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"*I would have everie man write what he knowes and no more.*"—MONTAIGNE

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EDITORIAL

DRUG ADDICTION

THERE will be general agreement with the first part of the interim report of the Inter-departmental Committee on Drug Addiction.* This committee, presided over by Sir Russell Brain, appears to be doing an excellent job of work, and its recommendation that in general "any drug or pharmaceutical preparation which has an action on the central nervous system and is liable to produce physical or psychological deterioration should be confined to supply on prescription" seems long overdue. There will be widespread hope that if implemented with expedition this may prevent the people of this country becoming "tranquillizer addicts". It is to be hoped that this recommendation will apply to those numerous drugs available for weight reduction, the excessive and unwise use of which may be disastrous. The report further recommends that "an independent expert body" should be responsible for advising which substances should be so controlled. This is again long overdue.

Anaesthetists are known to have given evidence before this commission and their testimony is reflected in the section of the report devoted to addiction to anaesthetic gases. While it was impossible to determine accurately the incidence of addiction of this kind, it appeared that in the past eleven years under twenty cases have come to notice

It should be remembered that there are some 1,500 doctors exclusively practising anaesthesia, excluding a number of general practitioners, resident medical staff, etc. Furthermore, all these cases "would seem to have been of essentially abnormal personality". The report concludes that the incidence of this irregularity has been very small indeed. The committee accepted the need for anaesthetists occasionally to sample by sniffing the mixture they are delivering in these words: "It was represented to us that with the apparatus at present in use, the preliminary sniffing of the gases immediately before administering them to the patient is a recognized and indispensable precaution. Neglect of this measure in the first place might be tantamount to professional negligence. Furthermore, of the great majority of anaesthetists, such a practice offers no encouragement to addiction." With these views we are in complete agreement.

The committee does not make recommendations as to how cases of irregularity in this matter are to be dealt with. There are discussions proceeding at the moment with the Ministry with the object of arriving at a satisfactory procedure. We would only point out that this is a matter which must be left to the medical profession and there is little doubt that with encouragement the medical staffs of hospitals are well able to deal with cases as they arrive. Failure to do so in the past has been uniquely exceptional and should not demand the establishment of any special committee of individuals to supervise and pass judgement on their colleagues. Indeed, it might be that with the passage of time the individuals on these committees might be the ones requiring advice or admonition.

* *Drug Addiction.* Interim report of the Inter-departmental Committee. H.M. Stationery Office, price 6*d*.

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THE INFLUENCE OF MORPHINE AND PETHIDINE IN COMBINATION WITH LEVALLORPHAN ON BILIARY DUCT PRESSURE AFTER CHOLECYSTECTOMY

BY

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IT has long been known that morphine causes contraction of the sphincter of Oddi (Kitakoji, 1930) and thereby raises the pressure in the biliary ducts. Gaensler, McGowan and Henderson (1948) demonstrated that pethidine had a similar action, although the rise in pressure in the ducts was somewhat less. The opiate antidote (-)-3-oxy-N-allyl-morphinan (levallorphan) is in several respects antagonistic to morphine and pethidine (Fromherz and Pellmont, 1953; Lendle, 1953; Malorny 1955). One may therefore wonder if this antagonism influences the action of morphine and pethidine on the sphincter of Oddi. Although Lipchik (1958) studied the effect of levallorphan on morphine-induced spasm in this sphincter, the smallness of his clinical material and the absence of controls precluded reliable inferences.

In the present study the pressure in the biliary ducts was measured in cholecystectomized patients after administration of morphine or pethidine alone and in combination with levallorphan.

MATERIAL AND METHODS

It is generally agreed that the sphincter of Oddi seems always to react to morphine by contraction. In hitherto unpublished experiments, however, I found that this reaction may be absent if the sphincter mechanism is disturbed by calculi in the common bile duct, inflammatory changes there or in the pancreas, or manipulations in the vicinity of the sphincter during operation. In consideration of these findings, the present study was limited to patients with uncomplicated cholecystolithiasis.

A series of 20 patients was investigated after the injection of morphine and morphine levallorphan. A further 10 patients were given pethidine and pethidine-levallorphan (Pethilorfan).

