systolic blood pressure was lowered by at least 10 mm.Hg, and in 35% by at least 30 mm.Hg.

Mean Values of Blood Pressure and Pulse Rate

	Drug	Placebo	Difference
<i>Systolic Blood Pressure (mm. Hg)</i>			
Erect	114.4	133.7	-19.3†
Lying	133.8	144.4	-10.7*
Difference	-19.4†	-10.8†	8.7†
<i>Diastolic Blood Pressure (mm. Hg)</i>			
Erect	79.8	89.5	-9.7†
Lying	86.2	91.4	-5.3*
Difference	-6.4†	-2.0	4.4†
<i>Pulse Rate (beats/min.)</i>			
Erect	90.1	88.7	1.4
Lying	81.3	80.9	0.4
Difference	8.8†	7.8†	1.0

*Significant at 5% level. †Significant at 1% level.

Discussion

These results show that L-dopa has a significant hypotensive action in man. As L-dopa is a precursor of noradrenaline this observation is somewhat paradoxical. Studies on the metabolites of catecholamines excreted by patients receiving L-dopa indicate that there are very large increases in dopamine turnover, and only relatively small increases in noradrenaline metabolism. It is possible that dopamine is responsible for the hypotension. Dopamine can release noradrenaline from adrenergic nerve endings to give a sympathomimetic effect (Spiers and Calne, 1969), which may be followed by depletion of noradrenaline stores in spite of the fact that dopamine is the immediate precursor of noradrenaline (Harrison *et al.*, 1963; Eränko and Räisänen, 1966).

It has also been shown (Collins and West, 1968) that L-dopa can be taken up into sympathetic nerve endings in the rabbit, after which the arrival of a nerve impulse leads to the release of dopamine in addition to noradrenaline. J. H. Burn (personal communication, 1969) suggested that the "dilution" of noradrenaline in this way may be responsible for the hypotension in Parkinsonian patients receiving large doses of L-dopa, because the direct action of dopamine on receptors in the blood vessels varies according to site and species from weak vasoconstriction to vasodilatation (Burn and Rand, 1958;

Goldberg and Sjoerdsma, 1959; Goldberg *et al.*, 1969). A further possibility is that dopamine may be exerting a more complex action in the central nervous system, or L-dopa itself may possess relevant central or peripheral pharmacological activity.

Patients with Parkinsonism often display autonomic disturbances such as excessive sweating and constipation. The cardiovascular reflexes may occasionally be severely impaired (Shy and Drager, 1960; Barbeau *et al.*, 1969). Our results in patients on placebo for six weeks show slight orthostatic hypotension, which is probably consequent on their Parkinsonism, though it might alternatively represent some persisting activity of L-dopa.

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REFERENCES

- Barbeau, A., Gillo-Jeffroy, L., Boucher, R., Nowaczynski, W., and Genest, J. (1969). *Science*, **165**, 291.
 Burn, J. H., and Rand, M. J. (1958). *Journal of Physiology*, **144**, 314.
 Calne, D. B., Stern, G. M., Laurence, D. R., Sharkey J., and Armitage, P. (1969). *Lancet*, **1**, 744.
 Collins, G. G. S., and West, G. B. (1968). *British Journal of Pharmacology*, **34**, 514.
 Cotzias, G. C., Papavasiliou, P. S., Gellene, R., and Aronson, R. B. (1968). *Transactions of the Association of American Physicians*, **81**, 171.
 Cotzias, G. C., Papavasiliou, P. S., Gellene, R., Aronson, R. B., and Mena, I. (1969). In *Parkinsonism and Parkinsonian Syndrome*, edited by F. J. Gillingham and I. M. L. Donaldson, p. 185 Edinburgh, Livingstone.
 Duvoisin, R., Scheer, M., Hoehn, M. M., and Yahr, M. (1969). In *Parkinsonism and Parkinsonian Syndrome*, edited by F. J. Gillingham and I. M. L. Donaldson, p. 185. Edinburgh, Livingstone.
 Eränko, O., and Räisänen, L. (1966). In *Mechanisms of Release of Biogenic Amines*, edited by U. S. Von Euler, S. Rosell, and B. Uvnäs, p. 73. Oxford, Pergamon.
 Godwin-Austen, R. B., Tomlinson, E. B., Frears, C. C., and Kok, H. W. L. (1969). *Lancet*, **2**, 212.
 Goldberg, L. I., and Sjoerdsma, A. (1959). *Journal of Pharmacology and Experimental Therapeutics*, **127**, 212.
 Goldberg, L. I., Talley, R. C., and McNay, J. L. (1969). *Progress in Cardiovascular Diseases*, **12**, 40.
 Harrison, W. H., Levitt, M., and Udenfriend, S. (1963). *Journal of Pharmacology and Experimental Therapeutics*, **142**, 157.
 Shy, G. M., and Drager, G. A. (1960). *Archives of Neurology*, **2**, 511.
 Spiers, A. S. D., and Calne, D. B. (1969). *British Medical Journal*, **4**, 333.
 Yahr, M. D., Duvoisin, R. C., Hoehn, M. M., Scheer, M. J., and Barrett, R. E. (1968). *Transactions of the American Neurological Association*, **93**, 56.

