TREATMENT OF CHRONIC OTORRHOEA WITH CHLORAMPHENICOL

BY

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The common causes of persistent ear discharge are chronic otitis media, chronic otitis externa, and infection in the cavities made by tympano-mastoidectomies and fenestration operations. It is difficult to assess the proportion of the population suffering from running ears, but Formby (1942) reported that just over 2% of recruits examined during the 1939-45 war were rejected because of chronic ear diseases. Otorrhoea formed the bulk of the cases. Johnston (1948) found that of 1,902 factory employees 3.3% had suppurating middle ears, and Asherson (1950) states that 1% of the school population of London in 1932 were treated for chronic otorrhoea. These figures apply to special sections of the population, but most otologists would agree that otorrhoea is equally common in many other groups as well.

Chronic suppurative otitis media ranges from a relatively benign condition to a cause of death. In most cases it is painless and the otorrhoea may be intermittent, appearing only when an upper respiratory tract infection occurs. The effect on hearing is variable: the loss is often slight, and even when both ears are affected there may be no serious economic or social handicap. The deafness from bilateral ear discharge, however, may interfere considerably with the education of a child.

It may be accepted that the longer the discharge persists the worse the hearing gets, and in some cases the deafness may become profound. This is especially so when nerve-deafness is added. Fortunately, bilateral cases of this kind are not common. Although a number of cases therefore suffer little more than the annoyance of running ears, the group as a whole are handicapped, and various occupations, such as nursing, the Post Office, the Services, the police, and food manufacturing, may be closed to them. They may have sub-normal health, headaches, giddiness, and deafness; and the continual presence of pus, which is often offensive, is distressing. The pus may be a source of danger to others by acting as a reservoir for the spread of organisms such as *Ps. pyocyanea*.

Another handicap is the amount of time that may have to be spent in treatment; in some cases it is a matter of years, and is only too often given up because of its tediousness and uncertainty. Long hours spent each week on treatment, if there is failure to cure the otorrhoea or if it recurs after the first cold, can hardly be justified in the simple cases of unilateral otorrhoea, in which the worst that can happen is a moderate degree of unilateral deafness and the annoyance of a persistent discharge. Present methods of treatment may be very

effective, but the best results can be obtained only by regular treatment, preferably undertaken by trained staff. Recurrent attacks are frequent, each one demanding a repetition of the regime. There is a great need for a simple and effective remedy which would save the time of the patient and the hospital.

Pathology of Chronic Suppurative Otitis Media

Before presenting the results of treatment with chloramphenicol, some consideration must be given to the pathology of the condition. It is a surprising fact that although mankind has suffered from infection of the middle ear at least since the days of Rhodesian Man, and that it is such a common disease, its aetiological factors are by no means clear. A discussion of the difficulties and theories would be out of place here, but a simplified exposition may help to explain the reasons for choosing either conservative treatment or radical surgery. Cases of chronic suppurative otitis media fall into two groups—the "safe" and the "dangerous." The "safe" ears are so called because complications threatening life practically never occur, since the infection is limited to the mucous membrane; but the pathological changes in the middle ear and mastoid process in the "dangerous" group give rise to bone destruction, which may lead to fatal intracranial complications. The clinical differentiation of the two groups is usually easy: the "dangerous" ears include all cases with an attic or posterior marginal perforation. Where the perforation is central—no matter how large—serious complications need not be feared. We have included inferior and anterior marginal perforations in the "safe" group.

The pathological differences between the two groups may be summarized briefly. In the "safe" group the infection is limited to the mucous membrane of the middle-ear cleft—a tympano-mucosal infection. Granulations and polypi can and often do occur, but they are not in these cases an indication of underlying bone infection, and with suitable local treatment they disappear and the otorrhoea ceases. In early cases the drum may heal, but as a rule the perforation is permanent and the ear remains liable to infection through the perforation or up the Eustachian tube. Treatment therefore cannot be said to have failed if the otorrhoea recurs some weeks or months later.