Cholangiography was routinely performed during cholecystectomy. At the end of the operation a cannula was inserted into the common bile duct through the stump of the cystic duct or through a choledochotomy. Pressure readings were taken 3 to 5 days after the operation. The biliary duct pressure was then conducted via the drain either to a simple indicator tube, where it was read against a scale graduated in centimetres, or to an electromanometer, where the tension changes caused by the fluctuations in pressure were taken up by a potentiometer, amplified and traced on paper by a recorder. The accuracy of registration in both procedures was 0.5 cm of water. The patients were supine during the pressure measurements. As zero point the confluence of the cystic duct and the hepatic duct was selected. The level of this was marked on the skin of the right flank during cholecystectomy.

Only resting pressures were registered. For present purposes no interest was attached to pressures during perfusion of fluid and subsequent residual pressures.

Each patient was studied twice, viz., after morphine and morphine-levallorphan or after pethidine and pethidine-levallorphan. As a rule the observations were made on two successive days. To eliminate the time factor as far as possible, half of the patients in the respective groups received morphine or pethidine alone on the first day, while the other half were given the same drug combined with levallorphan, and on the second day this arrangement was reversed.

The dose of morphine was always 10 mg. When morphine and levallorphan were given together, the dose of the latter was as follows:

0.5	mg	levallorphan	in	3 cases
1.0	„	„	„	3 „
1.5	„	„	„	2 „
2.0	„	„	„	12 „

The doses in the "pethidine group" were 100 mg of pethidine with or without 1.25 mg of levallorphan.

The drugs were given by subcutaneous injection Paired drugs were injected simultaneously.

RESULTS

Statistical treatment of the results would have been desirable but, because of the many individual variables that influence such results, this was considered to be scarcely warrantable. The wide variations in initial pressure (5.0–15.5 cm of water) in biliary flow and in intestinal function suffice as examples. One must therefore have recourse to comparison of observations in individual patients and means of these values.

All the diagrams are based on the increase of biliary duct pressure following administration of the various drugs. The pressure before the injection thus is stated as zero in all cases.

In figure 1 the effect of 10 mg of morphine may be studied. All 20 patients reacted with pressure elevation, which 60 minutes later had subsided in only 1 patient. In 17 patients the pressure was still elevated 90 minutes after the injection. The highest value on the graph of means was 5.6 cm of water.

Figure 2 shows the pressure measurements following injection of 10 mg of morphine with levallorphan according to the stated distribution of dosage. In 2 cases no pressure elevation resulted. In 8 of the other patients the pressure had returned to initial levels after 60 minutes. Ninety minutes after the injection only 6 of the patients still had elevated biliary duct pressure. The highest mean value was 4.7 cm of water.

Thus it seemed that the addition of levallorphan shortened the duration of the pressure rise produced by morphine, and that this rise was generally less after the combined drugs.

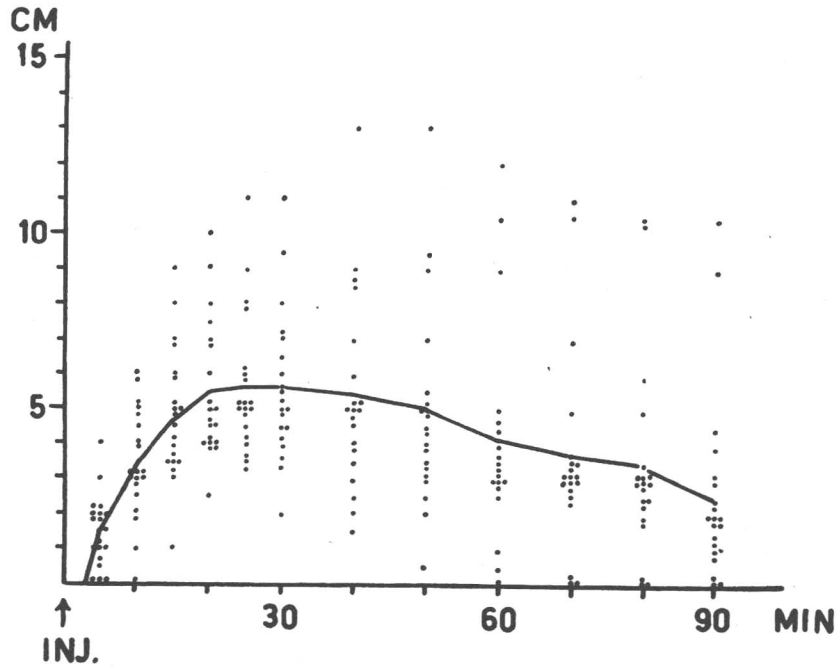

FIG. 1

The pressure increase in the common bile duct after the subcutaneous injection of 10 mg of morphine. The dots indicate individual readings and the graph denotes the mean of these readings.

