better ones with imipramine (Tofranil). Only two of the patients with secondary depression, however, required E.C.T., the rest being successfully treated by imipramine.

E.C.T. still remains a most valuable form of treatment, but our standard practice is to give a two- to three-week trial of an antidepressant drug first. Only if there is no improvement or in the presence of severe agitated or retarded depression with a risk of suicide would we proceed with E.C.T. The ultimate period of sickness is probably not prolonged by this regimen, which may in fact yield a more stable recovery. Certainly the retarded patient has no wish to indulge in explorative and interpretative psychotherapy, and his very inability to do so may be construed by him as yet another culpable failure. Thus the armamentarium of the general physician is here surely extended by such antidepressant drugs, aided by his knowledge of the natural history of the illness. Perhaps just as the physician of old recognized syphilis as the great diagnostic deceiver, so we in the twentieth century must recognize the multiform nature of depression, fortified by the better weapons at our disposal.

In conclusion, I would say that the trends in psychiatry which to me are the most optimistic are those which help to place the specialty back into the fold of medicine. To this end, the newer drugs are undoubtedly playing their part. "Putting psychiatry back into medicine" is a phrase that we owe to Ayd. However, I consider that it will be a long time before we reach an integrated practice of both medicine and psychiatry. Perhaps this will be achieved both by the general hospitals advancing towards psychiatry and the mental hospital advancing towards the general hospital. In this way a proper community of service will be set up without perhaps the series of parallel, and at times overlapping, facilities that exist at present. Until continuity of treatment is achieved, I think that our best efforts will always be to some extent vitiated.

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USE OF ALPHAPRODINE AND LEVALLORPHAN DURING LABOUR*

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THE EFFICIENCY and safety of pain-relieving drugs administered during labour must be assessed in the light of extreme sensitivity of fetal respiration to narcosis. Barcroft's[1] investigations on sheep revealed the pattern of development of the respiratory control mechanism in the medulla, and its response to the new environment after birth. Snyder[2] and many other workers have contributed further knowledge concerning the reactions of fetal respiration to many extraneous factors. It is generally accepted that analgesic and anesthetic agents can depress the respiratory system of the fetus and newborn infant, but it is essential to remember that the respiratory system practically always bears the brunt of any injury, direct or indirect, incurred during labour and delivery. Therefore, in attempting to establish the value of any analgesic or anesthetic agent, the whole process of labour must be reviewed with great care. At times it is extremely difficult to dissociate the effect of drugs from complications arising from labour itself, and thus carelessly conceived opinions can create unnecessary bias.

Adequate relief from pain during labour entails the use of the more powerful narcotics, the effects of which produce varying degrees of respiratory depression. Alphaprodine (Nisentil) is no exception to this rule, and in doses of 1 mg./kg. it has been found to reduce both the respiratory rate and the minute volume in adults.[3] The value of alphaprodine as an obstetrical analgesic has been investigated by many workers, as the sole agent, or in combination with scopolamine, or with the barbiturates. The general opinion has been that it is a satisfactory analgesic if given at frequent intervals, since its effect is comparatively short-lived, approximately an hour in duration.[4]

The introduction of narcotic antagonists has led inevitably to administration of larger doses of narcotics and to a tendency to rely on the good offices of the antagonist drug in the event of untoward reaction to the narcotic. Levallorphan tartrate (Lorfan), the allyl derivative of levodromoran, is one of the more recently synthesized narcotic antagonists. Studying the mode of action of this narcotic antagonist, Landmesser, Cobb and Converse[5] offer the hypothesis that narcotic analgesics and antagonists compete for cell sites in the sensory and respiratory centres. They suggest that administration of a narcotic antagonist results in displacement of the analgesic drug from most of the respiratory and some of the sensory receptor cells. This results in elimination of the respiratory depression produced by the narcotic.

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The use of alphaprodine and levallorphan in obstetrics has been described by Backner, Foldes and Gordon,[6] and their observations on 200 patients indicate the effectiveness of this mixture in reducing the time of onset of breathing and crying in the newborn infant. Previous observations by one of us (H.R.[7]) on the effect of levallorphan on respiratory depression at birth due to meperidine (Demerol) analgesia indicated that the antagonist was particularly effective when the dose of meperidine had been high.

