sensitivity to chlorpromazine (Popper and Schaffner, 1959). A delay in onset of jaundice, such as occurred in Case 1, has also been noted with chlorpromazine jaundice (Sherlock, 1962).

Prior to the introduction of this estolate of erythromycin there had been no reports of hepatic dysfunction associated with the drug. It is not known which fraction of the estolate is responsible for stimulating the immunological reaction. The drug appears in the blood as erythromycin-free base (40–50%) and erythromycin propionate (50–60%), but the fate of the lauryl sulphate, which is dissociated in the bowel, is uncertain (Griffith, 1960). Gilbert (1961) has suggested that the esterification of the free OH grouping on the desosamine side-chain of the erythromycin molecule confers the properties of a haptene on the molecule.

In view of the likelihood of this being a hypersensitivity type of reaction, it would seem advisable to avoid the use of repeated courses of the drug, particularly with patients who have a history of allergies (Havens, 1962).

Summary

Two cases of untoward reaction after treatment with "ilosone" (erythromycin estolate) are reported. The first patient developed prolonged jaundice, and occasioned sufficient diagnostic doubt to necessitate a laparotomy.

The liver was biopsied and the histological findings were those of an intrahepatic cholestasis.

The second patient presented with a pain simulating biliary colic after taking two capsules of ilosone. This was the third occasion on which she had reacted in this way. Jaundice did not develop on any of these occasions.

The findings in these and other reported cases suggest that the hepatic dysfunction is due to a hypersensitivity reaction.

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Preliminary Communications

Effect of Cooling on Pre-mixed Gas Mixtures for Obstetric Analgesia

The term pre-mixed is used here to denote a gas mixture which has been formed by placing two or more non-reacting gases together in the same storage cylinder. A mixture of nitrous oxide and oxygen (in equal volumes when measured at atmospheric pressure) compressed in the same cylinder to 2,000 lb./sq. in. (kg./sq. cm. 140.6) at room temperature remains in a single gas phase. Such a pre-mixed mixture was first used for self-administered inhalational analgesia by women in labour in 1961 (Tunstall).

The only problem with regard to safety which has appeared in the clinical use of pre-mixed gases is that due to exposure of full cylinders to temperatures in the region of 0° C. or below. Cole (1962, personal communication) was the first to point out that if a full cylinder of pre-mixed 50% nitrous oxide and 50% oxygen, v/v, was cooled to –8° C. (the point at which nitrous oxide begins to form a liquid in the most dependent portion of the cylinder) the reversion to a single gas phase in even mixture, identical to that before cooling, was not immediate after rewarming. This implied that if a cylinder were brought into the labour ward from out-of-doors in freezing weather it would not, even after the elapse of some hours to allow for rewarming, be safe to use. It suggested, for example, that if the cylinder were used upright a mixture containing a weak concentration of nitrous oxide would at first be inhaled and then, when the cylinder was nearly empty, perhaps a dangerously high concentration. This paper summarizes the work done to assess the nature of this problem and to discover whether it could be overcome by simple means.

METHOD

Twenty-one different cooling experiments were performed with full cylinders containing various percentage mixtures

of pre-mixed nitrous oxide and oxygen. The changes induced in the physical state of the contents of the cylinder were studied by measuring the percentage of the oxygen in the gas mixture which issued from the cylinder outlet under stated conditions and after stated manœuvres. Measurements were made with a Beckman paramagnetic oxygen analyser. After cooling to –25° C., to 0° C. or above, and after stated manœuvres, measurements were made within 15, 5, and 2 minutes respectively. Where applicable stated manœuvres were performed immediately after the last preceding measurement.

If the oxygen percentage of the sample of the mixture taken from the outlet of the cylinder was the same as before cooling or the same for various positions of the outlet valve relative to the cylinder (for example, upright and inverted), it was assumed that the contents were in a single gas phase in even mixture. If the oxygen percentage measured just before the cylinder became empty was the same as at the beginning of the experiment, it was assumed that the cylinder would have been safe to use under the circumstances set.

RESULTS

The results of 14 of the experiments are tabulated. In the seven others the results provided neither new nor contradictory information and are therefore not included.

The column marked oxygen % gives the percentage content of oxygen in the sample of gas mixture obtained from the cylinder outlet valve. The position of the cylinder at the time of sampling is of course vital and is recorded. (When the cylinder is upright the outlet valve is at the top.) The pressure shown on the cylinder contents gauge at the time of sampling is an indication of the temperature of the contents of the full cylinders. Each sample resulted in about two litres of gas at atmospheric pressure being expended. Readings taken on day 0 were those at the beginning of the experiment and before any cooling had taken place.

