oozing, but the injection area should not be massaged for fear of producing back-seepage of the injected material into a punctured vessel.

All nurses, and other personnel who may be required to give penicillin injections, should receive instruction on the minutiae of the injection technique.

6. *Precaution Against Repetition.*—All patients who have suffered an acute immediate reaction from the administration of penicillin should be given a card or disk indicating this fact, and this should be carried in the wallet or handbag.

Treatment

The fact that so many of the patients in this series recovered rapidly without treatment suggests that the claims made for this or that treatment may be unjustified, recovery occurring in spite of treatment rather than because of it. However, since it is impossible to forecast the train of events and there is a danger that severe bronchospasm may occur rapidly, it is best to regard every acute reaction as an anaphylactic one so far as immediate treatment is concerned. At the first sign of an acute reaction 0.5 ml. of a solution of adrenaline 1 in 1,000 should be injected intramuscularly. This should be repeated as required or injection of the solution continued at the rate of 0.1 ml. a minute until the attack shows signs of terminating. An intravenous antihistamine such as diphenhydramine hydrocloride in a dose of 50–100 mg., or of promethazine hydrochloride in a dose of 25–50 mg., may also have some value, but they tend to produce a state of drowsiness lasting several hours. Positive-pressure oxygen should be administered where indicated and if available, and in cases where recovery is delayed intravenous hydrocortisone has been found to be valuable.

Those patients who experience weakness and malaise for a considerable time after the reaction, such as Cases 5, 7, and 11 in this series and one of the cases described by Bell (1956), may benefit from the administration of neostigmine, as did three of the patients described by Winston and Nora (1955). Acute reactions believed to be due to procaine toxicity in which there is evidence of gross central stimulation, such as generalized convulsions, might be expected to benefit from the administration of an intravenous barbiturate.

Summary

Twelve instances, from general practice, of acute immediate reactions following injection of preparations of penicillin are recorded.

The nature of these reactions and their possible modes of production are discussed. It is suggested that they may be produced in one of three ways: (1) intramuscular injection of penicillin in sensitized individuals; (2) accidental intravascular injection or back-seepage in sensitized individuals; or (3) accidental rapid intravascular injection of procaine penicillin suspensions.

A scheme for minimizing the incidence and severity of these reactions is outlined and suggestions are made for treatment.

I am indebted to Drs. C. A. Brockbank, S. D. Singh, A. C. Cattanach, A. A. Fullerton, A. R. Montgomery, J. Macdonald, A. Gilston, and L. S. Calvert for allowing me to quote their case reports, to the other practitioners who sent reports on penicillin reactions which did not quite fall within the arbitrary definition of immediate reactions, and to the College of General Practitioners and the *Practitioner* for publishing my request for case histories.

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CHLORAMPHENICOL IN TREATMENT OF ACUTE RESPIRATORY INFECTION

BY

A. H. IOANNIDIS, M.B., Ch.B.
Clinical Assistant

AND

J. McC. MURDOCH, F.R.F.P.S., M.R.C.P.Ed.
Senior Medical Registrar

From the Royal Infirmary, Edinburgh, and the Department of Therapeutics, University of Edinburgh

During recent years medical teaching in this country has tended to limit the use of chloramphenicol primarily to the treatment of the typhoid group of infections in view of its alleged toxic effects on the haemopoietic system; it has been suggested that respiratory infections are more appropriately treated with other chemotherapeutic agents. The view is now generally held, however, that the micro-organisms commonly invading the human respiratory tract are of a mixed type. Of these, probably the most important in the United Kingdom are the *Haemophilus influenzae* and the pneumococcus (*Lancet*, 1955). The former organism is highly sensitive to chloramphenicol both *in vitro* (Fairbrother, 1956) and *in vivo* (May, 1953a, 1953b, 1954; Elmes, Knox, and Fletcher, 1955; Franklin and Garrod, 1953). Cohen and Schwartz (1950) believed chloramphenicol to be the antibiotic of choice in acute respiratory infections of undetermined origin, in the absence of an influenza epidemic or a "common cold."

Tunbridge (1953) points out that in infections usually of mixed origin it is advisable to use a chemotherapeutic agent which is effective against both Gram-negative and Gram-positive organisms, as well as against some virus infections. Penicillin alone is not always effective, as it has a limited action against Gram-negative organisms, especially *H. influenzae* (Stuart-Harris *et al.*, 1953), and May and Oswald (1956) have suggested that a combination of penicillin and streptomycin gives prompt and complete remission of exacerbation in the early stages of chronic bronchitis.