CASE MATERIAL AND METHOD

The survey presented here was carried out on 391 patients. Two groups were established by one of the methods of random selection; the patients in the treated group numbered 199 and received a mixture of alphaprodine and levallorphan while those in the control group totalled 192 and were given alphaprodine only. The drugs were administered in accordance with the following instructions:

When labour was well established, the uterine contractions regular and causing definite discomfort, and the cervix at least two fingers dilated

1. The patients in the *treated group* received alphaprodine 60 mg., levallorphan 1 mg. administered intramuscularly and repeated at 2-hourly intervals until the 2nd stage of labour was reached. The second and subsequent injections were delayed if the patient did not require further medication after the 2-hourly interval.

2. Patients in the *control group* received alphaprodine 60 mg. given intramuscularly and repeated as in the treated patients.

TABLE I.—ANESTHETIC TECHNIQUE USED FOR DELIVERY

Anesthetic technique	*Treated group (No. of patients)*	*Control group (No. of patients)*
Local infiltration of perineum	42	34
Pudendal nerve block	21	13
Epidural block	25	29
Subarachnoid block	1	0
Nitrous oxide and oxygen	84	73
Nitrous oxide, oxygen and trichlorethylene	33	29
Cyclopropane	36	38
Cyclopropane and ether	0	1
Halothane	2	3
$X^2 = 2.684$ 8 d.f.	P = .90	

It will be noticed that the total number of anesthetics listed in Table I is greater than the number of patients in the survey. This is because a large proportion of mothers delivered under local infiltration or pudendal nerve block also received nitrous oxide and oxygen inhalations. The distribution of the types of anesthetics in each group has been analyzed statistically, and according to the table of Chi square, P = .90. Therefore it is felt that the two groups can be compared without influence of the terminal form of anesthesia upon such comparison.

TABLE II.—DISTRIBUTION ACCORDING TO PARITY IN THE TWO GROUPS

Parity	*Treated group (No. of patients)*	*Control group (No. of patients)*
Primigravida	74	72
Multipara	125	120
$X^2 = .01$ 1 d.f.	P = .90	

The statistical analysis of data in Table II gives the probability value of .90, indicating no significant difference in the make-up of the groups in this respect.

TABLE III.—MATURITY DISTRIBUTION

Duration of pregnancy	*Treated group (No. of patients)*	*Control group (No. of patients)*
28 - 35 weeks	3	9
36 - 38 "	27	27
39 - 42 "	143	134
Over 42 "	26	22
$X^2 = 4.244$ 3 d.f.	P = .20	

The patients have been grouped according to maturity, and the distribution in the treated and control groups has been examined. The result is not significant, P = .20. Thus without subdividing the treated and control groups according to parity or maturity it seems reasonable to compare them as a whole, and the results produced by the administration of alphaprodine and levallorphan can be validly assessed.

RESULTS

The primary aim of this survey was to estimate the value of combining levallorphan with alphaprodine in order to reduce or prevent anoxia in the newborn. However, other important points have been recorded, such as relief of pain, length of labour, and any complications arising during the third stage. A specially designed proformata recorded the necessary data concerning the patient's progress throughout labour, and the condition of the mother and infant after delivery. The observations of the labour floor staff and those of the mother herself were taken into consideration. Careful note was made of the condition of the infant at birth and of his condition in the nursery the next day.

Relief of Pain

There were three classifications: (i) Good—indicating an unqualified success. (ii) Fair—when the relief was partial at some time during labour but the general impression was quite good. (iii) Poor—poor or no relief at all.

TABLE IV.—AMOUNT OF PAIN RELIEF PROVIDED BY THE TRIAL DRUGS

Degree of pain relief	*Treated group (No. of patients)*	*Control group (No. of patients)*
Good relief	98	83
Fair relief	73	79
Poor relief	28	30
$X^2 = 1.437$ 2 d.f.	P = .50	

The analysis in Table IV indicates that there is no effect on the part of the levallorphan to enhance or impair the sedation provided by the alphaprodine.