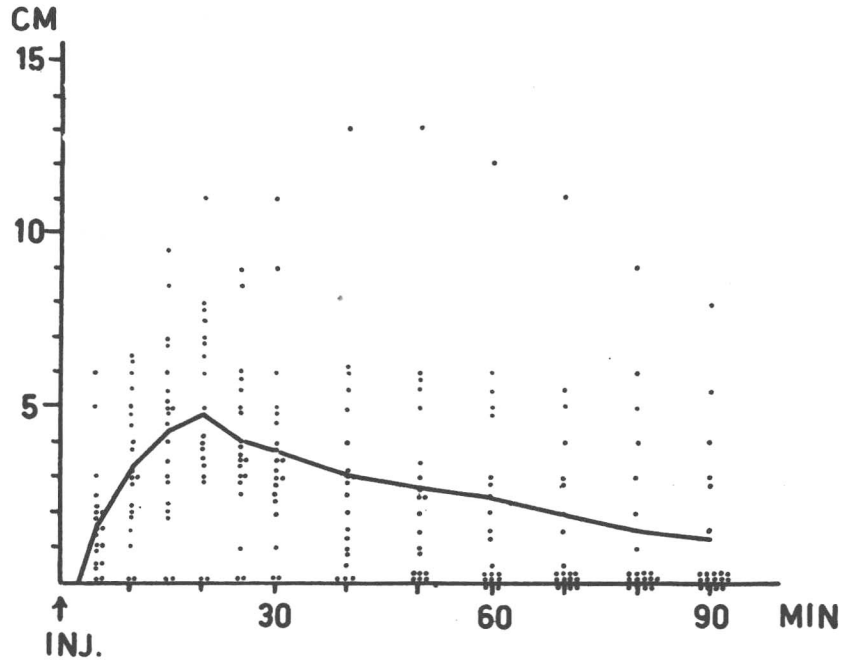

FIG. 2

The pressure increase in the common bile duct after the subcutaneous injection of 10 mg of morphine and 0.5–2.0 mg levallorphan. The measurements were made on the same patients as in figure 1. The dots indicate individual readings and the graph denotes the mean of these readings.

The amount of levallorphan appeared to be less important. Of the 2 patients without pressure elevation, 1 had been given 1 mg of this drug, and the other 2 mg. In 4 of the 20 patients no antidote action was observed; the pressure curves after morphine and after morphine-levallorphan being almost identical. Three of the 4 patients had received 2 mg of levallorphan and the fourth patient 1 mg.

The influence of pethidine on the biliary duct pressure is shown in figure 3. The elevation was less pronounced and was briefer than after the injection of morphine alone. Comparison with figure 4, which shows the pressures after administration of pethidine-levallorphan gives roughly the same impression as comparison between the pressure curves following morphine and morphine-levallorphan. Thus, elevation of pressure occurred in all of the 10 patients after pethidine alone and in 8 patients after pethidine-levallorphan The highest mean readings were 3.3 cm of water after pethidine and 2.2 cm after the combined drugs. Here, too, the duration of the rise was shorter after the combined drug injection. Sixty minutes after injection of pethidine-levallorphan the initial reading had been regained in 9 patients, whereas the corresponding figure after pethidine alone was 4.

In 1 patient the pressure curve after pethidine alone was virtually identical with that after combined medication.

Levallorphan in these experiments gave rise to no subjective or objective side effects.

The results of the investigations may be summarized as follows. Levallorphan seemed to counteract the contractile action of morphine and pethidine on the sphincter of Oddi. The rise in pressure in the biliary ducts that followed administration of these two drugs usually was reduced and shortened by simultaneous administration of levallorphan. In a few cases no pressure rise occurred when levallorphan was given.