Preliminary Communication

Respiratory Stimulants in Treatment of Perinatal Asphyxia

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Summary: The effects of two analeptic drugs—taloximine and ethamivan—have been studied in asphyxiated fetal and newborn rabbits. In primary apnoea ethamivan reduced the time before the onset of gasping, while during gasping taloximine increased the gasp rate. In secondary apnoea neither drug initiated respiration, though most animals could be resuscitated by using intermittent positive pressure respiration. From these results it is suggested that analeptic drugs have no place in obstetric or neonatal departments.

INTRODUCTION

Despite theoretical, clinical, and experimental evidence that analeptics are of no benefit in neonatal asphyxia (Cross, 1968) a recent authoritative publication (Bound, 1969) recommends their use, and replies to a questionnaire which we circulated in August 1969 to the 32 approved London institutions of midwifery training showed that 12 out of the 23 that answered favoured the use of one or more of them.

It seems necessary to reiterate the sequence of events in the asphyxia of the newborn mammal, exemplified by asphyxia in nitrogen of the newborn rabbit which passes through the following stages: (a) a short period of hyperventilation, (b) *primary apnoea* lasting some 5 minutes, (c) a *gasping phase* lasting a further 15 minutes, and (d) *secondary apnoea* lasting until death in the absence of effective intervention.

The behaviour of fetal monkeys, lambs, and rabbits is similar if useful respiratory exchange is prevented. It is clear also that

the asphyxiated human newborn is often born during its phase of primary apnoea, and when gasping begins in air or oxygen recovery follows. An animal reaching this gasping phase will recover spontaneously if left alone (Cross, Dawes, Hyman and Mott, 1964). Injection of analeptic drugs tends to reduce the length of primary apnoea (Daniel, Dawes, James, and Ross, 1966).

“Effective intervention” in secondary apnoea usually constitutes intermittent positive-pressure ventilation (I.P.P.V.) through a tracheostomy or, in the human infant, an endotracheal tube. The chances of success appear to be directly related to the state of the cardiovascular system and the blood pressure in particular (Godfrey, 1968). Injection of respiratory stimulants in secondary apnoea (Daniel *et al.*, 1966) does not initiate respiration but does cause hypotension, thus almost certainly reducing the chances of resuscitation by I.P.P.V.

Using the methods described by Godfrey (1968), we have studied the effects of two more analeptic drugs on asphyxiated fetal and newborn rabbits. One of these drugs, taloximine, is a known respiratory stimulant not specifically recommended for neonatal apnoea by the manufacturers; the other, ethamivan, is marketed for this purpose and was the commonest drug recommended to pupil midwives in the questionnaire referred to above.

RESULTS

Before Asphyxia.—Ethamivan caused a 30% increase in respiratory rate; taloximine caused a 100% increase. Neither drug had any significant effect on heart rate, but both caused a 10% rise in blood pressure. These effects began within 10 to 15 seconds of intravenous infusion and lasted for 80 to 90 seconds.