In experiment 1 the oxygen content on sampling rose from 40% at the original reading to 68% after cooling. This meant that some of the original (60%) nitrous oxide content, which was at the beginning entirely gaseous and

Results

No.	Day	Time	Position	Oxygen (%)	Pressure lb./sq.in.	Surface Temp. of Cylinder °C.
1	0	1600	Upright	40	1780	
	Stored five days at -25° C.					
	5	1535	Upright	68	1400	
	8	0930	"	67	1700	
	11	1120	"	62	1750	18-4
	Cylinder inverted three times.					
	11	1125	Upright	41	1700	15-0
	Mixture remained even in all positions and during use.					
	0	1600	Upright	40	1900	
	Stored five days at -25° C.					
2	5	1535	Horizontal	63	1360	
	5	2330	"	48	1730	
	6	1445	"	42	1780	
	Cylinder inverted three times.					
	6	1450	Upright	41	1770	
	Mixture remained even in all positions and during use.					
	0	1430	Upright	40	1880	
	Four days at -25° C.					
	4	1530	Upright	66	1180	
	4	1630	"	"	1000	
3	5	1345	"	63	1820	
	Cylinder inverted three times.					
	5	1350	Upright	"	1760	
	5	1355	"	41	1830	
	5	1825	"	41	1880	
	Cylinder inverted three times.					
	5	1830	Upright	41	1880	
	0		Upright	40	1850	
	Seven days at -25° C.					
	7	1555	Upright	64	1470	
4	8	1435	"	58	1750	17-5
	Cylinder inverted three times.					
	8	1440	Upright	43	1700	15-0
	Cylinders turned on to empty at rate of 10 l./min.					
	8	1545	Upright	42		12-0
	8	1630	"	42	1250	11-5
	8	1750	"	42	700	11-5
	8	1930	"	42	Empty	
	0		Upright	40	1825	
	Seven days at -2° C.					
5	7	1700	Upright	48	1450	
	Blast off in 15 minutes.					
	7	1715	Upright	0	0+	Frosted
	8		"	0	200	
	0		Upright	42	1750	
	Four days at 3° C.					
	4		Upright	42	1400	
	One day at approximately 0° C.					
	5	1615	Upright	45	1350	
	5	1617	Inverted	26		
6	Cylinder inverted three times.					
	5	1620	Upright	44		
	5	1622	Inverted	27		
	Seven days at 1° C.					
	12	1700	Upright	44	1350	
	12	1705	Inverted	30		
	In bath at 42° C. for five minutes.					
	Blast off for eight minutes.					
	12	1720	Upright	42	600	
	12	1725	Inverted	42	600	

Results (continued)

No.	Day	Time	Position	Oxygen (%)	Pressure lb./sq.in.	Surface Temp. of Cylinder °C.
7	0		Upright	39	2000	
	Eleven days at -25° C.					
	11	1655	Upright	67	1350	
	Rewarm in horizontal position at room temperature.					
	11	1715	Horizontal		1500	
	11	1730	"		1600	
	11	1735	Inverted	24		
	11	1815	"	38		
	11	1820	Upright	39	1750	
	11	1825	Inverted	39		
8	Used by patient from 1830 hours.					
	0		Upright	62	2100	
	Three days at 2-9° C.					
	3	1005	Upright	62		
	Run off in one hour and twenty-five minutes (400 gallon type N ₂ O cylinder).					
	3	1130	Upright	62	0+	
	Cylinder moist but not frosted. (Room temp. 21° C.)					
	0		Upright	58	2050	
	Eleven days at -25° C.					
	11		Upright	67	1500	
9	14		Upright	58	2000	
	Three days at 4-10° C.					
	17	1700	Upright	58	1850	
	Blast off in one minute.					
	17	1703	Upright	45		
	17	1705	Inverted	9	100	
	Cylinder in bath at 40° C. five minutes.					
	17	1712	All positions	20		
	0		Upright	52	2000	
	Three days at 4-10° C.					
10	3	1535	Upright	52	1830	
	Blast off in two minutes.					
	3	1540	Upright	14		
	3	1543	Inverted	11	50	
	Cylinder in bath at 42° C. for five minutes.					
	3	1550	All positions	11		
	0		Upright	52	1850	
	Twenty-three days at -25° C.					
	23	1350	Upright	67	1200	
	Cylinder in bath at 42° C. for five minutes, then inverted three times.					
11	23	1400	Upright	52	1900	
	Blast off in three minutes.					
	23	1405	Upright	52	0	
	0		Upright	50	2100	
	Three days at 2-9° C.					
	3	1035	Upright	50	1550	
	Run off to empty in 1½ hours (400 gallon type N ₂ O cylinder).					
	3	1140	Upright	50	Empty	
	Moist but no frost. Room temperature 21° C.					
	0		Upright	53	1825	
12	Five days at 1-3° C.					
	5	1020	All positions	53	1500	
	Run off to empty in 1½ hours (400 gallon type N ₂ O cylinder).					
	5	1150	Upright	53	Empty	
	0	1030	Upright	53	2550	
	Blast off in one minute (room temperature 23° C.).					
	0	1035	Upright	13	0+	

in even mixture with the (40%) oxygen content, had liquefied and settled in the most dependent portion of the cylinder. This resulted in a higher oxygen concentration in the gas phase, which was above the liquid phase. In this experiment the cylinder was kept absolutely still and free from movement after withdrawal from the refrigerator. It will be seen from the results on the eleventh day that the gas sample taken from the upper end of the cylinder still contained a higher proportion of oxygen than in the original mixture, even though the contents must have been at room temperature for several days. There was therefore still a pool of nitrous oxide, if not in liquid form at least in high concentration, in the most dependent portion of the cylinder. Three brisk inversions of the cylinder in rapid succession resulted in the dispersal of this pool and a reversion of the cylinder contents to its former state as a single gas phase in even mixture. The temperature drop of the surface of the cylinder recorded by an electrical thermometer suggested that the nitrous oxide pool was in a liquid or near liquid state, and conversion to the gas phase of course absorbs heat. The final reading of 41%, when it should have been 40%, is within the accuracy required of observer and instrument for the purposes of the experiments.

