becomes apparent when its ability to control postoperative pain is observed. Among the 164 patients receiving the drug parenterally during the postoperative period after laparotomy, 99.5 per cent of the 182 trials resulted in complete, satisfactory relief of the pain, discomfort and restlessness. After procedures other than laparotomy, postoperative pain was completely controlled in 91.5 per cent of 271 trials in 252 cases. An additional 5.2 per cent experienced a moderate effect, or relief for approximately three hours. The after effects of rectal operations are notoriously painful. In this group only 4 of 45 cases failed to give a satisfactory response to Demerol hydrochloride, 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.

44. Batterman, R. C., and Mulholland, J. H.: *Arch. Surg.*, 46:404, Mar., 1943.

Orally, Demerol hydrochloride was effective when the pain was not severe or after the acute postoperative symptoms had subsided. Satisfactory control of the pain was achieved in approximately 87 per cent of 123 trials on 118 patients. It is thus possible to continue using Demerol hydrochloride and to rely on the oral preparation if the postoperative discomfort should persist for several days.

In these studies on a group of postoperative surgical patients Demerol hydrochloride was found to be a safe drug, rarely causing untoward reactions; it is considered a more suitable drug for the control of pain than morphine or any of its derivatives. It produces respiratory depression only in exceptional cases. With several patients who had developed respiratory depression after morphine administration (during the transition period), it was possible to continue the treatment with Demerol hydrochloride for the control of pain without producing this serious side effect. Other preferable qualities of Demerol hydrochloride are its antispasmodic effect on gastro-intestinal tract and bronchi, its atropine-like drying action on mucous membrane and its lack of suppression of the cough reflex. A definite advantage is the absence of constipation.

Hori and Gold[42] used Demerol hydrochloride postoperatively in 200 patients as an analgesic in lieu of the opiates. The usual dosage prescribed was 100 mg. parenterally every three hours. However, of 200 patients 97 did not obtain sufficient relief from pain with this dosage and either more Demerol hydrochloride or morphine had to be given. Eight patients were given a total of from 600 to 700 mg. (12 to 14 cc. of solution) within the first twelve hours after the operation and in 57 patients 500 mg. (10 cc.) had to be given during a similar period. Morphine was given to the remainder of the 32 patients in one or more doses because of inadequate analgesia from Demerol hydrochloride. The analgesic value of 100 mg. of Demerol hydrochloride seemed to be equivalent to 1/6 grain of morphine. Even when the relief from pain was sufficient, a large number of patients were apprehensive and restless with Demerol hydrochloride as postoperative medication. Consequently morphine had to be used more for its sedative effect than for its analgesic action. Demerol hydrochloride had slightly less constipating effect than morphine and it lessened slightly the number of cases that needed to be catheterized. The effect of Demerol hydrochloride on intestinal activity was observed in one patient who had evisceration following breakdown of the laparotomy closure. A dose of 100 mg. given intravenously and repeated at the end of two hours caused no change in the peristalsis of the small bowel during the period of observation. In 4 patients with well functioning colostomy, Demerol hydrochloride had no appreciable effect on the activity of the intestine. In 25 patients undergoing laparotomy under a spinal anesthetic, the administration of Demerol hydrochloride produced no apparent effect on the intestinal tonicity or peristalsis. Six patients undergoing ureteral catheterization under spinal anesthesia were given 100 mg. of Demerol hydrochloride intravenously and the effect of the drug on the urinary secretion of the kidney was observed. In all cases, there was no appreciable change in the amount of urine secreted.

Trauma and Minor Surgery

Christie[25] reported on the value of the oral administration of Demerol

hydrochloride in the relief of pain due to trauma as studied by the war wounds committee of the British Medical Research Council. Observations were made by the medical and nursing staffs in 8 hospitals on the effects of Demerol hydrochloride given orally in doses of 100, 50 and 25 mg., respectively, to 335 patients suffering from pain. The information was collected by a large number of persons and differences of opinion on the value of the drug varied since in some wards there was bias against what was considered to be an experiment, while in others the drug was tested with enthusiasm.

Of 335 patients treated, 236 obtained complete or partial relief. In 203 of these, a further analysis of results was possible. Of the patients with "severe" pain, complete relief was obtained in 55 per cent and partial relief in 20 per cent, while of those with "moderate" pain, complete relief was obtained in 61 per cent and partial relief in 12 per cent. In neuralgic pain and in pain due to vascular disease, Demerol hydrochloride seemed to be particularly effective as compared with tablets containing codeine phosphate ¼ grain, acetylsalicylic acid 8 grains, phenacetin 8 grains, which were given to 109 patients. The effect of Demerol hydrochloride was usually apparent in from fifteen to thirty minutes, and its duration was almost invariably more than two hours and usually from four to five hours.

In 13 cases, Demerol hydrochloride in doses of 25, 50 and 100 mg. was compared with morphine, 1/4 or 1/6 grain given by mouth in tablets of similar size and appearance. In every case the effect of morphine was superior to that of Demerol hydrochloride.

Batterman[19, 24] found Demerol hydrochloride very effective for the control of skeletal pain associated with fractures and metastatic malignancies.

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 less pain if from 75 to 100 mg. of Demerol hydrochloride are administered intramuscularly one-half hour previously. Hoffman[21] also noted that Demerol hydrochloride was useful in cystoscopic work, ureteral catheterization and irrigation. Thoracentesis without local anesthesia was found to be relatively painless after preparation with Demerol hydrochloride; similar results were obtained in spinal punctures.

Control of Visceral Pain without Interference with Diagnostic Signs

Interesting observations have been made concerning the ability of Demerol hydrochloride to control certain types of visceral pain without interfering with diagnostic signs. Noth, Hecht and Yonkman[26] described an instance of severe biliary colic in which a complicating acute pancreatitis was subsequently found at operation. This patient obtained enough relief from Demerol hydrochloride to be fairly comfortable and yet the physical signs were not obscured. Later ¼ grain of morphine sulfate provided complete relief but it also masked the abdominal findings. The difference in this case between the effects of Demerol hydrochloride and morphine upon the physical findings is of some interest from the point of view of the diagnosis of acute abdominal conditions following the use of analgesic agents. Hoffman[21] observed in 4 cases of suspected appendicitis and 1 case of ruptured duodenal ulcer that Demerol hydrochloride relieved the pain but in no manner masked diagnostic signs.

Demerol hydrochloride when used in control of labor pain has been shown to produce satisfactory analgesia, to shorten labor in the primipara, and to be without significant effect upon the baby. With large doses of Demerol hydrochloride, a moderate sedative effect is noted and sleep is frequently induced between pains. In none of the obstetric patients so far observed was excitement, disorientation, or irrationality encountered, such as may frequently be seen with the barbiturates and other preparations used for the production of amnesia in addition to analgesia during labor.

Demerol hydrochloride alone produces analgesia but not amnesia. If amnesia is also desired, scopolamine or barbiturates also should be used. However, when barbiturates are used· the fact that their action is potentiated by Demerol hydrochloride should be kept in mind.

Gilbert and Dixon[45] used Demerol hydrochloride during labor as an analgesic in 150 women delivered vaginally during 1941 and 1942 at the Union Memorial Hospital, Baltimore, Md. Of the group, 124 were primiparous, 26 multiparous. In 70 cases, Demerol hydrochloride was used alone and in 80 cases it was combined with other drugs. For delivery, caudal anesthesia with 35 cc. of 1 per cent Novocain solution was used in 75 cases, nitrous oxide with oxygen and ether in 74, and no anesthesia in 1. Demerol hydrochloride was administered both orally and parenterally, but the majority of patients received intramuscular injections because of greater uniformity and rapidity of effect when so given.

Length of labor appeared to be shortened by Demerol hydrochloride medication, although definite conclusions can not be made with such a small series of cases. Shortening of labor may be the result of the drug's spasmolytic effect on the cervix or may result simply because the bearing down is more vigorous when the pain threshold is raised. In the 54 primiparas receiving Demerol hydrochloride alone, the average total length of labor was eleven hours and eighteen minutes. Demerol hydrochloride alone was used in 16 multiparas and in 10 in combination with a barbiturate. The authors believe that in analgesia of multiparas Demerol hydrochloride alone may prove to be particularly suitable since often the institution of a major amnesic regime to carry such cases through an easy labor seems unwarranted.

In none of the 70 cases in which Demerol hydrochloride was used alone was amnesia, as distinguished from analgesia, obtained in any degree. Analgesia was good in 51 and slight in 19; no patient reported "excellent" (painless labor) analgesia in the absence of amnesia. Of the 72 patients receiving Demerol hydrochloride and barbiturate, amnesia was excellent in 8, good in 36, slight in 27, and absent in 1.

With large doses of Demerol hydrochloride (300 to 500 mg.) a moderate sedative effect was noticed and women would frequently sleep between pains, awakening, however, when spoken to. No excitement, disorientation, or irrationality was observed in patients receiving Demerol hydrochloride alone. Dizziness and lightheadedness were occasionally noted. No increase in vomiting was observed. A euphoric effect was noted and patients seemed braver.

45. Gilbert, G., and Dixon, A. B.: *Amer. Jour. Obst. & Gynec.*, 45:320, Feb., 1943.

No postpartum depression, confusion, or "hangover" occurred. During the third stage of labor, there was no increase in bleeding and no atony of the uterus. Complaint of thirst and dryness in the mouth was frequent. With patients delivered under inhalation anesthesia, this depressed secretory activity in the nasopharynx has an obvious advantage.

No babies delivered of mothers receiving Demerol hydrochloride alone showed any persistent cyanosis, evidence of narcosis, or otherwise merited the term "sleepy baby."

The authors suggest the following program for the use of Demerol hydrochloride in obstetrics: (1) As soon as regular contractions are established, 100 mg. of Demerol intramuscularly. (2) A second 100 mg. dose one hour later. If labor has been rapid or if the cervix is thin and 2 to 3 cm. dilated at the first dose, the second dose may be given one-half hour later. (3) A third dose of 100 mg. one hour later or when the cervix reaches 4 cm. dilatation, if labor has been rapid. If, at this point, it is decided to conduct labor under Demerol hydrochloride alone, a fourth 100 mg. dose may be given when the cervix is 5 cm. dilated. In any event, it is advantageous to complete the total Demerol hydrochloride dosage early during labor. The action of the drug is sustained and its perceptible effect is maintained for six hours after a single dose. A total dosage of 400 mg. of Demerol hydrochloride given by the time the cervix is 5 cm. dilated, or 4 cm. if labor appears rapid, is believed to be optimum. Further doses are not recommended until five or six hours later. If amnesia is desired, concurrently with the third or fourth dose at 4 to 5 cm. dilatation, a barbiturate is given orally and repeated in from one-half to one hour. In the majority of cases, this dosage and sequence insure adequate amnesia for the ensuing four to six hours, and short quiet labors are the rule.

Roby and Schumann[46] and Schumann[47] recorded and analyzed over 1000 obstetric cases at the Boston Lying-In Hospital. Identical medication was given at fixed intervals to labor. The routine consisted of the following: Initial medication was 100 mg. of Demerol hydrochloride and 1/100 grain of scopolamine intramuscularly, followed by 1/150 grain of scopolamine forty-five minutes later. After four hours another dose of 100 mg. of Demerol hydrochloride with 1/200 grain of scopolamine was given. Thereafter, when necessary, 100 mg. of Demerol hydrochloride were given every four hours and 1/200 grain of scopolamine every two hours. New admissions expected to deliver within two hours received 100 mg. of Demerol and 1/100 grain of scopolamine intravenously, taking at least two minutes for this injection. The same amounts of Demerol hydrochloride and scopolamine, intravenously, were used as premedication for cesarean section, forty-five minutes prior to induction of anesthesia.

Entirely satisfactory amnesia was obtained in 70.5 per cent of 847 patients; 16.9 per cent had analgesia but no amnesia, and 12.6 per cent constituted failure of amnesia. In examining the partial and total failures it became apparent that a number of the patients had received medication too late to benefit materially from its effects.