During Primary Apnoea.—Ethamivan reduced the time before gasping started to 0.5 minute, compared with 5.5 ± 1.9 minutes for six untreated controls. The gasping phase in nitrogen was also greatly reduced.

During Gasping.—The gasp rate was increased by taloximine, and again the last gasp occurred much sooner than in a control given the same volume of saline (Fig. 1).

FIG. 1.—Rate of gasping and duration of gasping in three rabbits who were given the drugs shown at different periods after the onset of primary apnoea induced by exposure to nitrogen. Weights: 54, 46, and 57 g.

During Secondary Apnoea.—Neither drug initiated respiration. The time after the last gasp when the drugs were administered, usually about one minute, and the delay before I.P.P.V. was started in an attempt to salvage the rabbit are shown in the Table. One animal was left without I.P.P.V. and

Timing (Minutes) of Various Events During Asphyxia and Resuscitation

	Weight of Animal (g.)	Primary Apnoea		Gasping		Secondary Apnoea		
		Time of Drug	Time to Start of Gasping	Time of Drug After First Gasp	Total time to Last Gasp	Time of Drug After Last Gasp	Time of I.P.P.V. After Drug	Time of Resuscitation (I.P.P.V. to First Breath)
Ethamivan (0.25 mg.)								
Fetus	60	—	—	—	18.7	0.8	1.9	—
Newborn	60	—	6.7	—	27.5	3.0	1.0	1.8
Newborn	54	0.2	0.5	—	7.5	1.0	1.0	1.2
Taloximine (0.4 mg)								
Fetus	60	—	—	—	24.5	1.0	3.0	2.1
Fetus	46	—	—	—	20.0	5.7	2.8	—
Fetus	57	—	—	—	18.5	6.5	2.9	3.7
Newborn	65	—	6.0	—	23.4	1.1	1.6	4.3
Newborn	62	—	7.0	—	21.4	1.0	1.7	2.3
Newborn	40	—	7.5	2.0	18.5	1.8	2.2	—
Newborn	46	—	2.0	5.5	12.5	1.2	1.3	1.5
Newborn	58	—	4.0	—	20.0	1.3	—	—

no respiratory activity was seen, and it eventually died with cardiac asystole. Experience with these animal preparations suggests that most of the animals could be salvaged with I.P.P.V. even after five minutes of secondary asphyxia without drug intervention (Godfrey, 1968).

In the fetus given ethamivan cardiac arrest occurred 0.4 minute later, and in the two newborn there was a fall in heart rate and blood pressure, but both were subsequently resuscitated by I.P.P.V. No cardiac arrests followed the administration of taloximine, but two of the seven animals in which resuscitation by I.P.P.V. was subsequently attempted did not recover. The blood pressure showed a transient increase during the infusion of the drug as it did with infusion of saline, presumably due to the boosting of blood volume in a circulation deprived of vasomotor tone (Fig. 2).

FIG. 2.—Effect of ethamivan, taloximine, and saline on heart rate and carotid blood pressure of three animals who had just completed their last gasp. All injections were 0.4 ml. volume. Weights: 54, 60, and 57 g.

CONCLUSIONS

Taloximine and ethamivan are analeptics which act in the same general way as nikethamide and lobeline, and as such are unable to stimulate a central nervous system paralysed by asphyxia.

If a baby is born asphyxiated and apnoeic there is no way

of knowing whether it is in primary or secondary apnoea. If in primary apnoea it will recover without intervention, but if analeptic drugs are given it will start gasping more quickly and vigorously, giving rise to the clinical impression that the drug is life-saving. Effective I.P.P.V., though also unnecessary, would not be harmful and would similarly hasten recovery.

If the baby is in secondary apnoea it will die unless given I.P.P.V., and the administration of analeptics will be of no benefit. What evidence there is suggests that lobeline or ethamivan will seriously jeopardize the chances of resuscitation by I.P.P.V. because they induce hypotension at this stage.

We feel strongly that analeptic drugs have no place in obstetric or neonatal departments, as they are of no benefit in primary apnoea and potentially lethal in secondary apnoea. The availability of personnel trained in intubation of small babies is of paramount importance, as recommended by the Central Midwives Board (February 1968). The practice of putting a drop or two of ethamivan on the tongue while waiting for the anaesthetist or to see what happens should be discouraged.

