Conclusions

While there are still many difficulties in the diagnosis of acute appendicitis a considerable proportion of the children dying in hospital were suffering from potentially remediable effects of the disease. It seems that a more widespread application of accepted lines of treatment might reduce the mortality rate further.

Though we were looking only at deaths from acute appendicitis it is likely that the conclusions we have drawn about fluid balance, anaesthesia, and the treatment of hyperpyrexia and convulsions will be applicable to children suffering from other diseases and from trauma. This type of national medical audit should be used more extensively, on the lines of the Confidential Enquiry into Maternal Deaths.

There is a need in the health service to expend effort and money on absorbing knowledge and techniques into universal practice, and to ensure that patients are admitted to hospitals which can provide the facilities and skills appropriate to their requirements.

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Single-blind Comparative Trial of Trimethoprim-sulphamethoxazole and Ampicillin in the Treatment of Exacerbations of Chronic Bronchitis

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Summary: Fifty patients with exacerbations of chronic bronchitis were treated with either a combination of trimethoprim 320 mg. and sulphamethoxazole 1,600 mg. a day or ampicillin 2 g. a day. The trial, carried out as a single-blind procedure, showed that the combination was more effective as judged by clinical response and reduction in sputum volume and purulence, with eradication of pathogenic organisms. No appreciable side-effects were encountered with either treatment, and it is suggested that the trimethoprim-sulphamethoxazole combination may be a safe and useful drug in the treatment of chronic bronchitis.

Introduction

Trimethoprim (2,4-diamino-5-(3,4,5-trimethoxybenzyl) pyrimidine) is a dihydrofolate reductase inhibitor (Roth, Falco, Hitchings, and Bushby, 1962). Since it selectively inhibits the bacterial rather than the mammalian enzyme it can be used as an antibacterial agent in man. Its activity is much enhanced if it is combined with a sulphonamide, and, indeed, in vitro the two can be shown to have a synergistic effect (Elion, Singer, and Hitchings, 1954; Bushby and Hitchings, 1968). Darrell, Garrod, and Waterworth (1968) showed that while the action of either drug is bacteriostatic, when they are used in combination this becomes bactericidal. Besides its activity against Gram-negative bacilli such as *Escherichia coli* and *Proteus* sp., the combination is also effective in vitro against such pathogens as *Haemophilus influenzae* and *Streptococcus pneumoniae* (Bushby and Barnett, 1967). It has therefore been used in the treatment of exacerbations of chronic bronchitis. Clinical trials with the combination have been reported in urinary infections (Reeves, Faiers, Pursell, and Brumfitt, 1969; Grüneberg and Kolbe, 1969), but only brief reports of its efficacy in chest disease have appeared (Drew, Hughes, Fowle, and Cassell, 1967a; Hughes, 1968; Hughes, Drew, Johnson, and Jarvis, 1969). Further, in some of these a different dosage regimen was used from that now currently employed.

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Methods

Fifty cases fulfilling the Medical Research Council criteria for chronic bronchitis (M.R.C., 1965) were selected. All of them had had symptoms for more than five years. There were 44 men and 6 women. They all had acute exacerbations of bronchitis leading to an increase in dyspnoea, cough, sputum volume, and purulence. The majority of them needed hospital admission, though 10 (five from each of two treatment groups) were treated as outpatients.

Comparison was made between the effect of a week's course of ampicillin 500 mg. four times a day and trimethoprim (TMP)-sulphamethoxazole (SMZ). This was administered as two Septrin tablets twice a day, each containing 80 mg. of TMP and 400 mg. of SMZ, so that the total daily dosage was 320 mg. of TMP and 1,600 mg. of SMZ. TMP/SMZ combinations are administered only twice daily because of their relatively long half-life in the body of 13 to 15 hours. Because of the difference in presentation (capsules as compared with tablets) and in the number of times of administration a completely double-blind trial was not feasible. It was therefore carried out as a single-blind trial. Sufficient tablets or capsules to make up a week's course of either treatment were put up in 50 numbered boxes with a slip inside instructing the patient how to take them. There were 25 one-week courses of each treatment, which were randomly allocated to the patients without the medical attendants knowing which the patient was receiving, and the code was not broken until the trial was completed or, in two instances, when the treatment had failed (see below).

