logical group; 27% of the patients suffered from epileptic seizures, but in almost half uraemia was present; 27% had an abnormal mental state, usually associated with focal or generalized vascular lesions.

Three-quarters had an acute vascular episode (focal ischaemia in 48%, intracerebral haemorrhage in 38%, and subarachnoid haemorrhage in 5.5%); and some had more than one type of lesion. Criticism is levelled at the frequent misuse of the term "hypertensive encephalopathy," which should be reserved for the syndrome as described by Volhard; it seems to be very rare, and was found in only one of our cases.

An attempt should always be made to determine the cause of each cerebral event, and the term "focal brain ischaemia" used in appropriate cases.

There were eight isolated cranial nerve palsies (facial nerve in seven, abducens in one).

The C.S.F. pressure and contents were normal in 6 out of 42 cases. High pressure was found in 29, blood-staining in 11, and elevated protein content in 9 non-bloody fluids; some had more than one abnormality.

Treatment appears to have prolonged life where severe renal damage was not present at the start of treatment. The survival in this group when untreated averaged less than a year. Ganglioplegic drugs seemed to be more effective than sympathectomy.

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REFERENCES

- Adams, R. D. (1955). In Wright and Luckey's *Cerebral Vascular Diseases*. Grune and Stratton, New York.
- and Vander Eecken, H. M. (1953). *Ann. Rev. Med.*, **4**, 213.
- Adkins, G. H., Fahr, G., and Bernstein, I. C. (1955). *Minn. Med.*, **38**, 636.
- Allbutt, T. C. (1915). *Diseases of the Arteries, including Angina Pectoris*, **1**, 418. Macmillan, London.
- Aring, C. D., and Merritt, H. H. (1935). *Arch. intern. Med.*, **56**, 435.
- Attwater, H. L. (1911). *Guy's Hosp. Rep.*, **65**, 339.
- Ballantyne, A. J. (1943). *Brit. J. Ophthalmol.*, **27**, 383.
- Beaven, D. W., and Murphy, E. A. (1956). *British Medical Journal*, **1**, 77.
- Bechgaard, P. (1946). *Acta med. scand.*, Suppl. 172, p. 163.
- Blackfan, K. D., and Hamilton, B. (1925). *Boston med. surg. J.*, **193**, 617.
- Block, E. B., and Oppenheimer, R. H. (1924). *Arch. Neurol. Psychiat. (Chicago)*, **11**, 444.
- Bouveret, L. (1895). *Rev. Médecine*, **15**, 537.
- Brain, R. (1954a). *Lancet*, **2**, 831.
- (1954b). *Ann. intern. Med.*, **41**, 675.
- Cannon, B. W. (1951). *A.M.A. Arch. Neurol. Psychiat.*, **66**, 687.
- Clawson, B. J. (1928). *Amer. Heart J.*, **4**, 1.
- Cohen, M. M. (1955). *A.M.A. Arch. Path.*, **60**, 296.
- Corday, E., Rothenberg, S. F., and Putnam, T. J. (1953). *A.M.A. Arch. Neurol. Psychiat.*, **69**, 551.
- Cruz, I. de Gispert (1952). *Arch. Neuro-psiquiat. (S. Paulo)*, **10**, 70.
- Cushing, H., and Bordley, J. jun. (1908). *Amer. J. med. Sci.*, **136**, 484.
- Denny-Brown, D. (1951). *Med. Clin. N. Amer.*, **35**, 1457.
- Dodge, P. R., Richardson, E. P., jun., and Victor, M. (1954). *Brain*, **77**, 610.
- Epstein, A. W. (1951). *J. Neuropath.*, **10**, 426.
- Ferris, E. B. (1952). Cited by C. D. Aring, *Dis. nerv. Syst.*, **1952**, **13**, 183.
- Finnerty, F. A., jun., Witkin, L., and Fazekas, J. F. (1954). *J. clin. Invest.*, **33**, 1227.
- Fishberg, A. M. (1954). *Hypertension and Nephritis*, 5th ed., chapter 11. Baillière, Tindall and Cox, London.
- and Oppenheimer, B. S. (1930). *Arch. intern. Med.*, **46**, 901.
- Gardner, J. W., Mountain, G. E., and Hines, E. A., jun. (1940). *Amer. J. med. Sci.*, **200**, 50.
- Globus, J. H. (1938). *Proc. Ass. Res. nerv. Dis.*, **18**, 438.
- and Strauss, I. (1927). *Arch. Neurol. Psychiat. (Chicago)*, **18**, 215.
- Goodman, L. (1949). *Ibid.*, **62**, 445.
- Gowers, W. R. (1888). *A Manual of Diseases of the Nervous System*, vol. 2. Churchill, London.
- (1893). *Ibid.*, 2nd ed., **2**, 750. Churchill, London.
- Grant, F. C. (1932). *Arch. Neurol. Psychiat. (Chicago)*, **27**, 816.
- Greenfield, W. S. (1938). Cited by K. Stern, *J. Neurol. Psychiat.*, **1**, 26.
- Griffith, J. Q. (1933). *Arch. Neurol. Psychiat. (Chicago)*, **29**, 1195.
- Hicks, S. P., and Black, B. K. (1949). *Amer. Heart J.*, **38**, 528.
- Hughes, W., Dodgson, M. C. H., and MacLennan, D. C. (1954). *Lancet*, **2**, 770.
- Jaffé, R. H. (1937). *Radiol. Rev.*, **59**, 7.
- Janeway, T. C. (1913). *Arch. intern. Med.*, **12**, 755.
- Jefferson, A. (1955). *Quart. J. Med.*, **24**, 245.
- Keith, N. M., Wagener, H. P., and Kernohan, J. W. (1928). *Arch. intern. Med.*, **41**, 141.
- Knutson, J., and Baker, A. B. (1945). *Arch. Neurol. Psychiat. (Chicago)*, **54**, 130.
- Lafon, R., Pages, P., Minvielle, J., and Barjon, P. (1955). *Rev. neurol. (Paris)*, **92**, 536.
- Lecucq, J. (1945). Thèse de Lille.
- Madonick, M. J., Berke, K., and Schiffer, I. (1950). *Arch. Neurol. Psychiat. (Chicago)*, **64**, 431.
- Manschot, W. A. (1954). *Amer. J. Ophthalmol.*, **38**, 501.
- Meerloo, A. M. (1935). *Ned. T. Geneesk.*, **79**, 3868.
- Millikan, C. H. (1955). In Wright and Luckey's *Cerebral Vascular Diseases*, p. 90. Grune and Stratton, New York.
- Oppenheimer, B. S., and Fishberg, A. M. (1928). *Arch. intern. Med.*, **41**, 264.
- Paulin, J. E., Bowcock, H. M., and Wood, R. H. (1927). *Amer. Heart J.*, **2**, 613.
- Peet, M. M., and Isberg, E. M. (1948). *Ann. intern. Med.*, **28**, 755.
- Pickering, G. W. (1934). *Clin. Sci.*, **1**, 397.
- (1948). *J. Amer. med. Ass.*, **137**, 423.
- Pletscher, A., Shore, P. A., and Brodie, B. B. (1956). *J. Pharmacol.*, **116**, 84.
- Richardson, E. P., jun., and Dodge, P. R. (1954). *Epilepsia (Boston)*, **3**, 49.
- Riley, H. A., and Elsberg, C. A. (1926). *Arch. Neurol. Psychiat. (Chicago)*, **15**, 48.
- Riser, Planques, and Becq (1938). *Bull. Soc. Méd. Paris*, **54**, 62.
- Rose, W. McI. (1948). *Lancet*, **2**, 561.
- Rosenberg, E. F. (1940). *Arch. intern. Med.*, **65**, 545.
- Keith, N. M., and Wagener, H. P. (1938). *Ibid.*, **62**, 461.
- Saracoglu, K. S. (1939). *Dtsch. med. Wschr.*, **65**, 379.
- Scheinker, I. M. (1943). *Arch. Path. (Chicago)*, **36**, 289.
- Schottstaedt, M. F., and Sokolow, M. (1953). *Amer. Heart J.*, **45**, 331.
- Shelburne, S. A., Blain, D., and O'Hare, J. P. (1932). *J. clin. Invest.*, **11**, 489.
- Symonds, C. (1952). *J. Laryng.*, **66**, 295.
- Taylor, R. D., Corcoran, A. C., and Page, I. H. (1954). *A.M.A. Arch. intern. Med.*, **93**, 818.
- and Page, I. H. (1945). *J. Amer. med. Ass.*, **127**, 384.
- Traube, L. (1871). *Gesammelte Beiträge zur Pathologie und Physiologie*, **2**, 551. Hirschwald, Berlin.
- Vallat, J. N. (1938). Thèse de Bordeaux.
- Vancura, A., Chytil, M., and Fialová, V. (1956). *Acta med. scand.*, Suppl. **312**, p. 236.
- Vigne, A. R. de la, and Le Pourhiet (1951). *Ann. méd.-psychol.*, **109**, ii, 66.
- Volhard, F. (1918). In Mohr and Stachelin's *Handbuch der inneren Medizin*, **3**, 1342. Springer, Berlin. Cited by Fishberg (1954).
- (1935). *The Kidney in Health and Disease*, edited by H. Berglund and G. Medes, chapter 39. Kimpton, London.
- Walton, J. N. (1953). *J. ment. Sci.*, **99**, 521.
- Wolff, H. G. (1948). *Headache and other Head Pain*, p. 397. Oxford Univ. Press, New York.
- Wright, I. S., and McDevitt, E. (1954a). *Lancet*, **2**, 825.
- (1954b). *A.M.A. Ann. intern. Med.*, **41**, 682.

