arthritis, particularly with actively inflamed large joints, and ankylosing spondylitis. The fact that indomethacin is a rapidly effective, non-steroidal, anti-inflammatory agent, like phenylbutazone, makes it a useful alternative to predni-steroid therapy.

As with many other drugs used in the treatment of chronic rheumatic disorders, indomethacin causes undesired effects which are particularly apt to occur in the early stages of treatment. Fortunately most of these are trivial and clear rapidly after withdrawal of the drug. In view of the occurrence of severe neurological disturbance in seven of our cases we feel that it would be unwise to ignore and dangerous to suppress the headache and associated symptoms so commonly encountered. If these cannot be avoided by gradual induction or by subsequent reduction of dosage, they must be taken as an indication for stopping the drug. It would seem reasonable to insist that indomethacin should only be given with caution to any patient with a history of depressive illness. Active or recent peptic ulceration should be regarded as an absolute contra-indication, and therapy should not be resumed in any patient who exhibits a rash during treatment.

Summary

Clinical experience with indomethacin during a period of 18 months in a series of 137 patients comprising 70 with rheumatoid arthritis, 50 with osteoarthrosis, and 17 with miscellaneous rheumatic disorders is recorded. A progressive dosage regime was used beginning with 25 mg. daily, and the average daily maintenance dosage was 75 mg.

Striking benefit was obtained in osteoarthrosis with a satisfactory outcome of treatment in 69% of cases, which was significantly better than the rheumatoid group where 44% were satisfactory. An excellent response was also seen in three patients suffering from acute gout.

A total of 70 side-effects occurred in 47 patients and compelled withdrawal of treatment in 39 (28% of the total group). The principal undesired symptoms were headache associated with vertigo, etc., but major neurological disturbance occurred in seven cases. All these symptoms subsided rapidly on withdrawal of therapy. There was one instance of slight melaena, one perforated ulcer, and three rashes developed during therapy.

Indomethacin is thought to be a useful addition to the range of drugs used in the management of certain rheumatic disorders, notably in osteoarthrosis, acute gout, rheumatoid arthritis, and spondylitis.

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Antibiotic Treatment of Epidemic Bronchiolitis—a Double-blind Trial

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Epidemic bronchiolitis is a common and widespread disorder of infants in Great Britain (Heycock and Noble, 1962; Holzel, Parker, Patterson, Cartmel, White, Purdy, Thompson, and Tobin, 1965). It has been shown in the U.S.A. (Beem, Wright, Hamre, Egerer, and Oehme, 1960; Chanock, Kim, Vargosko, Deleva, Johnson, Cumming, and Parrot, 1961; McClelland, Hilleman, Hamparian, Ketler, Reilly, Cornfeld, and Stokes, 1961) and in Great Britain (Sandiford and Spencer, 1962; Holzel, Parker, Patterson, White, Thompson, and Tobin, 1963) that respiratory syncytial virus is the predominant cause of bronchiolitis in infancy. Previous studies in Northern Ireland in 1962 and 1963 have also shown this association (Connolly, Forsyth, Haire, Evans, and White, 1963).

There is not as yet general agreement on the therapy of bronchiolitis in infancy. Wide-range antibiotics are advocated by Holt, McIntosh, and Barnett (1962) and by Jolly (1964), though Shirkey (1964) does not consider them to be of value. In view of this difference of opinion and of their almost universal use in domiciliary practice it was decided to plan a trial in order to test the efficacy of one of the antibiotics. As tetracycline had been shown to cause abnormalities in the teeth of infants (Wallman and Hilton, 1962), ampicillin, which has been proved to be effective in certain respiratory disorders in children (Elliot, Stokes, and Maxwell, 1964), was chosen.

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Patients, Materials, and Methods

An epidemic of bronchiolitis occurred in Belfast in November 1964. The criteria of selection for the trial were coryza, paroxysmal cough, expiratory wheeze, and increased respiratory rate. All patients except three had fine crepitations at the lung bases and were sufficiently distressed to be using the accessory muscles of respiration. The progress of each case was reported daily on a special chart which listed pulse rate, temperature, respiratory rate, the use of accessory muscles of respiration, expiratory wheeze, adventitious sounds in the chest, and the presence of cyanosis.

The treatment consisted of ampicillin or placebo 125 mg. six-hourly, all children received ephedrine ¼ gr. (16 mg.) thrice daily, and most of them were nursed for a day or two in an oxygen tent with aerosol water vapour. One or other treatment was allocated to the children according to a randomized code. It was decided that patients who became dangerously ill owing to steady deterioration of their condition should be given an antibiotic and removed from the trial. This was a difficult

decision, and was based on a summation of all the signs and symptoms.