In the "dangerous" type the discharge is kept up by the epithelial formation known as cholesteatoma (cholesteatosis has been suggested as a better name) or by chronic bone infection—caries of the attic recess, tympanic ring, or antrum. Granulations are more common and return after removal. The pathological changes transcend the bony boundaries of the middle-ear cleft and endanger life. It is difficult to see how any medicament instilled into the meatus will effect a cure when this happens. However, in some cases the caries is limited to the annulus tympanicus and aditus, and in others the cholesteatoma is small and able to discharge freely through the perforation. In these, conservative treatment may suffice and healing may occur by an ingrowth of epithelium. It is impossible to estimate the proportion of ears in the "dangerous" group in which this happens. The recurrence of discharge in the "dangerous" type is more often due to a recrudescence of the disease arising from the chronically infected bone or cholesteatoma than a reinfection such as occurs in the "safe" type.

Treatment of Chronic Suppurative Otitis Media

Only a small proportion of the cases of chronic suppurative otitis media require a mastoid operation. In theory, all the "safe" types should respond to conservative measures, and even if the discharge persists temporal bone surgery is seldom justified. The term "conservative measures" includes operations on the nose and throat, removal of aural polypi and granulations, and even cortical mastoidectomy.

The percentage of successful results obtained by conservative means depends to a large extent on the skill and frequency with which treatment is applied. During and after the recent war otologists were impressed by the excellent results they could obtain when treatment was carried out regularly and personally (Banham, 1944; Scott Stevenson and Ballantyne, 1945; Johnston, 1948).

The most effective form of treatment so far has been careful removal of all discharge by mopping or syringing and the insufflation of an antibacterial powder such as boric and iodine or boric and sulphathiazole. Spirit drops and wicks also give good results provided the cleansing is thorough and the medicament is brought into contact with the infected parts. Treatment is often needed daily, rarely less frequently than twice a week, and may take anything from a week to seven months to produce a dry ear (Johnston, 1948). It is time-consuming, requires trained personnel, and in civilian practice is often impossible to carry out adequately. Any new drug or treatment, therefore, producing results equal to or approximating those possible under ideal conditions but with less trouble and loss of time to the patient and doctor would be welcome.

We hope to show in this paper that the use of chloramphenicol as a local treatment in chronic otorrhoea can effect a rapid cessation of discharge with comparatively little inconvenience to the patient. The use of antibiotics locally is not new. Penicillin has been, and still is, used enthusiastically, but a consideration of the type of organisms encountered in chronic otitis—mostly Gram-negative bacteria—makes it clear that its use is irrational. We consider it unwise to use streptomycin in otorrhoea because of the rapidity with which resistant strains of organisms are bred. There have been no reports so far on "aureomycin" and chloramphenicol. One drawback to aureomycin is its instability in solution, but chloramphenicol has certain advantages that make it the antibiotic of choice for a preliminary trial.

The properties of chloramphenicol attractive for local use are as follows: in solution it is neutral and almost indefinitely stable; its activity against organisms stretches from the Gram-positive bacteria to the larger viruses; and it is non-toxic in therapeutic concentrations. Its chief disadvantage lies in its poor solubility in water. However, it is soluble in propylene glycol. In turn, propylene glycol has certain advantages as a vehicle for local medication: it is non-toxic, it is miscible in water, and it is markedly hygroscopic. It seemed to us, then, that chloramphenicol in propylene glycol might have advantages for certain forms of treatment far superior to any at present known.

In this investigation, a 15% solution of chloramphenicol in propylene glycol was used: this gives a concentration of antibiotic of 150,000 $\mu\text{g.}$ per ml. Examination of a series of standard ear-droppers showed that they

delivered about 30 drops to the millilitre. Each drop of this solution then contains approximately 5,000 $\mu\text{g.}$ of antibacterial substance. The sensitivity of the organisms isolated from some of the reported cases varied from 5–10 $\mu\text{g./ml.}$ for coliforms and 10–15 $\mu\text{g./ml.}$ for *Staph. aureus* to about 120 $\mu\text{g./ml.}$ for *Proteus vulgaris*—the most resistant organism met. It might be argued that in view of the sensitivity range the concentration of antibiotic was far in excess of that required and that a more economical solution should be used. Further experience may show that this is possible. Two factors, however, governed the choice of concentration. First, a desire to sterilize the infected cavities with the greatest possible speed: some experimental work in this laboratory has shown that chloramphenicol is a bactericide, and that there is a rough correlation between the concentration of the antibiotic and the rate of bacterial death. Secondly, it was thought that an initial high concentration would prevent the emergence of resistant strains of organisms. Cavalli and Maccacaro (1950) have shown that it is possible to increase the resistance of a coliform from 10 $\mu\text{g./ml.}$ to 1,280 $\mu\text{g./ml.}$ by transfer of cultures containing increasing concentrations of the drug on a geometric scale.