ANALGESIC SUPPLEMENTS TO NITROUS OXIDE ANAESTHESIA

A REVIEW

BY

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The many advantages of nitrous oxide were for a long time overshadowed by its weak anaesthetic properties and by its inability to produce muscular relaxation. Although widely used for analgesia in midwifery, for anaesthetic inductions, and as one of the vehicles to carry the vapour in ether anaesthesia, nitrous oxide could not be relied upon to produce adequate anaesthesia in every case, even in well-premedicated patients.

The short-acting barbiturates awakened a new interest in nitrous oxide. Within a few years nitrous oxide and oxygen anaesthesia supplemented with thiopentone had become an established technique. For operations which required no muscular relaxation this combination seemed ideal, since it was easy to administer, afforded the patient a pleasant induction, and allowed the surgeon to use diathermy. Although thiopentone was a potent hypnotic, its lack of analgesic properties and its slow degradation in the body led to frequent complications, especially in prolonged operations that required large doses of the barbiturate. As experience accumulated, the triad of respiratory depression, circulatory failure, and prolonged post-anaesthetic recovery caused the technique to be regarded more critically.

Many anaesthetists added small but analgesic concentrations of ether or cyclopropane to the nitrous oxide and oxygen mixture, using thiopentone for the induction alone. Diathermy could not, however, be safely used with these otherwise valid techniques.