In our view, however, there are several possible objections to this combination of antibiotics in such cases. Firstly, in the absence of absolute negative evidence of a tuberculous basis for the bronchitis, the use of streptomycin carries the risk, albeit small, of inducing resistance in the causative tubercle bacilli, even with a relatively small total dose (Medical Research Council, 1948). Secondly, it seems irrational to subject a severely ill patient to frequent and possibly painful injections where simple oral therapy could be used. Thirdly, as Zinnemann (1953) has shown, chloramphenicol was the only one of five antibiotics capable of inhibiting 100% of strains of *H. influenzae* tested at the comparatively low concentrations obtained with the usual recommended therapeutic doses; it would therefore seem that this organism cannot always be eradicated by such a combination. Finally, there is no doubt that many staphylococcal infections, especially those seen in hospital, are due to penicillin-resistant strains (Barber and Burston, 1955).

As Hausmann and Karlish (1956) have suggested, staphylococcal infections are responsible for a considerable number of cases of pneumonia failing to respond to penicillin, and such infections are likely to present a major problem in the future. In a series of 17 cases of penicillin-resistant staphylococcal empyemata reported by Brownrigg (1955) chloramphenicol was found to be the most effective drug. De Vries and Pritchard (1955) isolated *Staphylococcus pyogenes* from 87 post-mortem specimens. Of these, 100% were sensitive to chloramphenicol, and 88% were resistant to penicillin, 48% being resistant also to the tetracyclines. Rantz and Rantz (1956), studying the resistance pattern of 242 strains of *Staphylococcus aureus*, showed 81.8% to be penicillin-resistant, 51.7% streptomycin-resistant, 52.5% tetracycline-resistant, and only 5.8% chloramphenicol-resistant.

It would seem, therefore, that oral antibiotic therapy is preferable in the treatment of acute respiratory infections, and the choice lies between chloramphenicol and the tetracyclines. For short-term therapy we elected to use the former antibiotic, in the belief that the tetracyclines were better reserved for the long-term treatment of more chronic advanced cases of bronchial infection, and there is some evidence (Helm *et al.*, 1956) that stopping such treatment and restarting after a short interval may encourage the development of resistant strains of *H. influenzae*.

We report here our observations and results of treatment with chloramphenicol in 80 consecutive admissions to the Royal Infirmary, Edinburgh, all of whom were suffering from acute and severe respiratory infection, either *per se* or complicating other conditions. This is a report of experience only and is in no way a controlled trial.

Materials and Methods

The 80 patients selected for treatment were consecutive admissions to the hospital during the period June 10, 1956, to February 7, 1957. There were 63 males and 17 females, whose ages ranged from 34 to 79 years, and all were suffering from acute respiratory infection, characterized by fever, dyspnoea, and cough with the production of a purulent or mucopurulent sputum. Of these, 54 were suffering primarily from respiratory disease with an acute exacerbation. The remaining 26 had an acute respiratory infection complicating another condition. Out of the total number, 24 patients had received previous treatment with penicillin alone, 6 with penicillin combined with streptomycin, and a further 6 with spiramycin. None of these 36 patients had shown a favourable response to such treatment, given in adequate total dosage by modern standards. Details of these patients are shown in Table I.

TABLE I.—*Patients' Main Disease and Previous Antibiotic Treatment, if Any*

Main Disease Complicated by Respiratory Infection	No. of Cases		Previous Antibiotics		
	Male	Female	Penicillin	Penicillin and Streptomycin	Spiramycin
Chronic bronchitis—emphysema ..	29	12	17	5	6
Bronchiectasis ..	6	—	1	—	—
Bronchial asthma ..	3	4	2	—	—
Pulmonary embolism	5	—	—	—	—
Mitral stenosis ..	2	1	—	—	—
Coronary artery disease	8	—	2	—	—
Diabetes mellitus ..	10	—	2	1	—
Total ..	63	17	24	6	6

Observations made in all cases before, during, and after treatment included assessment of general physical state, degree of fever, character, quantity and bacteriology of the sputum, and full peripheral blood counts.

The treatment consisted of chloramphenicol, 2 g. daily (500 mg. six-hourly) to a total of 10 g.—that is, five days' treatment. Careful observations on possible side-effects such as glossitis, skin rashes, sore throat, and alteration in the character and frequency of the stools were also made during treatment.

