Summary

During the winters of 1958-9 and 1959-60 a controlled trial was held in order to see if tetracycline in therapeutic dosage for two days at the start of an upper respiratory infection in children would prevent the development of bronchitis or disabling chesty colds. Ninety-six children entered the trial and were randomized into two groups. Those in one were given tetracycline and in the other a placebo. For each of the factors analysed there was a difference in favour of the tetracycline-treated group. Attacks of bronchitis were prevented in 58% of the upper respiratory infections treated with tetracycline, compared with 49% of those in the control group; the average durations of time off school per attack were 1.9 and 2.9 days respectively.

I am indebted to Dr. Ian Sutherland for his advice and help in planning this investigation, and for the statistical treatment of the results. I am grateful to Miss M. Arris, sister in charge of the chest clinic, for her valuable help in the supervision of the mothers. My thanks are due to the Clinical Research Committee of the North-West Metropolitan Regional Hospital Board for a research grant. The tetracycline ("achromycin V" paediatric drops) and identical placebo were kindly supplied by Lederle Laboratories.

REFERENCE

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TREATMENT OF INTRACTABLE PAIN WITH MORPHINE AND TETRAHYDROAMINACRINE

BY

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One of the disadvantageous side-effects of morphine may be depression of the central nervous system (narcosis). Shaw and Bentley (1952) were the first to discover a group of substances which completely restored to consciousness a dog narcotized with morphine. Some of these were also powerful respiratory stimulants. Such substances did not, however, interfere with the analgesic action of morphine. They were called partial antagonists, in distinction to the complete antagonists or competitive inhibitors of morphinoid structure such as N-allylnormorphine or levallorphan.

Amiphenazole

In a series of papers by various authors (for literature see Shaw, 1959) it was shown that if one of these partial antagonists, amiphenazole ("daptazole") was combined with morphine it was possible, with safety, to give enough morphine (up to 100 mg. q.i.d.) to keep the patient free from pain for at least six hours, while at the same time he remained alert, co-operative, and even happy. The main—though not the only—use of this combination was in the treatment of the intractable pain

of terminal carcinoma. The most recent exposition of the method is that of Shaw (1960b). The combination of amiphenazole and morphine has other uses also—for example, to relieve post-operative pain (for literature see Shaw, 1960a) and even to provide operative analgesia (Hayward-Butt, 1957). The treatment of the other side-effects of morphine—respiratory depression, and nausea and vomiting—has been dealt with by Christie *et al.* (1958). Amiphenazole has, however, two disadvantages: it is an unreliable respiratory stimulant and it is unstable in solution.

Tetrahydroaminacrine

Because of these disadvantages we have turned our attention during the last two years to another member of the original group, tetrahydroaminacrine (T.H.A.), which is a very reliable respiratory stimulant (Shaw, 1960a) and is extremely effective in arousing patients after the administration of a barbiturate or general anaesthetic (G. R. Harris, 1960, personal communication; McCaul, 1960). Moreover, it is stable in solution and has the distinct advantage that it can be supplied in the same ampoule with morphine. T.H.A. has been chiefly used in anaesthesia (McCaul, 1960). A few cases of myasthenia gravis have also been treated. The present paper deals with its use in conjunction with morphine to relieve intractable pain in a series of 60 patients with carcinoma.

Pharmacology.—T.H.A. may be classed as a stimulant; in lethal doses it produces convulsions in animals, but these have not been observed in man. It stimulates the respiration (Shaw and Bentley, 1952), and antagonizes the action of curare at the neuromuscular junction while extending the action of suxamethonium (Gershon and Shaw, 1958).

It is a powerful anticholinesterase and has anticholine acetylase activity (de la Lande, 1958). T.H.A. awakens barbiturized (cats and mice) and morphinized (dogs) animals and counteracts the coma of a nephrectomized kitten. It has little effect by itself on the cardiovascular system: the blood-pressure may rise or fall a few milligrams of mercury, and it may cause slight bradycardia. The drug can, however, prevent ventricular fibrillation precipitated by either digitalis or electric shock. It protects against the cardiac changes produced by volatile anaesthetic agents. The actions of adrenaline and noradrenaline are to a certain extent antagonized. In animals the alimentary canal is stimulated and defaecation may occur, though this effect is not produced in man. In animals it also increases the various mucosal secretions, but this hypersecretion occurs in man only when excessive doses are given, and it is counteracted by atropine. The LD₅₀ (rats) is about 35-40 mg./kg. (Herman *et al.*, 1960). T.H.A. produces no side-effects other than vomiting in about 1% of cases, but the incidence of vomiting rises in conscious volunteers as the dose increases above 30 mg. (intramuscularly or intravenously). When morphine, barbiturates, or general anaesthetics are also given there is scarcely any vomiting.