Before the advent of curare, muscular relaxation during general anaesthesia could be achieved only by deep anaesthesia with potent agents. Deep anaesthesia was therefore an invariable incident to an adequately relaxed abdomen. With the introduction of curare into clinical anaesthesia it became possible to maintain light anaesthesia throughout the longest operation. The ability to produce muscular relaxation irrespective of the agents used for general anaesthesia added great impetus to the interest in nitrous oxide. Curare could be administered during any general anaesthetic, and it was found easier to maintain uniform planes of light anaesthesia with nitrous oxide than with ether or cyclopropane. Ether had the additional disadvantage of having its own curare-like effect which made it difficult to gauge the dose of curare during its administration.

Curare has no analgesic properties. Prior to the introduction of curare, one of the indications for an additional dose of thiopentone was involuntary movement of the patient. The neuromuscular block induced by curare prevents reflex muscular activity, eliminating to a large extent this indication for additional thiopentone. As curare displaced thiopentone as a means of reinforcing nitrous oxide, certain disadvantages became apparent. A number of reports appeared of patients waking up in the middle of the operation or having a vivid memory of the procedure. Mushin (1951) aired this problem when he wrote:

"Our pharmacological colleagues warned us long ago of the possibility that the patient might be awake during the operation. . . . I am inclined to believe that this occurrence may be more common than we think. It is clear that with the present-day large doses of relaxants, little objective evidence is available for the anaesthetist to determine the presence or absence of unconsciousness. A patient who is motionless may be conscious but curarized, while one who kicks may be unconscious and acting reflexly."

Curare, in making it possible to use nitrous oxide and oxygen with thiopentone in a wider variety of operations, complicated rather than solved the problem of using nitrous oxide. There was a great need for a means by which this gas could be safely potentiated without completely resorting either to thiopentone on the one hand or curare on the other.

Pethidine

In 1947 Neff *et al.*, in the United States, suggested supplementing nitrous oxide and oxygen with pethidine and curare. Induction with nitrous oxide was slowly carried out and no thiopentone was used. They stressed the importance of first securing "pain relief" before the administration of curare, a view that was later reiterated by Mushin (1951).

After observing Neff's work at first hand, Mushin and Rendell-Baker (1949) further developed the conception and published a preliminary report of 100 cases. They modified the technique in two ways: (1) a "sleep dose" of thiopentone was administered before nitrous oxide and oxygen was begun; (2) 25 mg. of pethidine was administered about every twenty to thirty minutes, this dosage being needed for adequate depth of anaesthesia. The publication of this basic technique in Great Britain stimulated great interest, and it was not long before many clinical reports were forthcoming.

The analgesic properties of pethidine were discovered almost by accident. The drug was synthesized in 1939 (Eisleb and Schaumann) during a search for atropine-like compounds. About one-eighth as potent as morphine, it

shares some of morphine's undesirable side-effects. One of its chief disadvantages is the ease with which patients become addicted to it, a problem not encountered in its use in anaesthesia. Though small, the atropine-like action of pethidine on the bronchial tree makes it particularly useful during general anaesthesia. The action on the heart is one of vagal depression superimposed on a primary muscular depression (Duguid and Heathcote, 1940). In analgesic doses these effects are very small indeed.

Most investigators of pethidine as a supplement to nitrous oxide anaesthesia report rapid post-anaesthetic recovery. This may be attributed to the small dosage and the poor hypnotic qualities of pethidine. This finding is in sharp contrast to the frequent observation of the post-anaesthetic sleep seen after anaesthesia in which thiopentone was the sole additional agent. Other advantages claimed for pethidine in anaesthesia include the ease of administration, the flexibility of the technique, the absence of the explosion hazard, and the production of adequate planes of anaesthesia without undue depression of the respiratory or circulatory systems.

Brotman and Cullen (1949) used pethidine in this way, administering small doses of thiopentone to facilitate rapid induction as well as additional small doses in prolonged cases to provide supplemental hypnosis. They concluded that the technique is well suited for the poor risk. Their belief that pethidine produces less respiratory depression than morphine has not been substantiated (Prescott *et al.*, 1949; Loeschke *et al.*, 1953).

The use of nitrous oxide and oxygen supplemented with analgesics and muscle relaxants has been condemned as an unsatisfactory technique for junior anaesthetists (Cullen, 1950). The opposite view has been expressed by Mushin (1951), who wrote: "This method can be quickly picked up by well-trained juniors." Evidence of the flexibility of this form of anaesthesia is presented in a report by Mushin and Rendell-Baker (1950), who applied this technique to thoracic surgery. With this method, unconsciousness, immobility, and control of respiration and of reflex activity were easily maintained, awakening was immediate, and post-operative shock was absent.

In reviewing the status of pethidine-supplemented nitrous oxide anaesthesia, Neff *et al.* (1950) again stressed the importance of a slow, more complete induction with nitrous oxide and oxygen. Since his original report, Neff had decreased each increment of pethidine by 50%. It seems unlikely, however, that a prolonged induction with nitrous oxide and oxygen would prove to be practical in routine anaesthetic practice.

Depression of pulmonary ventilation is rarely severe in degree or prolonged, though its occurrence should dispel any idea that pethidine can be used without fear of respiratory depression (McDermott and Papper, 1950). Any respiratory depression due to pethidine is naturally masked during "controlled respiration." The few references to such depression in papers describing techniques of assisted respiration must be taken as an indication of the rarity of such an effect. If pethidine in the doses used in anaesthesia caused serious depression it would be easily detected with such techniques.