Pre-treatment sputum cultures on blood-agar medium showed the predominant organism to be *H. influenzae* in 15 cases, pneumococcus in 24 cases, *Staph. pyogenes* in 19 cases, and no predominant growth from mixed organisms in 22 cases. These figures are summarized in Table II. Of the

TABLE II.—*Culture of Sputum Before Treatment with Chloramphenicol*

	Mixed Organisms. No Predominant Growth	Predominant Organism Obtained from Mixed Growth		
		H. influenzae	Pneumococcus	*Staph. pyogenes*
No. of cases	22	15	24	19

19 cultures yielding a predominant growth of *Staph. pyogenes*, only two were found to be fully sensitive by routine laboratory methods—that is, to penicillin, streptomycin, chloramphenicol, and the tetracyclines. Seventeen were resistant to penicillin, seven to streptomycin, and eight to the tetracyclines. All were sensitive to chloramphenicol and five to this antibiotic alone.

Results

The results of treatment are shown in Table III. The general condition of 77 patients was regarded as improved at the end of the fifth day of treatment in that they were afebrile and free from respiratory symptoms and signs. Of these, 73 remained free from symptoms, continuing to be

TABLE III.—*Results of Treatment with Chloramphenicol*

Main Disease Complicated by Respiratory Infection	No. of Cases	Effect of Treatment with Chloramphenicol on				
		General Condition		Infection		
		Improved	Unchanged	Controlled	Initially Controlled	Uncontrolled
Chronic bronchitis—emphysema ..	41	40	1	39	—	2
Bronchiectasis ..	6	6	—	4	2	—
Bronchial asthma	7	6	1	6	—	1
Pulmonary embolism	5	4	1	4	—	1
Mitral stenosis ..	3	3	—	3	—	—
Coronary artery disease ..	8	8	—	8	—	—
Diabetes mellitus	10	10	—	9	1	—
Total ..	80	77	3	73	3	4

without sputum for periods varying from one to eight months after treatment. Relapse occurred in three patients within seven days of stopping therapy: return of fever and productive cough with infected sputum. One patient, although subjectively improved, had a mucopurulent sputum at the end of treatment, while three patients were totally unaffected.

As to the control of infection, the assessment of the change in purulence of the sputum before and after treatment is shown in the Chart. The bacteriological results are shown in Table IV. Forty-eight patients had no sputum at the end of treatment. Twenty-five produced mucoid sputum from which no growth of organisms was obtained on culture. Of the seven patients considered either to have been unaffected by treatment or to have relapsed within one week, mixed organisms were cultured from the sputum in four—*H. influenzae* in one, and pneumococcus in two. It is noteworthy that in none of the 19 patients whose sputa grew *Staph. pyogenes* before treatment could any growth of organisms be obtained on culture thereafter.

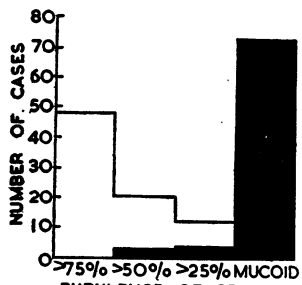

Chart showing purulence of sputum before (white areas) and after (black areas) treatment.

TABLE IV.—*Culture of Sputum After Treatment with Chloramphenicol*

	No Sputum Produced	No Growth Obtained	Mixed Org.; No Predominant Growth	Predominant Organism Obtained from Mixed Growth		
				H. influenzae	Pneumococcus	*Staph. pyogenes*
No. of cases	48	25	4	1	2	0

TABLE V.—*Side-effects Observed During or After the Treatment with Chloramphenicol*

	Side-effects				No Side-effects
	Blood Disorders	Diarrhoea	Skin Rash	Dry Mouth	
No. of cases ..	0	1	1	3	75
Percentage ..	6·25				93·75

Side-effects (See Table V).—Seventy-five patients (93.75%) in this series were completely free from any side-effects attributed to chloramphenicol. Of the remaining five (6.25%), one had slight transient diarrhoea for 24 hours, which did not necessitate stopping the drug. Three developed a dry mouth, detected only by direct questioning, and one of them had in fact a mild "black tongue." The fifth patient exhibited a slight erythematous rash over the arms and hands during treatment, although this may have been caused by concomitant phenobarbitone medication. No evidence of bone-marrow depression as a result of therapy was elicited by comparative blood counts before and after treatment in all cases.

