

THE LANCET

No. 7733

BOSTON, MASS. AND LONDON · SATURDAY 13 NOVEMBER 1971

VOL. II FOR 1971

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Editorial Office: 7 Adam Street, London WC2N 6AD, England. North American Edition published by and Company, 34 Beacon St., Boston, Mass. 02106. In U.S. and Canada, annual subscription \$18.50; \$11.50; single copy \$2.00. Second class postage paid at Boston, Mass., and at additional mailing offices 13 November 1971. Notification on Form 3579 is to be mailed to The Lancet, 34 Beacon Street,

Dr. Reddy's Laboratories, Ltd., et al.
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Editorial Office: 7 Adam Street, London WC2N 6AD, England. North American Edition published weekly by Little, Brown and Company, 34 Beacon St., Boston, Mass. 02106. In U.S. and Canada, annual subscription \$18.50; resident and intern rate \$11.50; single copy \$2.00. Second class postage paid at Boston, Mass., and at additional mailing offices. © The Lancet Ltd., 13 November 1971. Notification on Form 3579 is to be mailed to The Lancet, 34 Beacon Street, Boston, Mass. 02106.

We are now investigating these metabolic processes. They are partly the reason why a child is precipitated into a clinical episode of kwashiorkor. These factors and also the role of the immune response will be enlarged upon in future communications.

Few other studies have been made on the effects of infection on serum-albumin, except where these infections have led to specific loss of protein through the gut or kidney. There was no gross proteinuria in the children in this series, although a trace was sometimes observed during pyrexial episodes, as might be expected. Loss of albumin through the gut could not be investigated, but this possibility is now being pursued as a separate project, although it is anticipated this will be of only minor significance except perhaps during measles, gastroenteritis, or when there is severe worm infestation. Albumin concentration does fall significantly after surgery,⁸ but the cause is not known. Of particular relevance to the β -lipoprotein results are the investigations of Platt,^{9,10} who showed that infection could lead to a fatty liver in laboratory animals even when the protein content of the diet was apparently adequate.

It is becoming more obvious that the pathogenesis of kwashiorkor is complex and is a product of the child's whole environment. It is just as important to combat disease as it is to improve diet, and any public-health scheme aimed at eradicating malnutrition should give equal consideration to both these crucial aspects of the problem.

We thank the medical and nursing staff of this unit who run the outpatient clinics, and Mr. J. B. Kiwanuka, who analysed the blood specimens.

Requests for reprints should be addressed to R. G. W.

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"...I will not labour my own conviction that the normal state of most people is to feel faintly tired, harassed, and under the weather—and that my clinical observations lead me to believe that an abounding sensation of positive health usually presages either a cardiac infarction or incipient hypomania. The fact remains that the concept of positive health is as popular with some apostles of preventive medicine as with lay journalists. It postulates a state that could apparently be achieved by the careful observation of a set of rules that vary with the writer, but which are always inconvenient and uncomfortable and usually eccentric. I question the whole concept of positive health and the validity of the prescriptions claimed to ensure it."—HENRY MILLER, M.D., in *Medical History and Medical Care* (edited by GORDON McLACHLAN and THOMAS McKEOWN); p. 224. London, 1971.

COMPARATIVE EFFECTIVENESS OF TETRACYCLINE AND AMPICILLIN IN ROSACEA

A Controlled Trial

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Summary 56 patients with papular rosacea were treated with tetracycline, ampicillin, or placebo in a randomised double-blind clinical trial. Patients were evaluated by counting the number of papules in predetermined sites on the forehead and left cheek at fortnightly intervals over a six-week period. The results showed that both tetracycline and ampicillin produced a significant decrease, at the 5% level, in the number of papules, compared to the placebo treatment. When the results were assessed by a scoring system, tetracycline and ampicillin proved significantly better than placebo ($p=0.05$); tetracycline was better than ampicillin, but the difference did not quite reach the 5% significance level.

