In respect of the 9 slow babies Table II shows the dose of pethidine and the time between its administration and the birth of the child.

TABLE II

Parity	Degree of Dilatation of Cervix on Initial Dosage	Initial Dose	Time of Initial Dose before Birth	Final Dose	Time of Final Dose before Birth
1	4 fingers	100 mg. i.m.	2 hrs. 10 min.	100 mg. i.m.	30 min.
1	3 "	100 mg. i.m.	55 min.	—	—
1	3 "	100 mg. i.m.	2 hrs. 25 min.	100 mg. i.m.	20 min.
1	Anterior lip	100 mg. i.v.	20 min.	—	—
0	"	100 mg. i.v.	2 hrs.	—	—
0	3 "fingers"	100 mg. i.v.	2 hrs. 35 min.	100 mg. i.m.	1 hr. 5 min.
0	4 "	100 mg. i.v.	2 hrs. 35 min.	100 mg. i.m.	1 hr. 10 min.
0	3 "	100 mg. i.m.	2 hrs. 25 min.	100 mg. i.m.	1 hr. 25 min.
0	4 "	100 mg. i.m.	3 hrs. 15 min.	100 mg. i.m.	1 hr. 15 min.
		+ scopolamine gr. 1/150		+ scopolamine gr. 1/150	

In all these cases the progress of labour was much quicker than was anticipated clinically. From experience with them it was decided that it is undesirable to administer pethidine within 2½ hours of the expected delivery of the child. The average time between the final dose and the end of labour in Gilbert and Dixon's cases was 2 hours 22 minutes in primiparae.

Summary

In the dosage employed pethidine is an effective obstetric analgesic. It does not, however, produce amnesia unless given with adequate doses of other drugs—e.g., scopolamine and barbiturates.

Only 5% of the patients failed to obtain any relief from pethidine. Analgesia was complete or satisfactory in 60%.

Two dosage schemes were found to give satisfactory results: (a) Initial dose 100 mg. intramuscularly, repeated one hour later with a chloral-bromide-opium mixture or with scopolamine; (b) 100 mg. pethidine intravenously, followed by 100 mg. intramuscularly an hour later, either alone or with scopolamine gr. 1/150. In either technique further intramuscular injections of 100 mg. can be given up to a total of 400 mg. in 24 hours. The first injection is best given when the cervix is two fingers dilated and the patient is having regular contractions.

Pethidine and scopolamine form an effective combination for producing obstetric analgesia.

Given intravenously pethidine produces analgesia in 5 to 10 minutes; intramuscularly in 15 minutes. The duration of action is 3 to 4 hours. Intravenous administration produces a more rapid and powerful initial action, but intramuscular administration is highly satisfactory and equally effective. Intravenous administration is contraindicated in labour complicated by toxæmia or hypertension.

Pethidine has a definite antispasmodic action on the cervix.

Statistically, in comparison with controls pethidine appeared to prolong labour. This was probably due to the selection of the cases. The figures compare well with average figures for the duration of labour.

No increase in the incidence of instrumental delivery or obstetric complications was associated with the use of pethidine.

Reactions in the mother included vomiting, a temporary rise of blood pressure, dizziness, tingling of the limbs, and dryness of the throat. These were transient, and, although unpleasant, gave no cause for alarm.

Of the babies 91% were apparently normal and active at birth; 9% were slow, and required resuscitation.

There were no deaths among the babies that could be attributed to pethidine. The neonatal (three days) morbidity was nil.

This investigation was carried out in the obstetric unit of St. Mary Abbots (L.C.C.) Hospital, Kensington, from Jan., 1943, onwards. Thanks are due to the consultant obstetrician, Mr. W. C. W. Nixon, for his helpful criticism of the investigation and the manuscript.

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OBSTETRIC ANALGESIA WITH PETHIDINE

BY

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Pethidine hydrochloride has been studied in our maternity department since Oct., 1941, in regard to its analgesic and spasmolytic effects on normal labour. It is a pain reliever of fairly recent introduction, the hydrochloride of the ethyl ester of 1-methyl-4-phenylpiperidine-4-carboxylic acid, discovered by Eisleb and Schaumann in their search for an ideal analgesic with spasmolytic atropine-like properties. The drug is known on the Continent as "dolantin" and in the United States as "demerol," and was officially named pethidine by the G.M.C. a year ago.