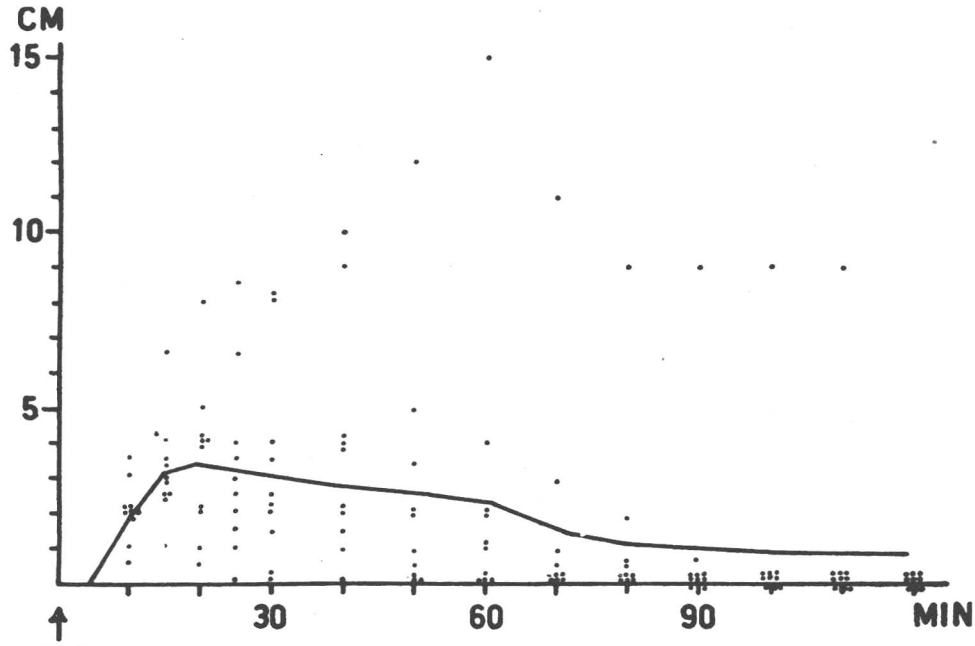

FIG. 3
The pressure increase in the common bile duct after the subcutaneous injection of 100 mg of pethidine. The dots indicate individual readings and the graph denotes the mean of these readings.

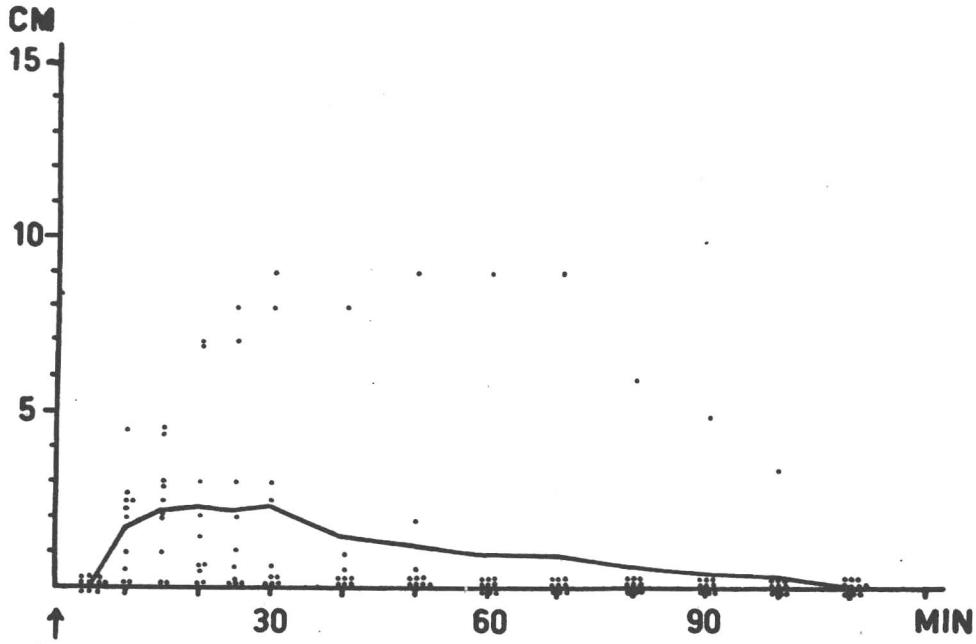

FIG. 4
The pressure increase in the common bile duct after the subcutaneous injection of 100 mg of pethidine and 1.25 mg of levallorphan. The measurements were made on the same patients as in figure 3. The dots indicate individual readings and the graph denotes the mean of these readings.

As regards pethidine-levallorphan, the reported results have received practical testing in a series of patients with cholelithiasis who were given this combination (pethidine-levallorphan) together with atropine as pre-operative medication (Kjellgren and Löf, 1959). Comparisons of the effect of premedication on the operative cholangiograms were made between these patients and others who had received morphine with hyoscine or a barbiturate together with atropine. The frequency of satisfactory cholangiograms was highest after pethidine-levallorphan and atropine.

