The cleansing of chronic varicose ulcers, the treatment of chronic osteomyelitis and of chronic sinusitis, and the control of infection in skin grafting seem fertile fields for an extension of its use. The possibility of local allergic reactions, which may be related to the lysis of bacteria by the antibiotic, must be kept in mind in any topical application of chloramphenicol.

Summary

The treatment of chronic infections of the middle ear and mastoid cavities with a 15% solution of chloramphenicol in propylene glycol is presented. The results appear to be as good as those produced by any method at present in use and they can be obtained with less trouble to the patient, hospital, or doctor. A wider application for topical chloramphenicol is suggested.

[Since writing the above we have found that a 10% solution of chloramphenicol seems to be as effective as the 15% solution. Under present conditions the saving in cost and material is important.]

We owe thanks to our colleagues at King's College Hospital and the Belgrave Hospital for allowing us to treat some of their cases; to Mr. W. I. Daggett and Mr. T. E. Cawthorne for their criticism; and to Mr. Hewlitt, Mr. Hollis, Mr. Jarrett, and Mr. Foxwell for their help in collecting material. We are also indebted to Dr. A. G. Cunliffe and the staff of the Bacteriology Departments of King's College Hospital Group for carrying out many investigations and sensitivity tests; to Mr. Daverson for the photographs; and to Dr. J. Stanley White, of Parke, Davis and Co., for the supply of chloramphenicol solution used.

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A delegation from the National Union of Students visited Russia in May, and on their return they published an account of what they had learned about higher education and other aspects of Soviet life, including the free State health service (*British Students Visit the Soviet Union*; from 3, Endsleigh Street, W.C.1, price 2s.). No fees are charged for doctors' or hospital services, but a small charge is made for medicines supplied on a doctor's prescription. Services provided are centred in polyclinics, sanatoria (special clinics), and hospitals; the latter are mostly in the large towns, and the polyclinics scattered throughout urban and country districts. The delegation visited a polyclinic in Moscow, and found that it provides treatment similar to that given in out-patient departments of British hospitals. If necessary the patient is referred to a hospital, since polyclinics have no hospital beds. Each clinic serves a specified district, and each doctor is responsible for the health of a certain group of people covered by the clinic. The service aims to provide one doctor to 1,500 people. Part of the medical course for students includes a period spent at a polyclinic. When the delegation visited the Bodkin Hospital in Moscow they were told that 1,000 beds were formerly set aside for infectious diseases, but that since the war the incidence had so decreased that now less than half that number were reserved. Nurses are required to undergo a five-year training before they qualify, and to work a minimum of 36 hours a week, though they may work longer hours if they wish. On the whole the hospital organization appeared to be similar to our own, and the most striking feature was the overcrowding in the wards, especially the surgical wards. Little or no midwifery is practised at home, and free nursing is available to all expectant mothers.

PETHIDINE AND GENERAL ANAESTHESIA

BY

MICHAEL JOHNSTONE, M.D., D.A.

(From the Bolton District General Hospital (Townleys), Lancashire)

Pethidine was synthesized by Eisleb and Schaumann (1939) during a search for a drug which would act anticholinergically in a manner similar to atropine. They observed that pethidine antagonized the effects of acetylcholine on smooth muscle, abolished the spasm in gut associated with the application of barium chloride, prevented the action of histamine on the bronchioles, and acted as an analgesic agent. Recent investigators (Gruber *et al.*, 1941; Batterman, 1943; Yonkman, 1948) have agreed that the spasmolytic action of pethidine is due to a strong papaverine-like effect combined with a weak atropine-like effect.