Introduction

THE tetracycline group of antibiotics has been used in the treatment of acne vulgaris since shortly after their introduction in the early 1950s. In controlled clinical trials some groups have found that the tetracyclines improve acne,^{1,2} whereas another has found that these antibiotics were of little help.³ The present consensus is that tetracyclines improve acne slowly, incompletely, and irregularly.

In contrast to many reports on the use of antibiotics in acne, there have been few similar reports on rosacea and even fewer which describe a controlled clinical trial.

In this study we have compared the effectiveness of tetracycline and ampicillin in the treatment of rosacea in order to determine (1) whether, with objective assessment, there is significant improvement, and (2) whether the action of the tetracyclines is unique or is shared by other antibacterial agents.

Patients and Methods

Patients were admitted to the trial if they had typical rosacea characterised by the presence of persistent erythema of the cheeks and nose, chin, and forehead and papules (and/or pustules) on these areas. Patients without easily definable papules were not included. In addition, patients who had received treatment with antibiotics in the previous six weeks were not included. Patients who satisfied these criteria were randomly allocated to one of three coded treatment groups by the hospital dispensary. The placebo, tetracycline, and ampicillin were supplied in identical capsules, and neither patients nor investigators knew the identity of the group to which each participant belonged. The instructions given to each patient were to take one tablet three times a day for the first week, and then to reduce the dose to one twice daily for the subsequent five weeks. No other treatment was permitted apart from the use of an aqueous cream as an emollient.

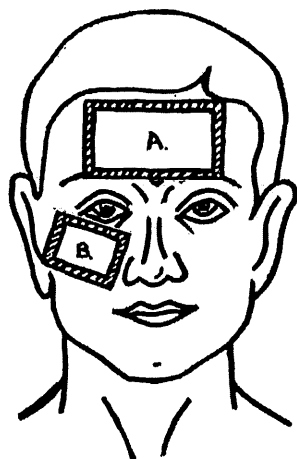
Patients were seen and assessed at fortnightly intervals, whenever possible, for six weeks. At each visit the number

* Present address: Slade Hospital, Oxford.

TABLE I—NUMBER OF PAPULES RECORDED AT EACH ATTENDANCE IN EACH PATIENT

Tetracycline									Ampicillin									Placebo								
Patient no.	Week								Patient no.	Week								Patient no.	Week							
	0	1	2	3	4	5	6	7		0	1	2	3	4	5	6	7		0	1	2	3	4	5	6	7
1	9		9		8		4		3	24		9				6	6	8	5		2				5	
2	10		6		6		9		4	10		7		4			4	9	12		17		4	12	16	
7	54		10		1		0		6	16		9		10		10		13	22						9	
10	17	8		5		0			11	12		14		7		11		15	17		12		11			
18	12		12		4		4		23	21		9	4			6		16	24				18		13	
20	11	5		3		4			26	6		13		6	6			21	7		6		10		9	
22	28		21		2		0		28	9		8		8		7		24	4		1		0		0	
27	14		16		13		5		29	8		2				3		25	28		10		14		10	
32	7	6			8		8		31	9	3			1		5		30	8				13		22	
33	14			5		0	0		41	84		73		19	18	7		35	20			10		11		
36	48				31		17		42	16	17			4		1		38	9		8		15		14	
37	25		22		25		7		44	28		23		16	15			43	7		18		15		28	
39	24		23		19		23		50	6				2		0		45	60				35			
40	32		17		14				52	20		35		15		36		47	11		8		1		0	
46	7			5		1	1		53	17		17		11		6		51	23		38		30		23	
48	25		11		1		0		57	13		11		10		8		54	24		75		20		28	
49	15		10		0		0		62	59		37		21				55	34		34		41		31	
59	16		12		9		2											56	17		21		23		18	
60	28		37		15		8											64	19		18		15		13	
61	25		1		1		0																			