Lorfan[R] and Pethilorfan[R] were kindly supplied by F. Hoffmann-La Roche & Co. A. G., Basle, Switzerland.

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TRANSIENT HYPOTENSION IN THE CAT INDUCED BY GALLAMINE*

BY

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WHILE investigating certain aspects of the neuromuscular blocking properties of gallamine in cats it was observed that in some animals the intravenous injection of small quantities of the drug was followed by a transient hypotension. As any activity displayed by a drug in the experimental animal may also reveal itself in clinical practice (Paton, 1959) it seemed desirable to examine this phenomenon more closely.

In a series of twenty cats hypotension occurred on four occasions. Characteristically the fall in blood pressure was constant for each animal (fig. 1) although the effect varied from cat to cat. The smallest change was a fall of 20 mm Hg, while the largest was over 100 mm. The remaining two dropped by 30 and 50 mm Hg respectively.

In one cat anaesthetized with chloralose it was possible to investigate the hypotensive response in some detail (fig. 1). In this animal a dose of gallamine (0.25 mg/kg) too small to produce any neuromuscular blocking effects was sufficient to lower the blood pressure by 50 mm Hg. On analyzing this response it was found that the

*Work done in the Department of Pharmacology, Royal College of Surgeons of England.

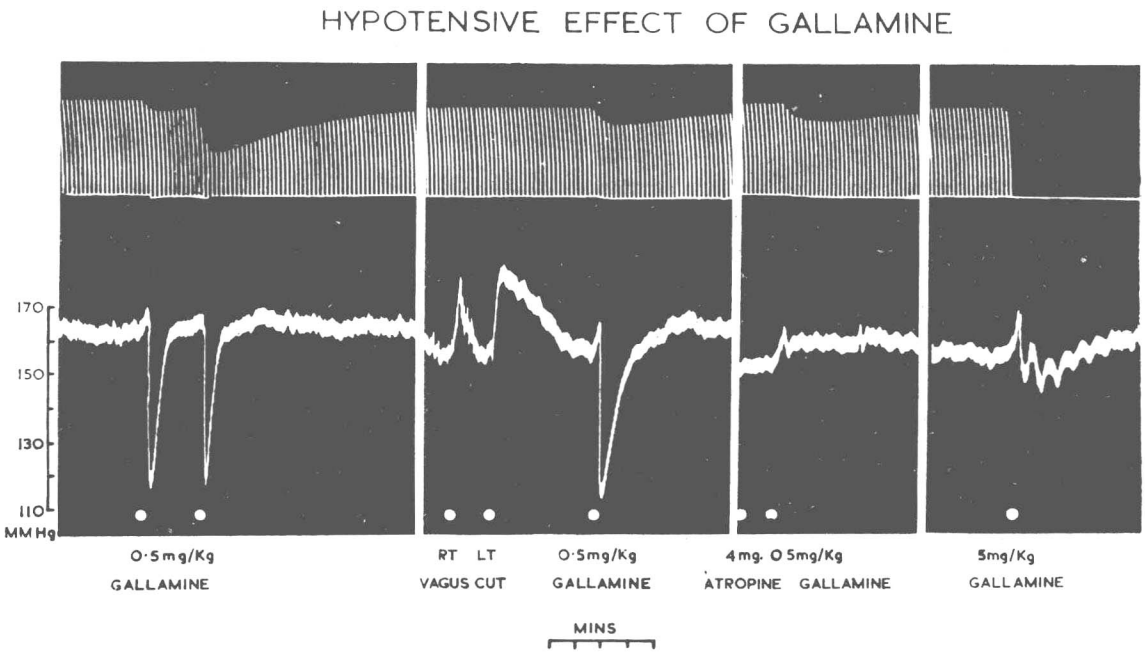

FIG. 1

Cat, male, 3.4 kg, chloralose. Ant. tibialis contractions in response to indirect stimulation. Blood pressure. Hypotensive effect of gallamine uninfluenced by bilateral vagal section but antagonized by atropine. No effect on neuromuscular blocking action.

blood pressure began to fall within 4 seconds of the injection of gallamine into the external jugular vein and the limit of the response was reached in a further 8 seconds. Recovery began 15 seconds later and was usually complete within 45 seconds of the time of the injection.