With regard to the effect of Demerol-scopolamine on the length of labor,

46. Roby, C., and Schumann, W. R.: *Amer. Jour. Obst. & Gynec.*, 45:318, Feb., 1943.
47. Schumann, W. R.: *Amer. Jour. Obst. & Gynec.*, 47:93, Jan., 1944.

it appeared that a substantial shortening of the time of labor could be obtained in comparison with a series of 500 cases delivered under barbiturate-scopolamine analgesia. Thus, under the Demerol hydrochloride routine, the average primipara's labor was apparently reduced by 2.5 hours, and the multiparous labor by 1.2 hours, representing a 17 per cent and 14 per cent reduction, respectively.

In order to gain an approximate estimate of the effect of Demerol hydrochloride on the quantity of the anesthetic agent required, comparative studies were made on 18 uncomplicated pelvic deliveries treated with Demerol and 19 identical cases with patients receiving barbiturates and scopolamine. The results suggest that Demerol hydrochloride and the barbiturates are equivalent in preanesthetic value.

The analgesic effect of Demerol hydrochloride was evident from a group of 37 patients who precipitated without anesthesia; 29 of these were delivered with no recollection of pain whatever in spite of the fact that several patients sustained lacerations requiring repair. No depressant effect of the analgesia was apparent.

To investigate the effect on the newborn infant, a detailed analysis was made of 897 cases. Of these, 737 babies were active, 107 slightly slow (all of these were normal and required no further attention), 30 were slow, and there were 6 neonatal deaths and 17 stillbirths. Each of the stillbirths and neonatal deaths could be explained on the basis of congenital deformity or pathologic state, and there was an adequate obstetric explanation for the slowness of the newborn infants, all of whom were discharged as normal with the mother.

An analysis of 44 premature infants showed that 91 per cent were in satisfactory condition; two prematures were "slow" and two were stillbirths. There is little to suggest a respiratory depressant effect in this group.

Demerol hydrochloride was used with satisfactory results as the premedication in 17 cesarean sections. The average length of medication was thirty minutes in 14 with active infants, one hour and forty-five minutes in 2 with slightly slow babies, and forty-five minutes in 1 patient with slow condition.

Patients treated with Demerol hydrochloride and receiving general anesthesia have been relatively free from mucus and excitement during the induction.

Schumann concludes that in view of the satisfactory amnesia, the absence of pulmonary complications, and the freedom from depressant effects upon the fetus, Demerol hydrochloride in conjunction with scopolamine is superior as an obstetric analgesic to other analgesics in common use.

Gallen and Prescott[48] used Demerol hydrochloride as an obstetric analgesic in 150 cases of which 100 are recorded in detail. These 100 cases comprised 70 primiparas and 30 multiparas all of whom were apparently normal on medical and obstetric examination. Two dosage schemes were found to give satisfactory results: (1) initial dose of 100 mg. intramuscularly, repeated one hour later with a chloral-bromide-opium mixture or with scopolamine; (2) 100 mg. Demerol hydrochloride intravenously, followed by 100 mg. intramuscularly an hour later, either alone or with scopolamine 1/150 grain. It was possible with either technic to give further intramuscular injections of

48. Gallen, B., and Prescott, F.: *Brit. Med. Jour.*, 1:176, Feb. 5, 1944.

100 mg. up to a total of 400 mg. in twenty-four hours without any harmful effect. The first injection was preferably given when the cervix was two fingers dilated and the patient was having regular contractions. When given intravenously, Demerol hydrochloride produced analgesia in from five to ten minutes, intramuscularly in fifteen minutes with a duration of from three to four hours. Intravenous administration produced a more rapid and powerful initial action, but intramuscular administration was highly satisfactory and equally effective.

Demerol hydrochloride had a definite antispasmodic action on the cervix, and in the dosage employed it was found an effective obstetric analgesic. It did not, however, produce amnesia unless given with adequate doses of other drugs — e. g. scopolamine and barbiturates. An effective combination was that of Demerol hydrochloride and scopolamine.

Only 5 per cent of the patients failed to obtain any relief from Demerol hydrochloride. Analgesia was complete or satisfactory in 60 per cent. There was no increase in the incidence of instrumental delivery or obstetric complications that could be associated with the use of the drug. Of the babies 91 per cent were apparently normal and active at birth, 9 per cent were slow and required resuscitation. When compared with patients not receiving the drug, there seemed to be a prolongation of labor in patients given Demerol hydrochloride, but this, in the opinion of the investigators, was due to the high proportion of apprehensive and nervous women in their studies. The actual duration of labor, however, from the time of administration of Demerol hydrochloride in both primiparas and multiparas was well within, if not below, average time limits.

Spitzer[49] studied the analgesic and spasmolytic effects of Demerol hydrochloride on normal labor in the maternity department of the Kingston County Hospital, Surrey, England, since October, 1941. Of the 80 normal patients 56 were primiparas, 24 multiparas. In this series of investigation the oral route of administration was preferred. The effect of the oral medication of a 25 mg. dose appeared in from twenty to thirty minutes and lasted from one to four hours. The optimum pain response seemed to occur with a 25 mg. dose repeated half hourly for two doses. (However, after completing this investigation 50 additional cases were treated with a higher dosage, i.e., a 50 mg. single dose with a 25 mg. dose occasionally added; an increase of complete analgesia was noted.)

The antispasmodic property of Demerol hydrochloride during labor was evident; after the first stage was established with cervical dilatation varying from 2 to 3 fingerbreadths, Demerol hydrochloride had a satisfactory influence on the course of labor in which regular, prolonged and rhythmic pains were present. Of all the patients with severe pain about 17.5 per cent were greatly relieved, 72.5 per cent had good relief, and 10 per cent obtained no relief. There was no striking difference between primiparas and multiparas in this respect. The behavior of excited patients was improved. No objectionable side effects on mother or baby were observed. In 3 mothers transient vomiting and bradycardia were noted. Twice a transient depression of the fetal heart sounds developed, and 5 babies showed a mild degree of asphyxia.

49. Spitzer, Walter: *Brit. Med. Jour.*, 1:179, Feb. 5, 1944.

In contradistinction to many other analgesics, the author found that Demerol hydrochloride had a remarkable shortening effect on the duration of normal labor, presumably by direct relaxing action on the uterine cervix. No harm was caused on uterine tone or perineum by shortening labor; there were 2 cases of postpartum hemorrhage and one second degree perineal tear. In elderly primiparas with rigidity of the soft parts the influence on the dilatation period was very favorable.

When carefully dosed and timed, Demerol hydrochloride was found to be a very useful analgesic and spasmolytic drug in obstetrics.

Donnelly,[50] in a review of the literature, considers the use of Demerol hydrochloride one of the outstanding new developments in obstetric analgesia. He points out that the frequency of stillbirths and neonatal deaths has been remarkably low in all reports, and that no serious maternal complications have been noted.

An interesting report on Demerol analgesia in labor is that of Cripps, Hall and Haultain[51] of the Royal Infirmary in Edinburgh. Their series consisted of 91 primiparas and 11 multiparas; 96 women received Demerol hydrochloride alone and 6 received scopolamine in addition. The following dosage of Demerol hydrochloride is recommended: 100 mg. by intramuscular injection, when the os is 3 to 4 fingers dilated and the pains are coming on about every four to five minutes. The second dose of 100 mg., when required, is given forty-five to sixty minutes later. In all, 44 of their cases received one injection and 40 two injections. A third injection of 100 mg. was necessary two hours later in 10 cases, and a fourth after another two hours in 2 cases. Demerol hydrochloride produced a successful analgesia in 78.4 per cent of the patients. There were no complications and no harmful effects on mother or child. There were no stillbirths in the 103 babies born. In only 4 cases was there any marked asphyxia; in two of these the asphyxia could be accounted for by a difficult forceps delivery, in one the asphyxia could be attributed to eclampsia and a forceps delivery, and in another to the cord being held tightly round the baby's neck. All of these babies responded to treatment and survived without giving any further cause for anxiety. In 22 cases the child did not cry immediately on delivery but responded in a few minutes; in only 8 of these cases was there no other possible reason found for the slight oligopnea. None of these babies gave any cause for anxiety at birth or later. Thus it can be stated quite definitely from this series of cases, which includes many complications that might have caused asphyxia and possibly stillbirth, that Demerol hydrochloride had no deleterious effect on the infant.

With regard to its effect on labor pains, the administration of Demerol hydrochloride seemed definitely to have hastened delivery in 33 cases, the average time from the first dose to delivery in these being 2.6 hours. The clinical explanation for this effect seemed to be that the "edge" was taken off the pains, thus allowing them to be more effective and the patient to cooperate more easily in the second stage of labor. Furthermore, the injections seemed in many cases to relieve spasm of the cervix and to enhance uterine polarity. The cervix therefore dilated more easily and the uterine contractions seemed to be accentuated, but were not so painful.

50. Donnelly, J. F.: *Amer. Jour. Med. Sc.*, 207:804, June, 1944.
51. Cripps, J. A. R., Hall, B., and Haultain, W. F. T.: *Brit. Med. Jour.*, 2:498, Oct. 14, 1944.

Hori and Gold[42] employed Demerol hydrochloride in 50 obstetric cases; 25 patients received Demerol hydrochloride 100 mg. every four hours, and 25 received Demerol hydrochloride 100 mg., with scopolamine 1/150 grain every four hours. Scopolamine was repeated only if indicated and usually in smaller doses. No alteration in blood pressure, pulse or fetal heart was noted and the sedation did not interfere with normal delivery. The voluntary expulsion pains were not diminished. Occasionally side effects appeared such as nausea, vomiting and dizziness. No maternal respiratory depression was noted. Demerol hydrochloride was in nearly every case given at the onset of labor and did not prolong or delay the progress of labor as judged by the frequency and strength of pains. Of the 50 cases, 30 demonstrated effective sedation, 11 fair sedation and 9 poor sedation. Analysis of the 50 babies in this series revealed that 42 babies breathed and cried spontaneously. Eight babies required resuscitation because of cyanosis and lack of respiratory movements. Three of the babies that required resuscitation were mid-forceps deliveries for transverse arrests. The author's impression is that the analgesic was more effective when Demerol hydrochloride was supplemented with scopolamine, since this added a fair degree of amnesia.

Grogan[52] states that in cesarean sections Demerol hydrochloride is an ideal preparation, apparently because it does not depress the respiration of the mother or the fetus and, therefore, may be used as follows: One hour before operation 100 mg. of Demerol hydrochloride plus 1/200 grain of scopolamine may be given intravenously and then a terminal anesthetic of gas and oxygen may be used. It has been the author's observation that there is very little effect upon the mother and baby. The baby cries immediately upon delivery either from vaginal delivery or cesarean section, which is the ultimate aim of any analgesic agent.

Marshall[53] considers Demerol hydrochloride to be a valuable addition to the obstetrician's list of analgesics. While the drug does not seem to cause as deep analgesia as the barbiturates, the patient is quieter and easier to manage during labor. Although Demerol hydrochloride seems safer than morphine or the barbiturates for the infant, Marshall believes it should be studied further. Demerol is much less depressing to the respiratory center of the mother and infant, but how safe it is, is not yet known. It may be used during premature labor, but not enough premature labors have been studied and reported upon as yet. Some persons have an apparent idiosyncrasy to the drug; transient cyanosis was observed in two mothers.