TABLE V.—VARIATION IN THE LENGTH OF THE FIRST STAGE OF LABOUR

Length of 1st stage of labour	*Treated group (No. of patients)*	*Control group (No. of patients)*
Less than 12 hours	141	129
12 to 24 hours	46	51
Over 24 hours	12	12
$X^2 = .670$ 2 d.f.	P = .70	

Table V shows the distribution of the length of the first stage of labour in both groups. The length of the first stage is difficult to calculate with any accuracy, but estimation of the time taken from the onset of regular uterine contractions and/or evidence of "show", to full dilatation of the cervix, gives a fairly standard value. Neither group shows a significant increase in length of time over the other.

TABLE VI.—INCIDENCE OF COMPLICATIONS OF THE THIRD STAGE OF LABOUR

Third stage complications	*Treated group (No. of patients)*	*Control group (No. of patients)*
Postpartum hemorrhage	5	3
Retained placenta	5	4
Retained placenta and postpartum hemorrhage	2	0

Table VI shows the incidence of postpartum hemorrhage and retained placenta. It is doubtful if there is any real significance in these numbers, even though the treated group shows a higher incidence of complications.

TABLE VII.—DISTRIBUTION OF SIDE EFFECTS

Side effects	*Treated group (No. of patients)*	*Control group (No. of patients)*
Dizziness	3	3
Nausea	1	1
Vomiting	1	3

Table VII indicates the distribution of side effects. These were minimal, although they appear slightly higher in the control group.

TABLE VIII.—PERINATAL MORTALITY AND THE INCIDENCE OF SEVERE ANOXIA

Perinatal mortality and morbidity	*Treated group (No. of patients)*	*Control group (No. of patients)*
Stillbirths	1	0
Severe anoxia (Apgar rating 1-4)	7	13
Perinatal deaths	1	4

Table VIII presents the major infant morbidity and mortality data. In the treated group the perinatal death is also included in the number of severely asphyxiated infants, and in the control group, four perinatal deaths are recorded among the 13 babies severely anoxic at birth. These cases are described in detail below. Severe anoxia was recorded whenever the Apgar rating was from 1 to 4 inclusive.

Apgar ratings were recorded for each infant in this series and the mean Apgar rating in each group was: treated group 8.56 and control group 8.37. Calculation of the significance of these values showed that the standard error of the difference (S.E.D.) between the means is 0.1758, t = 1.109, and P = 0.1. This indicates that there is no statistical difference between the two means.

DISCUSSION

From observations on the effect of alphaprodine on respiration in the conscious adult, Swerdlow, Foldes and Siker[8] have concluded that this drug has the power to depress the respiratory rate. Levallorphan given after or with the narcotic prevented the fall in respiratory rate to a satisfactory degree, although it appeared to be more effective in counteracting the decrease in depth of respiration than the rate. Machaj and Foldes[9] present three uses for the narcotic antagonists: (1) They are valuable in the treatment of overdosage of narcotic drugs. (2) They make possible the deliberate use of large doses of narcotic drugs for surgical and obstetrical analgesia. (3) They are useful for the prevention and the treatment of neonatal depression due to excess narcosis during labour.

Bearing these points in mind, it is possible to appreciate the value of levallorphan, but one should avoid being lulled into a false sense of security in which unnecessarily large doses of narcotic drugs are administered during labour. Moreover, it is essential that the antagonist should not be administered when the cause of the anoxia is other than the untoward effect of a narcotic. Hunter[10] is inclined to think that the antagonist drugs are most effective when given therapeutically rather than prophylactically. This point of view seems to be borne out by the results of this survey in which, even though the incidence of severe anoxia was higher in the control group, there was a correspondingly higher incidence of obstetrical complications to account for the increase. Prophylactic doses added to meperidine did not show any statistically significant improvement in the respiratory minute volume of the newborn when compared with a control series (Roberts and Please[11]). Stoetling and Hicks,[12] using the drugs during adult anesthesia, also state that levallorphan given with alphaprodine is apparently less effective than levallorphan given after alphaprodine, in the manner described by Foldes *et al.*[13] and by Gross and Hamilton.[14]

Consideration of the results of this survey leaves the authors with no doubt that some of the value in pain relief was lost when the time interval

STILLBIRTH IN THE TREATED GROUP

Parity	*Maturity*	*Wt. at birth*	*Length of labour*	*Analgesia*	*Anesthesia*	*Condition of infant at birth and treatment*
0	Post mature	9 lb.	1st stage—8 hr. 45 min. 2nd stage—1 hr. 45 min.	Alphaprodine, levellorphan. 1 injection 4 hr. 15 min. before birth of infant	Nitrous oxide and oxygen, trichlorethylene	Stillborn and very slightly macerated. Placenta described as gritty. Post-mortem examination revealed no abnormalities except evidence of intrauterine asphyxia.