The two treatment groups were comparable in that the mean length of the history of the 25 patients receiving ampicillin was 13·5 years and that of the group receiving the TMP/SMZ combination was 15·6 years. The rate of admission to hospital with exacerbations of bronchitis in the preceding three years was also comparable, the mean for the group receiving ampicillin being 1·04 and for the combination 1·2. They had all received various antibiotics during preceding winters. In this particular trial, however, ampicillin or TMP/SMZ was the primary treatment, with one exception. This was a 61-year-old man with severe purulent bronchitis who had spent most of the preceding winter in hospital. He was included in the trial as he had failed to respond to treatment with tetracycline and chloramphenicol, so that the *Pseudomonas pyocyanea* cultured from his sputum may not have been the primary pathogen.

Sputum Examination.—Specimens of sputum were examined fresh each day in order to assess the degree of purulence. They were graded on the M.R.C. (1965) scale, ranging from M1 (the most mucoid) to P3 (the most purulent). All sputum expectorated in the first two hours of each day was carefully collected in graduated cartons and its volume measured. The sputum was cultured on Oxoid diagnostic sensitivity medium with added 5% lysed horse blood, and the sensitivity of any organisms grown tested against standard discs of penicillin, ampicillin, streptomycin, tetracycline, and the combination (in this case containing 23·75 μg. of sulphamethoxazole and 1·25 μg. of trimethoprim per disc). In a few cases sensitivities to other antibiotics were also investigated. Cultures were taken before and after treatment.

Blood Counts.—All patients had haemoglobin estimations, white cell and differential counts, and platelet counts carried out before and after treatment.

Other Tests.—All patients had *x*-ray examinations, while many also had other investigations, such as electrocardiograms and pulmonary function tests.

Clinical Assessment.—A simple clinical assessment of the response to treatment was also made, taking into account changes in the patient's symptoms and signs.

Results

Sputum Volumes.—These were reduced by either treatment. The TMP/SMZ combination produced a significantly greater reduction in volume (Table I).

TABLE I.—*Changes in Sputum Volume*

	TMP/SMZ			Ampicillin		
	No.	Mean (ml.)	S.D. (ml.)	No.	Mean (ml.)	S.D. (ml.)
Before treatment ..	25	21·60	18·12	25	16·12	12·28
After treatment ..	25	12·20	13·20	25	13·04	11·26
After-before	25	−9·40 (1)	11·44	25	−3·08 (2)	8·55

(1) and (2) differ significantly (0·05 > P > 0·01).

Sputum Purulence.—This was more difficult to assess, particularly as in practice the difference between M.R.C. grades are not always easy to judge. A change from predominantly purulent (M.R.C. grades P1–3) to predominantly or wholly mucoid (M1–2) is more easy to be certain about, and this change was therefore sought. Treatment was judged to be successful if it converted sputum from grade P1–3 before treatment to grade M1–2 afterwards. This happened in 23 out of 24 cases treated with the combination but in only 16 out of 22 cases receiving ampicillin, as shown in Table II. The combination was significantly more effective in reducing sputum purulence.

TABLE II.—*Changes in Sputum Purulence. Paired Figures in the Two Columns Show the Proportion of Cases with Purulent Sputum (Grades P1–P3) Becoming Mucoid After Treatment*

Grade before Treatment	TMP/SMZ Combination	Ampicillin
P3	5/5	3/5
P2	13/14	6/10
P1	5/5	7/7
M2 (excluded) ..	1	3
Total success ..	23/24	16/22

These figures show that the success rate for the TMP/SMZ combination in rendering sputum mucoid is significantly higher than that for ampicillin. (P = 0·036 in a single tailed probability test.)

Eradication of Pathogens.—The organisms cultured before treatment are shown in Table III. The combination eradicated pathogens in 15 out of 16 patients, while ampicillin did so in only 9 out of 13 cases. Though these results favour the combination they are not statistically significant (see Table IV).

TABLE III.—*Organisms Cultured Before Therapy*

Organism	TMP/SMZ	Ampicillin
H. influenzae	8	7
Str. pneumoniae	4	5
E. coli	2	1
Ps. pyocyanea	2	0
Proteus sp.	1	1
K. pneumoniae	0	1
Staph. pyogenes ..	1	2
Total	18 (from 16* patients)	17 (from 13* patients)

* Owing to more than one organism being isolated from a single case.