The combined use of barbiturates and scopolamine has been compared with the use of Demerol hydrochloride and scopolamine by Irving,[54] who analyzed 14,676 cases receiving the former and 2446 cases receiving the latter group of drugs. The barbiturate-scopolamine medication produced complete and almost complete amnesia in 85 per cent of the patients, while the combination of Demerol hydrochloride and scopolamine resulted in only 70 per cent of complete or almost complete amnesia. However, there were 3 deaths associated with the use of pentobarbital, but no deaths were due to Demerol hydrochloride. The incidence of respiratory complications in mothers after Demerol

52. Grogan, R. L.: *Texas State Jour. Med.*, 41:28, May, 1945.
53. Marshall, C. J.: *New York State Jour. Med.*, 45:1432, July 1, 1945.
54. Irving, F. C.: *Rhode Island Med. Jour.*, 28:493, July, 1945.

hydrochloride was 2 in 2446 cases, as compared to as many as 44 in 14,676 barbiturate cases. This bears out the claim that Demerol hydrochloride is rarely a respiratory depressant and, in spite of its lessened effectiveness as an adjuvant in producing amnesia, it is a safer drug for routine use in a large clinic. The second disadvantage of the barbiturates is the production of excitement which is distinctly less often caused by Demerol hydrochloride and scopolamine. Excitement was usually controlled in those given barbiturates by 100 mg. of Demerol hydrochloride or retention enemas of paraldehyde. Only 62 per cent of babies breathed spontaneously after barbiturates and general anesthesia as compared with 82 per cent of the Demerol group.

PEDIATRICS

Experience with Demerol hydrochloride in pediatrics is limited. Sprockhoff[55] reported on its use as a spasmolytic in the croup of measles, diphtheria and pseudocroup. He believes that in some instances in these conditions, by relaxing spasm, tracheotomy may be avoided. While he found it difficult to stop the cough in pertussis, he was able to minimize its frequency and severity as well as to diminish the vomiting. Sprockhoff states that in general vomiting is favorably influenced by Demerol hydrochloride whether its origin is central or peripheral. The dosage advised is as follows: Infants, 2 to 4 drops of a 5 per cent solution by mouth, or a 25 mg. suppository, or 0.1 to 0.2 cc. (5 to 10 mg.) subcutaneously; older children, 5 to 8 drops by mouth, or a 50 mg. suppository, or 0.2 to 0.4 cc. subcutaneously; larger children may receive 8 to 12 drops by mouth, or a 75 mg. suppository, or 0.5 to 0.8 cc. subcutaneously.

Hori and Gold[42] state that they have used Demerol hydrochloride in children as young as 3 years for preoperative and postoperative medication. A child of 10 years, of average build, received from 50 to 75 mg. of Demerol hydrochloride, while a child of 5 years received from 25 to 35 mg. of Demerol hydrochloride. They have also used it in combination with atropine in children.

Glaser[56] found Demerol in combination with epinephrine very effective in the treatment of asthma in infants and children. He used the Demerol hydrochloride and epinephrine hydrochloride solutions mixed together in the same syringe, a procedure commonly employed by others. Glaser recommends, as a conservative hypodermic dose, 1.5 mg. per kg. (or 0.015 cc. per pound of the 5 per cent solution, available in ampuls). He points out that the tolerance in infants for Demerol hydrochloride is apparently quite high. In this connection Glaser mentions the case of a 5 lb. infant with meningitis complicating an inoperable myelomeningocele. For the relief of pain the infant was given 25 mg. of Demerol hydrochloride (0.5 cc.) by hypodermic injection without any apparent ill effects. This is a dosage somewhat in excess of 10 mg. per kg. In infants weighing 8 lb. or more with severe colic not relieved by phenobarbital in the usual doses, Glaser frequently used one half to three fourths of a 50 mg. tablet of Demerol hydrochloride orally with very good results and no undesirable side reactions.

55. Sprockhoff, O.: *Deutsch. med. Wchnschr.*, 67:383, Apr. 4, 1941.
56. Glaser, Jerome: *Ann. Allergy*, 3:373, Sept.-Oct., 1945.

SUMMARY OF INDICATIONS

Pain from whatever cause, particularly that associated with smooth muscle spasm in the gastro-intestinal, biliary and genito-urinary tracts.

Gastro-intestinal tract pain: gastric malignancy, pylorospasm, enteritis, ischiorectal abscess, peritonitis, etc.

Biliary tract pain: cholecystitis, cholelithiasis, biliary cirrhosis, etc.

Genito-urinary tract pain: renal or ureteral calculus, cystoscopic examination, perinephric abscess, cystitis, prostatitis, orchitis, salpingitis, etc.

Neuromuscular pain: neuritis, skeletal muscle spasm, acute arthralgia, sciatica, etc.

Intractable pain: malignancies (primary or metastatic), arthritis, etc.

Cardiovascular pain: angina pectoris, coronary thrombosis, congestive heart failure, intermittent claudication, etc.

Respiratory tract pain: in pleurisy, lobar pneumonia, etc., for the relief of pain. When suppression of the cough reflex is desired, codeine may be necessary.

Bronchial asthma: status asthmaticus refractory to epinephrine and aminophylline.

Surgery: to control preoperative and postoperative pain, and in the preoperative preparation of the patient.

Traumatic pain: osseous fractures, joint dislocations, extensive contusions, and pain incident to reduction of fractures and dislocations, and other manipulations in orthopedic surgery the nature of which does not necessitate the administration of an anesthetic.

Obstetrics: to produce analgesia during labor. (May be combined with scopolamine or barbiturates.)

Pediatrics: preoperative and postoperative use; intestinal colic.

SIDE EFFECTS AND CONTRAINDICATIONS

Demerol hydrochloride is generally well tolerated and nontoxic in therapeutic doses. Side effects, although generally of minor importance, occur more frequently in the ambulatory than in the hospitalized patient. They are of brief duration and usually insignificant and do not, as a rule, inconvenience the patient to any appreciable degree. They may occur with the first dose or only occasionally after several doses. After prolonged administration they usually subside completely.

Dizziness is the most common side effect. Ambulatory patients receiving Demerol hydrochloride should therefore be warned against driving a car or unnecessarily exposing themselves to hazards.

Nausea and vomiting occur materially less frequently than following administration of morphine. They are not an indication to stop Demerol hydrochloride since they subside promptly if the drug is continued. Perspiration and dryness of the mouth may at times be marked.

In contrast to morphine, respiratory depression occurs very rarely with Demerol hydrochloride. It is usually of short duration and responds readily to the usual stimulants.

Euphoria is sometimes noted. In view of this feeling of well-being that develops in some cases, particularly in those in which pain is not a factor, the drug should be considered as possibly habit forming.

More severe reactions are characterized by extreme weakness, syncope, profuse perspiration, marked dizziness, nausea and vomiting. They may occur occasionally in ambulatory patients. Such reactions can often be aborted or decreased in severity if the patient is advised to seek a recumbent position as soon as weakness is noted.

Excessive doses of Demerol hydrochloride, as employed in abuse of the drug, may result in tremors and possibly convulsions. The latter have occurred if the dose exceeded 200 mg. every two hours (as taken by previous opiate addicts). Convulsions have never been noted with therapeutic doses, although minimal signs of cerebral irritation such as tremors and uncoordinated muscular movements may occur in an occasional patient. In such cases the drug should be decreased in dose or discontinued.

Batterman,[19, 24] who bases his opinions on a series of over 4000 cases, states that with the exception of cerebral irritability with large doses, Demerol hydrochloride 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 has been found incompatible with Demerol hydrochloride.

Significant side reactions have been noted in 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 most common reaction is dizziness which occurs in approximately 22 per cent of the patients. It resembles a "feeling of being drunk," "floating on air," "lightheadedness," and may be described as a head-ache. Unless associated with other reactions it is not very disturbing and with repeated use of the drug may diminish in intensity or subside completely. Nausea and vomiting have been 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 of 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 hydrochloride possesses vasodilator 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 severity. 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 develops. Under no circumstances should the drug be given intravenously or in a dose higher than 35 mg. hypodermically if the patient is ambulatory.*

When a normal pain-free subject is given Demerol hydrochloride, the psychic effects are described variously depending on the psychologic make-up of the individual and perhaps the occurrence of the side effects previously mentioned. A good number may experience unpleasant dreams or disagreeable sensations. The majority, however, experience a sense of well-being or euphoria. Some subjects feel as if they had a "good cocktail," others feel "uplifted," stimulated or less despondent. However, the presence of pain and illness decreases the incidence of euphoria to no higher than 10 per cent. Nevertheless, the implications of this reaction are obvious since many subjects may request repetition of the drug. There is, therefore, little doubt that Demerol hydrochloride may result in habituation. However, repeated use of Demerol hydrochloride does not mean that a habit has developed. The patient may require continued use of the drug because of a specific beneficial effect such as analgesia. If the patient requests the drug for nonspecific reasons and no need for its administration is evident, then the possibility of habituation is to be considered. It is known, however, that patients receiving Demerol hydrochloride for many months may have the drug discontinued without encountering symptoms or signs of abstinence.

Respiratory depression and urinary retention are rare with Demerol hydrochloride. In several cases in which morphine had previously produced respiratory depression, it was possible to substitute Demerol hydrochloride without causing this reaction. Prolonged use of Demerol hydrochloride resulted in no alteration of the hematopoietic system or impairment of kidney function. Constipation, in contrast to the opiates, never resulted from Demerol hydrochloride. Sulfonamide therapy did not appear to affect the potency or safety of Demerol. There was no alteration in the electrocardiogram and basal metabolic rate, and the blood pressure and ventricular rates were unaffected. Unlike after morphine, the size of the pupil and the pupillary reflex are unchanged when Demerol hydrochloride is given. An unusual effect is the decrease or abolition of the corneal sensitivity noted in 80 per cent of the subjects. Drowsiness and sleep occur with the larger doses (usually following parenteral administration), are of short duration, and are not followed by depression and confusion.

Hoffman[21] found Demerol hydrochloride to be well tolerated except for occasional atropine-like or epinephrine-like reactions. Demerol hydrochloride did not alter blood sugar levels. It delayed the gastric emptying time about 20 per cent; there were no unfavorable effects in a number of peptic ulcer cases.

Fitzgerald and McArdle[31] noted transient giddiness, pallor, faintness,

*Demerol hydrochloride is best administered to ambulatory patients by mouth only.

sweating, blurring of vision, nausea, tremulousness and anxiety in 7 of the 10 cases in which Demerol hydrochloride was given intravenously.

Branwood[32] also found that dizziness and faintness often occurred after intravenous injections but never after intramuscular or subcutaneous administration. No changes in blood or urine were observed. After intravenous injection, a rapid and considerable fall in blood pressure (from 30 to 70 mm.) occurred and the patient experienced a sensation of dizziness and faintness. This initial fall was of short duration, the pressure returning to its original value within a few minutes. A secondary fall (from 2 to 14 mm.) usually occurred. Intramuscular or subcutaneous administration of Demerol hydrochloride resulted in a more prolonged and steady decline of both systolic and diastolic pressures which usually reached a maximum in forty minutes. While no alarming effects were observed, the hypotensive effect of Demerol hydrochloride would contraindicate its use in shock or in conditions in which a sudden reduction in blood pressure is dangerous.

In Hecht, Noth and Yonkman's[20] series of 111 cases, dizziness, nausea, vomiting, a choking sensation, momentary excitation, euphoria, dryness of the mouth and urticaria were occasionally noted immediately following administration, but in only 5 per cent of all cases were these reactions severe enough to necessitate withdrawal of the drug. Regular urinalysis, blood counts, electrocardiograms and liver function tests showed no alterations attributable to the drug. After prolonged intramuscular administration (0.1 Gm. six to eight times daily for periods exceeding one month) sudden withdrawal occasionally resulted in nausea, violent vomiting, profuse perspiration, itching of the skin, irritability, depression and apprehension. These symptoms began a few hours after the drug had been withdrawn and generally lasted for one or two days. These reactions could easily be overcome by the use of barbiturates and scopolamine. Symptoms of this kind were never observed following prolonged oral medication.

Guttman[57] pointed out that Demerol hydrochloride should be administered with caution, if at all, to patients with intracranial lesions. In such cases morphine sulfate is usually considered contraindicated because of its depressant effect on respiration and the alteration in pupillary response.