In the British journals 1951 was a popular year for reports concerning pethidine in anaesthesia. Johnson (1951), using the technique described by Mushin and Rendell-Baker (1949) and Mushin (1951), stressed the occurrence of relaxation of the bronchial tree and the absence of respiratory depression. Blazeby (1951) contended that: "In some cases, in which an additional dose becomes indicated shortly before the close of the operation, it may be wise to give a dose of thiopentone, 0.1 g., instead of a final repeat dose of pethidine." While this is left unexplained, it reflects the nebulous nature of specific indications for the administration of pethidine as opposed to thiopentone.

Also in 1951 Ruben and Andreassen recorded their observations on the effects of pethidine on the larynx. After routine premedication, pethidine alone was used for endotracheal intubation, the average dose administered

intravenously being 140 mg. They observed no case of apnoea, although a depression in the respiratory rate to six to eight a minute often occurred for a few minutes.

By utilizing intravenous pethidine in alternate cases, Wolfers (1953) reported the first "controlled" study of this technique. The method in the test group was that described by Mushin and Rendell-Baker (1949), although Wolfers found that 25-mg. increments of pethidine "did not produce satisfactory anaesthesia in a proportion of cases and supplementary doses of thiopentone were often needed." In the control group thiopentone alone was used to supplement nitrous oxide anaesthesia. It was found that the mg./minute dose of thiopentone in the control group was almost twice that in the pethidine group.

Johnstone (1951) reported that multifocal ventricular tachycardia and bigeminal rhythm which spontaneously appeared during trichlorethylene ("trilene") anaesthesia disappeared within four minutes of receiving 25 mg. of pethidine intravenously. Mushin and Rendell-Baker (1950) and others have also made the observation that the use of pethidine was associated with a decreased incidence of cardiac arrhythmia during anaesthesia.

Table I summarizes the literature concerning pethidine supplementation.

Codeine

In a report concerning anaesthesia for the fenestration operation, Meals (1948) wrote: "Our early patients were given rather large doses of thiopentone for adequate control and the surgical procedure was followed by a prolonged post-operative sleep. The intravenous use of analgesics was tried to reduce the thiopentone requirements." Meals found morphine too depressant to respiration and pethidine not very effective. He states that codeine sulphate was tried "with remarkable success," that the dose of thiopentone was reduced by one-third and the recovery time from hours to minutes. Mushin (1951) found that codeine was as satisfactory as pethidine but abandoned it because "no method of determining which is the better drug has so far been evolved." Brown (1953), reporting on codeine, concluded that it had no advantages over pethidine. The absence of further communications concerning codeine supplementation would seem to substantiate this conclusion.

Levorphanol

Levorphanol ("dromoran"; L-methorphan) has an analgesic potency four times that of morphine sulphate (Gross *et al.*, 1949). Its side-effects are similar to those produced by morphine. While the onset of peak analgesia is similar to that of morphine, the duration of effect is six hours or longer.

In utilizing levorphanol as an analgesic supplement, Brotman *et al.* (1950) gave a sleep dose of thiopentone followed by nitrous oxide and oxygen, with levorphanol administered in 1.5- to 3-mg. doses. The recovery times and duration of post-operative analgesia in this series were compared with

two other series in which morphine and pethidine, respectively, had been used as supplements. They concluded that equivalent doses of the three drugs provided comparable results as supplementary narcotics during nitrous oxide anaesthesia. Recovery times did not vary significantly among the three groups. Brown (1952) administered a "standard dose" of 0.5 g. of thiopentone to all patients, which was followed by nitrous oxide and oxygen and levorphanol in from 0.25- to 0.5-mg. doses. If Brown had used a sleep dose of thiopentone adjusted to the individual patient rather than a standard dose of 0.5 g., his findings would have had greater validity. In a subsequent report, Brown (1954) concluded that a continuous levorphanol drip was contraindicated because of the high incidence of respiratory depression. Crawford and Binning (1953) found that they used at least 2-mg. increments of levorphanol rather than the much smaller doses that Brown reported.

Alphaprodine

Alphaprodine ("nisentil"; 1,3-dimethyl-4-phenyl-4-propionoxypiperidine), similar in structure to pethidine, is one of the latest narcotic analgesics that have been investigated as a supplement to nitrous oxide and oxygen anaesthesia. In general, side-effects were less frequently encountered than with levorphanol or morphine (Lee and Hasegawa, 1950; Lee and Pfeiffer, 1951). The development of tolerance was not observed (Gross *et al.*, 1948). Siker *et al.* (1954) compared alphaprodine with pethidine supplementation in two large series. The thiopentone requirements in the pethidine group were almost consistently twice those of the alphaprodine group, and the percentage of patients reacting at the end of the surgery was greater in the alphaprodine group. The latter finding was attributed to the shorter duration of action of alphaprodine as compared with pethidine.

Lancaster and Levin (1956) reported on the use of alphaprodine and suxamethonium in a continuous drip. Foldes and Swerdlow (1956) concisely stated their objections to the combination of two such diverse agents in the same drip: "on repeated or continuous administration the degree of cumulative effect will not be the same for each drug. Consequently the mg./min. requirements of two different drugs are very unlikely to parallel one another as time progresses. . . . Combined administration of two drugs with such widely divergent pharmacological properties will frequently result in overdosage with one or both agents."