TABLE IV.—*Success or Failure to Eradicate Pathogenic Organisms*

	TMP/SMZ	Ampicillin	Single-tailed Probability
Success	15	9	
Failure	1	4	
Total ..	16	13	0·107

Sputum Sensitivity Testing.—The organisms from three patients were resistant to the TMP/SMZ combination. Two of these were *H. influenzae* and one was *Ps. pyocyanea*. One patient growing *H. influenzae* received penicillin, to which he responded. The other growing this organism and the one with *Ps. pyocyanea* responded clinically to the combination, which eradicated the organisms from their sputum. Organisms from four patients were resistant to ampicillin (1 *Klebsiella pneumoniae*, 1 *Staphylococcus pyogenes*, and 2 *Ps. pyocyanea*). The one case with *Staph. pyogenes* nevertheless responded with eradication of the organism, as did one of the cases with *Ps. pyocyanea* treated initially with the TMP/SMZ combination, to which it was sensitive. The other case growing *Ps. pyocyanea* and the one with *K. pneumoniae* both failed to respond to ampicillin but subsequently responded to the combination. The *K. pneumoniae* was sensitive to the combination but the *Ps. pyocyanea* was not. These results are not altogether helpful and only confirm the discrepancy not infrequently

TABLE V.—*Changes in Blood Counts*

	TMP/SMZ			Ampicillin		
	No.	Mean	S.D.	No.	Mean	S.D.
Haemoglobin (%):						
Before treatment	25	95·72	11·44	25	100·88	11·29
After treatment	25	96·80	10·47	25	101·36	13·00
After-before ..	25	1·08 (1)	5·22	25	0·48 (2)	10·38
White blood cells/ cu.mm.:						
Before treatment	25	8,200	2,040	25	8,360	2,610
After treatment	25	7,020	2,090	25	7,520	2,160
After-before ..	25	−1,180 (1)	2,440	25	−840 (2)	2,780
Polymorphs/ cu.mm.:						
Before treatment	25	5,980	2,140	25	5,640	2,360
After treatment	25	4,740	1,760	25	4,840	2,120
After-before ..	25	−1,240 (1)	2,300	25	−780 (2)	2,290
Platelets/cu.mm.:						
Before treatment	22	252,640	94,060	23	297,870	112,520
After treatment	22	259,000	143,050	23	291,870	106,160
After-before ..	22	6,360 (1)	125,520	23	−6,000 (2)	40,390

(1) and (2) not significantly different in any of these instances (P > 0·5).

found between in-vitro testing and clinical response. They do, however, confirm the in-vitro and in-vivo sensitivity of *K. pneumoniae* to the combination.

Clinical Assessment.—Clinically 24 out of 25 cases receiving the combination responded well as compared with 19 of those receiving ampicillin. These figures compare well with those for changes in sputum purulence shown in Table II.

Side-effects.—There was no significant effect on the blood counts produced by either treatment, nor was there a significant difference in the effect produced by each (Table V). The only abnormal white cell count was one of 2,400 cu. mm., with 1,200 polymorphs, which occurred before treatment in one case. After treatment with ampicillin the counts rose to normal limits. Otherwise no white cell count of less than 4,000/cu. mm. was encountered, nor was there any significant thrombocytopenia. The only side-effect was nausea and diarrhoea in one case receiving the combination.

Discussion

These results show that a combination of trimethoprim and sulphamethoxazole is an effective treatment in exacerbations of chronic bronchitis. Indeed, the comparison made in this study suggests that it is more effective than ampicillin. The exact part antibiotics play in producing improvement in such exacerbations is difficult to define. Many trials with different antibiotics have been made to assess this (for a good review see Stuart-Harris, 1968). Though patients can undoubtedly recover without use of these, few clinicians would withhold antibiotics from acutely ill persons with purulent sputum. This view is reinforced by a recent study by Pines, Raafat, Plucinski, Greenfield, and Solari (1968). They found that in a pilot study so many patients with such exacerbations deteriorated while on a placebo that they felt ethically unable to include a placebo instead of an antibiotic in their main comparative trial. Further, it is difficult not to conclude that a drug is effective if in addition to clinical improvement it produces objective changes such as reduction of sputum volume, purulence, and pathogens.