Doubling the dose and increasing it tenfold did not enhance the fall in blood pressure. Repeated doses (6) at 2-minute intervals did not modify the response nor did the provision of an interval of 60 minutes between injections. The division of both vagus nerves had little effect on the extent of the blood pressure fall although from figure 1 it is obvious that the recovery time has been prolonged. But when the injection of gallamine was preceded by the administration of intravenous atropine (4 mg) 1 minute beforehand, the hypotensive response was abolished. That this was a true atropine antagonism was shown by the fact that after sufficient time had been allowed for the effects of atropine to wear off gallamine again produced hypotension.

It is perhaps worth noting that despite the marked fall in blood pressure, the pulse rate was relatively slightly altered from 130 beats per minute to 145.

DISCUSSION

When hypotension follows the intravenous injection of a drug several possibilities need to be considered. A central action is not uncommon with many drugs and the possibility of vagal effects should not be ignored. Ganglionic block may be a side effect of certain relaxant drugs and histamine release is common to all of them. Finally, in this group the possibility of an anticholinesterase activity should be examined.

Except under markedly artificial conditions, the possibility of a central action by gallamine is too remote to be considered. The drug is a highly ionized compound containing three quaternary ammonium groups; such substances do not cross the blood-brain barrier and cannot act centrally when given intravenously.

The vagolytic action of gallamine demonstrated by Riker and Wescoe (1951) makes it unlikely that the fall in blood pressure is due to vagal stimulation, and the occurrence of hypotension when gallamine was injected after the division of both vagus nerves confirms this conclusion.

Riker and Wescoe further investigated the action of gallamine on ganglionic transmission and showed that even with doses as high as 10 mg/kg injected intra-arterially into cats there was no depression of transmission across ganglia. They concluded that gallamine cannot be regarded as a ganglionic blocking drug.

While histamine release must always be remembered when considering relaxant drugs, the absence of the typical response to histamine as described by Paton (1959) seems to exclude this possibility in the experiments under discussion.

According to Foldes (1957) all relaxant drugs show some anticholinesterase activity and the fact that the hypotension in this case was antagonized by atropine supports this view. Moreover, the pattern of response is closely similar to that obtained when acetylcholine is injected intravenously into cats in large doses (Payne—unpublished observations).

ACKNOWLEDGMENTS

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Able technical assistance was provided by Mrs. Dawn Gardiner and Mr. D. A. Green.

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ENDOTRACHEAL ASPIRATION AND OXYGENATION IN RESUSCITATION OF THE NEWBORN

BY

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THE indications for active intervention in neonatal resuscitation vary from hospital to hospital. There is little agreement as to whether the clinical control should be the immediate responsibility of the obstetrician, the paediatrician or the anaesthetist (Schmidt, McLandress and Cruickshank, 1956), and which of a large variety of methods should be used (Abramson, 1956).

Most physicians now agree that the administration of oxygen takes precedence over the administration of drugs, but there is no general agreement concerning the route of administration. The shortcomings associated with the administration of oxygen by mask are now appreciated and recently the effectiveness of intragastric oxygen, first advocated by Akèrrén and Fürstenburg (1950) and Waller and Morris (1953), has been questioned by Holme and Payne (1955), James et al. (1959) and Barrie (1959). Osborn (1958) has further shown that indwelling oesophageal catheters are not without their dangers, and rupture of the stomach due to overdistension has followed this method of resuscitation (Hodges, 1956).

It has been alleged that endotracheal intubation may lead to shock and trauma, so increasing the infant mortality rate (Bloxsom, 1951). Some therefore regard this procedure as contra-indicated (*Lancet*, 1951); especially in small infants (Lord, Powell and Roberts, 1953). Laryngeal ulceration has been cited as a complication, and even among those who advocate it, intubation is not always regarded as a primary measure (Peddie, 1957).

In this unit during operative obstetric deliveries when an anaesthetist is present the responsibility for neonatal resuscitation is, in the first instance, delegated to him.

In anaesthesia endotracheal suction and the administration of oxygen by intermittent inflation is an accepted form of therapy for obstructed, failing, or absent respiratory effort. We follow these principles which are applied to neonatal resuscitation also by others (Roberts, 1949; Kromm, 1955; Rees, 1958).

This paper analyzes the results obtained in 137 infants in whom endotracheal resuscitative measures were undertaken. Conclusions are drawn as to the difficulties, dangers and the effectiveness of the technique.