Discussion

In deciding to employ chloramphenicol in this series, we were well aware of the serious objections which have been raised against its use. Probably as a result of the negligible incidence of reported side-effects, chloramphenicol was extensively and often indiscriminately prescribed prior to 1952, by which time a number of blood dyscrasias, including aplastic anaemia, thrombocytopenia, and neutropenia had been reported. All of these were surveyed by the Food and Drug Administration of the United States of America in 1952 (Lewis *et al.*, 1952). As a result, a policy of restraint in its use was advocated thereafter. Since then exhaustive work, both experimental and clinical, has been carried out in an endeavour to elucidate the questions raised by such reactions. These have been admirably posed by Parker (1955–6) as follows: What is their true significance? Are they purely coincidental? Are they a toxic reaction to the nitrobenzene radical? Are they related to the total dosage of the drug? Are they precipitated by previous or concomitant medication?

Research workers now seem to be in a little doubt about the cause of the abnormal bone-marrow finding in experimental animals after the administration of large doses of chloramphenicol. They seem to agree that the earlier reports on the marrow findings (Radomski and Nelson, 1953; Rigdon *et al.*, 1954) are mainly, if not wholly, due to malnutrition of the animals resulting from the administration of chloramphenicol (Nelson and Radomski, 1954; Weston *et al.*, 1954; Saslaw *et al.*, 1954–5; Radomski *et al.*, 1955; Reutner *et al.*, 1955; Rigdon *et al.*, 1955; Reutner *et al.*, 1955–6). This malnutrition was shown to be due to the marked anorexia induced by chloramphenicol, noted earlier by Gruhzit *et al.* (1949).

Following the earlier reports attributing blood dyscrasias to chloramphenicol administration, a nation-wide survey was carried out by Lewis *et al.* (1952) in the U.S.A., which produced no definite clinical evidence incriminating chloramphenicol in this respect. Welch *et al.* (1954), in a similar survey two years later, emphasized that "it cannot be stated categorically that chloramphenicol actually caused the blood dyscrasias which developed following its use." In the United Kingdom Hodgkinson (1954) surveyed 31 blood dyscrasias attributed to chloramphenicol from 20 centres, 28 of which were classified as aplastic anaemia. Seventeen of these patients had received concomitant treatment with other drugs, including sulphonamide (12), pyribenzamine (2), and streptomycin (1), each of which has been reported to be associated with the occurrence of aplastic anaemia. In 24 cases the dosage was over four times that employed by us, and the average was more than double that calculated to be the maximum necessary to control most infections.

In an endeavour to determine whether or not early blood or bone-marrow depression occurred in a controlled group of 43 children receiving antibiotics—75% of whom had chloramphenicol for 10 days—Doyle *et al.* (1953–4) found by serial examinations no change in the normal pre-treatment marrow or peripheral blood findings either during treatment or three months thereafter. Among others, Bercovitz (1953–4) also reported no abnormal blood findings in 67 patients with ulcerative colitis treated intermittently with chloramphenicol for long periods. In our series of 80 patients there was no significant clinical or laboratory evidence of blood disorders as a result of chloramphenicol administration.

Accordingly, we feel that the risks incurred by giving chloramphenicol in short courses of 10 g. are negligible or, at most, no more than with any potent drug. It is worth recalling that following early reports of serious sulphonamide toxicity, such as that of Sutliff *et al.* (1943), a restricted total dosage has been in use for many years. Even penicillin administration carries the risk of anaphylactic reactions in susceptible individuals, amounting to 100 to 200 acute reactions in a single year (Welch *et al.*, 1954), and three deaths have recently been attributed to this cause (Andersen, 1955–6).

As has been stated already, the tetracyclines should be reserved for the long-term treatment of more chronic advanced cases of bronchial infection, rather than for short-term treatment of acute episodes. There is already some evidence that repeated short courses of tetracyclines may encourage the development of resistant strains of *H. influenzae* (Helm *et al.*, 1956). Moreover, the high incidence of tetracycline-resistant staphylococci may be attributed to repeated or prolonged exposure, or to hospital infection (Brownrigg, 1955; de Vries and Pritchard, 1955; Barber and Burston, 1955; Rantz and Rantz, 1956; May and Oswald, 1956). We would also hesitate to use the tetracyclines in such cases as diabetic ketosis aggravated by bronchial infection or

mitral stenosis with cardiac failure attributable to bronchial infection, where any diarrhoea caused by these drugs would be detrimental to the underlying disease.