At the Neurologic Institute, New York, Demerol hydrochloride was given to 20 patients with intracranial lesions of various kinds. The patients received 100 mg. of the drug parenterally (unless otherwise indicated) into the deltoid region. Data including blood pressure, pulse and respiratory rate were obtained before the drug was administered, and the so-called vital signs along with other pertinent observations were made every fifteen minutes for about three hours afterward. In 7 of the 20 patients the respiratory rate fell from 18-22 per minute to 12 per minute or less; of these, 5 patients showed a rate of 12 per minute while in one it dropped to 8 per minute and in another it reached a low of 4 respirations a minute. Of the remaining 13 patients, 9 showed a decrease to 16-18 per minute, 3 to 15 per minute and 1 to 14 per minute. A rate of 12 or less per minute for at least fifteen minutes was considered an unsafe respiratory depression; 7 individuals fell into this category. Instances of contracted pupils with sluggish response to light were observed also.

57. Guttman, S. A.: *J.A.M.A.*, 124:155, Jan. 15, 1944.

Christie[25] noted toxic effects from Demerol hydrochloride in 22 of 335 patients, but in no case were they serious. Vomiting occurred in 8 patients, nausea in 4, giddiness in 9, and "hangover" in 1.

In preoperative and postoperative use Demerol hydrochloride was found to be an exceptionally safe drug, rarely causing untoward reactions.[19, 20, 24, 40, 41, 44]

Similarly, the use of Demerol hydrochloride in obstetrics rarely gave rise to side effects. Mild reactions in the mother, such as vomiting, temporary rise in blood pressure, dizziness, tingling of the limbs and dryness of the throat have occasionally been observed.[45-50]

DOSAGE AND MANNER OF USE

The average adult dose of Demerol hydrochloride for most medical and surgical conditions is 100 mg. administered either intramuscularly or orally. Inasmuch as in many patients 50 mg. are sufficient for control of pain, it is suggested that the first dose be held to 50 mg. and subsequent doses be increased or decreased as necessary. For very severe pain 150 mg. may sometime be required.

As a rule, it is sufficient to administer Demerol hydrochloride at three or four hour intervals when prolonged relief from pain is necessary. In some cases, however, e.g. cardiac infarction, shorter intervals may be necessary at the beginning of medication.

In ambulatory patients Demerol hydrochloride is usually administered by mouth only. *Oral* administration is also preferable when long continued use is necessary for the relief of chronic pain. *Intramuscular* administration is the best method of use when rapid relief is needed. It is preferable to subcutaneous or intravenous use because the drug is better tolerated locally and systemically when administered by intramuscular injection. *Subcutaneous* administration is not recommended because it may be irritating on prolonged use. *Intravenous* administration does not offer sufficient advantages over intramuscular use to warrant the use of Demerol hydrochloride in this manner. If intravenous administration is indicated for special reasons, it should be done very slowly over a period of two minutes. This is facilitated by diluting the solution of Demerol hydrochloride with distilled water. Rapid intravenous injection increases the severity and frequency of side effects considerably.

For preoperative medication, Demerol hydrochloride is administered intramuscularly or orally in doses of 50 to 100 mg. from thirty to ninety minutes before the beginning of anesthesia.

Postoperatively Demerol hydrochloride is used as an analgesic in lieu of the opiates without the production of constipation or depression of the respiratory center, in doses of 50 to 100 mg. orally or intramuscularly. Doses are usually repeated at four hour intervals.

For the production of analgesia in obstetrics, several satisfactory methods may be employed. Demerol hydrochloride 100 mg. may be given intramuscularly as soon as contractions occur at regular intervals. The dosage may be repeated at from one to three hour intervals if necessary. When amnesia is

desired in addition to analgesia, scopolamine or one of the rapid acting barbiturates may be used with Demerol hydrochloride. However, when barbiturates are used, the fact that their action is potentiated by Demerol hydrochloride should be kept in mind.

Roby and Schumann at the Boston Lying-In Hospital, Harvard Medical School, have adopted the following routine: Medication is begun when the patient complains of pain, regardless of the state of dilatation of the cervix. Initially, Demerol hydrochloride 100 mg. and scopolamine 1/100 grain are administered intramuscularly, followed forty-five minutes later by scopolamine 1/150 grain. Four hours later 100 mg. dose of Demerol hydrochloride is given with 1/200 grain of scopolamine. When there is need for continuing the medication, Demerol hydrochloride (100 mg.) is given every four hours, and scopolamine (1/200 grain) every two hours.

DOSAGE TABLE

Indications	Adult dose	Route of administration[1]	Frequency — Remarks
Medicine			
Biliary colic	100-150 mg.	Intramuscular or oral	Repeated in 1 to 3 hours as needed
Renal colic	100-150 mg.	Intramuscular or oral	Repeated in 1 to 3 hours as needed
Gastro-intestinal colic	50-150 mg.	Oral or intramuscular	Repeated at 3 or 4 hr. intervals as needed
Pleuritic pain	50-100 mg.	Oral or intramuscular	Repeated at 3 or 4 hr. intervals as needed
Arthritic pain	50-100 mg.	Oral or intramuscular	Repeated at 4 hour intervals as needed[2]
Neuritic pain	50-100 mg.	Oral or intramuscular	Repeated at 4 hour intervals as needed[2]
Cardiovascular pain	50-150 mg.	Intramuscular or oral	Repeated in 1 hour or more as needed
Hypertensive headache	50-100 mg.	Oral or intramuscular	Repeated at 4 hour intervals as needed[2]
Bronchial asthma	25-100 mg.	Oral or intramuscular	Repeated at 4 hour intervals as needed
Surgery			
Preoperative medication	50-100 mg.	Intramuscular or oral	30 to 90 mins. before beginning of anesthesia
Postoperative pain	50-100 mg.	Oral or intramuscular	Repeated at 3 or 4 hr. intervals as needed
Fracture pain	50-150 mg.	Intramuscular or oral	Repeated at 3 or 4 hr. intervals as needed
Bone metastases	50-150 mg.	Oral or intramuscular	Repeated at 3 or 4 hr. intervals as needed
Obstetrics			
Labor pain	100 mg.	Intramuscular or oral	When pain becomes regular. Repeated 3 or 4 times at from 1 to 4 hour intervals as needed[3]

1. For ambulatory patients, only oral administration is advised.
2. Side effects usually subside with prolonged use.
3. May be combined with scopolamine, barbiturates, local or general anesthesia.

HOW SUPPLIED

Demerol hydrochloride is available as follows:
For oral use: Tablets of 50 mg., bottles of 25, 100, 250 and 1000. Elixir, 25 mg. per teaspoonful (5 cc.), bottles of 473 cc. (16 fl. oz.).

For prescription purposes: Powder in vials of 15 Gm.

For injection: Vials of 30 cc. (50 mg. per cubic centimeter) with rubber diaphragm stopper. *Ampuls* of 2 cc. (100 mg.) boxes of 6, 25 and 100. *Hypodermic tablets* of 50 mg. and 100 mg., tubes of 20 and bottles of 100 and 500.

NARCOTIC BLANK REQUIRED

On July 1, 1944, Demerol – designated by the name "isonipecaine" – was included by Act of Congress under the Harrison Act. Therefore, its distribution and sale are governed by the regulations of the Federal Bureau of Narcotics.

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SUBJECT INDEX

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SUBJECT INDEX (Continued)

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ABSTRACTS

from

the Medical Literature on

SULFADIAZINE

GENITOURINARY INFECTIONS

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Abstracts from the Medical Literature

ON

SULFADIAZINE

The Clinical Use of Sulfadiazine in Non-Specific Urinary Tract Infections. A Study of 100 Cases.

LaTowsky, Leroy W. (Urological Service and Harrison Department of Surgery, Research Medical Schools and Hospital, University of Pennsylvania, Philadelphia).

The Journal of Urology 50:625 (November) 1943.

THE excellent results obtained in the therapy of gonorrheal urethritis with sulfadiazine prompted the author to test it in nonspecific infections of the urinary tract. Sulfadiazine was tested in a group of 100 consecutive patients with a variety of these conditions, 85 per cent of which were severe enough to require hospitalization. The remainder were cases seen in the outpatient department.

The series presented a very good cross-section of the conditions in question. There were cases of benign and malignant prostatic hyperplasia, cystitis secondary to stricture, and other causes of urinary stasis, bladder diverticulum, calculous and noncalculous pyelonephritis, and epididymitis.

The causative agents were *Escherichia coli*, *Staphylococcus albus* and *aureus*, *Streptococcus hemolyticus* and *nonhemolyticus*, *Aerobacter aerogenes*, *Pseudomonas aeruginosa*, *Streptococcus viridans*, *Bacillus proteus*, *Bacillus mucosus capsulatus*, *Escherichia pyogenes*, and *Bacillus hemophilus*.

Sulfadiazine was efficacious to some extent against all of these microorganisms. The effect was poorest where *Streptococcus viridans* was encountered, but even there the response was favorable in 57 per cent of the cases. There was generally a good response in urinary tract diseases associated with benign prostate hypertrophy, cystitis secondary to stricture, pyelonephritis (both calculous and noncalculous), and epididymitis. Adenocarcinoma of the prostate or bladder and bladder diverticulum as cause of urinary infection did not respond well. Criteria for good response were sterile urine, clearing of the urine of pus and albumin, and disappearance of symptoms.

Most of the patients were given 2 to 4 Gm. of sulfadiazine for 4 to 60 days, the range being 1 to 6 Gm., with febrile pyurias on higher

dosages. An adequate fluid balance (3,000 cc. or more fluids daily) was insured throughout the time of the treatment. The author made a deliberate attempt to keep the urinary pH on the acid side, in contrast to Schwartz, Flippin, Reinhold and Domm[1], basing this on the evidence brought forth by Yeaw[2] that high pH levels favor the growth of bacteria in the urine, whereas a urinary pH on the acid side renders the urine bacteriostatic for the common invaders. No urinary calculi were produced by this form of treatment. Toxic reactions were minimal and subsided promptly on discontinuation of the drug.

An important point was the fact that sulfadiazine was readily excreted even in four cases of renal impairment severe enough to cause changes in blood urea nitrogen and phthalein excretion.

The author emphasizes the necessity for accurate urologic and bacteriologic study and of concurrent surgical treatment, if indicated, as removal of stones, tumors, diverticula, and urinary obstruction.

The author's figure of 74 per cent satisfactory responses with 2 to 4 Gm. of sulfadiazine compares favorably with the reports in the literature on the use of sulfathiazole. The lower toxicity of sulfadiazine with at least equal efficacy suggests that sulfadiazine is the drug of choice in nonspecific urinary tract infections alike, as it is in gonorrheal infections.

(1) Schwartz, L.; Flippin, H. R.; Reinhold, J. G., and Domm, A. H.: J. A. M. A. 117:514 (Aug. 16) 1941.

(2) Yeaw, R. C.: J. Urol. 44:699 (Nov.) 1940.

Medical Progress—Urology.

QUINBY, WILLIAM C. (Urological Clinic, Peter Bent Brigham Hospital, Boston, Massachusetts).

New England Journal of Medicine 229:972 (December 23) 1943.

THE sulfonamide compound that is today the one of choice in urinary tract infections is sulfadiazine.

The majority of bacterial infections of the urinary tract respond to its administration, with the exception of that produced by the enterococcus. Small doses (2 to 4 Gm. daily) suffice in most cases, and, therefore, the desired results are obtained without untoward manifestations. It is advisable to maintain an alkaline urine by means of sodium bicarbonate and a daily urinary output of at least 2 liters when the patient is given sufficient fluids. Should precipitation of the drug occur, with blockage of the ureter or kidney pelvis, it can usually be relieved by ureteral lavage, best performed with a low concentration of bicarbonate solution.

Literature on Sulfadiazine

Sulfadiazine: Further Clinical Studies of Its Efficacy and Toxic Effects in 460 Patients.

FINLAND, MAXWELL; PETERSON, OSLER, L., and GOODWIN, ROBERT A., JR. (Boston City Hospital and Department of Medicine, Harvard Medical School, Boston, Massachusetts).

Annals of Internal Medicine 17:920 (December) 1942.

THE results of treatment and toxic reactions encountered in 460 patients treated with sulfadiazine are described.