The fortifying effect of pethidine on the anaesthetic properties of nitrous oxide has been described by Brotman and Cullen (1949) and is now generally accepted. Its mode of action in this respect remains unexplained: I am of the opinion that it is too pronounced to be explained by synergism or by summation. The object of the present investigation is to try to throw some light on the problem by studying the effects of pethidine on the various cardiac and respiratory dysfunctions associated with general anaesthesia. The investigation has been divided into four sections: (1) the effects of pethidine on the cardiograms of normal subjects; (2) the effects of pethidine on the tachypnoea associated with trichlorethylene anaesthesia; (3) the effects of pethidine on the cardiac inhibition associated with general anaesthesia; and (4) the effects of pethidine on the ventricular arrhythmias associated with trichlorethylene anaesthesia.

Pethidine and Conscious Subjects

Fifteen patients with normal cardiovascular and respiratory systems were selected. Pethidine, 50 mg., was administered intravenously to each of them and followed 10 minutes later by atropine, 1/100 gr. (0.65 mg.) intravenously. Cardiograms were obtained immediately before the first injection, five minutes after it, and one minute after the injection of atropine.

Pethidine caused no changes in the rhythm or form of the cardiograms of any of the patients; there were slight increases—three or four beats a minute—in the sinus rates of a few of the patients, attributable to emotional factors; the sinus rates of the remainder were unchanged. There was no evidence of a narcotic effect, and respiration appeared to be uninfluenced. There was a marked increase in the sinus rate of each patient within 30 seconds of the administration of atropine.

Pethidine and Trichlorethylene Tachypnoea

Pethidine, 50 mg., was administered intravenously to each of 25 patients who had developed persistent tachypnoea after periods of trichlorethylene anaesthesia ranging from 20 to 30 minutes; atropine was the only pre-operative drug given. Before the administration of pethidine the average respiration rate for the group was 52 a minute, the most rapid being 72 a minute.

FIG. 1.—Pneumogram illustrating the effect of pethidine on trichlorethylene tachypnoea. Note the decrease in the respiratory rate and the increases in the amplitudes of the respiratory excursions which occur 70 seconds after the administration of pethidine.

FIG. 2.—(A) Pneumogram illustrating the occurrence of apnoea following overdosage with pethidine in the treatment of trichlorethylene tachypnoea. (B) Pneumogram of the same patient, taken three minutes later, showing the response to a small dose of carbon dioxide. Exogenous carbon dioxide had been eliminated when this tracing was recorded.

The injection of pethidine was followed within two minutes by a marked decrease in the respiratory rate of each patient. There also occurred considerable increases in the amplitudes of the respiratory excursions of 20 patients, the increases affecting both inspirations and expirations (Fig. 1). Complete apnoea occurred in the remaining five patients approximately two minutes after the administration of pethidine (Fig. 2, A); in each instance the apnoea was abolished by the administration of small amounts of CO_2 by manual compression of the rebreathing-bag, spontaneous respiration returning within one minute when the carbon dioxide was discontinued (Fig. 2, B).

The Coxeter-Mushin anaesthetic apparatus was used for a few patients outside the above series to facilitate the graphic registration of the respiratory changes associated with the use of pethidine; an ink writing-point was attached to the lever of the rebreathing-bag and tracings were recorded on a drum rotated by clockwork. Adequate precautions were taken to prevent interference to respiration by the accumulation of carbon dioxide in the circuit, and soda-lime was not used in view of the risk of a toxic reaction.

It was also noted that there was a marked decrease in the resistance of the lungs to manual inflation following the administration of pethidine. The appearance of each patient improved and the operating conditions, from the point of view of muscular quiescence and

capillary bleeding, were very much better. I have since used smaller doses of pethidine—25 mg.—with consistently satisfactory results and without the occurrence of apnoea; the intramuscular injection of slightly larger doses is equally effective.

