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A CLINICAL TRIAL OF TETRACYCLINE IN ROSACEA.*

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THERE must be few diseases which cause more emotional flushing in the supporters of the various theories of causation than rosacea. Whatever cause is suggested, be it achlorhydria (Brown *et al.*, 1935), emotional guilt (Klaber and Wittkower, 1939), alterations in the jejunal mucosa (Watson *et al.*, 1965), or the humble demodex (Robinson, 1965), there seem to be violent supporters of diametrically opposed views. Yet treatment based on the supposed causes has remained, to put it at its most favourable, unreliable. There is, in fact, no exhaustive study to show the natural history of rosacea. Unheralded by any fanfares, tetracycline as a method of treatment has come into current use in the last few years (in fact there is virtually no published work on the subject, though David Williams has certainly drawn attention to it). Early claims by French (Aron-Brunetiere *et al.*, 1951) and Belgian (Thulliez and Gillis, 1954) authors for the efficacy of chloramphenicol do not appear to have been followed up.

Many of the spate of dermatological textbooks published in the last two years mention tetracycline as a significant agent in treatment, and this must reflect the attitude of dermatologists as a whole, but there has been no statistical support for this opinion. Perhaps statistics are unnecessary when the treatment is so good that it obviously works.

We have used tetracycline in Sheffield in the treatment of rosacea since 1962 and felt that it was effective, but in order to determine how necessary or how successful this expensive remedy was, the following trial was started in December 1964 and run for a year.

INVESTIGATION.

All new patients with rosacea, and old patients re-attending with a recurrence at the Royal Infirmary, Sheffield and the Doncaster Gate Hospital, Rotherham were included in the trial. Cases were accepted whether they were of the erythematous and papular type, or the more usual pustular form. Since the aim of the trial was to evaluate the use of tetracycline, few investigative procedures were carried out. Haemoglobin estimations were done to exclude anaemia, and a number of the pustules were cultured to see whether there was a pathogenic organism, but these were universally negative.

On the first attendance patients were given one month's supply of tetracycline 250 mg. twice daily, or a dummy placebo indistinguishable in appearance, and these were dispensed by the pharmacist according to a random table. No local application was prescribed, and the patient was instructed to continue washing and the use of

* Based on a paper read at the Annual Meeting of the British Association of Dermatology in Oxford, July, 1966,

cosmetics in their accustomed way. No instructions to avoid hot drinks or alter the diet or their mode of living were given.

Progress was assessed at 2 weeks and 4 weeks, and the assessment was made by the same physician who had examined the patient in the first instance. After 4 weeks all patients were given active tetracycline 250 mg. b.d. and further progress recorded fortnightly for another month, and many of the patients followed up for far longer.

At the end of the year there were 85 patients who had been included in the trial, but 7 of these were not in the final analysis because 2 failed to attend, 2 refused to continue with tetracycline after two weeks (one said he was constipated, and the other had a sore mouth) and 3 patients were found to have incorrect diagnoses, one a papular light eruption, one discoid lupus erythematosus, and one acne vulgaris.

There remained 78, 52 women of average age 47, but with two-thirds in the age groups 35-55, and 26 men of average age 54, of whom half were over the age of 56. These figures would support other workers who have found rosacea is more common in women than men, and tends to affect an earlier age group.

RESULTS.

At the end of the first month's treatment it was considered that assessable improvement as shown by disappearance of pustules, flattening of papules and diminution of erythema, was detectable in 47 and no improvement in 31. Though the code was not broken until after the end of the trial, and in fact after all assessments had been made, it is more convenient to consider the relationship of active and inactive tablets in each of the groups at this stage.

Thus the results at the end of the first month are shown in Table I.

TABLE I.—*Results at the End of the First Month.*

Result.	Tetracycline.	Placebo.	Total.
Improved	28	19	47
Not improved	8	23	31
All	36	42	78
% improved	78	45	

Thus although after the first month there was a considerable placebo effect, the improvement with tetracycline is statistically significant. The findings are equally significant if the men and women are considered separately.

In the second phase of the investigation, after all had received active tetracycline, the results can be expressed as shown in Table II.

TABLE II.—*Results at the End of the Second Month.*

Results.	Tetracycline.	Placebo.
Improved 2nd month	4	17
Not improved	4	2
Did not complete	—	4
All	8	23
% improved	50	74

Again the improvement of 74% of those who had not previously received tetracycline is statistically significant.

A review of the 6 who did not improve revealed that there were 4 women and 2 men, all under the age of 50, anxiety appeared a prominent feature, and redness rather than pustulation was the main element of the rosacea. One of the women was a girl of 17 who afterwards was found to be pregnant and the tetracycline rapidly stopped.

Four patients who had rosacea and keratitis, 3 women and one man, all improved steadily after initiation into the trial, and were free from rosacea and keratitis within 8 weeks. As luck would have it, all had been given the placebo first.

Many of the patients have been followed for periods of over a year, and it has been observed that tetracycline has a suppressive effect on rosacea, which may soon pass off once it has been discontinued. For instance, one patient did not clear on the placebo, cleared in one month on tetracycline, relapsed in two weeks after tetracycline was stopped, cleared again on 250 mg. b.d., relapsed on 250 mg. on alternate days, and finally remained clear on 250 mg. daily. A number of other patients have been controlled completely by tetracycline 100 mg. daily but if this was stopped the condition recurred.

An attempt to estimate the relapse rate of those who had discontinued treatment and supervision for over six months was made by sending a questionnaire to 22 of those who had been clear when last seen. Nineteen replies were received, 5 patients were still completely clear, 8 were having slight trouble, and 6 reported themselves as bad as ever.

DISCUSSION.

In this investigation no attempt has been made to determine how tetracycline works, yet the observation of these cases has raised a number of queries. There is no doubt that tetracycline controls not only pustulation, which one could accept might be of bacterial origin, but the liability to flushing and the permanent dilatation of the capillaries also clear in favourable cases. I would agree with others such as Wittkower and Klaber (1939) that many rosacea patients are shy individuals often under great emotional stress, as instanced in the following case. A man aged 33 with marked rosacea of 1 year's duration. The onset of the rosacea coincided with the discovery that he was sterile, and also that the house he rented and on which he had spent a great deal of time and money, was the subject of a demolition order, surely enough frustration and feeling of inadequacy to explain the onset of rosacea. Yet within three weeks of commencing tetracycline the rosacea had virtually cleared, and was completely clear in six weeks. He remained well two months after the tetracycline had been discontinued, yet his circumstances were the same.

It is difficult to avoid a placebo effect in any trial. In a recent report (Witkowski and Simons, 1966) on a trial in acne vulgaris where every precaution was taken, 23% of patients on the placebo improved. In the present trial

the benefit of tetracycline was statistically significant and was successful in controlling rosacea in 87% of patients. Such improvement was maintained in two-thirds of a group of patients who had discontinued treatment for over six months. The mechanism of its beneficial action is as yet unknown, but the observation that it controls not only pustulation but erythema suggests that it is not entirely an antibacterial or antiodemodectic effect. Has it some action on intestinal absorption?

I would like to thank Ronald Church for his help and Professor Knoweldon for his assistance in designing the trial and working out the statistics.

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