introduced intravenously on the first and second days after the operation, and each contains 0.2 mg./kg. of body weight. Regular estimation of leucocyte and platelet counts are performed. After discharge the patients are seen in the out-patient department every three months and examined for signs of recurrence.

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- received. This was tried successfully by Eckenhoff *et al.* (1953), using a dose of 10 mg. of nalorphine to the mother. The difficulties arising from this method are that the exact time that the baby will be born is not known and that the time the drug takes to cross the placenta and enter the baby's brain is also not known. Thus an intravenous dose to the mother is usual.
2. A small dose can be given to the baby after birth if it fails to breathe in a reasonable time. This has also been reported on (Eckenhoff *et al.*, 1953; Paterson and Prescott, 1954). For a reasonably rapid effect the drug must be injected into the umbilical vein or the heart, to which procedure there are some objections.
3. The antagonist may be premixed with the opiate at each dose given to the mother in labour. This would appear to be the method of choice, as the other two methods require the presence of a doctor, whereas the mixture can be used by midwives without any special supervision. The correct mixture of the two drugs (called the ratio) is probably the least amount of the antagonist which, when mixed with a dose of the opiate, will, as near as possible, prevent respiratory depression. Much work has been done by others (Cullen and Santos, 1954, 1955; Eckenhoff *et al.*, 1955; Foldes *et al.*, 1955; Gaard, 1955; Baker, 1957) and myself (Bullough, 1957, 1958a, 1958b, 1959) in trying to find the correct ratios of antagonists and opiates. It is not known whether the antagonists cross the placental barrier at the same rate as the opiates; research on this point remains to be carried out.
- This paper describes the effects of pethidine and mixtures of pethidine with nalorphine and levallorphan, used to relieve pain in childbirth over the past five years in the maternity unit at the West Hill Hospital, Dartford. This is a busy unit in which 1,200 to 1,400 babies are born annually.
- In 1954 I introduced the use of premixed pethidine and nalorphine for the relief of pain in childbirth at Dartford, with the full co-operation of the obstetric staff, to whom my thanks are due. So far as I know, this unit was the first to employ premixed pethidine and antagonists in obstetrical analgesia. The first report on the use of such mixtures came from this unit in 1956* and was published later (Baker, 1957). After a pilot series of 75 mothers who received individual doses of pethidine 100 mg. premixed with nalorphine 5 mg., three series of cases were compared (see Table I). Series A: the mothers received pethidine 100 mg. in the customary way. Series B: nalorphine 2 mg. was added to each dose of pethidine. Series C: nalorphine 5 mg. was added to each dose of pethidine.
- As a result of this trial it was tentatively concluded that the use of the mixture of pethidine 100 mg. and nalorphine 5 mg. provided more effective analgesia than pethidine alone, as it could be used in larger quantities without interfering with labour and without increasing the incidence of neonatal asphyxia (which was actually reduced). After this trial all mothers received the mixture as a routine for two years, so that over 2,000 mothers were treated in this way. Details of 1,000 of these await publication.
- In 1957 it was decided to substitute the newer drug, levallorphan, in place of nalorphine, and compare the results. At that time the correct ratio of these two drugs was thought to lie between 1 and 2 mg. of

USE OF PREMIXED PETHIDINE AND ANTAGONISTS IN OBSTETRICAL ANALGESIA

WITH SPECIAL REFERENCE TO CASES IN WHICH LEVALLORPHAN WAS USED

BY

JOHN BULLOUGH, M.B., F.F.A.R.C.S.

Consultant Anaesthetist, Dartford, Kent

The introduction into clinical practice of the two specific opiate antagonists nalorphine (*n*-allyl derivative of morphine) and levallorphan (*n*-allyl derivative of levorphan) has opened up a new field in the relief of pain by morphine and all the drugs related to morphine. The main effect of these antagonists is to correct the respiratory depression which inevitably follows the administration of opiates. When pethidine is used in obstetrics the main hazard is that the baby will be depressed at birth by the drug administered to the mother, will fail to breathe immediately, will become asphyxiated, and will require resuscitation. If the baby is also suffering from shock due to some obstetric abnormality or to operative birth under general anaesthesia, the additional effect of the pethidine in its body might endanger its life.