The pharmacological virtues and faults of pethidine have been carefully surveyed by Rothschild (1941) of Basle. It possesses a powerful analgesic action like that of morphine; but is stimulating rather than depressing to the central nervous system. Because of its depressant effect on smooth muscle tissue its spasmolytic properties have been compared to those of atropine and papaverine. Several authors have claimed that it can antagonize the effects of acetylcholine and histamine on the intestine (Eisleb and Schaumann, 1939; Duguid and Heathcote, 1940; Schaumann, 1940). Gruber *et al.* (1941) could not acknowledge the spasmolytic action. It is relatively non-toxic, and has little effect on the pulse rate or the pupil. It lowers the blood pressure and depresses the respiration only in large doses.

Only a few clinical reports on pethidine are available in this country. Prof. Christie (1943) undertook an investigation on behalf of the War Wounds Committee of the Medical Research Council. Pethidine proved to be of value as an analgesic when given by the mouth to 335 patients of six different hospitals. Of the patients with "severe pain" 55% obtained complete relief and 20% partial relief; of those with "moderate pain" 61% were completely and 12% partially relieved. Toxic symptoms were uncommon and never serious. Fitzgerald and McArdle (1943) described the usefulness of pethidine in neurological cases.

The Continental literature on pethidine in a variety of conditions is very encouraging; and as regards obstetrics, Benthin (1940, 1942), Fuchs (1941), and Sonnek (1941) have described excellent results in the relief of pain in labour. Detailed literature is not accessible in this country.

It seemed to me to be advisable to investigate another method of inducing analgesia in the first stage of labour which would cover three important points—namely, (1) reduce pain without having a depressing effect on the respiration and circulation of mother or baby; (2) avoid psychic depression; (3) avoid prolongation of labour. The choice of obstetric analgesics in any particular case has often to be made according to existing conditions. That is why an ideal method has not yet been agreed upon and legions of analgesic and anaesthetic substances in a variety of methods of administration are used all over the world. The exhaustive studies of obstetricians in this country have shown that "twilight sleep" is, for the baby, a dangerous first-stage treatment. All general anaesthetics weaken uterine contractions and retraction. The barbiturates depress the prothrombin levels in mother and child by causing damage to the liver, in which prothrombin is formed (Browne, 1942; Fitzgerald and Webster, 1942). Barbiturates are sometimes responsible for delay, with deleterious effects on the third stage of labour.

In domestic practice chloral hydrate and bromide and/or morphine are still most commonly used. While the first two drugs are safe and fairly satisfactory, the use of morphine for analgesia is unsafe for both mother and baby. It is encouraging that Eardley Holland (1943) has reminded the profession again of the dangerous effects of morphine as regards the respiration of the foetus. Especially in the present era, in which there is an increase in the number of premature labours, the liability to primary apnoea and atelectasis or pneumonia after use of morphine or the popular derivatives has to be taken into account. In short, all narcotics depress the respiratory centre of the foetus far more than that of the mother, and occasionally

in attempting to quiet the mother in the first stage of delivery the foetus is rendered dangerously apnoeic. It is proved by experiments (Rosenfeld and Snyder, 1939) that non-volatile anaesthetics (chloral hydrate, paraldehyde, barbiturates, and morphine) depress or completely abolish foetal respiratory movements at a level of dosage well below that required to anaesthetize the mother. Volatile anaesthetics with enough oxygen (ether, nitrous oxide, and cyclopropane) can produce satisfactory anaesthesia of the mother without interruption of the intra-uterine respiration. The chief inference to be drawn, therefore, is that on clinical trial of a new drug for obstetric analgesia in the first stage of labour only brief action is justifiable, and in the later stages anaesthetics (nitrous oxide) alone should be used; for these are drugs of brief action and have relatively slight depressive effects on respiration (Yandell Henderson, 1939).

Clinical Trials

The effect of pethidine hydrochloride on 80 normal patients in labour was studied; 56 were primiparae, 24 multiparae. Of all these patients with severe pain in the early first stage of labour, 14 (17.5%) were greatly relieved, 58 (72.5%) experienced good relief, and 8 (10%) were unrelieved. There was no striking difference between primiparae and multiparae in the relief of pain. Pethidine can be administered by any of the parenteral routes as well as by the mouth.