Levallorphan and Opiates

Because further attempts to reduce the thiopentone requirements by increasing the alphaprodine dose had failed as a result of the marked respiratory depression that was encountered, Foldes and his colleagues (1955) tried a new tack. In unanaesthetized patients levallorphan tartrate (levo-3-hydroxy-N-allylmorphinan tartrate) afforded considerable protection against alphaprodine-induced respiratory depression (Swerdlow *et al.*, 1955). They therefore used a combination of alphaprodine and levallorphan tartrate in a

TABLE I.—Summary of Literature Concerning Pethidine for Supplementation of Nitrous Oxide and Oxygen Anaesthesia

Author	No. of Cases	Average Total of Pethidine per Hour	Initial Dose of Pethidine	Total Dose of Thiopentone	Recovery Time	%N ₂ O/%O ₂
Neff <i>et al.</i> (1947)	160	—	25–50 mg.	Not used	15–20 min.	80/20
Mushin and Rendell-Baker (1949)	100	75 mg.	25 mg.	"Sleep dose"	Rapid	—
Brotman and Cullen (1949)	317	106 "	—	144 mg.	30 min.	80/20
Mushin and Rendell-Baker (1950)	100	—	50 mg.	0.5–0.7 g.	Rapid	50/50
Blazeby (1951)	380	—	25 "	0.3–0.7 "	"	80/20
Boisson (1952)	400	—	50 "	0.2–0.35 g.	"	75/25
Johnson (1951)	200	—	20–50 mg.	0.27–0.75 "	"	—
Griffiths (1950)	150	—	25 mg.	0.2–0.4 g.	"	80/20
Ruddell (1950)	129	—	25 "	0.3–0.8 "	"	—
Pearce (1951)	330	80 mg.	15–50 mg.	250 mg. (av.)	10 min.	70/30
Auld (1952)	12	31 "	5 mg.	Not used	—	66.6/33.3
Wolfers (1953)	200	84 "	25–50 mg.	0.25–1.05 g.	56% awake in theatre	66.6/33.3
Murphy (1951)	40	—	—	—	Rapid	—
Verne (1952)	180	—	50 mg.	"Sleep dose"	"	80/20
Randall <i>et al.</i> (1952)	—	0.02–0.04% Pethidine drip	15–25 mg.	0.15–0.3 g.	"	75/25
Franks (1954)	202	—	25 mg.	0.3–0.8 "	"	75/25
Siker <i>et al.</i> (1954)	600	42 mg.	—	—	58% awake within 5 minutes	75/25

ratio of 50:1 as a supplement to nitrous oxide anaesthesia, hoping that the increased dose of alphaprodine would further reduce or completely eliminate the need for thiopentone. This seemed desirable to them, in view of the relatively slow rate of thiopentone degradation in the body (Brodie *et al.*, 1950). This technique permitted an approximately 50% reduction of the thiopentone requirements, as compared with the thiopentone used when alphaprodine was employed without levallorphan tartrate. Although the doses of alphaprodine were four to five times that reported by Siker *et al.*, no serious respiratory depression was seen.

Hamilton and Cullen (1955) also reported on the use of levallorphan tartrate in combination with narcotic analgesics. In 40 patients who underwent operations requiring no muscle relaxation large doses of narcotics (average initial doses: pethidine, 180 mg.; levorphanol tartrate, 7.3 mg.) in conjunction with levallorphan tartrate were used to supplement nitrous oxide anaesthesia. It was noted that, while the action of levallorphan was to prevent respiratory depression, the patients were often very sleepy post-operatively, some continuing to sleep for several hours. No untoward effects from levallorphan tartrate were noted in this series. That some effects of the opiates which provided useful supplementation to nitrous oxide are not antagonized by levallorphan has been demonstrated by the work of Hamilton and Cullen (1955) and of Foldes *et al.* (1955).

Miscellaneous Drugs

Many other analgesics have received clinical trials as supplements to nitrous oxide. Heroin, methadone ("phys-eptone"), phenadoxone ("heptalgin"), and ketobemidone ("cliradon") were used by Mushin (1951). Of these, he found ketobemidone as satisfactory as pethidine. Thompson and Neff (1950) reported their findings with ketobemidone, and also concluded that it compared favourably with pethidine as a supplement. Bemidone, which they also investigated, was unsatisfactory because of respiratory depression and the undesirable side-effect of stimulation of the central nervous system.

Assessment of Analgesic Effect

The cortical appreciation of pain and the individual response to pain are highly complex mechanisms. Although a discussion of this subject is not within the scope of this paper, it is important to relate a few elementary conceptions of pain perception to the problems of assessing the effects of narcotic analgesics when used to supplement nitrous oxide anaesthesia. Irrespective of the type or degree of pain, its perception is primarily a product of the pain threshold and the emotional state of the subject. In addition, both the emotional state and the pain threshold of any individual are subject to wide deflections within relatively short periods of time.

The analgesics are drugs whose main effect is to reduce the reaction of the central nervous system to pain. This definition echoes the suggestion of Hardy *et al.* (1940) that morphine acts by altering the response to pain—that is, the pain is still perceived but seems remote and causes no anxiety. It is important to differentiate pain perception and the reaction to pain in the conscious subject and in the anaesthetized patient. The point at which the conscious patient can appreciate pain (pain threshold) loses its meaning in the anaesthetized patient. While the conscious subject may react to cortically perceived pain, the anaesthetized patient may also react, but to subcortical levels of afferent pain impulses.