The antagonists can be used to prevent respiratory depression occurring when an opiate is given, or to correct or relieve existing respiratory depression already caused by opiates. In obstetrics there are thus three possible ways in which they can be used (Baker, 1957).

1. A single adult dose is given to the mother a sufficient time before the baby is born for the drug to enter the baby's respiratory centre and antagonize the effects of pethidine or other opiates the mother has

*A paper read at the Royal College of Surgeons to the Association of Anaesthetists of Great Britain and Ireland.

TABLE I

	Series			
	A	B	C	D
Ward to which patients admitted	II	I	I and II	I
Drugs used for each injection* (mg.)	P. 100	P. 100 N. 2	P. 100 N. 5	P. 100 L. 2
No. of patients in series	100	98	100	130
Average age (years)	25.3	25.6	25.8	26
Proportion primigravidae (%)	63	68	65	63
Incidence of all antenatal abnormalities (%)	14	19	17	20
Pre-eclamptic toxæmia (%)	8	16	13	17
Prematurity (%)	2	6	4	3
Post-maturity (%)	6	10	6	26
Surgical induction of labour (%)	1	4	6	15
Average duration of first stage:				
Primigravidae (hours/minutes)	14/38	16/45	15/55	15/15
Multigravidae ()	9/14	10/34	9/27	10/0
Average duration of second stage:				
Primigravidae (minutes)	64	62	70	70
Multigravidae ()	24	31	23	38
Forceps deliveries (%)	4	8	7	10
Caesarean sections (%)	1	0	0	1.5
Post-partum hæmorrhage (%)	0	2	2	3
Manual removal of placenta (%)	1	2	4	3
Mean total dose of pethidine (mg./patient)	173	200	227	242
Mean dosage of pethidine per hour of labour (mg.)	12.4	12.8	15.5	15.8
Analgesia produced according to patient's reply next day:				
Good (%)	58	66	76	76
Fair (%)	26	29	19	21
Unsatisfactory (%)	6	5	6	3
Amnesia, according to midwife's assessment next day:				
Good (remembers little or nothing) (%)	20	45	50	33
Nil (remembers all) (%)	28	4	3.5	3.2
Incidence of asphyxia at birth:				
None (class 1 baby) (%)	76	79	90	89
Slight or moderate (class 2 baby) (%)	15	14	4	8
Severe (class 3 baby) (%)	8	6	5	2
Stillbirths (%)	1	1	1	1

* P.=pethidine; N.=nalorphine; L.=levallorphan.

levallorphan to each 100 mg. of pethidine. It was decided to use the ratio of 100 to 2, and the series was designated series D.

Material and Methods: Series D

The material was 130 patients admitted consecutively in early labour to one of the two wards in the unit (ward I), the same ward as in series B. This ward receives a higher proportion of abnormal cases, especially patients with pre-eclamptic toxæmia; also of patients having surgical inductions of labour for this reason and for post-maturity; also premature and trial labours. (The only cases excluded from these studies are those with multiple pregnancies.)

The conduct of labour and pain relief was the same as in the previous three series. Chloral in doses of 30 gr. (2 g.) was given in early labour (83 patients received 125 doses). When labour was well established at two fingerbreadths' dilatation of the cervix, premixed pethidine was injected intramuscularly in doses of 100 mg. (with levallorphan 2 mg.) and was repeated an hour later, if necessary, and thereafter as required. (One patient received a double dose, as described later.) Gas-air or "trilene"-air inhalation was given later as considered appropriate by the obstetric staff. 124 patients received gas-air, 8 also received trilene-air; and six patients received trilene-air only.

Other drugs were used in labour as indicated. Seven patients received morphine $\frac{1}{4}$ gr. (16 mg.); in six of these it was given for artificial rupture of the membranes. Quinalbarbitone ("seconal") 3 gr. (0.2 g.) was given to eight patients, chlorpromazine ("largactil") 50 mg. to 24 patients (one received 125 mg., see later, case 51).

[NOTE.—Since 1957 2,000 mothers have received a mixture of pethidine and levallorphan in the ratio of 100 mg. pethidine to 1.25 mg. levallorphan (commercially available as "pethilorfan"); some results of this study were presented at the Annual Meeting of the B.M.A., Edinburgh, Scientific Exhibition, July, 1959.]