The combination of trimethoprim and sulphamethoxazole is effective against *H. influenzae* and *Str. pneumoniae,* the two commonest pathogens isolated from the sputum during exacerbations of chronic bronchitis (Burns and May, 1967). In the present study these were again the commonest organisms found. A number of Gram-negative bacilli were also isolated from the sputum, however. This may reflect a change in the bacterial flora causing chest infections, especially in hospital, and it is such Gram-negative bacilli that may be more difficult to treat (Watt and Okubadejo, 1967 ; *Lancet,* 1969). There is also evidence that some of these organisms may play the part of pathogens in the chest. For example, Tillotson and Lerner (1967) described a number of cases of pneumonia caused by *E. coli,* while Burns (1968) demonstrated precipitating antibodies to *K. ozaenae* in the serum of bronchiectatic patients with purulent sputum from which this organism could be cultured. So this new combination may prove to be a valuable weapon against such infections.

Trimethoprim-sulphamethoxazole in the present dosage appeared effective in treating the exacerbations encountered. Because of the difficulties in using such a combined preparation the present dosage regimen is recommended by the manufacturers. Reeves *et al.* (1969) have pointed out that such a fixed ratio of 1:5 TMP/SMZ with these particular amounts of each compound per day may not be the ideal dosage for all urinary infections. There was some suggestion that a 1:2 ratio with 500 mg. of trimethoprim might be more effective. This also appeared to be the case in chronic bronchitis as shown by Hughes *et al.* (1969). Pines (1969) also found that a larger dose of the present combination (480 mg. of trimethoprim and 2,400 mg. of sulphamethoxazole) was more effective in treating severe cases of chronic bronchitis. Thus though the dosage of 320 mg. of trimethoprim and 1,600 mg. of sulphamethoxazole would seem effective for most cases of urinary and chest infections, larger doses of trimethoprim may occasionally be required.

The effect of an antibacterial substance in chronic bronchitis may depend on its concentration in the sputum. Indeed, May and Delves (1964) suggested this as a rationale for treating exacerbations of chronic bronchitis with 4 g. of ampicillin a day rather than 1 g. This dosage achieves a higher level of the drug in the sputum and more effective eradication of *H. influenzae.* Animal studies have shown that the concentration of trimethoprim in lung tissue may reach between 15 and 20 times that in serum (Bushby and Hitchings, 1968). In a recent clinical study Pechere and Beck (1969) found that after oral administration of the combination the level of trimethoprim in the sputum was always greater than that in the blood by a factor of about 2·5. The level of sulphamethoxazole in sputum, however, was always lower than that in serum by a factor of about 0·3. This means that in sputum the ratio of the drugs may be quite different from that in which it was administered by mouth—namely, TMP:SMZ=2·5:1·7. It therefore appears that trimethoprim may reach a higher concentration in the lung and bronchial secretion than sulphamethoxazole. Be that as it may, this combination, with its sequential blockade of folate metabolism, is undoubtedly an effective one and relatively small doses of the two constituents need be used.

The combination may also be useful in the long-term chemoprophylaxis of chronic bronchitis. In spite of a number of trials, including some quite extensive ones carried out by the Medical Research Council and the British Tuberculosis Association—for example, Pridie *et al.* (1960), Francis, May, and Spicer, 1964 ; M.R.C., 1966)—the value of long-term antibacterial therapy in chronic bronchitis is not unequivocally established. Many physicians feel that certain bronchitic subjects do benefit from such therapy, and tetracycline or ampicillin seems to be superior to a sulphonamide alone. In 10 patients with crippling bronchitis or bronchiectasis Drew, Hughes, and Jenkins (1967b) showed that administration of TMP/SMZ 1:2, with a daily dosage of 500 mg. of trimethoprim and 1,000 mg. of sulphamethoxazole over a three-month period in the winter was effective in reducing the number of bouts of infection, and, in fact, kept them out of hospital for the period of trial, whereas in preceding winters they had all needed prolonged admissions.

Though trimethoprim has a much greater affinity for the bacterial than for the mammalian dihydrofolate reductase enzyme by a factor of about 10,000, there is at least a theoretical risk that it could interfere with folate metabolism in man—especially so if it were administered for long periods. Drew *et al.* (1967b) found relatively trivial haematological changes in their patients, and Kahn, Fein, and Brodsky (1968) also found some changes in a study carried out largely on volunteers: these consisted of hypersegmentation of the polymorphonuclear leucocytes in several cases and reduced serum folate levels in a few. In the present study no haematological effects were encountered (see Table V) ; and indeed no significant reduction in haemoglobin, or in white cell, polymorph, and platelet counts has occurred to date in any of the 200 patients treated for one week with TMP/SMZ combinations at the London Hospital. This is in contrast to a report by McCarthy (1969) suggesting that neutropenia may occur after treatment with the combination for between 7 and 14 days.