Pethidine and Cardiac Inhibition

Pethidine, 100 mg., was administered intramuscularly to each of 15 patients 30 minutes before the induction of anaesthesia; no other pre-operative drugs were given. Anaesthesia was induced with 0.5 g. of thiopentone intravenously and continued with cyclopropane and oxygen in a closed circuit with carbon dioxide absorption, assisting gently the respirations when necessary. After five minutes of cyclopropane anaesthesia, atropine, 1/100 gr. (0.65 mg.), was given intravenously to each patient and the anaesthesia continued. Only those patients whose air passages remained completely patent, with no evidence of laryngeal or bronchial spasm, have been included, as these complications may cause changes in cardiac rate and rhythm. Cardiograms were obtained immediately before induction, after the administration of thiopentone, after five minutes of cyclopropane anaesthesia, and 30 seconds after the administration of atropine.

Well-marked bradycardia occurred in every patient within a few minutes of the start of cyclopropane inhalations, being of S-A nodal origin in 12 patients and of A-V

FIG. 3.—Male, 45 years; herniorrhaphy. All Lead II. Premedication: pethidine 100 mg. (A) Before induction; (B) after thiopentone, 0.5 g. intravenously; (C) after cyclopropane inhalations for three minutes; (D) 15 seconds after atropine, 1/100 gr. (0.65 mg.) intravenously; (E) 30 seconds after the atropine.

nodal origin in 3. The injection of atropine was followed within 30 seconds by the appearance of sinus tachycardia in every patient (Fig. 3); the selective action of atropine on the A-V node was apparent in several patients (Fig. 3, D and E).

Pethidine and Ventricular Arrhythmias

Pethidine, 25 mg., was administered intravenously to each of a series of 25 patients in whom ventricular arrhythmias had occurred spontaneously during trichlorethylene anaesthesia: multifocal ventricular tachycardia was present in 12 patients, and bigeminal rhythm (SA-V) in the remainder; the arrhythmia was present in each patient for 20 minutes before

the injection of pethidine (Fig. 4, C, D, and E).

The arrhythmia disappeared in each patient within four minutes after the injection of pethidine, with the return of regular sinus rhythm (Fig. 4, F). It was noted that the arrhythmia did not disappear spontaneously if apnoea followed the administration of pethidine; under these circumstances sinus rhythm was restored in a few minutes by assisting the respirations manually. The ventricular ectopic rhythms showed no tendency to recur during the subsequent 30 minutes of anaesthesia; after this period the respiratory rate tended to increase and an occasional ventricular ectopic beat appeared on the electrocardiograph; the administration of a further small dose of pethidine restored normal rhythms to both the heart and the lungs.

Discussion

The most dramatic and probably the most important effect of pethidine during anaesthesia is in the abolition of respiratory dysfunctions, of which tachypnoea is the most common. Since the completion of this investigation I have observed that it also abolishes the severe bronchospasm which may follow the insertion of an endotracheal tube, normal respiratory rhythm returning within two minutes of the administration of the drug.

The genesis of trichlorethylene tachypnoea is not quite clear. Whitteridge and Bülbring (1946) were of the opinion that it was due to hyperirritability of the inflation and deflation reflexes produced by trichlorethylene on the pulmonary vagal receptors. I doubt whether this is the complete explanation, because the degree of tachypnoea associated with trichlorethylene anaesthesia is considerably in excess of that associated with other agents which have somewhat similar effects on the pulmonary receptors.

Dixon and Ransom (1921) observed the occurrence of bronchoconstriction in animals inhaling chloroform vapour; the constriction occurred during induction and disappeared as the depth of anaesthesia increased; the reaction was equally well defined in atropinized animals. I believe that a more persistent degree of bronchoconstriction may follow the inhalation of trichlorethylene, which is a much less potent anaesthetic agent than

chloroform; prolonged constriction of the bronchioles would lead to retention of carbon dioxide, with consequent increase in the respiratory rate.

It is probable that pethidine abolishes tachypnoea by causing bronchiolar dilatation and facilitating the elimination of carbon dioxide. It probably also prevents the occurrence of bronchoconstriction when an anaesthetic vapour is inhaled, thereby permitting larger volumes of the anaesthetic agent to reach the alveoli; this effect would potentiate the anaesthetic properties of the agent used. In support of this hypothesis may be cited: the marked decrease in the resistance of the lungs to manual inflation after the administration of pethidine; the apnoea which may follow the injection of pethidine, perhaps due to a sudden elimination of carbon dioxide, as it is abolished by the inhalation of small amounts of carbon dioxide; the abolition of the bronchospasm which may follow the insertion of an endotracheal tube.