Method

The method used in administering T.H.A. to relieve pain is the same as that for amiphenazole (Shaw and Shulman, 1955). The patient is given the usual therapeutic dose of morphine, 10 mg. (1/6 gr.), with T.H.A. (10-15 mg.), and if he is not completely relieved of pain for six hours the dose of morphine is increased at each injection until this ideal is attained. The increments are usually

morphine 15 mg. ($\frac{1}{2}$ gr.), 20 mg. ($\frac{1}{2}$ gr.), and 30 mg. ($\frac{1}{2}$ gr.), but a dose of 10–20 mg. is usually sufficient in the first instance. Each injection of morphine is accompanied by T.H.A., either separately or, more conveniently, in the same syringe from the same ampoule of mixed morphine and T.H.A. The dose of T.H.A. is not precisely related to the morphine; usually 10–15 mg. is enough to keep the patient alert, but up to 30 mg. may be required. As it is easier to prevent the onset of pain than to relieve it, injections should be given four times a day.

If the mixture has to be used continually, as for patients with cancer, the dose of morphine has to be increased at approximately monthly intervals. In all probability this increase is due as much to the increasing severity of pain as it is to tolerance. The usual increases are made in 25% increments and the maximum we have reached after one year is 150–200 mg. (2–3 gr.) q.i.d. It is seldom necessary to increase the dose of T.H.A. Sensitivity to morphine is rare, but if it does occur it will be observed before large doses are given. One of the great advantages of T.H.A. is that if palliative treatment lessens the pain it is possible to reduce the morphine without the appearance of withdrawal symptoms. Although we have on occasion stopped the administration of morphine suddenly without ill effect, it is advisable to reduce it over a period of 48 hours. Care should be exercised in treating elderly people as morphine alone will often cause mental disturbances. In such cases, dihydrohydroxy-codernone ("proladone") has been found satisfactory.

Vomiting occurs in only about 1% of cases and may be treated with cyclizine ("marzine"), 50 mg., either orally or parenterally (Christie *et al.*, 1958). More recently trifluoperazine ("stelazine"), 5 mg., and flupromazine ("vesprin"), 5 mg., have been used successfully.

If a sedative is necessary, chloral or one of the barbiturates is usually sufficient. Chlorpromazine has been used in a few cases, but as our object is to keep the patient alert it should be avoided as much as possible. As death approaches T.H.A. may be discontinued if the patient is distressed by insight into his condition. A report of one case is given in detail as it illustrates all the points of treatment.

Case History

The patient was a man aged 25. In 1953 he had a lump on the forehead. The growth, attached to bone, was progressive but there was no pain. In 1958, when an epithelioma was removed from the front of the right ear, pain developed in both legs and later extended to the shoulder. It was eased by DXRT. In 1959 radiographs showed widespread osteolytic secondary deposits in the pelvis, femora, carpus, etc., and a biopsy of an ulcer on the scalp showed squamous-cell carcinoma (these findings were confirmed at necropsy). The patient was very disturbed and had a great deal of insight into his condition. He had been receiving morphine for some months at another hospital but said that the pain had never been completely relieved.

After his admission on March 16, 1959, he complained continually of pain, especially at night, and always requested more morphine, although he eventually received 30 mg. q.i.d. He gave the nursing staff a great deal of trouble, and, as a result, their attitude was rather unsympathetic and he was considered to be malingering. On April 16 he was given morphine 30 mg. ($\frac{1}{2}$ gr.) and T.H.A. 15 mg. q.i.d., with the result that he no longer complained of pain, asked for injections, or worried the staff, and was able to get up. The treatment was continued until July 9, when morphine was discontinued abruptly (the T.H.A. remained at 15 mg.). No morphine was given for 36 hours, during which time no withdrawal symptoms appeared (he had received morphine for more than 12 weeks). When he complained of pain, however, morphine and T.H.A. were given as before. He died on August 6. He had been on the same dose of morphine for more than 17 weeks, and until the terminal stage of his illness he remained bright, alert, co-operative, and ambulatory, and his mood throughout was in great contrast to that on admission.