The detailed explanation of this experiment should make it simpler for the reader to interpret the results of the other experiments. One can see that, provided rewarming has taken place in the pre-mixed gases under discussion, nitrous oxide pooling is easily and permanently reversed by agitation of the cylinder. For the 50:50 mixtures rewarming above 0° C. should be sufficient to produce a single gas phase in even mixture after agitation.

Further, it may be seen in experiment 11 that adequate rewarming of full cylinders after being cooled to -25° C. occurs after immersion of the cylinder in water at 42° C. for five minutes. (The steel cylinders in the water rewarming experiments were of the light-weight variety.) In experiment 7 there was adequate rewarming of the cylinder after it had been left lying flat in the labour room for two hours and subjected to a certain amount of movement.

The cooling occasioned by emptying the cylinder at about 10 l./min. in experiments 8, 12, and 13 was not sufficient to cause unevenness of the mixture, even though the cylinder was already cold at the beginning of the experiment.

Experiment 14 shows that the intense cooling which results from widely opening a cylinder valve and blasting off the contents might cause a dangerous unevenness of the mixture in the cylinder.

Experiment 2 (in which the cylinder was kept still) shows that nitrous oxide pooling is not nearly so prolonged (cf. 1) in a cylinder allowed to rewarm in the horizontal position.

DISCUSSION

Pure nitrous oxide gas at 20° C. forms a liquid when compressed above 750 lb./sq. in. (kg./sq. cm. 52.7). But compressed oxygen has a solvent effect on liquid nitrous oxide. At 2,000 lb./sq. in. (kg./sq. cm. 140.6) the maximum amount of nitrous oxide v/v with oxygen that will remain in a single gas phase is 75% at 20° C., 60% at 0° C., and 50% at -8° C. These figures are approximate.

The results suggest that the temperature problem may be readily overcome. If there is no frosting of the surface of a full cylinder of pre-mixed nitrous oxide 50% and oxygen 50%, v/v, when in room air, and if it has been inverted briskly three times, it appears to be perfectly safe to use. The inversion manoeuvre would of course be necessary only

in winter weather when the possibility arises that the cylinder may have been cooled.

It is suggested that the time has come to replace nitrous oxide and air by nitrous oxide and oxygen for the relief of pain in labour (Cole and Nainby-Luxmore, 1962). The future of pre-mixed gases is based on several important considerations.

1. Gas and oxygen analgesia machines at present available are too bulky for domiciliary use.

2. If midwives are to be allowed to administer nitrous oxide and oxygen on their own responsibility, they will require a machine of specified accuracy and performance to deliver the gases. With pre-mixed gases the accuracy is incorporated and only a simple demand valve is required.

3. A light-weight cylinder of the 400 gallon nitrous oxide type filled with 50:50 pre-mixed nitrous oxide and oxygen at 2,000 lb./sq. in. (kg./sq. cm. 140.6) at room temperature, attached to a Merlin demand valve, corrugated rubber tubing, expiratory valve and face-piece, is lighter, cheaper, easier to breathe from, and contains more nitrous oxide than a portable gas and air machine with a full 100 gallon nitrous oxide cylinder.

CONCLUSION

The use of pre-mixed nitrous oxide and oxygen for the relief of pain in domiciliary confinements appears to be practical.

Any unevenness of the gas mixture due to accidental exposure of the cylinders to temperatures below 0° C. in winter can be readily and permanently reversed.

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M. E. TUNSTALL, M.B., B.S., F.F.A. R.C.S.,
D.Obst.R.C.O.G.

Department of Anaesthetics,
Aberdeen Royal Infirmary.

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Medical Memoranda

Diverticulum of Female Urethra containing Multiple Calculi

The following report of a case of this uncommon but not rare condition may be found of interest.

CASE HISTORY

A married woman aged 72 attended the surgical out-patient department on June 8, 1960, complaining of an uncomfortable feeling as if her womb was dropping. This symptom had been present for many years. Frequency of micturition was thrice daily and twice nightly, but she was continually wet from urinary incontinence. She had borne four full-term children, the deliveries being normal. Nothing else of significance appeared in her clinical history.

Vaginal examination revealed a diverticulum of the distal part of the urethra projecting into the anterior vaginal wall. Straight x-ray examination of the pelvis confirmed the presence of a diverticulum containing many radio-opaque calculi, situated below the level of the bladder (Fig. 1). A micturating cystourethrogram indicated that the diverticulum was lying posterior to the urethra (Fig. 2).