It has been demonstrated that the inhalation of an irritant anaesthetic vapour may lead to cardiac arrest as the result of stimulation of the pulmo-cardiac reflexes (Johnstone, 1951a). The anaesthetic agent stimulates vagal receptors in the air passages, resulting in reflex inhibition of the heart with the appearance of bradycardia, S-A nodal and A-V nodal blocks, ventricular standstill, and complete cardiac arrest; atropine modifies the vagal effect considerably. Brodie and Russell (1901) were of the opinion that the vagal receptors were situated in the bronchioles and alveoli, and they observed that the most intense degree of cardiac inhibition followed artificial inflation of the lungs in the presence of an open thorax; the cardiac inhibition was equally well marked in curarized and non-curarized animals.

Judging from the results obtained in the third section of this investigation, it would seem that cardiac inhibition occurs more readily in patients premedicated with pethidine: severe degrees of inhibition appeared in several patients within two to three minutes of the start of cyclopropane inhalations, whereas in non-premedicated patients inhibition is not so pronounced till several minutes later (Johnstone, 1951a). The absence of any significant increases in the sinus rates of conscious patients after the intravenous administration of pethidine is in marked contrast to the effect of atropine. The briskness of the pulmo-cardiac reflexes in pethidinized patients may be due to increased exposure of the vagal receptors as the result either of bronchiolar dilatation or

FIG. 4.—Woman, 33 years; colporrhaphy. All Lead II. Premedication: atropine, 1/100 gr. (0.65 mg.). (A) Before induction; (B) after thiopentone, 0.5 g. intravenously; (C) after seven minutes of trichlorethylene anaesthesia; (D) after 15 minutes of trichlorethylene anaesthesia; (E) after 20 minutes of trichlorethylene anaesthesia; (F) three minutes after pethidine, 30 mg. intravenously; (G) five minutes after the pethidine.

of the prevention of bronchiolar constriction following the inhalation of the anaesthetic vapour.

To return momentarily to the problem of trichlorethylene tachypnoea: it may be argued that pethidine abolishes tachypnoea during anaesthesia by producing analgesia of the vagal receptors, with diminution in the activity of the Hering-Breuer reflexes; the inability of pethidine to protect the heart from reflex vagal inhibition tends to discount this theory.

It has been demonstrated that carbon dioxide retention is responsible for the occurrence of ventricular arrhythmias during cyclopropane anaesthesia (Johnstone, 1950) and during thiopentone anaesthesia (Johnstone, 1951b); efficient elimination of carbon dioxide prevents the occurrence of the arrhythmias and abolishes them when present. I have recently administered small doses of carbon dioxide to a series of 25 patients who had been anaesthetized with trichlorethylene and in whom there was no evidence of cardiac arrhythmias; the inhalation of carbon dioxide was followed by the appearance of multifocal ventricular tachycardia in 14 patients, bigeminal rhythms in 7, and sinus tachycardia in the remainder. These observations indicate that the ventricular arrhythmias which appear spontaneously during trichlorethylene anaesthesia may be due to the retention of endogenous carbon dioxide as the result of tachypnoea. Pethidine abolishes the arrhythmias probably by permitting the more efficient elimination of carbon dioxide; the failure of pethidine to abolish the arrhythmias when apnoea follows its administration indicates that the drug has no direct influence on the cardiac conducting mechanism and that its probable action is indirect through the more efficient elimination of carbon dioxide.