Results

Over a period of a year 60 cases have been treated. Table I summarizes the results in five typical cases. Table II provides a résumé of such important points as the absence of withdrawal symptoms when treatment with the mixture was discontinued, the reduction in the amount of morphine given during treatment, the greater relief of pain induced by T.H.A., the use of pethidine or other drugs, failure of treatment, and the relative value of T.H.A. and amiphenazole. The treatment produced safe, pleasant, and complete analgesia in more

TABLE I.—Summary of Five Cases

1 (M)	10/2/59: M., aspirin	17/2/59: M. 10. Pain not adequately controlled and M. gradually increased	15/4/59: M. 65. Still some pain. Drowsy	16/4/59: M. 65, T.H.A. 30. Pain relief complete only when T.H.A. added. Not drowsy. Ambulatory	2/7/59: M. 90, T.H.A. 30. M. increased because c/o pain. Now pain-free. Ambulatory	10/9/59: M. nil, T.H.A. 20. No M. for 17½ hours. No withdrawal symptoms	11/9/59: M. 20, T.H.A. 10. M. now reduced but pain relief complete. Ambulatory
1 (M) Cont'd.	17/9/59: M. nil, T.H.A. nil. No M. for 24 hours. No withdrawal symptoms	18/9/59: M. 30, T.H.A. 10. M. still reduced but no pain	30/10/59: M. 45, T.H.A. 15. No pain. Condition worse	24/11/59: M. 65, T.H.A. 15. No pain. Terminal	3/12/59: M. 65, T.H.A. 15. Confused. T.H.A. stopped sl. less confused	14/12/59: M. 65, A. 60. No better. Replaced on T.H.A. and less confused	29/12/59: M. 90, T.H.A. 20. Mental confusion in last week. Died 6/1/60
2 (M)	23/4/59: M. 30, T.H.A. 15. Still complained of pain	1/5/59: M. 60, T.H.A. 20. No pain, except when moved	15/5/59: M. 60, T.H.A. 20. Path. fracture, no pain when moved	22/5/59: M. 90, T.H.A. 20. M. increased as complained of slight pain	12/6/59: M. nil, T.H.A. nil. No pain, no withdrawal symptoms. 7 weeks on M.	19/6/59: Died	
3 (M)	9/2/59: M. 15. Still pain on M. 30	8/5/59: M. 30, T.H.A. 15. No pain, alert	22/5/59: M. 30, T.H.A. 15. V. good. Injections only b.d.	12/6/59: M. nil, T.H.A. 15. No pain. No withdrawal symptoms. 17 weeks on M.	19/6/59: M. nil, T.H.A. nil. Went home		
4 (F)	14/8/59: M. 30, A. 30. Not bright. Path. fracture pain when moved	15/8/59: M. 30, T.H.A. 10. V. bright. No pain on movement	2/10/59: M. 45, T.H.A. 15. V. bright. No pain	9/10/59: M. nil, T.H.A. 15. No pain. No withdrawal. V. bright. 8 weeks on M.	23/10/59: M. 10, T.H.A. 10. Had slight pain	30/10/59: M. 30, T.H.A. 15. Pain relieved. Alert	
5 (F)	25/9/59: M. 20, T.H.A. 10. No pain. Bright	2/10/59: M. 15, T.H.A. 10. Able to reduce M. No complaint of pain	23/10/59: M. nil, T.H.A. 10. Good	22/11/59: M. nil, T.H.A. 10. Difficult to assess	13/11/59: Peth. 50, T.H.A. 10. Better	16/11/59: Peth. 50, T.H.A. nil	26/11/59: No drugs

A. = Amiphenazole. M. = Morphine. T.H.A. = Tetrahydroaminacrine. Numbers refer to dose in mg. q.i.d.

than 90% of the cases, and has been so successful that a day-room has been created in the hospital in which these severely ill patients may enjoy the normal amenities.