The patients were separated into three degrees of illness—mild, moderate, and severe. The mild cases had no moist sounds in the lungs and only a minor degree of cough and wheeze; moderate cases had fairly severe respiratory distress, though cyanosis was either absent or rapidly relieved; the severe cases were very distressed and cyanosis persisted for some time.

Bacteriology.—Throat swabs were taken from 35 of 44 patients on admission to hospital.

Virology.—Throat swabs were obtained from 13 babies. One swab was immediately transferred to a tube of second-passage monkey-kidney-cell culture in Earle's lactalbumin medium without serum and another swab to a tube of HEp2 cell culture in Eagle's medium containing 1% foetal calf serum. The tubes were examined daily for cytopathogenic effects and haemadsorption tests were carried out on the monkey-kidney tubes on the fourth and eighth days after inoculation. Monkey-kidney-cell cultures were observed for 10 days and HEp2 cultures for 20 days. Acute and convalescent sera were obtained from 18 babies, the interval between the two sera varying from 9 to 20 days. The sera were stored at −20° C. until used. Complement-fixation tests were performed on doubling dilutions of the patients' sera, with overnight fixation at 4° C. Four units of respiratory syncytial virus, influenza virus A, B, and C, parinfluenza virus 1 and 3, adenovirus or *Mycoplasma pneumoniae* antigens, and 2½ MHD_{50} of complement were used.

Results

Of the 52 infants with acute bronchiolitis admitted to the trial between 30 October and 30 November 1964 (Table I), five whose conditions had deteriorated and who became gravely ill were removed from the trial and treated with intramuscular penicillin and streptomycin. In none of these was there a dramatic response to this change in therapy, though all infants recovered. Two patients who developed diarrhoea with pyrexia and one patient with otitis media were also removed from the trial. There were no deaths and no apparent side-effects from the ampicillin.

TABLE I

	Ampicillin Group	Placebo Group	Total
Number of patients	28	24	52
Patients removed from trial owing to:			
Severity of symptoms and signs	3	2	5
Diarrhoea and pyrexia	0	2	2
Otitis media	0	1	1
Patients remaining in trial	25	19	44

TABLE II.—*Age Distribution*

Age	Ampicillin Group	Placebo Group	Total
Under 3 months	12	5	17
3 months to under 6 months	5	10	15
6 months and over	8	4	12
Total	25	19	44

$\chi^2 = 5{\cdot}15$. D.F. = 2. $0{\cdot}1 > P > 0{\cdot}05$.

TABLE III.—*Severity of Illness*

Illness	Ampicillin Group	Placebo Group	Total
Mild*	2	0	2
Moderate*	19	17	36
Severe	4	2	6
Total	25	19	44

* These frequencies were combined in both groups; an exact probability test applied to the resultant 2 × 2 table indicated a value of P (double tail) = 68·43%. Severity distributions are not significantly different at P = 5%.

Of the 44 patients remaining on trial the age distribution is shown in Table II and the severity of illness in Table III. The placebo and ampicillin groups were compared for age and severity, and tests of significance were carried out.

There is no significant difference between ampicillin and placebo groups either in age or in severity of symptoms. Though the age distributions show relatively large differences these are not statistically significant.

Bacteriology.—The organisms isolated from the throat swabs are shown in Table IV. No organisms were isolated from 37% of the patients and no single organism predominated in the others. The finding of a potentially pathogenic organism in the throat swab did not affect the severity of the illness.

TABLE IV.—*Organisms Isolated from Throat Swabs*

	Ampicillin Group	Placebo Group	Total
No growth	7	6	13
Escherichia coli	6	2	8
Staphylococcus aureus	2	3	5
Staphylococcus albus	1	3	4
Streptococcus pneumoniae	1	2	3
Haemolytic streptococci	1	3	4
Candida albicans	3	0	3

Virology.—Virus was not isolated from any of the throat swabs in either tissue-culture system. These included swabs from six babies who had serological evidence of infection with respiratory syncytial virus. The paired sera from 10 babies out of 18 showed a fourfold or greater rising titre to respiratory syncytial virus antigen. There was no antibody rise to influenza A, B, or C, parainfluenza 1 and 3, adenoviruses, or *M. pneumoniae* in any of the children. Six out of the eight babies who showed no serological response to respiratory syncytial virus were aged 12 weeks or less.

Response to Treatment.—The duration of the illness was determined from the date of admission until the symptoms and signs disappeared (Table V), and the total duration of the illness was calculated from the history of when the symptoms started until they disappeared (Table VI). It will be seen that there was no significant difference in the duration of symptoms in the two groups.