Nothing is more frustrating than an attempt to measure the effects of an analgesic in the already anaesthetized patient. In only one respect is the task easier than in the conscious: the unpredictable effect of emotion on the individual response to pain is eliminated. The reaction to pain in the anaesthetized patient may be characterized by increase in the pulse rate or blood pressure, sweating, phonation, involuntary movements, and changes in the respiratory pattern. However, one or more of these signs may result

from the very drugs producing the anaesthesia, or from oxygen lack or carbon dioxide excess during anaesthesia. Involuntary movements and irregular respirations are completely hidden by a dose of muscle relaxant large enough to cause apnoea. The interrelationship of all these cause-and-effect mechanisms makes it difficult or impossible to select any of these signs as a criterion for the measurement of analgesia.

The observation that these supplements are valuable because they "work" offers a suitable hypothesis by which these drugs may be clinically assessed. It may be inferred from the many advantages attributed to the use of narcotic supplementation that certain specific goals are being sought. These goals include the safe production of adequate planes of anaesthesia and rapid post-anaesthetic recovery without post-operative restlessness. If our relative success in attaining these goals could be effectively measured, the advantages of narcotic supplementation could be more accurately judged. Certain clinical measurements may be selected whereby the effects of two or more analgesics may be compared. The basis for such comparisons that have appeared in the literature are: (1) the mg./min. dose of thiopentone (Wolfers, 1953; Siker *et al.*, 1954; Foldes *et al.*, 1955); (2) the percentage of patients reacting at the end of the operation (Brotman *et al.*, 1950; Wolfers, 1953; Siker *et al.*, 1954; Foldes *et al.*, 1955; Lancaster and Levin, 1956); (3) the duration of post-anaesthetic analgesia (Brotman *et al.*, 1950). Complex methods of statistical analysis may sometimes be needed to elucidate the results (Wilkins *et al.*, 1951).

The duration of post-anaesthetic analgesia and the reaction time are both simple numerical expressions. Any reduction in thiopentone requirements that results from the use of a narcotic supplement may be viewed as one expression of the efficiency of the narcotic. Table II summarizes the findings of the authors, who calculated the mg./min. dose of thiopentone in their cases.

The percentages of patients reacting within specified intervals recorded in five publications are given in Table III.

Despite carefully controlled experiments and accurate statistical analysis, the wide range of techniques and results make it difficult to list any incontrovertible conclusions. By comparing the analgesics using the methods mentioned above, much valuable information has been gathered con-

TABLE II.—Nitrous Oxide and Oxygen Anaesthesia. Dose of Thiopentone Expressed in mg./min.

Author	No Analgesic	Pethidine	Alphaprodine	Alphaprodine and Levorphanol
Wolfers (1953)	12	6.4		
Foldes <i>et al.</i> (1955)	No relaxant	20	9.8	4.1
Siker <i>et al.</i> (1954)	Relaxation for intubation	14	8.4	3.8
	Relaxation for maintenance	12	6.4	3.4

TABLE III.—Percentage of Patients Reacting to Tactile and Auditory Stimuli Following Nitrous-Oxide-Oxygen-Thiopentone Anaesthesia With:

Author	No Analgesic	Pethidine	Alphaprodine	Alphaprodine and Levallorphan	Morphine	Levorphanol
Wolfers (1953) (before leaving theatre)	32	56				
Brotman <i>et al.</i> (1950) (on return to ward)		28			31	39
Siker <i>et al.</i> (1954); Foldes <i>et al.</i> (1955) (within 5 minutes of completion of surgery):						
No relaxant		53	77	98		
Relaxant for intubation		59	87	94		
Relaxant for maintenance		60	84	95		
Lancaster and Levin (1956) (in theatre) ..			47			

cerning how much less thiopentone is required, how much sooner the patient awakens, and how much longer it is before the patient requires additional pain relief after surgery.

Any objective expression of analgesic effect during anaesthesia is still an unknown quantity. One promising method whereby this might be determined is electroencephalographic monitoring during anaesthesia. There is a considerable literature concerning electroencephalography during anaesthesia, but little attempt to show the electroencephalogram

FIG. 1

FIG. 2

FIGS. 1 and 2 (after Mushin, 1955).—Changes in E.E.G. with level of pain appreciation. Incidence of alpha rhythm with increasing ether analgesia in two volunteers. The vertical black bars above the abscissa indicate the strength of a standard pain stimulus as judged by the subject. The hollow box below the abscissa shows the period during which the subject was judged to be unconscious.

tracing during application of graded pain stimuli during anaesthesia. A start in this direction was made by Mushin (1955), who, during induction and maintenance of ether anaesthesia in volunteers, recorded electroencephalograms while painful stimuli were applied. Two samples of his results are shown in Figs. 1 and 2. It seems that the ability to appreciate pain can be correlated with the amount of alpha rhythm in the electroencephalogram. The electroencephalogram may therefore prove of great value in the future in measuring the effect of narcotic analgesics during general anaesthesia.

Indications for Administration of Analgesic Supplements

The most difficult problem encountered in the use of analgesic supplements has been to decide what constitutes the indications for the administration of the first, or addi-

tional, increments of the drug. The anaesthetist's difficulty is to differentiate between an elevated pulse or blood pressure due to a response to pain and a reaction to an elevated plasma carbon dioxide; between a movement representing a response to pain and a spinal-cord reflex resulting from surgical traction; between tachypnoea due to pain and that due to hypoxia. The problem is made more difficult when muscle relaxants are used, since movements of the patient and changes in his respiratory pattern which may yield valuable information about the depth of anaesthesia are obtunded. Most of the authors writing on analgesic supplementation are vague about their indications for additional analgesic. Some merely state that further doses are given when the anaesthetic becomes "too light." The following represents a list of all the indications given for the administration of an additional dose of analgesic: (1) any obvious reaction to painful stimuli such as a towel clip; (2) wrinkling of brow or other movement of patient; (3) phonation; (4) rise in blood pressure or pulse rate in the absence of elevated plasma carbon dioxide or decreased plasma oxygen; (5) any increase in the respiratory rate: breath-holding; (6) perspiration; (7) lacrimation.

