The trial has shown that with these doses there is no difference in results obtained with ampicillin and tetracycline in the long-term treatment of chronic bronchitis as judged by symptoms, work record, and bacteriology of the sputum. Side-effects were troublesome with both drugs. *In vitro*, ampicillin has the advantage in being a bactericidal drug, and in high doses might conceivably prove more effective than tetracycline in treating the bacterial complications of chronic bronchitis, especially those due to *H. influenzae*; further work on this point is needed.

Continuous chemotherapy was used to compare ampicillin and tetracycline, for with the limited number of patients available comparison would not have been possible by any other method. Although continuous treatment may be valuable for individual patients in whom infection cannot be controlled by short courses of chemotherapy, there is evidence that the immediate and short-term treatment of an acute exacerbation of infection may be just as effective and should be tried in the first instance (Elmes *et al.*, 1957; Moyes and Kalinowski, 1959; Berry *et al.*, 1960).

Summary and Conclusions

Fifty-two patients with chronic bronchitis were treated alternatively with ampicillin and tetracycline from November, 1961, to April, 1962.

The dose of both drugs was 500 mg. twice daily.

There was no significant difference between the clinical and bacteriological response to the two drugs, except that patients given ampicillin noticed a greater reduction in the quantity of sputum than those given tetracycline.

Sputum cultures showed a decrease in the incidence of *H. influenzae* with both drugs and no significant increase in the incidence of resistant organisms.

Ampicillin is a useful alternative to tetracycline in the long-term treatment of chronic bronchitis.

ADDENDUM.—While this paper was being prepared the results of a trial on the treatment of exacerbations of chronic bronchitis with ampicillin have been published (Ayliffe, G. A. J., and Pride, N. B. (1962). *Brit. med. J.*, 2, 1641). The trial suggested that ampicillin was effective treatment, but it was not possible to show any difference between treatment with ampicillin compared with demethylchlortetracycline or with phenoxymethylpenicillin and streptomycin.

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NIKETHAMIDE FOR SEVERE CO₂ RETENTION IN EXACERBATIONS OF CHRONIC BRONCHITIS

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Inadequate pulmonary ventilation leading to confusion and coma is a familiar and dangerous complication of exacerbations of chronic bronchitis. Once the patient becomes drowsy and fails to cough, secretions accumulate and a further drop in alveolar ventilation may occur. In recent years treatment with tracheostomy, bronchial suction, and artificial ventilation has enabled an increased number of patients to survive the acute episode, but these measures make heavy demands on skilled nursing care. If ventilation and consciousness could be improved by respiratory stimulants treatment would be simpler to administer and less distressing to the patient. Westlake and Campbell (1959) measured the change in arterial carbon-dioxide tension (Pco₂) following intravenous infusions of nikethamide in seven men with acute exacerbations of chronic lung disease. Their results suggested that nikethamide might be of some value; others (Hugh-Jones, 1958) have reported a favourable clinical impression. As this impression of nikethamide is not universally held, the following trial was carried out in two different centres in a further attempt to assess the effects of nikethamide in the treatment of severe carbon-dioxide retention.

Selection of Patients

Our aim was to study patients with chronic bronchitis who had an acute deterioration resulting in severe underventilation and carbon-dioxide retention. These three requirements were defined as follows:

Chronic bronchitis was diagnosed if there was a history of at least three years of chronic cough with expectoration and persistent breathlessness of effort, not

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solely attributable to other lung disease. In most cases the presence of irreversible airway obstruction was confirmed by spirometry, either before or after the acute episode.

An acute deterioration was diagnosed on the history. In most cases the deterioration was associated with a bronchial infection, but in some instances it was unexplained. No case in which a deterioration followed an operation or the giving of sedatives was included.

Severe underventilation was defined as being present when the arterial PCO_2 was 70 mm. Hg or more after the patient had been breathing 100% oxygen for 20 minutes. One severely ill patient was included whose initial PCO_2 was lower (55 mm. Hg.)

Twelve patients were studied.

Methods

100% oxygen was given continuously by facemask under supervision throughout the period of study except for brief intervals of up to three minutes for expectoration and occasionally vomiting. If an interruption occurred a blood sample was not taken until the mask had been replaced for at least 10 minutes.

Arterial Blood Gas Analysis.—Samples of arterial blood were taken through an indwelling needle before and during the infusion of nikethamide. The arterial PO_2 and PCO_2 were measured by the bubble equilibration method. At St. Thomas's Hospital the method of bubble analysis described by Riley *et al.* (1957) was used with the modification and correction factors quoted by Semple and Young (1959). At Hammersmith Hospital the mass spectrometer was used for the analysis of the equilibrated bubble (Strang, 1961). By both methods values for PO_2 above 95 mm. Hg are inaccurate and are reported as >95 mm. Hg.