SEVERE ANOXIA IN INFANTS IN THE CONTROL GROUP

0	Post mature	7 lb. 8½ oz.	1st stage—21 hr. 2nd stage—3 hr.	Alphaprodine. 5 injections. Last dose 2 hr. 10 min. before delivery	Cyclopropane and ether	Difficult forceps delivery. Infant severely anoxic. Intubation attempted. Levallorphan 0.25 mg., i.m. Satisfactory within 10 minutes.
0	At term	7 lb. 4½ oz.	1st stage—11 hr. 2nd stage—20 min.	Alphaprodine. 2 injections. Last dose 2 hr. before delivery	Nitrous oxide and oxygen, trichlorethylene	Infant breathed once, then became severely anoxic. Intubation, oxygenation. Levallorphan 0.25 mg., i.m. Satisfactory within 10 minutes.
0	At term	7 lb. 1½ oz.	1st stage—7 hr. 2nd stage—1½ hr.	Alphaprodine. 3 injections. Last dose 2½ hr. before delivery.	Nitrous oxide and oxygen, pudendal block	Suction, oxygenation, levallorphan 0.25 mg., i.m., breathing but lacked tone at 10 minutes. Large caput. Grunting respirations, ABO incompatibility. Died 4 days later.
1	34 weeks	4 lb. 15½ oz. (2nd twin)	1st stage—6½ hr. 2nd stage—55 min.	Alphaprodine. 1 injection 50 min. before delivery	Pudendal nerve block	1st twin spontaneous vertex delivery, cried lustily. 2nd twin assisted breech and forceps to aftercoming head. Limp, little response to resuscitation. Levallorphan 0.25 mg., i.m. Died within 24 hours.
0	At term	8 lb. 14½ oz.	1st stage—12 hr. 2nd stage—45 min.	Alphaprodine. 3 injections. Last one 2 hr. before delivery	Epidural	Apneic at birth. Low forceps delivery. Intubation, oxygenation, levallorphan 0.1 mg., i.m. Responded within 4-5 minutes. Maternal toxemia.
0	At term	7 lb. 3 oz.	1st stage—12¼ hr. 2nd stage—48 min.	Alphaprodine. 2 injections. Last one 1½ hr. before delivery	Nitrous oxide and oxygen, trichlorethylene	Cord tightly around neck, gasped once, then apneic and cyanosed. Oxygen under positive pressure. Levallorphan 0.25 mg., i.m. Crying within 5 min.
0	38 weeks	5 lb. ¼ oz.	1st stage—16 hr. 2nd stage—1 hr. 12 min.	Alphaprodine. 2 injections. Last one 2 hr. before delivery	Epidural	Cried at birth, then became pale and apneic. Intubation, oxygenation, levallorphan 0.25 mg., i.m. Respiration established and crying within 10 minutes. Low forceps delivery.
7	At term	7 lb. 3½ oz.	1st stage—12 hr. 2nd stage—30 min.	Alphaprodine. 2 injections. Last one ½ hr. before delivery	Nitrous oxide and oxygen	Cried at birth, then cyanosed and apneic. Levallorphan 0.25 mg. into umbilical vein. Responded dramatically.
0	At term	7 lb. 3 oz.	1st stage—30 hr. 2nd stage—45 min.	Alphaprodine. 5 injections. Last one 1½ hr. before delivery	Epidural	Poor, but cried at birth, then apneic, flaccid, and heart rate slowed. Intubated and oxygen insufflation. Levallorphan 0.1 mg., i.m. Respirations re-established in 5 mins. Crying in 10 minutes.
3	37 weeks	6 lb. 3 oz.	1st stage—5 hr. 2nd stage—40 min.	Alphaprodine. 1 injection 1½ hr. before delivery	Nitrous oxide and oxygen	Limp at birth. Considerable meconium and the cord tightly around the neck. Oxygen by mask and the infant was crying within 5 minutes.
1	At term	7 lb. 8½ oz.	1st stage—11 hr. 45 min. 2nd stage—27 min.	Alphaprodine. 4 injections. Last one 1 hr. before delivery		Apneic at birth. Intubation, oxygen insufflation. Respirations established in 3 minutes.