Among this series there were 6 patients with gonococcal infections of the genital tract, all of whom had complications such as epididymitis, orchitis, conjunctivitis, or salpingitis. In all cases, fever, symptoms, and discharge promptly subsided with sulfadiazine therapy and there were no relapses.

There were 18 patients with gonococcal arthritis. In 13 of these, the symptoms were relieved within 1 to 5 days and did not recur. Five of the patients with acute gonococcal arthritis had been previously treated with sulfathiazole for 10 days or longer, but failed to improve. In all of these, improvement was noted 24 to 48 hours after the administration of sulfadiazine was begun.

Urinary tract infections were treated in 60 patients, 39 of whom suffered from acute and 21 from chronic conditions of a variety of urinary infections. As a rule, the patients with uncomplicated acute infection responded very well to sulfadiazine. Even 2 cases with acute glomerular nephritis showed definite improvement. The 21 chronic cases had associated severe surgical or systemic disease. The results therefore were difficult to interpret. Four deaths occurred in this group from the primary disease.

There was no evidence of sensitization in the 21 patients receiving a second or third treatment with sulfadiazine.

These favorable results present a confirmation of the earlier conclusions drawn from a series of 446 patients from the same hospital as to the efficacy and low toxicity of sulfadiazine[1]. Sulfadiazine may be considered the drug of choice, compared to sulfathiazole, in acute infections of the urinary tract and in acute gonococcal infections, due to its lower toxicity. This is particularly true in all cases requiring prolonged treatment.

Toxic effects attributable to sulfadiazine were relatively few and mild. Of the various toxic reactions noted, the most frequent were encountered in the urinary tract; 7.4 per cent of the cases had crystalluria and 5.2 per cent hematuria, although the latter was only micro-

scopic in 4.3 per cent. If oliguria occurs, the fluid intake should be immediately increased and the dosage of the drug reduced. With marked suppression of the urinary output and particularly with concomitant ureteral pain, fluids must be forced and ureteral catheterization should be carried out, since by so doing, a fatal outcome may be avoided.

Full courses of sulfadiazine were given to a number of patients who had previously been treated with another of the sulfonamides. Side effects in these cases were similar to those seen in patients who had no previous experience with other sulfa preparations. This was true regardless of whether or not the patients had shown side effects from these other drugs.

(1) Finland, M.; Strauss, E., and Peterson, O. L.: J. A. M. A. 116:2641 (June 14) 1941.

Treatment of Gonococcic Vulvovaginitis— A Study of 442 Children.

COMPTON, BEVERLEY, C.; BIEREN, ROLAND E.; JONES, EDWARD GOMER; INLOES, BENJAMIN HARRISON, JR.; KARDASH, THEODORE, and HUNDLEY, J. MASON, JR. (Department of Gynecology of the University of Maryland School of Medicine, Baltimore, Maryland).

Journal of the American Medical Association 127:6 (January 6) 1945.

THE authors found 318 cases of gonococcic vulvovaginitis among 442 children examined for vaginal discharge; i.e., 72 per cent. In most cases the secretion is loaded with gonococci, so that the diagnosis can easily be made by smear.

The diagnostic, therapeutic, and follow-up methods can be duplicated in any office practice or outpatient department. The child should be isolated at home, since the disease is spread by the purulent discharge. The parents should be given instructions in the use of towels, commode, and clothing.

Sulfadiazine and estrogens have been found highly successful in vulvovaginitis of gonococcic origin.

With sulfonamide therapy, the discharge usually decreased in 2 to 3 days, the smears remaining positive at the end of 1 week and becoming negative by the end of the second week. Sulfonamides, as a rule, may be stopped by the end of the second week.

In none of the children treated were toxic reactions observed. The dosage was 0.25 Gm. of sulfadiazine per day for children from 6 months to 1 year; 0.5 Gm. per day for children from 1 to 4 years; 0.75 Gm. to

1 Gm. per day for children between 5 and 10 years. These are half the doses which must be given of sulfathiazole.

The sulfonamides should be used in cases with complications or when estrogen treatment is unsuccessful. All cases should have a follow-up at increasingly longer intervals for at least one year before being pronounced cured.

Sulfonamide Therapy in Gonococcal Infection in Women (Sulfanilamide, Sulfapyridine, Sulfathiazole, and Sulfadiazine).

HESSELTINE, H. CLOSE; HAC, LUCILE R.; ADAIR, FRED L., and HIBBS, DONALD K. (Department of Obstetrics and Gynecology, University of Chicago and the Chicago Lying-in Hospital, and the Chicago Municipal Social Hygiene Clinic, Chicago, Illinois).

American Journal of Obstetrics and Gynecology 49:746 (June) 1945.

THIS report is the result of a thorough four-years' investigation to determine to which of the various sulfonamide compounds women with gonococcal infection respond most surely and promptly. The well established value of sulfa chemotherapy in gonorrhea was formerly based primarily upon results obtained in men.

One thousand one hundred and twenty-six female patients with acute and chronic gonococcal infections were observed and treated with sulfanilamide, sulfapyridine, sulfathiazole, and sulfadiazine. Insofar as was practical, patients were assigned in rotation to these drugs. Of these 1,126 women, 551 had to be discarded; they could not be considered as responding to the therapy, because they did not complete the course of treatment. The remaining 575 patients fulfilled the criteria required by the authors, viz., observation through at least 2 months following sulfa treatment, with diagnosis and cure based on cultures and provocative tests.

Seventy-five per cent of the 575 women could be discharged as cured while 25 per cent had repeated positive cultures and needed further treatment. This was effected by a single course of therapy.

The differentiation between what was to be considered an actual failure of treatment, and what as a reinfection, was often a difficult problem, as is easily understood in an infection such as gonorrhea in ambulatory cases.

The 4 sulfonamides were given in 4 daily doses, and 6 days constituted one course of therapy (only sulfanilamide required 14 days). Sulfadiazine and sulfathiazole were effective in the smallest dosage (2 Gm. daily), the dose for sulfapyridine was higher (3 Gm.), and for sulfanilamide highest (6.6 Gm.).

Careful computation and clinical scrutiny revealed clearly that sulfadiazine was the most effective of the four tested sulfa compounds. Following it 94 per cent were cured; following sulfanilamide, 71 per cent; with sulfapyridine, 82 per cent; with sulfathiazole 87 per cent. When the patients exposed to reinfection were deleted, the percentage failure with sulfadiazine was lowest (only 1 per cent); highest with sulfanilamide (17 per cent); with sulfapyridine 6 per cent, and with sulfathiazole 3 per cent. Chronic infections and cases with secondary complications responded as readily as did acute ones, whereas the gonococcal infections in the pregnant patients were more resistant if treated with sulfathiazole, sulfapyridine, and sulfanilamide, but not if treated with sulfadiazine. Among the latter there was no failure in the pregnant women, while the percentage failure for sulfathiazole was 6, for sulfapyridine 27, and for sulfanilamide 57. The efficacy of sulfadiazine in gonorrhea of pregnancy is particularly noteworthy. The fact is well borne out by many investigators that the gonococcus infection in pregnant women is highly resistant[1].

None of the newborn was adversely affected by the cure of the mother during pregnancy. All of the patients tolerated sulfadiazine and sulfathiazole better than the other two preparations.

In every respect then, sulfadiazine was found to be the outstanding curative drug and is designated by the authors as the drug of choice in the treatment of gonococcal infection in women.

(1) Blair, H. I.: The Venereal Disease Problem in a Woman's Federal Reformatory. Am. J. Syph., Gonor. & Ven. Dis. 30:165 (Mar.) 1946.

Treatment of Gonococcus Infection.

Ill, Herbert M. (Medical Corps, U. S. N. R.).

Military Surgeon 96:78 (January) 1945.

THE author, disappointed with earlier methods of gonorrhea therapy using small doses of sulfa drugs in combination with irrigations and instillations, decided to try massive doses of sulfadiazine and to do without the local treatment. The latter, it was felt, had been responsible for many of the complications, especially prostatic infections.

Sulfadiazine was chosen because of its outstanding effectiveness against the meningococcus. In view of the bacteriological similarity between the meningococcus and the gonococcus, the assumption seemed justified that gonococcus infections would respond as well to sulfadiazine.

Thirty grains were given every 3 hours during the first day and 22½ grains every 3 hours during the following 48 hours, 640 grains

in all, irrespective of body weight. During the three-day period, 10 grains of sodium bicarbonate were administered with abundant fluids every hour, day and night. The patients had to stay in bed and to refrain from spicy food. The sulfadiazine blood level was determined daily. At the end of the three-day period, treatment was discontinued, and no sulfadiazine, alkalis, or forced fluids were given.

Of 56 patients, 45 (79 per cent) had no pus in the urine after 4 weeks. Forty-two patients (74 per cent) had no discharge after 3 days and no pus in their urine 2 weeks thereafter. Thirty-six patients (63 per cent) had no discharge after discontinuance of therapy, and no pus in the urine after 10 days. None of the patients discharged from the hospital returned with a recurrence. Twelve cases were not helped. Examination of these patients showed large amounts of pus in the prostatic secretions containing the gonococcus. These patients were then treated with penicillin.

From his results the author concluded that large sulfadiazine doses are to be preferred in the initial treatment of gonorrhea. With small doses the gonococci become gradually sulfa-resistant, and once they have invaded the prostate gland, no amount of chemotherapy will remove them. There were no serious reactions, which proves that large doses of sulfadiazine are well tolerated over a short period, provided alkalis and sufficient fluids are given.

The Modern Treatment of Gonorrhea in the Male.

McLachlan, A. E. W. (Consultant in Venereal Diseases. Lecturer in Venereal Diseases, University of Bristol, England).

Practitioner 154:295 (*May*) 1945.

THE addition of the sulfonamides to the armamentarium of the physician has dramatically improved the outlook in gonorrhea therapy. It has shortened the cure and decreased the incidence of refractory or complicated cases. Thus, the objectives of treating venereal diseases, viz., the eradication of the infection at the earliest possible time and the curtailment of the period of infectivity, have been reached with much greater certainty than was the case formerly.

The treatment of gonorrhea comprises (1) general therapy, (2) chemotherapeusis, and (3) local application.

There are two sulfa compounds now chiefly employed, sulfadiazine and sulfathiazole. They have replaced sulfapyridine which shows lesser effectiveness and greater toxicity.

Sulfadiazine, of equal therapeutic activity, has been less productive

of side effects than has sulfathiazole, in the experience of the author, which is in accordance with all other reports.

The latter point is essential, since optimal doses of the drug are desirable for an effective blood concentration. Suboptimal amounts lead to immediate failure as evidenced by the persistence of clinical signs and the development of sulfa-resistant strains.

Five Gm. of the sulfa preparation daily are given in 3 doses, 1½ Gm. after breakfast, the same dosage 8 hours later, and 2 Gm. before retiring. The sulfonamide therapy is extended over 5 days. The author sees no advantage in continuing it beyond this period; the cure rate is not increased thereby, but the toxic sequelae become more frequent.

With successful treatment, there is rapid decrease of the urethral discharge within 24 hours and complete disappearance in 48 to 72 hours. The urine clears promptly with only a fine flocculate of threads by the third day. After 24 hours no gonococci are found, while a varying amount of pus might be noted, which disappears after the third day. The general condition of the patient parallels the bacteriological progress.

Observation and repeated examinations over a period of at least 3 months are needed to consider a cure as certain.

The criteria for a cure are consistently negative findings during the period of surveillance and a normal condition of the mucous membrane in urethroscopy.

Fifty to 60 per cent of the patients are cured after the first course of sulfa treatment. Failures are due to various causes. There are sometimes sealed-off foci of infection; the gonococci may become chemoresistant; complications (prostatitis, vesiculitis) may develop, usually a month after discontinuance of an apparently successful therapy. For these cases local treatment, gonococcal vaccine, fever therapy, and penicillin have been advocated.