A number of reports indicate that there is a strong correlation between the respiratory rate and the degree of effect from the narcotic analgesic. Blazeby (1951) states: "Marked slowing of respiration is a sign of relative overdose. Marked increase of respiration rate may conversely be taken as an indication that the analgesic effect is wearing off. . . ." Apart from the usual signs of light anaesthesia, an increase in the respiratory rate to over 20 a minute is regarded as an indication for the administration of a supplementary dose of alphaprodine (Siker *et al.*, 1954). However dependable the respiratory rate may be in judging the degree of analgesia, it can be utilized only during assisted respirations or in the absence of muscle relaxants. Using controlled respiration, the anaesthetist must depend upon pulse and blood-pressure changes, lacrimation, slight movements that may occur during brief periods of incomplete relaxation, and, most important, his own experience concerning the needs of the occasion.

Discussion

Analgesic supplementation is enjoying a vogue characteristic of many new agents and techniques. Although the technique is still widely used, there has been a gradual reduction in dosage of analgesics over the past four years. This decline in dosage has not been as great in cases where no muscle relaxation is used, because in these cases more reliance is placed on the analgesic to prevent the patient moving during surgery. Since the technique was first suggested by Neff *et al.* (1947) and elaborated by Mushin and Rendell-Baker (1949), the brief span of nine years has almost seen the completion of the parabolic curve of analgesic dosage. The reasons for this decline are becoming clearer. The difficulties of assessing the value of this technique may be attributed to the lack of specific indications for the administration of the analgesic supplements.

Paradoxically, the analgesics themselves are largely responsible for the reduction in their use. The analgesics and relaxants made it possible to use nitrous oxide and oxygen for most surgical procedures. In so doing, they enabled the anaesthetist to become progressively more experienced and familiar with nitrous oxide. As skill with nitrous oxide and oxygen increased, dependence upon analgesic supplements decreased. Saturation with nitrous oxide is a slow process. At the end of two hours the body is still absorbing as much as 75–100 ml. of nitrous oxide a minute (Severinghaus, 1953). As the duration of the anaesthesia increases, so does the efficiency, therefore, of the nitrous oxide. Evidence of this appears in the inverse relationship between the duration of anaesthesia and the dosages of thiopentone, pethidine, and alphaprodine needed (Siker *et al.*, 1954).

Any attempt to predict the ultimate direction that the practice of analgesic supplementation will take would be

presumptuous. The never-ending progression of new drugs and techniques changes anaesthetic practice almost overnight. Over the years, since the use of analgesics became widespread, one can trace an evolution that seems to point towards greater dependence upon nitrous oxide and less upon the analgesic. There is always the possibility that new methods will enable us to measure the effects of the analgesics during anaesthesia more accurately than hitherto. We will then have a more exact knowledge of what part the analgesic really plays, whether one drug is preferable to another, or even whether these drugs ought to be discarded altogether.

Summary

The ability to use nitrous-oxide-oxygen as a safe general anaesthetic was increased with the introduction of thiopentone. The advent of curare further widened the scope of nitrous oxide anaesthesia. Too much reliance upon thiopentone supplementation led to frequent complications, while too much reliance on curare to maintain immobility led to patient-awareness during an otherwise inadequate anaesthetic.

Pethidine was originally used to increase the depth of nitrous-oxide-oxygen anaesthesia. Investigations of pethidine as a supplement to nitrous oxide revealed many advantages associated with its use. Other narcotic analgesics such as levorphanol, alphaprodine, and ketobemidone were soon investigated as supplements.

Throughout these investigations the great shortcoming has been the lack of any clear-cut criterion for the assessment of analgesia during general anaesthesia. Such clinically measurable values as the mg./minute thiopentone requirements, the reaction time, and the duration of post-operative analgesia have been used both to measure and to compare the efficacy of analgesic supplements. They give valuable but incomplete information in this direction.

Many narcotic analgesics have been used successfully as supplements to nitrous oxide anaesthesia. Only when more precise methods for measuring the effects of these supplements during anaesthesia are found, however, will we have an idea of their proper role in anaesthesia, whether one drug is preferable to another, or whether they need be used at all.