of papules and pustules in predetermined areas on the forehead and right cheek were counted (see accompanying figure). In order to use the identical area, in each patient at each visit two flexible frames were used. The internal measurements for the forehead frame were 8×4 cm., and those for the right cheek frame were 4×5 cm. When counting lesions on the forehead the centre of the frame was made to coincide with the midline of the nose and its lower margin was placed on the supraorbital ridges. When using the frame for the cheek the upper and outer angle of the rectangle was placed on the lateral orbital tubercle so that one of the longer 5 cm. edges touched the lower border of the orbit. Lesions touching the lower and left margins of the frames were not counted. All palpable lesions were counted. To check that this method of assessment was reliable, repeated lesion-counts were made on the same patients by both observers at the beginning of the investigation. The values obtained were almost always identical, occasionally differing by one or, when many papules were present, two lesions. At each visit the patient's assessment of his progress and the observer's subjective assessment of the amount of erythema present were also recorded. In addition, patients were asked at each attendance whether the prescribed treatment had agreed with them, and any symptoms present were recorded.



Tested areas on forehead and right cheek.

56 patients completed the trial—20 in the tetracycline group, 17 in the ampicillin group, and 19 in the placebo group. The mean age of the 56 patients was 47.8 years (range 20–69) and there were 27 men and 29 women.

Results

Table I gives the number of papules and pustules for each patient at each attendance in the three treatment groups. Table II shows the mean numbers of papules and pustules before and at the end of the treatment period.

TABLE II—MEAN NUMBER OF LESIONS \pm STANDARD DEVIATION IN EACH TREATMENT GROUP

	Tetracycline	Ampicillin	Placebo
Pre-treatment	21.05 \pm 12.79	21.06 \pm 20.48	18.47 \pm 13.14
Post-treatment	4.60 \pm 6.20	9.53 \pm 8.79	16.63 \pm 12.81

These means were subjected to analysis of variance, which indicated significant differences between some of the means. Duncan's multiple-range test showed that:

- (1) The pre-treatment means were not significantly different from each other or from the post-treatment mean of the placebo group.
- (2) The post-treatment mean for the ampicillin group did not differ from the post-treatment means for the tetracycline and placebo groups, but was significantly lower than the pre-treatment means.
- (3) The post-treatment mean for the tetracycline group was significantly lower than all the other means except the ampicillin post-treatment mean.

The overall significance level is 5%.

The results were also analysed by giving a score to the change in the number of lesions between the first and last attendance in each patient, thus: a decrease in lesions by 75% or more (+3); a decrease by 50–75% (+2); a decrease by 30–50% (+1); a change in the number of lesions $\pm 30\%$ (0); an increase in lesions by more than 30% (–1). The scores that result from this analysis are shown in table III. The mean scores

TABLE III—NUMBERS OF PATIENTS WITH SCORES FROM +3 TO -1 IN EACH OF THREE TREATMENT GROUPS

Score	Tetracycline	Ampicillin	Placebo	Totals
+3	9	3	2	15
+2	8	6	2	16
+1	0	4	4	8
0	3	3	5	11
-1	0	1	6	7
Totals	20	17	19	57

TABLE IV—RESULTS OF PATIENTS' OWN ASSESSMENTS

Category	Tetracycline	Ampicillin	Placebo
Much better	5	8	6
Better	9	6	3
Same	4	2	7
Worse	2	1	3

for each group are as follows: tetracycline 2.15, ampicillin 1.41, placebo 0.42. The tetracycline and ampicillin scores differ significantly from placebo score at the 5% level. The difference between tetracycline and ampicillin does not quite reach the 5% significance level but is probably real.

Erythema

There did not seem to be any significant change in the extent or depth of erythema present during the trial.

Patients' Subjective Assessment

When patients were asked whether they considered themselves much better, better, the same, or worse, both tetracycline and ampicillin appeared to score better than placebo. Ampicillin seemed marginally better than tetracycline (table iv).