MATERIAL AND METHOD

All the patients were in-patients in the obstetric unit and formed a series of 754 operative procedures from an overall 6,574 patients delivered.

All the anaesthetics were administered by members of the anaesthetic department, and consisted of a sleep dose of thiopentone followed by suxamethonium, nitrous oxide and oxygen with endotracheal intubation. This method has been described, found to have advantages over the more traditional methods, and further to be associated with little or no neonatal depression referable to anaesthesia (Hodges et al., 1959, 1960).

After delivery the infant was placed on a special neonatal trolley near the head of the operating table. The infant lay on a padded rest which could be tilted as desired. Resuscitative equipment was available on this trolley.

Immediately after delivery, if the clinical observations suggested that aspiration of liquor or regurgitated gastric contents had occurred, endotracheal suction was undertaken.

After the establishment of a clear airway, with or without endotracheal suction, the indications for endotracheal oxygen and intermittent positive pressure inflation were signs of anoxia associated

*Present Appointment. Captain, R.A.M.C.

with apnoea, subsequently cyanosis, or failure to establish regular spontaneous respirations within 2 to 3 minutes. Each case was judged individually according to these criteria. Bradycardia and cardiac irregularities were regarded as indicative of anoxia. Intubation was carried out using size 00 Magill tube, or a Foregger shouldered tube. Oxygen was administered by manual compression of an open-ended bag on a T-piece circuit with manometric control. Pressures of between 30 and 40 cm H_2O were obtained, but were maintained for the shortest possible period. The movement of the chest was carefully observed. Suction was carried out as rapidly as possible, and was continued intermittently for short periods only. Between these periods of suction the infant was allowed to inhale oxygen, or in the absence of spontaneous respirations intermittent positive pressure inflation was continued. The infants were extubated as soon as the airway was cleared and regular spontaneous respirations were established.

All premature infants and those in whom the response to resuscitative measures was considered unsatisfactory, were transferred to the paediatric department.

The state of the infant at birth and the resuscitative measures applied were recorded on the anaesthetic-obstetric punch card previously described (Hodges, 1959). These observations together with the subsequent obstetric, paediatric and, when necessary, pathological records form the basis of this paper.

All stillbirths and neonatal deaths were classified at special monthly obstetric meetings held for this purpose by the obstetric department, and attended by representatives from the departments of paediatrics, anaesthesia, and pathology.

RESULTS

The group of 137 infants considered here represented 18 per cent of the operative deliveries, the incidence of intubation following Caesarean section being the highest. In 74 infants (54 per cent) pre-operative foetal distress in utero had been diagnosed. Six infants were delivered pulseless and apnoeic, being apparently stillborn. Resuscitative measures restored regular pulse and respirations in one patient but with short-lived success. Subsequently 11 other neonatal deaths took place.

Thirty-three per cent of the infants were premature according to their dates, and 15 per cent weighed less than 2,500 g. The majority of the group of premature infants was delivered by Caesarean section.

Most of the infants were intubated because of primary apnoea (or because they had only gasping respiratory efforts), subsequent clinical hypoxia, or failure to establish regular respiratory effort within 2 minutes of birth. Seventeen per cent of the infants breathed regularly at birth, but either relapsed later and had only a weak respiratory effort associated with hypoxia, or aspirated mucus and liquor and became obstructed or depressed. This was regarded as secondary respiratory depression. Twenty per cent of the infants suffered primarily from obstruction and were intubated for the purpose of aspiration (table II).

TABLE I

Details of 137 infants intubated for endotracheal toilet and/or oxygenation after delivery.*

From 754 operative obstetric deliveries all conducted under a standard anaesthetic technique.† (From a total of 6,574 deliveries in a 32 month period).

	Total	Infants intubated			
		Number of intubations	Pre-operative foetal distress	Failures (stillbirth)	Neonatal deaths
Caesarean section	333	80 (24%)	43 (54%)	4	6
Midcavity forceps	245	41 (17%)	20 (49%)	—	3
Outlet forceps	153	12 (8%)	8 (75%)	—	2
Breech delivery	23	4 (17%)	3 (75%)	1	1
Total	754	137 (18%)	74 (54%)	5 (3.6%)	12 (8.7%)

* According to the criteria outlined in text. † Thiopentone-suxamethonium-nitrous oxide-oxygen.