In our first series of clinical trials pethidine was given by mouth only, in order to determine its safety for mother and baby. The results are set out in Table I.

TABLE I.—*Relief of Pain according to the Dose of Pethidine in 80 Cases*

Dose	Severe Pain		
	Great Relief	Good Relief	No Relief
25 mg. for 2 doses, repeated $\frac{1}{2}$ -hourly ..	4	11	—
25 mg. for 2 doses, repeated hourly ..	1	6	1
25 mg. for 2 doses, repeated 2-hourly ..	—	2	—
25 mg. for 2 doses, repeated at long intervals ..	1	3	—
25-mg. single dose ..	7	35	7
25 mg. for 3 doses, repeated $\frac{1}{2}$ -hourly ..	—	1	—
25 mg. for 3 doses, repeated at long intervals ..	1	—	—
Total ..	14	58	8
% of relief ..	17.5	72.5	10

The effect of oral medication appears in 20 to 30 minutes, and, in doses of 25 mg., lasts from 1 to 4 hours. From the figures in Table I it seems that in the majority of cases a single dose of 25 mg. gave a good relief of severe pain in the early first stage of labour. The 25-mg. dose repeated half-hourly for 2 doses was tried in a series of patients, and gave, in my opinion, the most satisfactory analgesic effects. In a recent series of patients a 50-mg. single dose, with a 25-mg. dose repeated in 40 minutes, led to an increase of complete analgesic effects. In Table II I have summarized the side-effects of pethidine on both foetus and mother. The ill effect on the foetus was evident in only 2 cases. In the first a single 25-mg. dose produced a diminution in the foetal heart sounds for several minutes, without changing their quality. In the second case a dose of 25 mg. given half-hourly for 3 doses resulted in a depression of the foetal heart sounds for several minutes. No other signs of foetal distress were evident, and oxygen inhalation with 1 c.cm. of anacardone brought the foetal heart rate

TABLE II.—*Side-effects of Pethidine*

Dose	On Foetus		On Mother	
	F.H.S. Drop	Asphyxia	Stillbirth	Toxic Symptoms
25 mg.	1	2 mild (1 blue, 1 white)	None	1 vomiting ++
50 mg.	—	2 mild, blue	"	1 " (bradycardia)
75 mg.	1	1 " "	"	"
Total	2	5	—	3

back to normal. Among the 80 babies born of the mothers with pethidine analgesia 5 showed signs of mild asphyxia (4 blue, 1 white), which responded quickly to the routine treatment for asphyxia. There was no stillbirth or neonatal death in the whole series. All babies had a healthy cry. In 3 mothers

toxic manifestations were noticed that did not seem to depend on the total dosage of pethidine (see Table II). No patient showed excitement or psychic depression. Several patients improved in behaviour after pethidine administration. The antispasmodic property of pethidine seems to me especially worthy of observation during labour. After the first stage is established with cervical dilatation varying from 2 to 3 finger-breadths, pethidine had a satisfactory influence on the course of labour, in which regular, prolonged, and rhythmic pains were present. In contradistinction to many other analgesics pethidine does not delay labour.

Results

Table III shows in brief the action of pethidine on the uterus. Among the 56 primiparae the first stage was shortened in 17 cases (well under 4 hours), and among the 24 multiparae

TABLE III.—*Action on the Uterus*

	Dilatation of the Cervix (T Stage)			After-effects
	Rapid (1-4 hrs.)	Normal (6-12 hrs.)	Slow (Over 12 hrs.)	
Primiparae ..	17	32	7	Post-partum haemorrhage: 2 (1 rapid, 1 normal dilatation) 1 perineal tear 2nd degree
Multiparae ..	1-2 hrs.	6 hrs.	Over 6 hrs.	
	8	12	4	