Side-effects

No serious side-effects were encountered in this study. 2 patients developed troublesome diarrhoea after the first few days' treatment and were withdrawn from the trial; these were found to belong to the ampicillin group. 1 patient in the tetracycline group experienced diarrhoea on 750 mg. daily but not on 500 mg. daily; and 1 other in the ampicillin group complained of "persistent slight looseness of the bowel" not necessitating withdrawal from the trial. Interestingly, 1 patient (who was later found to be in the placebo group) developed a transient maculopapular erythema and was withdrawn from the trial. Other mild transient complaints included "a funny taste in the mouth", "nausea", "constipation", and "secretions drying up".

Discussion

Rosacea is a common and troublesome disease characterised by persistent erythema and crops of papules and pustules. Its cause is unknown, and various hypotheses on its aetiology have been found unacceptable when their assumptions have been put to the test.⁴⁻⁶ In particular, cultures from biopsy material and pustules have not revealed pathogenic bacteria, and histologically there is no evidence that the disease is caused by microorganisms.⁷ None the less the tetracycline group of antibiotics has been used

by dermatologists because of their successful use in acne and because in rosacea they were found empirically to be effective.

The lack of evidence for a bacterial cause raised the question of how the tetracyclines work in this condition. It was decided to determine whether an antibacterial action is involved, by comparing the clinical effectiveness of tetracycline with an antibacterial agent that worked in a different way to the tetracyclines—i.e., ampicillin. Our finding that both ampicillin and tetracycline are statistically better than placebo in the treatment of papular rosacea is presumptive evidence for the involvement of bacteria in the pathogenesis of the disease.

In acne it is believed that *Corynebacterium acnes*, a member of the normal skin flora, is responsible for hydrolysis of the triglycerides of sebum, with the liberation of irritant and comedogenic fatty acids.⁸ The tetracyclines have been shown to reduce the fatty-acid content of sebum, and this may explain their action in acne.⁹ It is difficult to accept that antibiotics act in a like manner in rosacea. In rosacea the inflammatory response is characterised by oedema and a loose admixture of lymphocytes and large histiocytes which is not markedly centred around the follicles, while in acne there is an acute folliculitis. Comedones are not usual in rosacea, and, in addition, rosacea is not common around puberty when sebum is secreted at a high rate. None the less, it appears likely that bacteria play some as-yet undefined role in the disease, and that antibiotics are effective clinically by virtue of their action on these microorganisms.

It has been shown that tetracyclines are deposited preferentially in the skin,^{10,11} and this may explain the better result that we obtained with tetracycline than with ampicillin.

In this trial we tested the effect of antibiotics on the papules of rosacea because these lesions can be readily counted. Furthermore, it had previously been observed that they are more readily affected than the erythematous component of the disease. In the short time that we observed our patients there did not seem to be any pronounced or consistent change in the depth or extent of erythema in any of the treatment groups. The persistence of the erythema may explain the less dramatic results obtained when the patients' own subjective assessments were compared.

There are few published reports of formal clinical trials involving the use of the tetracyclines in rosacea. Sneddon¹² reported that in a controlled clinical trial tetracycline was effective in 87% of 78 patients. Wereide¹³ also noted "excellent or good" results in 82% of 74 patients treated with methyl-L-lysine tetracycline. Both these workers noted that small doses of tetracycline sufficed to suppress the appearance of papules. The present trial seems to have been the first in which objective criteria have been adopted to show that the tetracyclines are effective in the treatment of rosacea.

We are grateful to Pfizer Ltd. for supplying the tetracycline, ampicillin, and placebo packed in identical capsules; and to Miss C. Pullin, of the Wellcome Research Laboratories, for statistical analysis of the results. R. M. is in receipt of a grant from the Medical Research Council.

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BRAIN TRAUMA AND THE POSTCONCUSSIONAL SYNDROME

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Summary In a retrospective case-note study of 474 patients with head injury admitted consecutively to a specialised unit, the hypothesis was tested that the outcome would depend on the severity of the initial trauma. The hypothesis was confirmed in regard to survival without definite brain damage, survival with brain damage, and death. But within the first group the difference between the "post-concussional" and recovered patients in terms of severity of the initial brain trauma was small. Patients with the postconcussional syndrome were better distinguished by psychosocial factors and by disturbances of the special senses.