There is no general agreement whether or not local treatment should be employed in acute cases, but there is consensus that it is indicated in refractory cases and in relapse. Urethral irrigation with potassium permanganate, albargin, or oxycyanide of mercury, in combination with increasing doses of a detoxicated polyvalent gonococcal vaccine is usually followed by marked improvement. It is, however, advisable to administer a second course of sulfonamide therapy, preferably changing to a drug other than that used before. Closed foci in the prostate or vesicles call for prostatic massage with subsequent vesicourethral lavage. A third course of sulfa treatment should follow the local treatment, whereby the majority of refractory

cases will respond successfully. A further course of the sulfonamide should also be given if fever therapy was employed in those refractory cases. It is to be expected that penicillin will further simplify the gonorrhea problem.

The Treatment of Gonorrheal Urethritis in the Male with Sulfonamide Derivatives—A Study of 199 Cases.

LaTowsky, Leroy W.; Knight, Frank; Uhle, Charles A. W., and Baker, Richard B. (Genito-Urinary Clinic, Philadelphia General Hospital, Philadelphia, Pennsylvania).

Journal of Laboratory and Clinical Medicine 27:1001 (May) 1942.

THE authors who had previously evaluated the sulfonamides in a number of papers on the therapy of gonorrheal urethritis in the male, report another study of 199 patients with gonorrhea.

The special purpose of this paper was to compare the therapeutic efficiency of sulfadiazine, sulfathiazole, and sulfapyridine, it being an established fact that sulfanilamide is no longer indicated in gonococcic infections, since these three sulfa drugs have been shown to be superior.

Of the 199 patients, there were 130 cases with acute anterior urethritis, 3 with subacute anterior urethritis; there were 59 with acute, 6 with subacute, and 1 with chronic posterior urethritis. The diagnosis was based on smears and cultures of the urethral exudate in every case.

The dosage of the 3 sulfonamides was kept as uniform as possible, though in individual cases it had to be fitted to the patient's condition.

One hundred sixty-seven of the patients could be followed to the completion of the cure or failure. Ninety-three and one-half per cent of these were apparently cured. The criteria of cure were: (1) after repeated prostatic massages, smear, and culture of the prostatic fluid to be negative in at least two examinations; (2) negative after passing a sound into the urethra; (3) negative after alcoholic indulgence, and (4) a negative condom test.

There were no significant statistical differences in the cure rates of the three sulfa compounds, but with sulfadiazine the average dose to effect a cure was significantly smaller (17.5 Gm.) than with sulfathiazole (28 Gm.) and sulfapyridine (23.5 Gm.).

The time elapsing between the start of treatment and the first negative prostatic culture was also lowest in the case of sulfadiazine (average 13 days) as compared with sulfathiazole (28 days) and sulfapyridine (51 days).

The so-called carrier state (the time that elapsed from the cessation of symptoms until the last positive prostatic culture) was also remarkably reduced in sulfadiazine treatment (average: 3 days, range: 0 to 18 days), while the corresponding figures for sulfathiazole were an average of 17 days and a range of 3 to 50 days.

The use of sulfadiazine was attended by the least toxic reactions (8.8 per cent), sulfapyridine showed the most (75 per cent), and sulfathiazole 11.5 per cent. Complaints were minor among the patients treated with sulfadiazine and sulfathiazole. They were severe in the case of sulfapyridine.

The authors conclude that sulfadiazine has a high cure rate, a low toxicity, and makes the prostatic fluid free from gonococci sooner than any of the other sulfa drugs used. Sulfathiazole is very effecuve too, and causes few toxic reactions. Sulfapyridine would better be excluded from the therapeutic armamentarium in treating the ambulatory patients with gonorrhea, because it causes too many and too severe toxic reactions.

The Sulphonamides in Ophthalmia Neonatorum.

Sorsby, Arnold, and Hoffa, Elizabeth L. (White Oak (L. C. C.) Hospital).

British Medical Journal 1:353 (March 11) 1944.

THE authors confirm their earlier (1942) findings as to the effectiveness of sulfonamides in both gonococcal and nongonococcal ophthalmia of the newborn.

In the present series a standard dose of 4 sulfa compounds (sulfapyridine, sulfathiazole, sulfadiazine, sulfamethazine) was used in 258 cases. The initial dose was 0.25 Gm., the maintenance dose 0.125 Gm., four-hourly during the active phase as well as for 3 days after apparent cure. They found sulfapyridine probably the least satisfactory of the four owing to its greater toxicity and have discontinued its previous routine use. Sulfadiazine proved to be the best tolerated of the sulfa drugs employed.

In the 258 cases, clinical cure was obtained in 85.7 per cent within 8 days, and 29.9 per cent were cured within 3 days. Fifty-five and eight-tenths per cent required 4 to 8 days, and 14.3 per cent took a delayed course.

The present study shows that the sulfa drugs are effective both in nongonococcal ophthalmias and in those caused by the gonococcus, but that the cures are quicker in the specific infection. Fifty-one and

seven-tenths per cent of the gonococcal variety showed a clinical cure within 3 days, as compared with 23.2 per cent of the nongonococcal cases. By the eighth day 90 per cent of all gonorrhoic ophthalmias had become resolved and 84.3 per cent of the nongonococcal infections. The causative agents in the nonspecific cases were various bacilli (mostly diphtheroids), staphylococci, other coccal organisms, and inclusion bodies.

Only occasionally was a case wholly resistant to sulfatherapy. More often it was more a matter of sluggish response than of total resistance.

There were few relapses and, apart from minor side effects, no toxic reactions.

Sulfadiazine and Sulfathiazole Therapy in Lymphogranuloma Venereum and Chancroid—A Report of Thirty Cases.

NOOJIN, RAY O.; CALLAWAY, J. LAMAR, and SCHULZE, WILLIAM (Section on Dermatology and Syphilology of the Department of Medicine, Duke University School of Medicine, Durham, North Carolina).

American Journal of Syphilis, Gonorrhea and Venereal Diseases 27:601 (September) 1943.

THE authors give a report on the diagnosis, treatment, and clinical results in 10 patients with lymphogranuloma venereum, 10 patients with chancroid, and 10 patients with lymphogranuloma venereum and/or chancroid.

All patients showed inguinal lymphadenopathy. The diagnosis of lymphogranuloma venereum was confirmed by a positive Frei test. Both yolk-sac antigen (*Lederle*) and human antigen were employed as test materials. For chancroid diagnosis the intradermal reaction to Ducrey Vaccine (*Lederle*) and the identification of the Ducrey bacillus were used. Half of each group received sulfadiazine therapy, and half were treated with the thiazole compound. The drugs were administered orally.

Each patient was given 6 Gm. of the sulfa drug on the first day and 3 Gm. daily thereafter.

With sulfadiazine therapy, the blood concentration level was higher than with sulfathiazole. Drug reactions were relatively infrequent following sulfadiazine. In no patient was it necessary to discontinue the sulfonamide because of urinary or hematological complications.

The clinical efficacy of both drugs appeared to be the same. Twenty-eight out of the 30 patients reported improvement after institution of treatment. Pain in the region of the lymphadenopathy and at the site

of the genital lesion subsided. Lymph node suppuration was prevented, unless fluctuation or drainage was already established. The Frei and Ducrey tests were unchanged at the end of the therapy.

With one exception, all patients could continue their daily activities while under treatment, an important point in regard to the economic value of the sulfa therapy.

The authors conclude by stating that, in view of the more frequent toxic reactions with sulfathiazole, sulfadiazine is the drug of choice in ambulatory patients.

An Evaluation of Urinary Antiseptics.

BURNS, EDGAR (Department of Surgery, Tulane University School of Medicine, and the Section on Urology, Ochsner Clinic, New Orleans, Louisiana).

Southern Medical Journal 37:320 (June) 1944.

THE value of urinary antiseptics can be properly assessed only by using appropriate methods. First of all, the adequacy of the renal function has to be determined before any medication is started because a damaged kidney cannot concentrate the drug in sufficient strength to kill the bacteria.

Urine from female patients must be obtained by catheter (voided samples may contain discharges from cervix and vagina); in the male, the last portion of the two-glass test should be used for examination (the first portion may carry infectious material from the prostate, seminal vesicles, and urethra). The laboratory report should identify the condition as coccal or bacillary and as Gram-positive or negative. Cultures should be made at least in resistant cases.

Such preliminary determinations would also allow for a better selection of the drug to be employed in the individual case.

The established efficacy of the sulfonamides in combating urinary infections has earned for these drugs a permanent place in this field. They act as well in acid as in alkaline urine, which makes them superior to methenamine and mandelic acid.

Sulfadiazine has proved to be effective in acute infections, particularly those caused by the colon bacillus and by certain strains of streptococci and staphylococci. It produces less gastrointestinal irritation and is, therefore, better tolerated in pregnancy and in the aged than any other sulfonamide.

Since the author has used sulfadiazine in pyelonephritis of pregnancy, he could do without indwelling catheters and cystoscopy, except in cases where there was complete obstruction.

Dosage was 45 to 60 grains sulfadiazine daily in divided doses. As soon as the acute symptoms subsided, the dose was reduced to 30 grains daily. Intravenous administration of sodium sulfadiazine (3 to 4 Gm.), followed by 15 grains every 6 hours orally, was found valuable in severe acute urologic infections, such as those flaring up after delivery and acute pyelonephritis of pregnancy.

Renal reaction due to sulfa precipitation should be prevented by giving appropriate amounts of alkali during the period of treatment.

Mandelic acid is not a good medicament in the treatment of acute pyelonephritis with chills and fever, since it is not well tolerated, but it is valuable in infections caused by the *Streptococcus fecalis*.

Chemotherapy in the Treatment of Obstetrical and Gynecological Urinary Tract Infections.

DOUGLAS, R. GORDON (New York Hospital, Cornell University Medical College, New York, New York).

Connecticut State Medical Journal 7:388 (June) 1943.

PREGNANCY, labor, and puerperium present certain predisposing factors for the development of infections in the urinary tract. The hyperplasia, increased vascularity, edema, atony of the genital organs, and hormonal changes in the maternal organism combine to produce conditions favorable to infection. Trauma during labor is an additional element of great importance, since the bladder is highly susceptible to injury which almost invariably entails infection. Gynecological abnormalities and diseases, because of the proximity of the two systems, frequently affect the urinary tract.

The author, who had directed the treatment of several hundred women with urinary tract infections for 5 years, this time reports on the use of sulfonamides in this category, with special regard to sulfadiazine.

Since sulfanilamide, sulfapyridine, sulfathiazole, and sulfadiazine were introduced, the therapy of urinary infections has been completely revolutionized. The older drugs, with the possible exception of mandelic acid, are now of historical interest only, since sulfadiazine has replaced them.

This paper gives an analysis of 34 antepartum and 54 postpartum urinary tract infections. Sulfanilamide, formerly largely used, is at present practically never administered by the author. Sulfapyridine was employed in few cases and then discontinued because of objectionable properties, especially precipitation in the urinary passages.

Sulfathiazole was used in 1939-40, but in the past two years the author has confined his therapy mainly to sulfadiazine, which is slightly superior to sulfathiazole and less toxic.

A "drug cure," i.e., the elimination of the causative agent during the course of the treatment, was effected with sulfadiazine in all antepartum and all postpartum cases. There was one failure in the sulfathiazole series, and 24 with sulfanilamide.

Sulfadiazine and sulfathiazole were given in equal amounts (6 Gm. per day), in divided doses, and rarely for more than 6 days. The author holds that, if a therapeutic effect is not obtained within one week, beneficial results are rarely obtained by continuing the administration for a longer time, but the incidence of toxic drug reactions would certainly be increased by prolonged treatment.

All of the postpartum infections and over 90 per cent of the antepartum infections were associated with the colon or the *aerogenes bacillus*.

Three cases are reported in detail and illustrate the value of sulfadiazine by its excellent therapeutic effect. The author also points out the prophylactic value of sulfadiazine in controlling urinary tract infection prior to gynecologic operations. Bladder retention and repeated catheterization or indwelling catheters frequently cause infection. The prophylactic administration of 3 Gm. sulfadiazine or sulfathiazole prevents the danger of infection.