The effectiveness of combinations of trimethoprim and sulphamethoxazole in treating exacerbations of chronic bronchitis with a low incidence of side-effects suggests that it may play a valuable part in the treatment of this condition—particularly, perhaps, in those patients who have already received other antibiotics on numerous occasions, or whose infections are caused by Gram-negative bacilli. This particular trial would also suggest that the TMP/SMZ combination is superior to ampicillin for that purpose.

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Medical Memoranda

Management of Pregnancy in a Woman with Hb H Disease

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Hb H disease is one of the α-thalassaemia syndromes. The α-thalassaemias are a heterogeneous group of conditions due to an inherited defect of the synthesis of the α-chains of Hb A ($\alpha_2\beta_2$) (Huehns, 1965; Weatherall, 1965). According to current concepts there are believed to be two α-thalassaemic genes involved in these syndromes, α^1 and α^2 (Weatherall, 1969).

The homozygous inheritance of two α^1-thalassaemia genes is believed to result in the complete suppression of α-chain synthesis. The fetus is unable to synthesize Hb F ($\alpha_2\gamma_2$) and only produces tetramers of γ-chains, Hb Bart's (γ_4). This results in the fetus being stillborn between 28 and 34 weeks with hydrops fetalis. The homozygous inheritance of the α^2-thalassaemia genes is as yet unrecognizable.

The heterozygous inheritance of both genes (α^1/α^2) is thought to result in Hb H disease. In this condition there is a moderate suppression of α-chain synthesis and the excess β-chain form tetramers of β_4 or Hb H. Hb H disease can be diagnosed in the laboratory by the following criteria: a blood film appearance suggestive of thalassaemia, decreased osmotic fragility of the red cells, the finding of inclusions typical of Hb H in the majority of red cells after incubation with new methylene blue at 37° C., and the presence of a fast-running haemoglobin (10–30% of the total) on zone electrophoresis at *p*H 8·6.

The heterozygous inheritance of either α-thalassaemia gene with the normal α-chain gene (α^1/α and α^2/α) results in a very mild clinical condition in adult life. Only the α^1-thalassaemia trait can be recognized, the α^2/α trait being undetectable by available techniques.

The various genotypes of α-thalassaemia are more easily recognized by examination of the cord blood at birth for Hb Bart's (Wasi, Na-Nakorn, and Suingdumrong, 1964). The amount of Hb Bart's present is indicative of the degree of α-chain suppression and the type of α-thalassaemia inherited—25% = α^1/α^2 (Hb H disease), 5–10% = α^1/α (α^1-thalassaemia trait), and 1–2% = α^2/α (α^2-thalassaemia trait).

We report the management of a pregnancy in a woman suffering from Hb H disease.

CASE REPORT

FAMILY STUDY

The patient was a 34-year-old Greek Cypriot. In 1958 she was investigated at Hammersmith Hospital for a chronic haemolytic anaemia, which proved to be Hb H disease. She returned to Hammersmith Hospital in 1968 for management of her pregnancy, and the following haematological investigations were carried out to confirm the diagnosis. Incubation of the red cells with new methylene blue showed that 85% of them contained inclusions of typical Hb H, and on starch-gel electrophoresis at *p*H 8·6 25% of the haemoglobin was fast-running. The globin of the fast-running haemoglobin was prepared by acid acetone precipitation after separation and elution of the haemoglobin by starch-block electrophoresis. The peptide chains of the globin were examined by CMC chromatography in 8M urea/mercaptoethanol buffers (Clegg, Naughton, and Weatherall, 1966), and it was found to consist entirely of β^A-chains. Thus the Hb H disease was confirmed.

Her husband and her father were investigated at the same time to determine whether they were affected by one of the α-thalassaemia syndromes. Neither her father nor her husband was anaemic, but both had slightly hypochromic blood films, a decrease in the osmotic fragility of their red cells, an occasional Hb-H-containing red cell, and trace amounts of Hb H, detectable by starch-gel electrophoresis at *p*H 7. These findings suggest that both her father and her husband had α^1-thalassaemia trait (α^1/α). The patient's mother was not available for study, but she was believed to be normal haematologically. Nevertheless, because the patient had inherited both α^1- and α^2-thalassaemia genes, the mother must carry the α^2-thalassaemia gene.