We wish to thank Mrs. S. Moonsaffie for her invaluable technical help and Riker Products for supplies of Vandid (ethamivan) and Numotac (taloximine) and for information on dosage.

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REFERENCES

- Bound, J. P. (1969). *Prescribers' Journal*, **9**, 104.
 Cross, K. W. (1968). *British Heart Journal*, **30**, 483.
 Cross, K. W., Dawes, G. S., Hyman, A., and Mott, J. C. (1964) *Lancet*, **2**, 560.
 Daniel, S. S., Dawes, G. S., James, L. S., and Ross, B. B. (1966). *British Medical Journal*, **2**, 562.
 Godfrey, S. (1968). *Quarterly Journal of Experimental Physiology*, **53**, 97.

Medical Memoranda

Pulmonary Tuberos Sclerosis Presenting with Pleural Effusion

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Tuberos sclerosis in all its forms has been calculated to occur with an incidence of 1:150,000 in the general population of the United Kingdom and an incidence of 1:300,000 for those forms of the disease with mental defect (Dawson, 1954).

Pulmonary complications are uncommon, only 17 cases having been described. Dawson (1954) reviewed the nine cases then reported in the literature and described four others. Green (1968) described four more. The pulmonary complications in these cases usually presented with dyspnoea, haemoptysis, and spontaneous pneumothorax. The following case is of interest in that, although having typical signs and symptoms and classical radiological appearances, the predominating feature was a large pleural effusion, the nature of which is described.

PATHOLOGY

Tuberos sclerosis usually affects several systems, embracing the brain and eye, skin, viscera, bones, and lungs. These may be briefly summarized as follows: sclerotic areas in the brain consisting of glial fibres with few cell bodies which may calcify and be visible radiologically. The patients usually present with epilepsy or mental defect. The retinal lesions, phakomata, consist either of single white glistening masses protruding into the vitreous or of multiple white or grey flat plaques. Skin changes include subungual fibromata, the adenoma sebaceum of the face, and "peau chagriné". This last is a sheet of thick nodular skin in the lower thoracic or lumbar region. The facial eruption consists of papules extending across the nose on to both cheeks with small superficial adenomata. There may also

be "café au lait" spots. The commonest visceral abnormalities are renal tumours of mixed epithelial, fatty, fibrous, and vascular tissue—occasionally malignant. Tumours are also found in other viscera; rhabdomyomata of the heart, polypi in the duodenum and small intestine, and occasionally tumours in the liver, uterus, and larynx. The limb bones and the skull may show cyst-like spaces and periosteal thickening on radiological examination. The lungs when involved usually show multiple pea-sized cysts, air filled, with brown walls consisting of bundles and tumours of smooth muscle with angiomatous new formations containing excessive iron pigment. A mucus-secreting adenoma has also been described in the lung.

CASE REPORT

A married woman aged 46 was first referred to the outpatient department in 1959, when she complained of shortness of breath and was found to be myxoedematous. She had adenoma sebaceum and had been aware of the facial rash for 10 years. She was noted to be of slightly reduced intelligence. She responded well to thyroxine and remained well until 1966, when she again complained of shortness of breath and fatigue and was found to have a large left pleural effusion. She was admitted for pleural aspiration. Intracerebral calcification and subungual fibromata were noted at this time and laboratory investigations were as follows: haemoglobin 12.7 g./100 ml.; white cell count 8,400/cu.mm. (neutrophils 62%, eosinophils 2%, lymphocytes 34%, monocytes 2%); E.S.R. 24 mm. in one hour; urea and electrolytes normal; cholesterol 418 mg./100 ml.; sputum: no malignant cells. Chest x-ray examination confirmed the presence of a large left pleural effusion with cystic mottling throughout both lungs (Fig. 1). Pleural aspiration: 880 ml. of slightly blood-stained fluid, protein 5.1 g./100 ml., no organisms, culture sterile, no malignant cells, scanty red cells, lymphocytes, and endothelial cells; L.E. cells were not seen and pleural biopsy was normal. After pleural aspiration her breathing returned to normal.