The use of pethidine in conjunction with nitrous oxide, oxygen, and trichlorethylene produces an excellent and safe method of anaesthesia provided that patients are premedicated with atropine. I have used the technique extensively for colporrhaphies, thyroidectomies, mastectomies, and numerous other operations not requiring profound muscular relaxation. Anaesthesia is less precariously light than when nitrous oxide, oxygen, and pethidine are used. Recovery is prompt, with a complete absence of restlessness, provided respiratory and cardiac dysfunctions are carefully controlled. Recovery resembles closely the awakening from natural sleep, and analgesia is well marked for three to four hours after the recovery of consciousness.

I have not been satisfied with this technique for robust patients or for patients undergoing operations which entail traction on the abdominal viscera or dilatation of the anal sphincter: these manipulations precipitate severe laryngo-bronchial spasms in lightly anaesthetized patients. It has not been my experience that the combination of light anaesthesia and curare eliminates the activities of the traction reflexes; the spasms which I have observed in lightly anaesthetized curarized patients have been much more severe and prolonged than those which have occurred in lightly anaesthetized non-curarized patients, presumably as the result of paralysis of the accessory muscles of respiration. I consider it advisable to use more potent anaesthetic agents for those surgical procedures which involve stimulation of the traction reflexes, in conjunction with minimal doses of curare. The greatest care must be taken to avoid the occurrence of reflex laryngo-bronchial spasm in patients with myocardial disease; so far as I can ascertain, it

can be avoided only by maintaining the first or second plane of surgical anaesthesia with either diethyl ether or cyclopropane.

Through the courtesy of Messrs. A. C. Cossor, Ltd., of London, in conjunction with Tytherington Products, Ltd., of Cheadle, Manchester, electrocardiographic equipment incorporating a specially adapted oscillograph was provided for part of this investigation; preliminary observations indicate that the oscillograph is ideally suited for the immediate detection of cardiac arrhythmias during anaesthesia.

Summary

It is demonstrated that pethidine abolishes and prevents the tachypnoea and ventricular arrhythmias associated with trichlorethylene anaesthesia. It is suggested that these complications of trichlorethylene anaesthesia are due to retention of endogenous carbon dioxide. Pethidine seems to act by causing bronchiolar dilatation, thereby ensuring the efficient elimination of carbon dioxide.

Pethidine appears to increase the sensitivity of the vagal pulmo-cardiac reflexes, thereby increasing the risk of cardiac inhibition during anaesthesia in non-atropinized patients.

In atropinized patients, the use of pethidine in conjunction with nitrous oxide, oxygen, and trichlorethylene is advocated as a safe and satisfactory method of anaesthesia for operations not requiring profound muscular relaxation or entailing traction on viscera.

Equipment for conveniently recording respiratory activity during anaesthesia is described.

The application of the cathode-ray oscillograph to clinical anaesthesia is explained.

I wish to record my gratitude to Mr. E. S. Gawne, recently my chief and medical superintendent, for the provision of facilities; to Professor W. Schlapp, Manchester University, for the loan of the pneumographic equipment; to Mr. J. Latham, S.R.N., and Mr. J. D. Rigby, clinical photographer, for valuable technical assistance.

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The fourth annual week-end school of the Association of Public Health Lay Administrative Officers was held at Oxford in September. Attended by over 100 representatives of local health authorities, the school opened with a visit to the Pressed Steel Company at Cowley, where in addition to a tour of the factories—refrigeration and car bodies—Dr. Reynard, principal medical officer to the company, gave an address on the industrial health services. Dr. J. A. Scott, deputy county medical officer, addressed delegates on the National Health Service. After a historical survey of the political launching of the Act, Dr. Scott dealt with anomalies—the ambulance services, the ludicrous situation of the supplier having little control over the demand; the maternity service with present loss of work for the domiciliary midwives; the difficulty of the medical officer of health in the field of infectious diseases; the complexity of the tuberculosis service; the difficulties of the aged, elderly, and chronic sick; and mental health. The last two days were spent in discussing care of mothers and young children, the ambulance service, prevention of illness, care and aftercare, home help service, and welfare services.