

and Stores, 1970; Jensen and Olesen, 1970; Ralston, Snaith, and Hirley, 1970). It is unlikely that the differences between these results and those of Reynolds (1967) and Neubauer (1970) can be explained by shorter exposure to folic acid; Neubauer (1970) noticed mental improvement in younger children from 5 to 8 weeks after starting folic acid and the adults reported by Grant and Stores (1970) received folic acid for 6 months with no effect. We have now shown that normal levels of folate are achieved very rapidly in both the red cells and serum when folic acid is given to folate-deficient patients on anticonvulsants; these results taken together with the lack of behavioural response in the controlled trials suggests that, in this context, folic acid has little direct effect on mental function. The possibility remains that the very slow deterioration in mental performance noted in some epileptics might be related to chronic folic acid deficiency.

We also confirmed the results of the controlled trials in adults (Grant and Stores, 1970; Jensen and Olesen, 1970; Ralston *et al.*, 1970) in not showing an increase in fits due to folic acid. Folic acid has undoubtedly provoked fits in some individuals (Chanarin *et al.*, 1960; Reynolds, 1967), but this response seems unusual.

Summary

Significantly lower serum folate levels were found in 39 children taking anticonvulsant drugs than in 25 controls ($P = 0.01$). Because of reports of improved mental function after folic acid replacement in folate-deficient epileptics, 19 children entered a trial of folic acid versus placebo. There was no significant difference in simple reaction times, in numbers of hours slept, or in fit frequency. The increase in fits due to folic acid which has been reported seems to be an uncommon response to the vitamin.

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Trimethoprim/Sulphamethoxazole in Pertussis: Comparison with Tetracycline

Antibiotics, if given early in the disease, are moderately effective in reducing the frequency and severity of cough in pertussis (MRC Report, 1953). Tetracycline, chloramphenicol, and erythromycin have all been recommended (MRC Report, 1953; Christie, 1969; Bass *et al.*, 1969).

Trimethoprim/sulphamethoxazole is a bactericidal combination active *in vitro* against *Bordetella pertussis* (Bushby, 1969), and it was considered that it might prove a suitable alternative agent in the treatment of pertussis. It was therefore decided to undertake a direct comparison between this agent and tetracycline, during a recent outbreak of the disease in Nigeria.

Materials and Methods

Patients were included in the trial if *Bord. pertussis* was isolated from the naso-pharynx, or if they had a typical 'whooping' cough, and a relative and absolute lymphocytosis. No account was taken of previous vaccination history. Patients accepted into the trial were randomly allocated to one of two treatment groups.

(a) *Tetracycline group*. Children under 2 years old were given 62.5 mg tetracycline 6-hourly, and older children 125 mg 6-hourly, for one week.

(b) *Trimethoprim/sulphamethoxazole group*. Children under 6 months old were given 20 mg trimethoprim with 100 mg sulphamethoxazole twice daily

for one week; older children received double this dose.

All children received phenobarbitone 15 mg t.d.s. until vomiting and spasmodic cough had ceased, and were also given a simple linctus for use as required. They were treated at home by their mothers who were asked to bring the children back after one week for assessment by the same doctor who saw the children at first attendance. This assessment was based on a full clinical examination, together with a detailed history from the mother concerning cough, sleep patterns, vomiting, feeding, and general behaviour of the child. The doctor examining the children was not informed as to the treatment group.

Nasal swabs were taken on first and second attendances and plated directly on to charcoal-blood agar plates containing suitable antibiotics for suppression of contaminants. Cultures were examined after 48 hours incubation in a humidified, CO₂-enriched atmosphere. Suspicious colonies were tested for agglutination with polyvalent and monovalent antisera to Andersen factors 1, 2, and 3 (Preston, 1965). Sensitivity tests were carried out by the disc diffusion method against tetracycline (25 µg per disc) and trimethoprim/sulphamethoxazole (2.5 µg and 50 µg, respectively, per disc).