As this is a saturated solution of chloramphenicol in propylene glycol it should not be stored in a refrigerator, otherwise the antibiotic will crystallize out; furthermore, by virtue of its concentration it is self-sterilizing. A bottle has been left open on the laboratory bench, shaken with a thumb over the mouth, had unsterile wool dipped in, and maltreated in ways which the untutored public might attempt—but no evidence of any growth was ever obtained.

Present Investigation

The cases selected have all been "chronic"—that is to say, the discharge has been present for at least six weeks and in most cases very much longer. Two main groups have been treated: those in which otorrhoea was due to chronic suppurative otitis media and those in which it followed a previous tympano-mastoid or fenestration operation.

No control series has been done: all the operation cavities and more than half the cases of chronic suppurative otitis media had failed to improve on out-patient treatment for two or more weeks before chloramphenicol solution was started. For comparison Table I gives the results of pre-chloramphenicol treatment in 31 other cases of chronic suppurative middle-ear disease at King's College Hospital. These patients were seen by the otologist on an average of once a fortnight. They were told how to mop out their ears, and spirit drops were given for instillation twice a day. The results do not approach those achieved at special centres or military hospitals, where up to 82.5% dry ears have been recorded (Banham, 1944), but probably present a fair average of what is obtained in many general hospitals.

TABLE I.—Results of Pre-chloramphenicol Treatment of Chronic Suppurative Otitis Media

	No.	Drum Healed	Dry	Failed	Duration of Treatment
"Safe" ears	18	—	13	5	From 1 to 24 months
"Dangerous" ears	13	—	5	8	From 1 to 10½ months
Total	31	—	18	13	

Methods Used

All through the investigation we were exercised to make the most effective use of rather scanty supplies of solution. The early cases of suppurative otitis media had a few drops put into the meatus four- to six-hourly, but later it was found that instillation twice a day was enough in most cases. In order to make certain that the chloramphenicol solution reaches the middle ear it is important to show the parent or patient how to use it. The patient should be lying down with the affected ear uppermost; the discharge is mopped away as much as possible, but the patient is not encouraged to clean deeply into the meatus itself. Enough of the solution to half fill the external auditory meatus should be used—for an adult, about half the amount contained in an ordinary hospital ear-dropper. The tragus is pressed in and out a few times to persuade the chloramphenicol solution to enter the middle ear. Without careful instruction, or better a demonstration, it is possible that none of the solution will reach the middle ear. If the drops are instilled properly the bitterness of chloramphenicol can often be tasted in the throat.

The cavities left by tympano-mastoid operation and fenestrations for otosclerosis can also be treated by drops, but they need a considerable quantity at each instillation, and, as the amount available for each patient was restricted, it was decided to try the more economical application of wicks of gauze or cotton-wool soaked in the solution.

In the more recent cases of chronic suppurative otitis media treatment has been started by the insertion of a wick soaked in the chloramphenicol solution down to the perforation. This is left *in situ* for two days, then removed by the patient himself, who continues with the drops. By using the wick first, the amount of pus and congestion is considerably reduced, allowing more effective penetration by the solution. In a few cases the wick alone was sufficient to stop the discharge.

TABLE II.—Results of Chloramphenicol Treatment of Chronic Suppurative Otitis Media

	No.	Drum Healed	Dry	Failed	Duration of Treatment
"Safe" ears . . .	26	5	20	1	From 1 to 21 days
"Dangerous" ears	10	—	4	6	From 14 to 30 days
Total ..	36	5	24	7	

Remarks on Table II.—Daily observation and more intensive treatment by the otologist would possibly reduce the number of days' treatment required, and it is worth emphasizing again that the reduction in length of treatment shown in Tables I and II from months to days has been achieved with little, if any, extra care and attention by the otologist. For several days after treatment has stopped, a clear exudate may be seen in the tympanic cavity. This is sterile on culture, and we believe it is due to the hygroscopic action of propylene glycol. Its presence does not call for interference, for it soon disappears. The comparative poorness of results in "dangerous" ears is not surprising. As we have pointed out, the pathological state allows little prospect of success by local measures. It is to be noted that the "dangerous" ears respond more slowly than the "safe." No cases have recurred as yet, but, since the perforation persists in the majority, the possibility of such an event remains.