in 8 cases (under 2 hours). The condition of the cervix was recorded for each case, and we were often surprised how satisfactorily the dilatation developed. The *second stage* was within normal limits, with the exception of 3 cases in which, in view of secondary inertia, deep transverse arrest, and maternal fatigue, a low-forceps delivery was effected. Only 1 episiotomy (rigidity) and 1 second-degree perineal tear (rapid labour) occurred among the 80 patients. The third stage of labour was normal, apart from 2 cases of post-partum haemorrhage—one case after rapid delivery (25 mg. pethidine at hourly intervals for 2 doses), and one after normal delivery (25 mg. pethidine at hourly intervals for 2 doses). In three cases of elderly primiparae (35 years) with some rigidity of the cervix and perineum, pethidine had a very favourable influence, especially on the dilatation period. It seems to me that pethidine may have a considerable field in many cases of cervical dystocia and lower the number of obstetrical interventions, which is so high in this age group. But also in elderly multiparae (35-45) we noted extremely quick dilatation of the often rigid parts, without ill effects on mother or baby. Pethidine may have a place in a definite group of cases in which the cervix is the cause of delay and in which it will aid in completing the dilatation and so avoiding uterine inertia. The exact mechanism of the effect of pethidine on uterine tone needs to be proved by further pharmacological experiments. The clinical experience of the shortening of labour by its definite relaxing effect on the cervix is valuable proof of its antispasmodic property. Mackenzie (1943) also acknowledged it recently. In our investigation we have only studied the effect of pethidine as an analgesic in the course of normal labour. We will have ample opportunity of trying the drug in various fields of abnormal labour and in combination with different analgesics. Meanwhile I have been much impressed with its immediate effect in severe after-pains and in pyelitis in pregnancy, in which it gave practically complete relief of the colicky spasmodic contractions. We have just started the use of pethidine in gynaecology and hope it will prove a useful drug in some severe types of dysmenorrhoea. Solomons and Widdess (1943) recently reported relief in 60% of their dysmenorrhoea cases which they considered due to central analgesic action of pethidine.

Summary

Pethidine hydrochloride was studied for its analgesic and spasmolytic effect on 80 normal mothers in the early first stage of labour. About 17.5% were greatly relieved, 72.5% had good relief, and 10% had no relief. The behaviour of excited patients was improved. Primiparae and multiparae were relieved equally.

For reasons of safety the oral route was used in this series of investigations. The effect of the oral medication of a 25-mg. dose appeared in 20 to 30 minutes and lasted 1 to 4 hours. The optimum pain response seemed to occur with a 25-mg. dose repeated half-hourly for 2 doses. A 50-mg. single dose and a 25-mg. dose repeated in 40 minutes will probably yield more complete analgesic effects. [Since submitting this paper for publication we have followed up a further 50 cases with a 50-mg. single dose and a 25-mg. dose occasionally added. 22% of the cases showed complete relief.]

Pethidine had in the majority of cases no objectionable side-effects on mother or baby. In 3 mothers transient vomiting and bradycardia were noted. Twice a transient depression in the foetal heart sounds developed, and 5 babies showed a mild degree of asphyxia. No other harmful effects on the child were observed.

It was found that the progress of labour was not delayed. Pethidine had a remarkable shortening effect on the duration of normal labour, possibly by its direct relaxing action on the uterine cervix. In elderly primiparae with rigidity of the soft parts the influence on the dilatation period was very favourable.

No harmful effects on uterine tone or perineum, by shortening labour, were observed, apart from 2 cases of post-partum haemorrhage and 1 second-degree perineal tear.

Definite conclusions about pethidine in normal labour can only be obtained from observations by several investigators on a large amount of clinical material.

So far as can be judged, pethidine hydrochloride, if carefully dosed and timed, is a very useful analgesic and spasmolytic drug in midwifery.

I wish to thank the medical superintendent, Mr. H. A. Kidd, and Mr. J. V. O'Sullivan, consulting obstetrician, for kind advice; and Dr. M. R. E. Boyd, assistant resident obstetrician, and the nursing staff for their help and co-operation. I am also greatly indebted to Roche Products Ltd. for abstracts of Continental literature and for a generous supply of the drug.

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BONE MARROW AS A SITE FOR THE RECEPTION OF INFUSIONS, TRANSFUSION, AND ANAESTHETIC AGENTS

A REVIEW OF THE PRESENT POSITION

BY

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As my experience in several surgical centres separated by some distance is precisely the same, I have assumed—I think correctly—that it represents a cross-section of the present attitude of the profession towards bone marrow as a site for infusion and transfusion: there are but few who have used this route a dozen times, and many are apprehensive about introducing a cannula into the sternum.