TABLE V

	Ampicillin Group	Placebo Group	Total
Number of patients	25	19	44
Average duration of symptoms and signs in hospital	6·36 days	6·05 days	

Difference in means = 0·31 days. Standard error of difference = 0·57. t = 0·54. D.F. = 42. $0{\cdot}6 > P > 0{\cdot}5$.

TABLE VI

	Ampicillin Group	Placebo Group	Total
Number of patients	24	18	42
Average total duration of symptoms and signs	9·54 days	9·7 days	

No tests of significance were carried out on these figures, as it was felt that the history from the parents might not be entirely reliable. In one case in each group the day of onset of symptoms could not be ascertained.

Discussion

It is difficult to be sure that the infants in whom we were unable to demonstrate respiratory syncytial virus, either on culture or serologically, were indeed infected with that virus. However, it should be noted that the laboratory diagnosis of respiratory syncytial virus infection has several difficulties. The virus isolation rate is low and there is no serological response to infection in about half the cases (Ross, Stott, McMichael, and Crowther, 1964). It has been shown (Gardner, Elderkin, and Wall, 1964) that the immunological responsiveness

increases with the age of the child, and that it is poor under 4 months of age (Chanock *et al.*, 1961). As already noted, six out of eight children in this trial who had no serological response to respiratory syncytial virus antigen were 12 weeks old or less. Other viruses have also been implicated in respiratory disorders of infants (Clarke, Corner, Gambier, Macrae, and Peacock, 1964 ; Gardner *et al.*, 1964 ; Holzel *et al.*, 1965), but the fact that 10 out of 18 cases showed a fourfold rise in titre to respiratory syncytial virus, and that all cases had very similar symptoms and occurred in an epidemic, would strongly suggest that most cases were due to infection with respiratory syncytial virus.

It is evident that ampicillin did not influence recovery of children with bronchiolitis in this trial. Patients with this disorder are often treated with antibiotics in the belief that these will at least prevent secondary infection (Heycock and Noble, 1962). The only evidence for this in the present series was in one case of otitis media. The duration of symptoms and signs was very similar to that found in previous cases treated by us with other wide-spectrum antibiotics, suggesting that had they been used in the trial instead of ampicillin the results would have been the same.

It is rare in domiciliary practice and uncommon in hospital to find infants with bronchiolitis who are not being treated with antibiotics. The results of this trial would suggest that their use does not hasten recovery. Apart from the question of cost the use of unnecessary antibiotics may not only cause iatrogenic illness but may increase the number of drug-resistant organisms. It is suggested that, in epidemic bronchiolitis of infants, antibiotics are used more to treat the physician's peace of mind than the patient's disease.

Summary

A double-blind study of the effect of ampicillin in an outbreak of bronchiolitis was carried out on 52 patients. Eight were removed from the trial because of complications. In the 25 treated with ampicillin and the 19 given a placebo there was no significant difference in the duration of symptoms and signs. Respiratory syncytial virus was shown to be the cause of infection in 10 out of 18 patients investigated. There were no deaths in the trial.

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Catatonic Stupor in Elderly Woman with Hyperparathyroidism

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The patient whose case is reported below presented in a manner not previously described in hyperparathyroidism nor, indeed, in hypercalcaemia. One of the oldest patients from whom a parathyroid adenoma has been removed during life, she presented an interesting differential diagnosis between hyperparathyroidism and hypercalcaemia from immobility in Paget's disease.

Case History

A widow aged 75 was admitted to hospital under the care of Sir George Pickering because one morning she had been found in bed, apparently unconscious. Many notes were scattered about the room, and most were attempts at making a will. There was no evidence that she had taken any tablets or had suffered a recent injury. Her daughter, who lived near, said that her mother had been behaving strangely for some four weeks before admission. The most florid example was when she wrote some cheques for large sums of money that she did not possess. Her letters and conversation were sometimes confused. Three months before admission she had fallen, with loss of consciousness for a few moments, but quickly recovered except for some unsteadiness in walking. A week before admission the daughter went away on holiday, and received three curiously phrased letters from her mother.

About eight years ago she had complained for a few weeks of leg and back pain and of difficulty in walking. These symptoms did not recur until a few months before the present admission. She then attended an orthopaedic hospital, where osteoarthritis of both hips and Paget's disease of the pelvis were diagnosed, and she was provided with two sticks and a surgical belt.

Her weight had been steady in recent years. She had been constipated for at least eight years, and this had recently become an increasing problem. For about two years she had felt unduly thirsty, but her daughter had not noticed that she drank excessively. There had been no notable change in skin, hair, or nails. She had no personal or family history of mental illness. Since leaving her

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