Treatment of Tympano-mastoid and Fenestration Operation Cavities

Twenty radical and modified radical and ten fenestration cavities were treated. It is difficult to convey in tabular form the results of the treatment, because the cases varied in severity of infection. Considerable clinical improvement was observed in 26 of the 30 cases, although complete "skinning" over of the cavities was not obtained each time. It was especially gratifying to see the improvement taking place in those cases infected by the usually troublesome *Proteus* and *Ps. pyocyanea* organisms.

Before the treatment of the operation cavity was started, any large granulations were cauterized or removed with a curette, loculations were broken down with a myringotome or fine punch forceps, and the cavity made as smooth as possible. The wick was thoroughly soaked in chloramphenicol solution and packed loosely into all parts. If the patient was to remove it himself the end was brought through the meatus so that he could pick it up without difficulty. We prefer cotton-wool wicks to gauze because they hold more solution. Pieces of wool have not become detached or been lost in the ear so far in our experience. The wick was left in place for 48 hours in most cases. The patient was instructed to move it and report in a week. If infection was still present the wick was replaced by another. The number of wicks required in successful cases was never more than four, and sometimes one was sufficient. Drops without wicks were used for one to three weeks in four cases: healing was rapid in three of these, but granulations persisted in the fourth.

These cases require a little more care and attention than a "safe" chronic otitis media, but the cleansing action of the chloramphenicol wick is striking.

Bacteriology

The commonest organism encountered in this investigation was *Proteus vulgaris*, closely followed by *Staph. aureus*, *Ps. pyocyanea*, and coliforms. Friedländer's bacillus was isolated in one case. In some the flora was mixed—that is, *Proteus vulgaris*, and *Staph. aureus* were found together. Others in combination were *Str. haemolyticus* and non-haemolytic streptococci.

At the Belgrave Hospital all the organisms isolated in the early cases were tested for chloramphenicol sensitivity by the disk method of Thompson (1950). This was soon abandoned, however, because in two cases a *Proteus vulgaris* isolated from each, which was apparently non-sensitive by the disk titration, vanished within 48 hours of treatment with the chloramphenicol solution. Consideration shows that, volume for volume, the solution used for treatment is 60 times more concentrated than that used in the preparation of the disks. The standard used in the sensitivity test contains 50 µg. of chloramphenicol per 0.02 ml. The same quantity of the solution used in the treatment of the cases described has 3,000 µg. Therefore the results of the disk titration for sensitivity bear no relation to the effect of treatment. In using the chloramphenicol solution described in this report the routine testing for the sensitivity of organisms is unnecessary.

As already stated, the chloramphenicol wicks were left *in situ* for 48 hours. In order to estimate the amount of antibiotic activity which might still be present in them, the following experiment was made. The treatment wicks

were removed with sterile precautions and laid across an agar plate; three streaks of an 18-hour Sonne broth culture up to the wick were made on the left half of the plate, and similar streaks of an 18-hour coliform broth culture were made on the right half. The *Sh. sonnei* had a known chloramphenicol sensitivity of 3 $\mu\text{g.}/\text{ml.}$, the coliform 12 $\mu\text{g.}/\text{ml.}$ The plates were incubated overnight. Fig. 2 shows the result. Fig. 1 is a culture wick soaked in propylene glycol only and left in a mastoid

FIG. 1.—Control. Wick removed from mastoid cavity at the end of 48 hours. Soaked in propylene glycol only. Organisms on left, *Sh. sonnei*; organisms on right, coliforms; organisms growing out from wick, *Ps. pyocyanea*.