As shown in Table I, the patients are alike in all four series as regards age and proportion of primigravidae. Duration of labour is not notably different. Owing to the admission procedure already mentioned (ward I receiving the higher number of abnormal cases), Series A has the lowest number of antenatal abnormalities, Series B and D the highest, and Series C a figure between.

Dosage, Analgesia, Amnesia, Co-operation, and Incidence of Neonatal Asphyxia

Tables I and II show that, as confidence in the method of using premixed drugs grew, an increasing dosage was used, providing better analgesia for the mothers, without any corresponding increase in the incidence of neonatal asphyxia. Amnesia was greater in the three series in which antagonists were used, being more pronounced with nalorphine than with levallorphan. This confirms an impression that, in the doses used, nalorphine has a greater narcotic action than has levallorphan. However, co-operation was as good in the series in which antagonists were used as in the pethidine-only series (Baker, 1957).

The incidence of operative deliveries is a little higher in the series in which antagonists were used, but this reflects the admission procedure already mentioned (Baker, 1957).

The baby's condition at birth was classified according to the time taken to breathe or cry, and the necessity for resuscitative measures. Babies in class 1 cried within 60 seconds and required no treatment other than clearing of the air passages. Babies in class 2 either did not cry within one minute or required nasal oxygen. Babies in class 3 did not cry within five minutes, and required oxygen or stimulants or artificial respiration.

The lowest incidence of neonatal asphyxia should have occurred in series A for three reasons: (1) on account of the admission procedure, this series having the lowest number of abnormal cases; (2) the lowest incidence

TABLE II.—Dosage of Pethidine in the Four Series

	Series			
	A (P.100)	B (P. 100, N. 2)	C (P. 100, N. 5)	D (P. 100, L. 2)
Patients receiving:				
100 mg.	47	39	28	26
200 "	38	46	45	42
300 "	10	7	7	11
400 "	5	4	13	11
500 "	0	1	6	4
600 "	0	2	1	3
700 "	0	1	0	0
800 "	0	1	0	1
900 " and over	0	0	0	1
Patients receiving:				
300 mg. and over	15	16	27	31
400 " " "	5	9	20	20
500 " " "	0	5	7	9
Percentage with good analgesia	58	66	76	76
Percentage with good amnesia	20	45	50	33
Percentage of first-class babies	76	79	90	89
Percentage of operative deliveries	5	8	7	10

of operative deliveries under general anaesthesia; and (3) because the lowest dosage of pethidine was used in this series. The results show that the incidence of neonatal asphyxia was in fact highest in this series, suggesting that addition of the antagonists in the other three series protects the babies from pethidine-induced neonatal asphyxia.

Further Details of Series D

There were 13 forceps deliveries in the series (11 in primigravidae and two in multigravidae), the indications for which were as follows (more than one indication being sometimes present): inertia, 4; persistent occipito-posterior presentation and transverse arrest, 5; disproportion, 1; maternal distress, 1; foetal distress, 3; delay in second stage, 5.

There were two caesarean sections in the series. One was for disproportion and the other for prolonged labour with foetal distress. In the latter case the last dose of pethidine mixture had been given 23 hours before delivery and was thus unconnected with the operation. This gives operative intervention in 15 cases, or 11.5%, which is not significantly higher than in previous years (see Table III).

The mothers in this series were asked to comment on their general care as regards pain relief in childbirth (including inhalational methods): 93% appreciated their treatment, and a third of these were enthusiastic; the other 7% were not appreciative.

Forty-eight patients were asked to give an opinion on the relative merits of the injections (of premixed pethidine) and gas-air inhalation: 33% preferred gas-air, 60% preferred the injections, and 7% could not say which they preferred.

Side-effects noted in this series were vomiting in 5%, drowsiness in 34% (of these a third were very drowsy), and two patients behaved in a peculiar manner (this aspect will be described in a subsequent report).

The circumstances relating to the three severely depressed babies were as follows. Case 24: toxæmia, long second stage, foetal distress, forceps delivery under general anaesthesia. Case 61: persistent occipito-posterior presentation; foetal distress. Case 92: premature labour at 37th week; baby weighed 2 lb. 4 oz. (1,020 g.).

All the babies in this series recovered satisfactorily after having their air passages cleared by suction in a head-down position and by the administration of oxygen through a nasal catheter. None of them were given injections of stimulants (nikethamide and lobeline) and none required gastric oxygen or endotracheal intubation, nor artificial respiration.