Results

Patients studied. The total number of children satisfying criteria for inclusion in the trial was 88, with equal numbers in each treatment group. Ages varied widely, but 90% were less than 5 years old. Details of the age-sex distribution are given in Table I. Only 12 children had been immunized, 3 in the tetracycline group and 8 in the trimethoprim/sulphamethoxazole group; in addition, one child in the tetracycline group had been partially immunized.

TABLE I

Total Number of Patients, Age, and Sex Distribution

Age groups	Tetracycline Group		Trimethoprim/Sulphamethoxazole Group		Total All Ages
	0-4 years	5-10 years	0-4 years	5-10 years	
Males	22	2	15	1	40
Females	19	1	24	4	48
Totals	41	3	39	5	88

Bacteriology. *Bord. pertussis* was isolated from 62 patients at the first visit; the other 26 patients were included in the study as they had a typical clinical history, typical cough, and a relative and absolute lymphocytosis. Of the 62 isolates, 50 (80.6%) possessed factors 1, 2, and 3; 10 (16.1%) had factors 1 and 2 only, while 2 (3.2%) had factors 1 and 3 only. All 12 previously immunized

TABLE II
Progress After One Week: All Cases

	No. of Patients			
	Trimethoprim/Sulphamethoxazole Group	Tetracycline Group	Total	%
Better	17	16	33	50.0
Same condition	13	14	27	40.1
Worse	2	4	6	9.9
Total	32	34	66	100

TABLE III
Progress After One Week: Patients with Cough for Less than 7 Days

	Trimethoprim/Sulphamethoxazole Group		Tetracycline Group	
	No.	%	No.	%
Better	15	58	8	38
Same condition	9	35	10	48
Worse	2	8	3	14
Total number of patients	26		21	

children were infected with strains possessing all three factors. All strains of *Bord. pertussis* were sensitive to both chemotherapeutic agents. No strains were isolated at second attendance of patients.

Duration of symptoms. Of the 88 patients in the study, 56 had a cough for less than 7 days: 34 of these were in the trimethoprim/sulphamethoxazole group and 21 in the tetracycline group. In the former group the mean duration of cough before attendance was 5.6 days (SD 2.7) and in the latter group it was 6.8 days (SD 3.8). This difference is not significant ($P > 0.05$). Patients from whom *Bord. pertussis* was isolated were seen slightly earlier than those with negative cultures, the mean duration of cough being 5.8 days (SD 3.0) and 6.9 days (SD 3.9), respectively. Again, this difference does not reach a level of statistical significance ($P > 0.05$).

Effect of treatment. Out of the 88 patients, only 66 returned for follow-up: of these, 33 were judged to have improved, 27 remained the same, and 6 had deteriorated. Details are given in Table II and it can be seen that there is little difference between the 2 groups.

When, however, only those patients with a history of cough for less than 7 days were considered (Table III), it was found that those in the trimethoprim/sulphamethoxazole group appeared to do slightly better than those in the tetracycline group. With the small numbers in each group, the differences do not reach a level of statistical significance ($P > 0.05$). The mean duration of cough before treatment did not differ significantly between these 2 groups, nor was there any difference in results between patients with or without a positive isolation of *Bord. pertussis*.

Discussion

The present trial was a direct comparison between tetracycline and trimethoprim/sulphamethoxazole. We were not concerned with the value of chemotherapeutic treatment *per se*, and thus no untreated control group was included.

It is known that chemotherapy is only effective in the early stages of pertussis. One major difficulty in the treatment of the disease is that by the time the child presents for treatment—seldom if ever before the cough has developed—the pathology of the illness is already well advanced. Nevertheless, tetracycline is known to be of some benefit (MRC Report, 1953), and our results indicate that there may be a slight advantage of trimethoprim/sulpha-

methoxazole over tetracycline, but only in children with a history of less than 7 days' cough.

Summary

A trial of trimethoprim/sulphamethoxazole against tetracycline as a treatment for pertussis was made in 88 Nigerian children. Results were slightly in favour of trimethoprim/sulphamethoxazole when treatment was instituted within 7 days of the onset of cough, but not significantly so.

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