The author took care to administer large quantities of fluids in order to maintain a sufficient output of urine and did not encounter precipitation with either sulfadiazine or sulfathiazole.

Pyelitis of Pregnancy.

GALLOWAY, CHARLES E. (Evanston, Illinois).

Urologic and Cutaneous Review 49:428 (July) 1945.

THE incidence of pyelitis (or pyelonephritis) in pregnancy is approximately 2½ per cent. Three etiologic factors are generally acknowledged: urinary stasis, presence of bacteria in the urinary passages, and dilatation of the ureters and renal pelves. Controversy still remains as to the mechanism of the stasis, the source of the bacterial agents and the cause of the dilatation.

Escherichia coli accounts for about 90 per cent of the microorganisms in pyelitis. Pyogenic cocci are found in 10 per cent, but they are the original offending agents in the majority of cases, the colon bacilli being the secondary invaders.

Prevention rather than cure of pyelonephritis should constitute the aim of the obstetrician, and he can fulfill this purpose by the early administration of the sulfonamides in pregnancy if the history and/or examination of the woman reveals previous attacks or present bacteriuria. The prefebrile therapy gives the best results. Small doses of sulfadiazine or sulfathiazole are quite effective. Concentrations of as little as 2.5 mg. per cent of urine will kill 90 per cent of the colon bacilli. The author administered usually 0.5 Gm. of sulfadiazine or sulfathiazole with a small quantity of sodium bicarbonate 5 times a day and saw the infected urine become sterile within 3 to 5 days. With such small doses, there is very little concern as to crystallization or untoward reactions.

The author stresses the point that, with such gratifying resuits obtained by small amounts of the newer sulfa drugs, the obstetrician really is in a position to protect his patient from pyelitis *before* the bacteria have become destructive. He closes with the statement that pyelitis in pregnancy can be looked upon in the majority of cases as caused by the neglect of the obstetrician.

Once the pyelonephritis has become febrile and fully established, and stasis has resulted in a bacterial concentration of millions per c.c. with little or no diuresis, one cannot expect the same striking effect in employing the sulfa drugs. A big reserve of highly infectious urine may interfere with their bacteriostatic action. Large sulfa doses are not indicated in severe cases, since the drug is concentrated in the kidney. Three to 4 Gm. on the first day, and 2 Gm. then for 7 days will suffice in febrile cases. A fluid intake of at least 3,000 cc. daily should be maintained, sodium bicarbonate given, and the renal function carefully checked. With these precautions, the mere presence of crystalluria should not be looked upon as a danger signal. Mandelic acid should then be tried and an acid urine (pH of 5) maintained, although this is often difficult because of the renal damage usually associated with those severe cases.

Maternal Deaths Due to Infection.

Minnesota Maternal Mortality Committee.
Minnesota Medicine 28:635 (August) 1945.

ALTHOUGH maternal mortality has definitely decreased in Minnesota, in accordance with the general trend throughout the United States, there were 18 of 26 deaths caused by puerperal infection in one year, which the Committee felt were preventable and were the responsibility of the attending physician.

Among the lessons to be learned from a study of these maternal deaths were the following:

There was a lack of proper prenatal care, improper evaluation of the relative size of the fetus and mother's pelvis, too many vaginal examinations, questionable asepsis, inadequate postpartum care, and failure to utilize fully what the Committee calls "the chemotherapeutic attack" with sulfonamides.

The choice of the right sulfa drug in the individual case frequently was not the wisest, or the dosage was too small, or the sulfonamide therapy was not instituted early. Sulfanilamide was used where sulfadiazine or sulfathiazole would have been more effective.

Sulfadiazine has become the drug of choice for almost all infections developing in obstetric practice. Its low toxicity and rapid rise in blood concentration allow for the maintenance of the efficient blood level with less frequent administration. The initial dose for an adult patient is 2 to 3 Gm. of sulfadiazine together with 4 Gm. of sodium bicarbonate. It is followed by 1 Gm. of sulfadiazine and 4 Gm. of sodium bicarbonate every 6 hours, providing an average blood level of 6 to 8 mg. per cent.

Sodium sulfadiazine is given intravenously or subcutaneously when the drug cannot be taken by mouth. The intravenous application is begun with 3 Gm. of the sodium salt as a 0.5 per cent solution in physiological saline and followed with 1 Gm. every 6 to 8 hours. For subcutaneous administration similar doses are used in a 1 to 2 per cent concentration. A fluid intake must be secured to produce a urinary output of at least 1,000 cc. daily. The Committee states that, at present, there seems to be little justification to use the other sulfa compounds in purely obstetrical infections. Penicillin therapy may be combined with the sulfadiazine treatment. Early and active chemotherapy is essential in the control of these infections.

The Management of Abortion.

PURDIE, ANTHONY W. (North Middlesex County Hospital, England).

Practitioner 155:35 (July) 1945.

FOLLOWING an outline of symptomatology and diagnosis of threatened inevitable, complete, incomplete, and missed abortion, the therapy of the various types is reviewed.

Special attention is devoted to the frequent septic cases. The author's practice is to evacuate the uterus with the utmost gentleness. Intrauterine glycerin is employed and a sulfonamide given if there is toxic appearance and the uterine content frankly offensive. A high

vaginal swab culture is then taken and the drug continued when hemolytic streptococci predominate.

There is diversity of opinion whether it is wise to evacuate the uterus in these cases or to adopt an expectant attitude. The author is inclined to follow Rutherford's method, who gives sulfadiazine routinely, takes cervical smear, and awaits the bacteriological report.

If the evidence is positive for hemolytic streptococci as predominant organisms, sulfadiazine is continued and the treatment remains conservative and expectant, until the temperature has been normal for 3 days. If the culture does not show a predominant hemolytic streptococcus and examination does not reveal a parametrial involvement, the uterus is curetted, even with fever present and a history of previous instrumentation.

Should general peritonitis be present with incomplete abortion, the author opens the abdomen with a small incision, inserts a drain down to Douglas' pouch, using sulfatherapy. Before laparotomy, the uterus is usually evacuated.

The outlined methods of the author for the treatment of abortion, not committed wholly to either school of strictly active or purely expectant therapy, appear definitely to shorten the period of hospitalization.

Spontaneous and Induced Abortion. Modern Concepts of Their Significance, Pathogenesis, Diagnosis and Treatment.

RUTHERFORD, ROBERT N. (Seattle, Washington).

The Western Journal of Surgery, Obstetrics, and Gynecology 51:257 (July) 1945.

THE author presents a plan of active therapy in spontaneous and artificial abortion with the aim of controlling hemorrhage and infection.

Sulfadiazine plays an important role in this therapeutic routine. As soon as the cultures are taken from the cervix, the patient is placed on sulfadiazine. The latter is preferred since it has a wider range against pathogens than sulfathiazole and is better tolerated than sulfanilamide. The author gives 2 Gm. doses of sulfadiazine hourly for 3 hours, and then 1 Gm. every 4 hours until a definite improvement can be noted. Blood and urine examinations are made every day or at least every other day. If, in rare cases, no microorganisms grow on the cultures, chemotherapy may be stopped.

When the cervical cultures show the hemolytic streptococcus to be the predominant invader, no active surgical procedure is instituted.

Bed rest, pelvic heat, and sulfadiazine are employed. When there is no predominance of hemolytic streptococci, curettage may be performed. Packing of the uterus is done only if the hemorrhage is severe, and one is definitely certain that no fragments are retained in the uterus. Packings impregnated with sulfa drugs have been employed with gratifying results.

The cultures are often of mixed variety, showing *Escherichia coli*, staphylococci, and saprophytes besides the streptococcus. Chemotherapy has given spectacular results in gas bacillus infections.

This more active therapy compares favorably in its late effects with the conservative treatment before the days of chemotherapy, and there is definite evidence of diminished infection and hemorrhage.

The Lignin Test.

(The following test is so extremely useful that it has been included, although it does not represent the work of any one author.)

THIS is a simple, rapid, and reliable test which gives evidence of previous sulfonamide therapy and has proven to be of practical value.

It allows immediate therapy if there are no facilities or no time to wait for the more laborious laboratory determination of sulfonamide in blood and urine. In the armed forces, culpability may sometimes keep the patient from reporting self-medication with sulfa drugs against venereal infection.

Put a drop of patient's urine on a piece of wood-pulp paper (paper towel, toilet paper, newspaper; but not filter paper). Add a drop of 5 per cent hydrochloric acid. If a sulfa drug has been taken, a yellow color appears immediately which on standing deepens to orange.

This color response occurs within 45 minutes to 1 hour after the first ingestion of a sulfonamide and remains positive up to 60 hours after the last dose. The presence of as little as 0.01 per cent of a sulfa drug gives a positive response. Nothing apt to occur in the urine will give a false test.

Lignin, the insoluble constituent of wood cells, is probably responsible for the color reaction.

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EVIPAL

Trademark Reg. U. S. Pat. Off. & Canada

SOLUBLE

"Evipal Soluble," *brand of* Hexobarbital Soluble

INTRAVENOUS ANESTHETIC

DESCRIPTION Evipal is chemically N-methylcyclohexenylmethylbarbituric acid. Evipal Soluble, its sodium salt, dissolves readily in water, but the solutions are not stable and therefore should be freshly prepared. For this reason Evipal Soluble is furnished as a powder in ampuls of 0.5 Gm. and 1 Gm. By the addition of distilled water shortly before use, a solution of the desired concentration is made.

PHARMACOLOGY Weese determined the hypnotic, narcotic and fatal doses of Evipal Soluble for the cat and mouse after oral administration, for the mouse after subcutaneous injection, and for the cat and dog after intravenous injection. In the cat an intravenous dose of 25 mg. per kilo usually produces full narcosis, while from 100 to 110 mg. per kilo are required to cause death. Thus the therapeutic ratio in the cat is somewhat less than 4; in the dog it is 3.3. Weese pointed out that the action of Evipal Soluble is brief after intravenous injection because the drug is destroyed rapidly in the liver, and that the action is prolonged when the function of the liver is impaired.

Parsons found in the cat that the anesthetic action of the drug is rapidly induced and of short duration. His figures suggest a therapeutic safety factor of 2, but the rate of injection is not stated. In rabbits half of the maximal narcotic dose is decomposed within thirteen minutes. Side effects in animals were found to be slight. The blood pressure decreased somewhat; the pulse remained regular and full. Overdosage caused cessation of breathing, the heart continuing to beat for some time after apnea set in.

Kennedy described the action of Evipal Soluble on mice, rats, guinea pigs and frogs. Considerable variation was found in the fatal dose, the therapeutic ratio according to the smallest dose being about 3 in mice and somewhat less in guinea pigs. It was also observed that waking from the anesthetic is rapid. Respiratory failure was found to be the cause of death in those animals which did not recover. After cessation of respiration the heart beat strongly, and if the thorax was opened after several minutes in which no respiratory movement was visible the heart was frequently seen to be still contracting. Artificial respiration, or the administration of carbon dioxide, was effective in restoring respiration in mice whose breathing had been markedly depressed.

In experiments on the frog heart Kennedy and Narayana showed that, while Evipal Soluble exerts a depressant action on the heart, the drug is not fixed by the cells since even high concentrations are readily washed out, with recovery of function to the original state.

Storm obtained results of a similar nature in perfusion experiments performed on the heart of the monkey.

Maloney and Hertz carried out toxicity studies in rats and rabbits. Ten rats were given (intraperitoneally) a dose of 100 mg. per kilogram; all survived. In another series of 10 rats a dose of 150 mg. per kilogram was injected and 9 survived. It was only when the dosage was increased to 280 mg. per kilogram that a 50 per cent mortality was recorded (5 of 10 rats). Surgical anesthesia was observed in the dosage ranges beginning at 60 mg.; at 80 mg. the anesthesia lasted ten minutes, and at 100 mg. its duration was twenty minutes. Recovery was rapid and no ill effects seemed to follow awakening.