Introduction

POSTCONCUSSIONAL syndrome is used to describe symptoms—headache, dizziness, emotional instability, and impairment of concentration—which frequently develop after head injury. Sometimes these complaints become persistent and disabling despite the absence of obvious physical signs. As Critchley¹ pointed out, opinion has swung from a concept of organic to mainly neurotic causation and back again. The case for an organic cerebral aetiology has been forcefully argued by Taylor.² But if brain trauma is a factor, the trauma must be of a subtle kind, since neither neurological signs nor the characteristic intellectual or personality changes associated with brain damage are present.

A study of a consecutive series of head injuries³ presented an opportunity to investigate retrospectively the relationship between the severity of the initial brain trauma and the outcome as expressed in terms of recovery, postconcussional syndrome, residual brain damage, or death. The hypothesis tested was that the head injury would be found to have been more severe the worse the outcome and that patients with the

postconcussional syndrome would have been more severely injured than those who recovered but less severely injured than the brain-damaged group. Absence of such a gradation in severity of injury would indicate that other factors were involved.

Patients and Methods

Patients

The material consisted of 474 patients aged fifteen years or more admitted consecutively to the neurosurgical unit at Newcastle General Hospital from April, 1963, to March, 1964. The criterion for admission was a period of unconsciousness after a head injury. 20% had been transferred from other hospitals. All except 6 patients had closed head injuries. 75% of the survivors were seen in the clinic one month after discharge, and 59% attended for a second or third time three to six months after discharge. The last outpatient visit that we took into account was in March, 1965.

Outcome

Patients were allocated to one of four outcome groups on the basis of the information contained in the inpatient files and the records of the follow-up clinic.

Group 1.—268 patients (56.4%) were regarded as *recovered*. One-fifth complained of headache at some stage after the injury, but if more than one symptom of postconcussional type (see below) was recorded the patient was placed in group 2. Table 1 shows the characteristic pattern of symptoms of groups 1, 2, and 3. Some of the group 3 patients also complained of postconcussional symptoms.

Group 2.—94 patients (19.9%) complained of headache, lack of concentration or fatigue, dizziness, depression, anxiety, or irritability, but showed no evidence of residual brain damage. *Postconcussional syndrome* is used here as a purely descriptive term for this group of symptoms.

Group 3.—61 patients (12.9%) who survived but who showed unequivocal signs of *residual brain damage*. This was defined by the presence of any one of the following: neurological deficits such as hemiparesis, spasticity or tremor, dysphasia or dyspraxia; gross personality change, or demonstrable impairment of memory or intellect. About a third of the patients showed a mixture of neurological and mental deficits.

Group 4.—51 patients (10.8%) who died in the neurosurgical unit.

Indices of Severity of Brain Trauma

The indices of severity related to two aspects: the degree of disturbance of consciousness, and the presence or absence of two direct complications of head injury—skull fracture and intracranial hæmorrhage.

TABLE 1—FREQUENCY (%) OF VARIOUS SYMPTOMS IN GROUPS 1, 2, AND 3 ON DISCHARGE AND INCLUDING FOLLOW-UP PERIOD

Symptoms	Group 1 (recovered) (268) at follow-up	Group 2 (post-concussional) (94)		Group 3 (brain damaged) (61)	
		Dis-charge	Follow-up	Dis-charge	Follow-up
<i>Residual brain damage:</i>					
Pyramidal signs ..	0	0	0	64	66
Gnostic disorders ..	0	0	0	41	44
Personality change ..	0	0	0	18	23
Memory/intellectual loss	0	0	0	20	23
<i>"Postconcussional" symptoms:</i>					
Headache	22	44	77	26	39
Dizziness	2	14	44	16	30
Depression	0	13	37	7	23
Anxiety	0	10	31	7	18
Irritability	1	11	21	12	21
Impaired concentration	0	3	14	10	25
Fatigue	1	4	18	3	10
Hypochondria	0	2	12	0	3