TABLE II

Total No. of patients	60
Discontinuance of morphine for more than 17 hours without withdrawal symptoms	17
As above, but slight withdrawal symptoms	2
Reduction of morphine during treatment	10
Increase in analgesia due to T.H.A.	7
Patients commenced on pethidine subsequently requiring morphine	6
Patients reacting better with amiphenazole (when both used)	4
Patients reacting better with T.H.A. (when both used)	3
Patients receiving only partial relief from treatment	2
Patients receiving no relief from treatment (T.H.A.)	2
Patients successfully changed to heroin	3

Discussion

The success of T.H.A. and morphine complements that produced by morphine and amiphenazole, as there are now two partial antagonists available, and in a few cases only one of these was suitable for the particular patient.

Advantages of T.H.A.—T.H.A. has the following advantages over amiphenazole: (1) It is a more reliable antinarcotic agent and respiratory stimulant; (2) it does not interfere with sleep, as may amiphenazole; (3) it is chemically stable and can be prepared in the same ampoule as morphine; (4) in some instances the analgesic action of morphine is increased—this follows from its anticholinesterase activity, as the same effect has been reported with neostigmine.

In other ways T.H.A. and amiphenazole appear to have the same effects: the constipation induced by morphine is lessened, pin-point pupils are not observed, and the patient's vision is undisturbed; he can cough voluntarily, and there is no euphoria—although even without T.H.A. or amiphenazole euphoria is rare.

Addiction.—The problem of addiction when large doses of morphine are given has been dealt with elsewhere (Gershon *et al.*, 1958; Shaw, 1960b). In this series when morphine was combined with T.H.A. the patients did not experience euphoria, they did not crave for their injections, it was possible to reduce or withdraw the morphine without withdrawal symptoms, and though increasingly large doses were given we never felt that we had "lost control" of our patients. Indeed, it has been our policy to check from time to time the continued presence of pain by withholding morphine and substituting a placebo. Similarly, we can check whether complaints of pain are genuine by giving either an injection of distilled water or a single injection of double the usual dose of morphine (with T.H.A.).

Other Side-effects.—Vomiting is rare. In the aged there may be mental disturbances. Some patients may be idiosyncratic to morphine, and in such cases heroin (with T.H.A.) has been found useful; in three cases heroin relieved pain more effectively than morphine and at a lower dosage. One patient was relieved by pethidine and even morphine-aspirin mixture by mouth. The small number who did not respond had to be treated empirically.

Domiciliary Patients.—The combination of morphine and T.H.A. offers another advantage in the treatment of pain in carcinoma in that it can be used for patients being treated at home. It has usually been considered inadvisable for a non-qualified person to administer morphine by injection, but most diabetics give their own insulin, and there have been many cases where a competent member of the family has looked after a

relative suffering from cancer, including the administration of morphine by injection. As for the necessity of keeping morphine under rigid control because of the danger of addiction, it must be stressed that morphine made up with T.H.A. in the same ampoule is useless to the addict as it will not produce euphoria and cannot produce addiction. Finally, accidental or intentional poisoning is impossible if only limited amounts of the mixed drugs are issued. We can see no danger in the domestic use of morphine thus dispensed, and our own experience with home treatment shows that it is quite feasible. In view of these observations it seems that the use of surgical measures such as cordotomy for the relief of pain should be reconsidered. While elaborate surgical procedures may in some cases be of value they may also fail; in such cases resort can be had to our pharmacological techniques. This view is particularly advocated by the surgical member of the team (V.S.).

Morphine and T.H.A. may be used for post-operative analgesia in the same manner as morphine and amiphenazole. The patient is alert and co-operative, especially with respect to coughing, and has normal respiratory exchange. This should be of great advantage after thoracic surgery (Weber, 1958; Glatzl, 1958).

Conclusion

The recent practice of safely relieving the intractable pain of carcinoma with a combination of morphine and a partial antagonist has been rendered easier by the introduction of tetrahydroaminacrine (T.H.A.). This substance is a partial antagonist to the narcotic analgesics, enabling morphine to be given (10–100 mg. q.i.d.) without producing narcosis or respiratory depression. The patient does not become addicted, and, though tolerance still develops, the dose of morphine may be reduced or withdrawn without withdrawal symptoms. An additional advantage of T.H.A. is that it is stable and can be combined in the same ampoule with morphine, thus making administration a very simple matter.

The successful use of the combination in a series of 54 patients over a period of more than a year is described.

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The report of a conference organized in 1959 by the National Association for Mental Health on "Truancy—or School Phobia" is still available from N.A.M.H., 39 Queen Anne Street, London W.1, price 3s. 6d.