It is probable that I should be less inclined to voice an opinion on a comparatively new procedure were it not for past memories. Ten years ago, when I pressed for the more general adoption of *continuous* intravenous saline (Bailey and Carnow, 1934), I met with initial reluctance, if not active opposition, towards the (then) unfamiliar procedure. At that time, although I had divided my previous ten years among surgical posts in three university cities and one London teaching hospital, I had never seen a *drip* infusion or transfusion performed. To-day there is no difficulty in getting continuous intravenous fluid therapy carried out. On the contrary, one

has to exercise constant vigilance in curtailing its use; for, as sometimes happens, enthusiasm, particularly enthusiasm unyoked to physiological understanding, leads to the abuse of good remedies.

It was from the American and Canadian literature that my interest in continuous intravenous saline infusions was stimulated. So with bone marrow as a receptor; I had never even thought of a medullary cavity in connexion with the reception of parenteral fluid until I read the paper by L. M. Tocantins and J. F. O'Neill (1941).

At first I employed bone puncture as a last resort, for instance, in those occasional cases in which most of the available veins had been utilized previously. As time went on I found an increasing field of usefulness for marrow infusion, and now I am prepared to state that the medullary cavity of the manubrium is as good a receptor as a vein for infusions of all kinds and for pentothal anaesthesia. In a few instances I consider bone marrow is a better avenue for infusion than a vein, and to bring this belief to the notice of those who may be called upon to resuscitate the very shocked and the very young is the main object of this communication.

Advantages

1. In very shocked patients there is difficulty, sometimes considerable difficulty, in cannulizing a vein. Even when the cannula is *in situ* the veins may be so collapsed that the reception of parenteral fluid is unsatisfactory, and one must stay with the patient and employ various devices to expedite the flow. Sternal puncture is a more crude procedure which is effected mostly by "feel." Once entry to the medullary cavity has been gained, the flow of fluid into the marrow is unaffected by those factors which militate against unhampered intravenous fluid therapy.

2. Sternal puncture can be carried out in a comparatively poor light—a most important consideration under black-out conditions. With experience and good organization, it should be possible for a medical officer to cannulize the sterna and start infusions more rapidly and more certainly than he could hope to do when cannulizing veins under similar circumstances.

3. Those who have had to give intravenous infusions to dehydrated infants will welcome the tremendous advantages of bone marrow as a receptor. It is certain; it is safe—at least I have neither seen nor heard of any ill effects from inserting a Witts sternal-puncture needle into the tibia and gravitating saline, glucose, or plasma into the bone marrow. At any rate, I am sure that I am correct in stating that this procedure is safer than utilizing the superior longitudinal sinus.

4. A cannula in the sternum is "out of the way" when an operation is being performed on the abdomen or lower extremity. In such circumstances, the whole of the infusion paraphernalia being near the head of the patient, it is convenient for the anaesthetist to attend to the infusion without moving from his accustomed position.

5. Thrombosis and phlebitis, of course, cannot occur. These inseparable complications of intravenous fluid therapy are admittedly infrequent: with correct technique they should not exceed 1%, but my impression is that this incidence is exceeded.

Disadvantages and Dangers

1. Theoretically, osteomyelitis may result. In an experience of over 60 cases I have seen no sign of it.

2. Whole blood cannot be introduced as rapidly as into a vein by gravity.* The apparatus designed by Messrs. Evans Sons Lescher and Webb overcomes this difficulty, for introduction is speeded up by oxygen pressure. Raising the intramedullary pressure is inclined to give pain.

3. The only real danger is that both plates of the manubrium may be perforated and the fluid be introduced into the superior mediastinum. This is not a theoretical conception, for it occurred in my practice when performed by an extremely capable house-surgeon. It is desirable to add that in this instance an "unwinged" Witts needle was employed and, fortunately from our point of view, the patient was suffering

* We are having increasing success with gravity drip blood-saline transfusions by this route. As with all blood-saline transfusions Officer's mixing chamber cannot be bettered.