Nikethamide Infusion.—An intravenous infusion of 5% dextrose in water was set up and the first blood sample taken while this was being given. An infusion of nikethamide in 5% dextrose was then substituted, usually at a dose rate of 20 mg./minute, which was increased until either a response or side-effects appeared. Close supervision was required, fine facial twitching and vomiting being signs that the rate of infusion should be reduced, since it is known that convulsions may follow an overdose. Evidence of overdosage was more

likely in the first half-hour but occasionally appeared after several hours. The second arterial blood sample was usually taken after the infusion had been running for 60 minutes, but in a few cases where the dose of nikethamide was high it was taken after a shorter interval.

Assessment of Mental State.—This was made as follows: grade 1, normal; grade 2, confused but able to obey simple commands; grade 3, very confused and unable to obey simple commands; and grade 4, coma.

Results

The results are all recorded in the Table, together with the patient's age, sex, and the dose and duration of the nikethamide infusion. Thirteen infusions were given to 12 patients; Case 4 received an infusion during each of two exacerbations of chronic bronchitis.

Arterial PCO_2 .—Nine patients showed a fall of 8 mm. Hg or more in PCO_2 while in three there was a rise of 9 mm. or more. Only in Case 12 was the PCO_2 restored to a normal figure.

Arterial PO_2 .—Five patients had an initial PO_2 of less than 95 mm. Hg despite breathing 100% oxygen. In Case 11 there was a rise in PO_2 following the nikethamide infusion, but there had been difficulty with the initial oxygen administration and it seems unlikely that the rise in PO_2 was entirely attributable to the effect of the nikethamide. In only one other case (No. 7) did the PO_2 rise after nikethamide. In Case 4(a) there was a definite fall in PO_2 (from >95 to 80 mm. Hg).

Mental State.—After 6 of the 13 infusions there was a sufficiently obvious improvement in mental state to change the grade in which the patient was placed. Four of the remaining seven patients became more restless or apprehensive, and there was an increase in respiratory rate. Those who showed the most obvious improvement in mental state were not necessarily the patients in whom there was the greatest fall in PCO_2 .

Side-effects.—These were sweating, skin irritation, nausea, vomiting, apprehension, restlessness, and facial twitching. One or more of these were seen during 8 of the 13 infusions, partly because the policy of the investigation was to go on increasing the dose of nikethamide until either a clinical effect or minor side-effects such as restlessness or skin irritation became

Effects of Intravenous Nikethamide on Arterial PCO_2 , PO_2 , and Mental State of 12 Patients (13 Observations) with an Acute Exacerbation of Chronic Bronchitis

Case No.	Sex and Age	Nikethamide		Initial Art. PCO_2 (mm. Hg)	Change in PCO_2	Initial Art. PO_2 (mm. Hg)	Change in PO_2	Mental Grade		Side-effects	Subsequent Course
		Rate mg./min.	Duration min.					Before	After		
1	M 69	41	60	166	-23			4	4		
2	M 55	270	20	133	-17			4	4	None	Died
3	M 64	200	20	130	-15	72	-4	4	2	"	Tracheostomy.
4	M 62	170	60	117	-8	>95		4	2	Skin irritation, sweating, apprehension, restlessness	Died
5	M 61	71	70	115	-10	>95	$> -15^*$	2	2	Tracheostomy.	Recovered
6	M 62	135	25	110	-9	>95		3	2	Restlessness	
7	M 51	50	60	103	+9	82	$> +13^*$	2	2	Skin irritation, nausea, vomiting	Recovered
8	M 66	38	60	97	+9	>95		3	3	Apprehension, restlessness	Died
9	M 54	125	40	90	-21	>95		3	2	None	
10	F 64	65	70	90	-2	>95		2	2	Apprehension, restlessness	Recovered
11	F 74	42	60	80	-10	43	+27	3	2	Nausea, vomiting	"
12	M 74	33	60	55	-19	51	-7	3	2	Skin irritation, restlessness, facial twitching	Died

All PO_2 values of more than 95 mm. Hg have been reported as >95 mm. Hg.

*These changes are approximate, since the initial PO_2 in Case 4(a) and the final PO_2 in Case 7 were both more than 95 mm. Hg.

apparent. The difference between the dose which produced a significant clinical response and that at which signs of serious toxicity such as facial twitching or vomiting developed was small.