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REFERENCES

- Auld, W. (1952). *Anaesthesia*, 7, 161.
 Blazeby, R. H. (1951). *Ibid.*, 6, 168.
 Boisson, P. (1952). *Acta anaesth. belg.*, 3, 7.
 Brodie, B. B., Mark, L. C., Papper, E. M., Lief, P. A., Bernstein, E., and Rovenstine, E. H. (1950). *J. Pharmacol.*, 98, 85.
 Brotman, M., and Cullen, S. C. (1949). *Anesthesiology*, 10, 696.
 ——— and Wilkins, D. S. (1950). *Ibid.*, 11, 527.
 Brown, A. K. (1952). *British Medical Journal*, 2, 1331.
 ——— (1953). *Anaesthesia*, 8, 26.
 ——— (1954). *British Medical Journal*, 2, 967.
 Crawford, J. H., and Binning, R. (1953). *Ibid.*, 1, 272.
 Cullen, S. C. (1950). *Ibid.*, 2, 276.
 Duguid, A. M. E., and Heathcote, R. St. A. (1940). *Quart. J. Pharm.*, 13, 318.
 Eisleb, O., and Schaumann, O. (1939). *Dtsch. med. Wschr.*, 65, 967.
 Foldes, F. F., and Swerdlow, M. (1956). *British Medical Journal*, 1, 686.
 ——— Lipschitz, E., Weber, G., and Pirk, L. A. (1955). *Canad. Anaesth. Soc. J.*, 2, 362.
 Franks, E. H. (1954). *Brit. J. Anaesth.*, 26, 418.
 Griffiths, H. F. (1950). *British Medical Journal*, 2, 763.
 Gross, E. G., Brotman, M. A., Nagyfy, S. F., Sawtelle, W. W., and Zager, L. L. (1949). *Fed. Proc.*, 8, 297.
 ——— Holland, H. L., and Schueler, F. W. (1948). *J. appl. Physiol.*, 1, 298.
 Hamilton, W. K., and Cullen, S. C. (1955). *Anesthesiology*, 16, 22.
 Hardy, D. W., Wolff, H. G., and Goodell, H. (1940). *J. clin. Invest.*, 19, 649.
 Johnson, P. D. (1951). *British Medical Journal*, 2, 705.
 Johnston, M. (1951). *Ibid.*, 2, 943.
 Lancaster, F. M., and Levin, J. (1956). *Ibid.*, 1, 381.
 Lee, R. E., and Hasegawa, A. K. (1950). *J. Pharmacol.*, 98, 20.
 ——— and Pfeiffer, C. C. (1951). *J. appl. Physiol.*, 4, 193.
 Loeschcke, H. H., Sweel, A., Kough, R. H., and Lamberts, C. J. (1953). *J. Pharmacol.*, 108, 376.
 McDermott, T. F., and Papper, E. M. (1950). *N.Y. St. J. Med.*, 50, 1721.
 Meals, W. G. (1948). *Anesthesiology*, 9, 644.
 Murphy, M. (1951). *Irish J. med. Sci.*, p. 535.

- Mushin, W. W. (1951). *Proc. roy. Soc. Med.*, 44, 840.
 ——— (1955). Joseph Clover Lecture, Royal College of Surgeons. Personal communication.
 ——— and Rendell-Baker, L. (1949). *British Medical Journal*, 2, 472.
 ——— (1950). *Brit. J. Anaesth.*, 22, 235.
 Neff, W., Mayer, E. C., and DeLaLuz Perales, M. (1947). *Calif. Med.*, 66, 67.
 ——— and Thompson, R. (1950). *British Medical Journal*, 1, 1400.
 Pearce, C. (1951). *Brit. J. Anaesth.*, 23, 205.
 Prescott, F., Ranson, S. G., Thorp, R. H., and Wilson, A. (1949). *Lancet*, 1, 340.
 Randall, H. S., Belton, M. K., and Leigh, M. D. (1952). *Canad. med. J.*, 67, 311.
 Ruben, H., and Andreassen, A. K. (1951). *Brit. J. Anaesth.*, 23, 33.
 Ruddell, J. S. (1950). *Lancet*, 1, 953.
 Severinghaus, J. W. (1953). Univ. of Pennsylvania, Seminar: "Recent Advances in Pharmacology."
 Siker, E. S., Foldes, F. F., Pakh, N. M., and Swerdlow, M. (1954). *Brit. J. Anaesth.*, 26, 405.
 Swerdlow, M., Foldes, F. F., and Siker, E. S. (1955). *Amer. J. med. Sci.*, 230, 237.
 Thompson, R. C., and Neff, W. B. (1950). *Cur. Res. Anesth.*, 29, 77.
 Verne, D. (1952). *J. oral. Surg.*, 10, 152.
 Wilkins, D. S., Cullen, S. C., and Brotman, M. (1951). *Anesthesiology*, 12, 145.
 Wolfers, P. (1953). *British J. Anaesth.*, 25, 244.

NEONATAL BLOOD PRESSURE IN RELATION TO MATURITY, MODE OF DELIVERY, AND CONDITION AT BIRTH

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This paper compares the average systolic blood pressure at birth of groups of infants differing in various respects. It also describes the course of the pressure during the first few months of life.

Method and Material

The systolic blood pressure was estimated by palpating the brachial artery below an inflatable cuff. The cuff was 2.5 cm. wide, as recommended by Robinow *et al.* (1939). The artery was palpated in the antecubital fossa—this is more reliable than palpation of the radial artery. The average of two or three readings, taken with the child quiet, was recorded. Pressures were measured within an hour of birth and often much sooner. Further measurements were made on the first, third, and ninth days after delivery, at 3 and 6 weeks, and at 3 and 6 months.

Most of the neonatal pressures were measured by one observer, and the later pressures by the other, but there were frequent opportunities for cross-checking. There was always good agreement.

Initially, all cases in which one of us could record the pressure within an hour of delivery were included. Later only abnormal cases were studied. For analysis the infants were divided into groups as described in the results. The groups are mutually exclusive.

Results

Unless otherwise stated, the figures quoted are the mean of all the readings in a group, and significance has been calculated by the *t* test.

Normal Deliveries

No Anoxia.—There were 54 normal pregnancies and spontaneous deliveries in the series. The mean systolic pressure rose slowly from 69 mm. Hg at birth to 93 mm. Hg at 6 months; the rise was most rapid during the first month