SEVERE ANOXIA IN INFANTS IN THE CONTROL GROUP

Parity	*Maturity*	*Wt. at birth*	*Length of labour*	*Analgesia*	*Anesthesia*	*Condition of infant at birth and treatment*
1	At term	5 lb. 12¾ oz.	1st stage—3 hr. 2nd stage—50 min.	Alphaprodine. 1 injection 1 hr. before delivery	Cyclopropane and ether	Apneic. Intubated and oxygen insufflation. Hare lip, cleft palate and abdominal distension. When respirations established there was indrawing of lower costal area. Died 24 hours later.
0	34 weeks	4 lb. 15¼ oz.	1st stage—6½ hr. 2nd stage—55 min.	Alphaprodine. 1 injection 1 hr. before delivery	Local infiltration of perineum	Limp and slow to breathe. Assisted breech with forceps to the aftercoming head. Died 24 hours later.
1	32 weeks	3 lb. 11¼ oz.	1st stage—1 hr. 45 min. 2nd stage—10 min.	Alphaprodine. 1 injection 1½ hours before delivery	Cyclopropane	Cried at birth, then became apneic and cyanosed. Intubated and oxygen insufflation. Respirations established in 10 min., but did not maintain colour well out of oxygen. Died in 24 hours.

SEVERE ANOXIA IN INFANTS IN THE TREATED GROUP

0	39 weeks	7 lb. 6½ oz.	1st stage—18 hr. 2nd stage—45 min.	Alphaprodine, levallorphan. 3 injections. Last dose 2 hr. 50 min. before delivery	Nitrous oxide and oxygen	Cried once when delivered, then became anoxic. Endotracheal intubation, oxygenation. Satisfactory after 3 minutes.
3	At term	6 lb. 12½ oz.	1st stage—1 hr. 40 min. 2nd stage—32 min.	Alphaprodine, levallorphan. 1 injection, 1 hr. 12 min. before delivery	Nitrous oxide and oxygen	Endotracheal intubation, gastric suction, oxygenation. Levallorphan 0.25 mg., i.m. Satisfactory within 10 minutes.
1	Post mature	7 lb. 4 oz.	1st stage—6 hr. 40 min. 2nd stage—25 min. Manual removal Placenta	Alphaprodine, levallorphan. 1 injection, 2 hr. 5 min. before delivery	Cyclopropane and oxygen	Intubation, oxygenation, gastric suction. Satisfactory after 5 minutes.
3	At term	7 lb. 1½ oz.	1st stage—42 hr. 2nd stage—10 min.	Alphaprodine, levallorphan. 2 injections. Last dose 15 min. before delivery.	Nitrous oxide and oxygen	Slow to breathe, but satisfactory in 10 minutes. Erythroblastosis.
0	Post mature	8 lb. 1 oz.	1st stage—14 hr.	Alphaprodine, levallorphan. 2 injections. Last dose 2 hr. 15 min. before delivery	Nitrous oxide and oxygen, pudendal nerve block	Breech delivery. Suprapubic pressure for delivery of head. Responded to suction and oxygenation within 10 minutes.
1	38 weeks	7 lb. 13¾ oz.	1st stage—6 hr. 45 min. 2nd stage—23 min.	Alphaprodine, levallorphan. 1 injection 2 hr. before delivery	Nitrous oxide and oxygen, trichlorethylene	Pale, limp, apneic. Intubated, oxygen insufflation. Levallorphan 0.25 mg., i.m. Responded within 10 minutes.
1	38 weeks	7 lb. 7¼ oz.	1st stage—3 hr. 30 min. 2nd stage—30 min.	Alphaprodine, levallorphan. 1 injection 1 hr. before delivery	Cyclopropane	Apneic, considerable meconium. Multiple congenital deformities. Intubated, oxygen insufflation. Respirations established in 15 minutes. Died few hours later.