In rabbits a dose of 60 mg. per kilogram produced hypnosis three minutes after injection; the hypnosis lasted an average of forty-five minutes, and the period of deep anesthesia was from five to twenty minutes. A dose of 70 mg. induced hypnosis within two minutes in most instances, and anesthesia lasting thirty-five minutes within five minutes. All animals in the several series of these experiments recovered. To each of a series of 10 rabbits 100 mg. were injected with no fatalities; with a dose of 150 mg. (in a series of 6 animals) there were 2 fatalities. Maloney and Hertz, as well as others, believe that the intraperitoneal route is accurately representative of slow intravenous injection. They state that the hazard of toxicity is inherent not in the drug per se, but rather in its absorption in any unit of time. Safety and therapeutic efficiency are

functions of rate and degree of absorption and detoxification. Applied to the clinical use of Evipal Soluble this would indicate that the drug should be given slowly, intermittently and in cases where there is no evidence of definite or pronounced liver dysfunction.

Weese has shown also why Evipal Soluble should not be administered to patients with purulent processes in the area of the parotid, the floor of the mouth, and in the anterior triangle of the neck. In elucidating the mechanism of the sudden cessation of respiration that may occur in such cases when intravenous anesthesia is employed, he produced abscesses in the carotid bifurcation of dogs and then studied the effects of pressure in this area. He found that if an abscess develops in the area of the carotid sinus, the nerve elements become more sensitive than normally when a certain stage of inflammation is reached. Should the nerve elements then be stimulated, the physiologic inhibition (through perceptive nerves from the carotid bifurcation) on the respiratory center will be greatly intensified. Consequently, pressure on such an altered area gives rise to a temporary or permanent respiratory failure with corresponding change in blood pressure, instead of only a transitory inhibition. However, this hypersensitivity diminishes during the course of anesthesia. If the anesthesia is deep enough, the sensitivity vanishes completely on the affected side as well as on the unaffected side. This gradual disappearance of the respiratory reflex seems to be due to the slowly induced anesthesia of the nervous elements in the carotid bifurcation itself.

CLINICAL CONSIDERATIONS AND INDICATIONS

Evipal Soluble was first employed clinically in 1933. Since then it has been used for intravenous anesthesia throughout the world in several millions of cases. The suggestions and recommendations presented in the following paragraphs are based upon many clinical articles, more particularly recent publications by notable anesthetists and surgeons.

Evipal Soluble is employed as a general anesthetic for surgical procedures and painful examinations that can be performed within a relatively *short period of time.* Intravenous anesthesia is preferred principally when other forms of anesthesia—inhalation, spinal, local—are contraindicated, or when the use of the former is deemed advisable in selected cases for certain special advantages characteristic of the intravenous method. Thus, intravenous anesthesia may be the choice for a patient with some complicating disorder who requires an operation which can not be carried out under inhalation, spinal or local anesthesia. Or, when considerable electric equipment is to be employed for a short operation, as in certain cystoscopic manipulations, intravenous anesthesia may be induced in order to avoid the risk of explosion which accompanies the use of inhalant anesthetics.

Evipal Soluble has been employed for many types of operative procedures. Its field of usefulness has included general surgery and the surgical specialties, particularly gynecology, urology, ophthalmology and rhinolaryngology.

Some of the operations and procedures carried out under intravenous anesthesia are as follows: Incision of boils and carbuncles, excision of small tumors and cysts, extraction of bullets and foreign bodies, reduction of fractures and dislocations, débridement, suture of wounds, painful change of dressings and removal of drainage tubes, treatment of burns, thoracotomy, biopsy, painful examinations, etc.

In *gynecology* intravenous anesthesia has proved serviceable for painful pelvic examinations and for those requiring muscular relaxation, for dilatation and curettage, perineal suture, cauterization of cervix, removal of cysts and polyps, cauterization of venereal warts and Skene's glands, etc.

Various *urologic procedures* have been carried out under intravenous anesthesia. Among these are cystoscopy, suprapubic cystotomy, passage of sounds, dilatation of stricture, meatotomy, circumcision, fulguration of tumors, lithotrity, incision and drainage of prostatic abscess.

In *ophthalmology,* intravenous anesthesia has been used for the removal of intra-ocular foreign bodies, incision of lacrimal abscess, tenotomy, trephining, lid operations, etc.

In *rhinolaryngology,* intravenous anesthesia has proved serviceable for drainage of the paranasal sinuses, myringotomy, removal of nasal polyps, tonsillectomy, bronchoscopy, etc.

In *psychiatry,* intravenous administration of short acting barbiturates such as Evipal Soluble has been found to

be a valuable aid in psychoanalysis and psychotherapy. Evipal Soluble is usually injected only at intervals frequent enough to maintain the patient in a preanesthetic state in which he loses inhibitions and talks freely. This semiconscious state may also be utilized for suggestion, persuasion and reeducation.

Control of ether convulsions with Evipal Soluble has been reported by a number of anesthetists. The convulsions usually stop promptly after injections of relatively small doses (3 to 5 cc. of 10 per cent solution).

Evipal Soluble should be employed *only by experienced anesthetists and surgeons.* An attempt should not be made to secure with Evipal Soluble alone anesthesia lasting longer than from twenty to thirty minutes. The contraindications to its use should be kept in mind and at all times there should be available the measures usually employed to combat respiratory depression.

MANNER OF USE

Preoperative Preparation. — Preoperative medication, such as morphine, scopolamine, etc., is seldom necessary. In the majority of reports, the administration of these agents before operation is not recommended. If a preliminary injection of morphine is made, it should be done from one-half to one hour before operation, and the dose should be as small as possible to avoid a depressing effect upon the respiratory center. However, whether or not morphine is given, it is helpful to administer atropine in order to decrease mucus in the respiratory tract. The preoperative administration of hypnotic agents, particularly barbiturates, is contraindicated.

Preparation of Solution.—Shortly before use the Evipal Soluble powder is dissolved in sterile distilled water (free from carbon dioxide) to make a 10 per cent solution. Dissolve the contents of the 1 Gm. ampul in 10 cc. of distilled water, and the contents of the 0.5 Gm. ampul in 5 cc. The water should preferably be warmed to body temperature. Care should be taken that all the powder is completely dissolved. This is best assured by withdrawing the distilled water into a syringe and injecting it into the ampul containing the powder. Then by aspiration and reinjection into the ampul a completely clear solution is made. The presence of undissolved particles or a discoloration of the solution indicates that the powder has been affected by carbon dioxide in the distilled water or by exposure to air and moisture, owing possibly to a fine crack in the ampul; such a solution should not be injected.

There is no objection to using the solution remaining in the syringe, provided it has been kept under aseptic conditions for not more than two or three hours, does not contain a precipitate, and is not discolored. Unused portions of Evipal Soluble solution or powder that have been exposed to the air for a longer time should be discarded.

Dosage and Injection.— The dosage of Evipal Soluble should not be determined arbitrarily on the basis of the patient's weight, age or size. There is considerable variation in individual reactivity to any of the barbiturates. Hence, the dose must be strictly individualized.

However, experience has demonstrated that the amount of drug required to produce satisfactory anesthesia in the majority of patients is well within certain limits. The injection is made intravenously, using a vein at the elbow, in the back of the hand or foot. To avoid any possible local irritation, care should be taken so that none of the solution, which is alkaline, escapes into the perivenous tissues. (If this should occur accidentally, hot moist compresses should be applied for some hours thereafter. Immediate injection of sterile normal saline solution in the affected area has also been recommended.) A 10 cc. syringe, with No. 19 or No. 20 needle, is employed. For most adult patients from 2 cc. to 4 cc. of the 10 per cent solution are required to induce unconsciousness. This fraction is injected at the rate of 1 cc. per ten seconds. During or immediately following the injection of this first fraction there occasionally occur twitching of the muscles of the face and generalized movements lasting for a few moments.

After the injection of this initial amount, about thirty seconds are allowed to elapse so that the effect may be observed. Then the injection of the solution is resumed to produce the degree of anesthesia and relaxation required for the contemplated procedure. Usually this stage of anesthesia is reached when an additional amount of 1 cc. or 2 cc. is injected. This second fraction is given intermittently according to indications. The experienced anesthetist or surgeon usually has no difficulty in determining the speed with which the second fraction is to be administered, as the signs of

anesthesia generally relied upon are the guide. The needle is kept in the vein throughout the operative procedure. A total dosage of from 3 cc. to 6 cc. is sufficient for most minor procedures, such as incision of an abscess, changing of a painful dressing, or short painful examinations.

When more profound anesthesia is required or when more time consuming procedures (lasting from twenty to thirty minutes) are being carried out supplemental amounts of the anesthetic agent are administered in small quantities from time to time as needed during the operation. Return of tonicity of the muscles, slight movements of the fingers or toes or eyeballs, or phonation call for an additional quantity of from 0.5 cc. to 1 cc. of the 10 per cent solution. The whole amount of the drug is given in divided dosage and injected in small quantities intermittently during the operation, much as when ether is administered by the open drop method. A total amount of 10 cc. of this 10 per cent solution is seldom required for adults, and it can not be exceeded without danger.

Throughout the entire period of anesthesia attention should be given to the lower jaw, care being taken that it is always kept forward so that a free airway is maintained. In some patients it is advisable to insert an airway as soon as this can be done. The effect on respiration must also be watched closely. Too rapid injection may produce transitory cessation of respiration. With the establishment of surgical anesthesia the

respirations are somewhat slower but generally deeper than normal. To follow the respiration easily a good plan is to place a wisp of cotton over the nostrils and mouth, as suggested by Lundy. The narrowed center of this "cotton butterfly" is attached to the upper lip by adhesive tape so that one wing comes in contact with the nostrils and the other with the lips.

A fall in blood pressure may occur after the injection of the first fraction of Evipal Soluble; usually this does not exceed 20 mm. of mercury. In some patients additional amounts of the drug may produce a greater fall; hence the drug must be used with caution in hypotensive individuals. In others there is a definite rise in the pressure, and in still others a fall may occur which is followed by a rise.

Recovery from Anesthesia.— In the majority of cases consciousness is restored in from fifteen to thirty minutes, depending upon the amount of drug injected. The mind is then clear and cooperation of the patient, should it be required, is easily elicited. Not uncommonly there follows some drowsiness or sleep if the patient is left undisturbed. Prolonged sleep, sometimes with unresponsiveness lasting several hours, may be encountered, but usually only when a relatively excessive dose has been administered. Because of the tendency to a hypnotic effect which gradually wears off, and also some ataxia and occasionally transient amnesia, intravenous anesthesia should not be looked upon as an office procedure; furthermore, the patient should not be allowed to walk unescorted shortly after its use.

CONTRAINDICATIONS Evipal Soluble is contraindicated in patients with hepatic disease or jaundice; and in all cases of respiratory disease with evidences of dyspnea or obstruction. In children, the air passages are relatively smaller and more readily obstructed. Consequently, particular caution should be exercised if for good reason intravenous anesthesia is used in young subjects. Evipal Soluble should not be employed in inflammatory processes of the throat and neck, in bronchiectasis or asthma. As with all general anesthetics, the use of Evipal Soluble is not considered preferable in severe septic conditions, paralytic ileus, peritonitis, extensive hemorrhage, and depressed state of the circulatory or respiratory system. Skill and experience are required in many cases to determine whether these conditions constitute an absolute bar to the drug. The total dosage should be decreased in old, debilitated or cachectic individuals and those with severe anemia. In the presence of arteriosclerosis, and especially when either hypertension or hypotension exists, Evipal Soluble should be employed with great caution.

HOW SUPPLIED Evipal Soluble is supplied in ampuls of 0.5 Gm. and 1 Gm. of the powder, boxes of 1 each, with an ampul of sterile distilled water. Also in ampuls of 0.5 Gm. of the powder, boxes of 1 and 10, and ampuls of 1 Gm., boxes of 1, 10 and 25, without distilled water.

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