Some Exceptional Cases

Case 89.—Multigravida aged 28. Normal full-term delivery. Labour lasted six hours. The only patient who received a double dose (pethidine 200 mg. and levallorphan 4 mg.), which was given three hours before delivery. She became confused; co-operation was only fair. She had no other drugs, but received gas-air later. The next day she could remember nothing of her labour. (A double dose was tried as pre-operative medication for gynaecological patients, and was found often to cause oversedation, occasionally semiconsciousness, and was abandoned.)

Case 51.—Primigravida aged 22. Ante-partum haemorrhage and premature labour at 37th week. Labour

lasted four days; the second stage 30 minutes. She received 150 gr. (10 g.) of chloral; a total of 900 mg. of premixed pethidine, the first dose 86 hours and the last dose 1½ hours before delivery; also morphine ¼ gr. (16 mg.) and chlorpromazine 125 mg. Nevertheless, the foetus was never distressed, and cried immediately at birth; it weighed 7½ lb. (3,400 g.).

Case 133.—Primigravida aged 26. Normal full-term delivery; labour lasted 13 hours. She received 60 gr. (4 g.) of chloral; two injections of premixed pethidine, the first six hours and the second five hours before delivery, followed by gas-air. Analgesia was good. The next day she could remember nothing of having her baby. (Some mothers have complained of their inability to remember their labour, and, although amnesia is generally regarded as an advantage in a method, it seems that it is advisable to consult the mother in advance on this point when using these mixtures.)

Comparison of Clinical Reports from the Maternity Unit, 1952-7

Some relevant statistics from the reports of the maternity unit at Dartford over the years 1952 to 1957 are given in Table III. Antagonists were introduced

TABLE III.—Statistics of Reports from the Maternity Unit, Dartford, 1952-7

	1952	1953	1954	1955	1956	1957
Drugs in use	P.	P.	P. or P. & N.	P. & N.	P. & L. or N.	P. & L. or N.
Total deliveries	1,122	1,277	1,209	1,364	1,453	1,450
P.E. toxæmia (% incid.)*	3.4	5.5	5.9	4.5	5.4	6.6
Toxæmia cases, foetal mortality (%)	10	14	10	18	9	17
Prolonged labour (%)	1.0	1.6	0.5	1.3	1.1	1.3
Forceps rate (%)	7.6	6.5	8.1	5.9	6.3	5.0
Forceps cases, foetal mortality (%)	8.1	2.4	5.0	3.7	3.3	2.8
Caesarean section rate (%)	4.4	5.6	5.4	6.3	4.9	6.4
Caesarean cases, foetal mortality (%)	8.2	7.0	6.0	9.3	8.4	4.5
Operative intervention (caesarean and forceps)	12.0	12.1	13.5	12.2	11.2	11.4
Post-partum haemorrhage incidence (%)	3.0	4.2	4.0	2.5	2.5	2.8
Manual removal of placenta: incidence (%)	2.0	1.6	2.0	2.0	2.1	1.6
Stillbirth rate (%)	2.6	2.7	2.2	2.0	1.6	2.5
Neonatal mortality rate (%)	3.5	2.2	1.5	2.4	1.9	1.6
Total foetal mortality (%)	6.2	4.9	3.8	4.5	3.6	4.1

* These figures do not include mild cases, whereas in Table I they are included.

late in 1954. It is not proposed to deal with these figures in detail; they are given to show that ill effects on mother or child have not followed the introduction of this method of relieving pain in childbirth. This is in spite of the fact that the mothers are now given approximately 40% more pethidine than previously, with a corresponding improvement in relief of pain.

There has been little change in the incidence of prolonged labour, forceps deliveries, caesarean section, post-partum haemorrhage, manual removal of the placenta, and stillbirths. There has been a fall in the mortality in babies born by forceps or by caesarean section, which could be attributable to the use of the antagonists in labour. On the other hand, it would probably be true to say that the care and resuscitation of the newborn have been improved since 1952 by the use of a regime more or less as outlined previously (Bullough, 1958a).