FIG. 2.—A 15% chloramphenicol solution wick removed from a mastoid cavity after 48 hours' insertion. Organisms on left, *Sh. sonnei*; organisms on right, *Bact. coli*; organisms isolated prior to treatment, *Staph. aureus*, haemolytic streptococcus, and diphtheroids.

cavity for the same length of time: it will be seen that colonies have grown out from this wick, swamping the Sonne and coliform streaks. The organisms isolated from the cavities prior to the implantation of the wicks were: Fig. 1 (control), *Ps. pyocyanea*; Fig. 2, *Staph. aureus*, haemolytic streptococcus, diphtheroids.

The photograph shows that not only is the wick still sterile after 48 hours' exposure to the infected cavity but that enough active chloramphenicol is left to create a large zone of inhibition about it. This is a striking illustration of the extreme potency of the chloramphenicol solution.

Discussion

There are many reports in the literature of series of

cases of chronic suppurative otitis media treated by conservative measures. We believe that equally good results can be obtained by the use of chloramphenicol solution, with less trouble and loss of time to the patient, hospital, clinic, or doctor. It is not a panacea: a thorough examination of the ears, nose, and throat must always precede its use. Granulations, polyps, loculations, etc., must always be treated as the experience of the surgeon dictates. It is important also to explain carefully how the drops should be used, for unless this is done the chances are that none will reach the affected parts. The use of a solution of chloramphenicol can have only an indirect effect on the healing of a drum by getting rid of infection. Healing has been observed five times in our series, and in most cases the perforation is

permanent. An ear with a perforated drum is liable to infection, and recurrences of discharge are bound to happen occasionally, whatever method is used. Johnston (1948) reports that 45% recur within six months, and Banham (1944) 25%. The recurrences should react quickly to treatment, especially if it is immediately restarted. Chloramphenicol solution in a 15% concentration keeps indefinitely, and a small supply kept by the patient for early use in a recurrence should be useful.

In infected mastoid cavities similar conditions exist. There is no bone infection and the discharge clears with treatment and granulations disappear. In most cases epithelium grows over the raw areas to line the cavity completely. In a few long-standing cases, although the discharge stops, the epithelium does not spread and the granulations take on a flat, glazed, indolent appearance that otologists will readily recognize. In these, recurrence of infection is likely.

The possibility that the results could have been due to the extra care and attention that tends to be given in an investigation of this sort has been borne in mind and guarded against so far as is possible. The figures strongly suggest that chloramphenicol has a marked effect, and justify further and more extensive trials.

The only cases in which an accurate record of the hearing has been kept are the fenestrations, but no patient has reported that his hearing has been made worse, nor have any vestibular symptoms developed. The audiograms of the otosclerotic cases, with the exception of one, showed no change. In the exception a slight loss developed three to four weeks after the wick was removed—a loss which might have occurred in any event.

Two cases, both radical mastoidectomies, showed a local allergic reaction, a dermatitis of the auricle developing. They settled with diphenhydramine hydrochloride ("benadryl"), and the healing of the cavities was not delayed. Whether this reaction was due to a drug sensitivity, either for propylene glycol (which is unlikely) or for chloramphenicol, or to the release of bacterial protoplasm due to the lysis of organisms by the antibiotic we are unable to say.

This investigation was made with a 15% solution of chloramphenicol in propylene glycol: whether equally good results can be obtained with a 10% solution only further work can show. On theoretical grounds the lesser concentration should be satisfactory. A 10% solution would contain 0.1 g. of antibiotic per ml. of propylene glycol, or an equivalent of 100,000 $\mu\text{g.}$ In a 30-dropper pipette a potency of 3,300 $\mu\text{g.}$ per drop is thus reached, which should be adequate in relation to the resistance of the organisms likely to be met in chronic surgical infections. It would have the advantage of a saving in cost and stability in cold. However, the point of primary importance is that the concentration should be such that the antibiotic available at the periphery of any cavity will overwhelm the organisms. If the amount of chloramphenicol in a solution is too critical there may be insufficient in the hidden recesses of the area under treatment to be effective, or, worse, resistant types of bacteria may breed.

It seems fairly obvious that if a solution of chloramphenicol of the potency we have described is effective in the treatment of probably the most difficult of all chronic surgical infections—those of the middle ear—it should have a much wider scope than the limited trial we have reported.

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.]

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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

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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.