Dose of Nikethamide.—The tolerable dose for eight patients lay between 30 and 70 mg./minute. In five (Cases 2, 3, 4(a), 6 and 9), a higher rate of infusion was tolerated before the appearance of side-effects. These patients were very drowsy or comatose, and four subsequently died or were treated by tracheostomy and artificial ventilation. In Cases 3, 6, and 9 an attempt was made to produce large changes in the gas tensions by further increasing the rate of infusion after either a definite clinical response had been obtained or the first signs of toxicity had appeared. The resulting gas-tension changes were, however, not larger with this increased dose.

Discussion

The reduction in arterial PCO_2 obtained in most patients during the infusion of nikethamide was small and is unlikely to have been of any benefit. A more significant effect was the improvement in the mental state of six patients. The fall in arterial PCO_2 in these cases was probably insufficient to account for such an improvement, which is more likely to have been due to the activity of nikethamide on the central nervous system rather than as a respiratory stimulant. We have not been able to predict which patients will show a useful response, nor what factors determine the size of dose they will tolerate.

These results are in broad agreement with those obtained by Westlake and Campbell (1959). Like these authors, we found that the dose which produced the maximum clinical response was only slightly less than that which resulted in serious side-effects. In none of our patients was it necessary to stop the infusion because of side-effects, which were troublesome in only two (Cases 3 and 6) in whom the dose had been further increased following a satisfactory clinical response.

Similar changes in the arterial PCO_2 and mental state of patients with chronic bronchitis have been reported after the intramuscular or intravenous administration of vanillic acid diethylamide (Silipo *et al.*, 1961) and of amiphenazole (Little, 1962). The side-effects of vanillic acid diethylamide, which include generalized pruritus, muscular twitching, and restlessness, are probably similar to those which we have experienced with nikethamide; Little (1962), however, found that although transient nausea, vomiting, and generalized pruritus occurred with amiphenazole, side-effects were not distressing with this drug. There does not seem to be any basic difference in action or complications between nikethamide, vanillic acid diethylamide, and amiphenazole.

A suitably controlled clinical trial is needed to establish definitely the place of nikethamide in the treatment of severe carbon-dioxide retention in patients such as ours. We have not demonstrated any important increase in ventilation, and the improvement in mental state and stimulation of coughing which often occurred may have been partly caused by the disturbance and attention of the experimental procedure. We doubt whether this drug is of value in the treatment of the majority of patients with an acute exacerbation of chronic bronchitis, but its use was associated with an improvement in mental state of half of our patients with severe carbon-dioxide retention, and we cannot exclude

the possibility that it may be of benefit. The arousal effect seems particularly likely to be helpful when the patient is conscious when breathing air but becomes unrousable on oxygen; in these circumstances it may be worth while making a trial of nikethamide as outlined in the methods. We would stress that frequent assessment of the patients is required, and that alternative treatment such as tracheostomy and artificial ventilation should not be unduly delayed.

Summary

Thirteen intravenous infusions of nikethamide in doses ranging from 30 to 270 mg./minute have been given to 12 patients with severe carbon-dioxide retention which occurred during an exacerbation of chronic bronchitis. All the patients were breathing oxygen before and during the infusion.

Arterial Gas Tensions.—After nine of the infusions there was a fall in PCO_2 (range 8–23 mm. Hg). In spite of this the PCO_2 remained high except in one patient. There was a rise in PCO_2 in three patients (9–12 mm. Hg). Changes in PO_2 were mostly small and probably of no significance.

Mental State.—There was an improvement in the level of consciousness after six of the infusions.

Side-effects.—These were sweating, generalized skin irritation, vomiting, and facial twitching. They could be satisfactorily controlled by adjusting the rate of the infusion.

There was no dramatic improvement in the condition of the 12 patients after the administration of nikethamide. The value of this drug in the treatment of carbon-dioxide retention occurring during an exacerbation of chronic bronchitis is discussed.

We are grateful to the physicians of the Hammersmith Hospital and St. Thomas's Hospital for allowing us to study their patients.

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"A common complaint is that in far too many cases where there is the mildest deviation from strictly normal behaviour, other social agencies are quick to label the case 'mental,' to refer it to the mental welfare officer and to retire precipitately. Conversely, cases which have once had contact with the mental health service, however slight, are regarded with the deepest distrust by other agencies, who will only move in the matter with great reluctance. Mental welfare officers generally feel that far too many cases come to them which could, and should, be more satisfactorily dealt with elsewhere. Some mental welfare officers are deeply worried about the numbers of aged people admitted to psychiatric hospital who could be dealt with in some other manner if facilities existed. There is a strong feeling that more accommodation should be provided for the care of the mildly disordered whose condition would cause difficulties in existing welfare homes, but which does not really need the full facilities of a psychiatric hospital. It is felt that the Minister should encourage local authorities to provide such accommodation and at the same time realize that the encouragement that would be most appreciated, and acted upon, would be financial encouragement." (*Mental Health*, February, 1963.)