Discussion

When pethidine alone is used as an analgesic in labour it has been found that from 9 to 21% of the babies are depressed at birth (Gilbert and Dixon, 1943; Gallen and Prescott, 1944; Cripps *et al.*, 1944; O'Reilly, 1948; Davis and Tupper, 1949; Paterson and Prescott, 1954) even though the drug is withheld for a few hours before delivery. Series A confirmed this. By mixing an antagonist with pethidine this effect can largely be eliminated. However, if too much antagonist is used the analgesic action of pethidine may be interfered with, so that the least amount of antagonist required to prevent respiratory depression is thought to be the correct amount to use.

In series D depression at birth attributable to the pethidine mixture was virtually unrecognizable, so that it is likely that there is no lack of levallorphan in the mixture used. The results of using a mixture of pethidine 100 mg. with levallorphan 1.25 mg. in a larger series of 1,000 cases will be offered for publication.

Summary

A series of 130 patients consecutively admitted in early labour to one of two maternity wards were given intramuscular doses of pethidine 100 mg. premixed with levallorphan 2 mg., with the object of preventing neonatal respiratory depression. In all, 317 injections were given. The mean dosage of pethidine to each patient was 242 mg. Injections were started at two fingerbreadths' dilatation of the cervix, and were repeated as required through labour. Gas-air or "trilene"-air was given in the later stages.

Of the patients 42% had two injections, 26% had one, one patient had nine, and the remainder (33%) had three to eight injections. Analgesia from the injections was good in 76%, poor or nil in 3%, and fair in the remainder. Of 48 patients questioned on the point, 60% preferred the injections to gas-air as more effective. Amnesia was good in 33%, nil in 3.2%. 89% of the babies cried within 60 seconds and required no treatment; 8% were moderately and 2% severely depressed at birth, but none required stimulants, intubation, or intragastric oxygen. There was one stillbirth due to ante-partum haemorrhage. The incidence of operative deliveries, prolonged labours, and post-partum haemorrhage was not increased. The results of this series are compared with three previous series from the same unit, in which pethidine alone and mixtures of pethidine and nalorphine were used.

It is suggested that, by mixing an antagonist with pethidine, more of the latter drug can be given, providing better analgesia without causing an increased incidence of neonatal asphyxia.

Relevant statistics from the maternity unit at Dartford over the years before and after the introduction of pethidine-antagonist mixtures are given, showing no evidence of adverse effects on mothers and babies.

Roche Products Ltd. supplied ampoules of premixed pethidine and levallorphan. Burroughs Wellcome Ltd. supplied ampoules of premixed pethidine and nalorphine. The patients were under the care of Drs. G. Dalley, W. A. Chester, and W. Gross, obstetricians to the maternity unit, West Hill Hospital, Dartford. Anaesthetics were given by the consultant and junior staff of the Dartford Group of Hospitals. Labours were conducted by, analgesia was administered by, and statistical data were collected by the

staff midwives (superintendent Miss M. Gantry), to whom special thanks are due for their co-operation.

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SUBACUTE COMBINED DEGENERATION OF SPINAL CORD AFTER EXTENSIVE RESECTION OF ILEUM IN CROHN'S DISEASE

REPORT OF A CASE

BY

C. N. BEST, M.B., M.R.C.P.Ed.

Senior Medical Registrar, St. Peter's Hospital,
Chertsey, Surrey

Subacute combined degeneration of the spinal cord (S.C.D.) due to non-Addisonian megaloblastic anaemia is a rare but well-authenticated entity, and the subject has been comprehensively reviewed by Richmond and Davidson (1958).

This report records a case following extensive ileal resection performed for Crohn's disease.

Case Report

A man aged 46 was admitted to this hospital in August, 1958, complaining of paraesthesiae in the feet and hands, tightness and a burning sensation affecting the feet, with weakness of the ankles and knees for six weeks. For about three months he had noticed progressive visual fatigue during his clerical occupation and had become progressively irritable, depressed, and disinterested. He had been unable to feel the ground with his feet for a few days, and admitted that his tongue had recently been sore around the margins.

Past History

In 1940, after appendicectomy at another hospital, a faecal fistula developed, and in 1941 a short-circuit operation was performed for what was found to be Crohn's disease. In 1942 the diseased area of bowel was excised and an end-to-end anastomosis performed.

He was first seen at this hospital in 1949 with recurrent abscess formation in the right inguinal fossa and small-