between doses was allowed to exceed two hours, and even the latter appeared too long. This confirms the findings of most workers that the narcotic, alphaprodine, is effective for a short duration only. The addition of the antagonist to the alphaprodine did not appear to diminish the degree of pain relief. At the most, any analysis of pain relief can give only a general idea of the efficiency of a drug, as the accurate measurement of pain defies any standard estimation. Our degree of analgesia obtained appears to fall below that presented by Backner[15] and we think that this is because scopolamine was not employed and also because the interval between doses was longer.

The levallorphan administered to anoxic infants, described in detail, produced satisfactory and sometimes dramatic results. The same response was seen when the antagonist was given intramuscularly to nine infants suffering from moderate anoxia (Apgar 5-7). It is now considered that a

dose of 0.1 mg. is more suitable than 0.25 mg., since the former can be repeated without risk of subsequent depression due to the antagonist itself. In two infants receiving levallorphan after birth there was some mild secondary depression. Whether this was due to the narcotic, the antagonist, or to some other factor associated with delivery was not easy to decide.

SUMMARY

A total of 391 patients have been observed during labour. Two groups were formed by a method of random selection: 199 patients formed the treated group, who received a combination of alphaprodine 60 mg. and levallorphan 1 mg. intramuscularly at 2-hourly intervals until the second stage was reached; and 192 patients formed the control group, who received alphaprodine 60 mg. at intervals similar to the patients in the treated group. Facts recorded were pain relief, length of labour, complications of the third stage, side effects, and the condition of the infant at birth.

Levallorphan was found to be extremely effective when used to counteract anoxia due to alphaprodine, but it did not appear to influence the results, according to statistical analysis, when combined with alphaprodine.

We wish to thank Dr. Geraldine Maloney for permission to make these observations on patients under her jurisdiction. The excellent co-operation given by Miss Percival, supervisor of the labour floor, and her nursing staff made this work possible. Miss Margaret Robins, R.N., research assistant to the anesthetic department, kept meticulous records on all cases. We would like also to express our gratitude to the board of governors of Women's College Hospital for the research grants given to the authors and to Miss Robins from the Dorothy Graham Research Fund. Hoffmann-LaRoche Ltd. supplied the drugs used in this survey and made a valuable contribution to the research fund.

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HUMAN BIOASSAY OF A NEW ANTITUSSIVE AGENT*

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THE POTENCY of cough suppressants has previously been found to be amenable to assessment by inducing cough in normal persons,[1] rather than by attempting to study the action of the drug on subjects with chronic cough. In cough-free individuals, cough can be induced by inhalation of an aerosol spray of citric acid. This causes a reproducible and relatively constant cough reaction in successive trials. Various drugs can then be administered and their antitussive action measured and compared with the normal response in unmedicated persons. We consider that this technique leads to a much more accurate determination of antitussive action than observations made on subjects with chronic cough.

Similar investigations of antitussive agents have previously been made,[2, 3] but we have not considered them to be completely satisfactory because of the absence of placebo control and because of possible bias introduced by the investigator's knowledge of which agent had been administered.

These objections were met in the present investigation by the use of a double-blind method of drug administration and inclusion of a placebo among the agents administered. It was also considered, because of previous experience, that the period during which coughs were counted, after inhalation of the aerosol, should be decreased from 5 minutes to 1 minute, as almost all coughs fell within this shorter interval, and those that did not could possibly be due to extraneous factors.

OBJECT

The object of the present study was to compare the cough-suppressant activity of an as yet untested compound with that of codeine. This preparation, called R-1132 by the manufacturer,‡ is a true synthetic material which has previously been investigated as an antidiarrheal agent and found to be an effective inhibitor of gastrointestinal motility. Its analgesic action is slight, and it is free of parasympatholytic activity.

MATERIAL AND METHODS

The procedure followed was modified from that described by Bickerman and Barach[1] in 1954 and repeated by Shane *et al.* in 1957 and 1958.[2, 3]

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