Summary and Conclusion

Eighty patients with acute respiratory infection of mixed bacterial origin either *per se* or complicating other conditions were treated with chloramphenicol, 2 g. daily for five days. Clinical improvement resulted in 77, three being totally unaffected. Relapse occurred in three patients within one week. The infection was controlled in 73 patients for periods varying from one to eight months after treatment.

Seventy-five patients were quite free from side-effects; dry mouth was observed in three, a mild skin rash in one, and slight transient diarrhoea in one. No blood dyscrasias of any kind were detected.

The potential toxicity of chloramphenicol has been overstressed. If it is given in short courses of 10 g. over five days to patients with acute and severe respiratory infections a satisfactory and prompt response is obtained, with a very low failure and relapse rate, and with negligible toxicity. Chloramphenicol has therefore a definite place in the treatment of such cases, but should not be employed in prolonged dosage or for trivial infections. It may well be that the avoidance of its extensive use in recent years has had the advantage of enabling us to deal effectively with organisms now frequently resistant to the other antibiotics more commonly employed.

We are grateful to Professor D. M. Dunlop for helpful advice and criticism on the preparation of this paper, and for allowing us to study the patients under his care. We also thank Dr. J. H. Bowie and the staff of the bacteriology department of the Royal Infirmary, Edinburgh, for carrying out the sputum cultures and sensitivity tests.

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ORAL TREATMENT OF TRICHOMONAS VAGINITIS WITH AMINITROZOLE

BY

JOSEPHINE BARNES, D.M., F.R.C.S., F.R.C.O.G. M.R.C.P.
Consultant Gynaecologist

ANNE BOUTWOOD, M.B., D.Obst.R.C.O.G.

ELIZABETH HAINES, M.R.C.S., D.Obst.R.C.O.G.

WENDY LEWINGTON, M.B., F.R.C.S. M.R.C.O.G.

ELAINE LISTER, M.B., F.R.C.S.
Gynaecological Registrars

AND

B. JOAN HARAM, M.R.C.S., L.R.C.P.
Pathologist

Elizabeth Garrett Anderson Hospital, London

The work described below is a controlled trial of oral treatment of trichomonas vaginitis, using the oral product aminitrozole (2-acetylamino-5-nitrothiazole, " tritheon "). During the course of the trial, attempts have been made to culture the *Trichomonas vaginalis*, using the simplified trypticase serum medium of Kupferberg.

Literature

Cuckler, Kupferberg, and Millman (1955) showed that aminitrozole administered orally is effective against trichomonas infection *in vitro* and *in vivo*. It was shown to have a therapeutic effect in experimental vaginal trichomoniasis in monkeys and mice. It is also effective against amoebae and against schistosomiasis. Aminitrozole was well tolerated in six species of animal for extended periods when administered by various routes. In some cases in dogs, brown urine was produced, and this has also been noted in humans.

Perl, Guttmacher, and Raggazoni (1956) treated a series of 174 cases of trichomonas vaginitis with aminitrozole and a cure was obtained in 35%. Out of 48 husbands of infected women, trichomonads were found in the semen of 28 (58%). Of these, 16 who brought further seminal specimens after treatment with aminitrozole were cured after one course of treatment, while a further two were cured after two courses of treatment. The remaining 10 defaulted. In the female trichomonas infection was found to be heaviest one week before and one week after menstruation. When husband and wife both received treatment the percentage of cures was increased.

Plentl, Gray, Neslen, and Dalali (1956) treated a series of cases of trichomonas vaginitis, using aminitrozole in a dose of 150 mg. three times a day. Severe side-effects were noted, including nausea, abdominal pain, anorexia, and dark urine. When the dose was reduced to 100 mg. three times a day, using enteric-coated tablets, side-effects were minimal. Eradication of trichomonas was achieved in 35% and clinical improvement in 67%.

Kupferberg, Johnson, and Sprince (1948) gave a detailed description of the method of preparing a simplified trypticase serum medium for the culture of *Trichomonas vaginalis*. Kean and Day (1954), using this medium for the diagnosis of trichomonas infection, found that culture was more reliable than the hanging drop method for the diagnosis of infection. In 500 consecutive patients examined from a gynaecological clinic the hanging drop was positive in 12.2%, while culture was positive in 18%. They concluded that culture of the organism was essential for diagnosis.