CORRESPONDENCE:
RE-TREATMENT OF SERIOUS PULMONARY TUBERCULOSIS WITH TB1 AND TETRACYCLINE

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To the Editor of the Acta Tuberculosea Japonica:

At present it is one of the most important problems for the physicians concerned with tuberculosis to treat serious pulmonary tuberculosis patients for whom surgical operations look not to be efficacious and whose bacilli have become resistant to SM, PAS and INH. On the other hand, we have TB1 as an anti-tuberculous drug, which nowadays is not widely used because of its considerable side effects.

We planned to make TB1 clinically useful by finding an effective co-partner, and found that Tetracycline was suitable for this purpose.

Table 1 shows our results of *in vitro* experiment, using Kirchner's liquid medium containing bovine serum at the concentration of 10 per cent and 0.00mg/ml H37 Rv as inoculum.

Table 1. Minimum inhibitory concentration of Tetracycline (TC) and TB1 in combination (γ/ml) for *Mycobacterium tuberculosis* H 37 Rv.

pH	5.6		6.6		7.6	
Drugs	TC	TB1	TC	TB1	TC	TB1
TC alone	12.5	—	12.5	—	9.3	—
TB1 alone	—	22.0	—	18.6	—	12.5
TC+TB1	4.7	4.7	4.7	4.7	4.7	4.7
TC+1/10 TB1	9.3	0.93	9.3	0.93	6.25	0.63

Here we find a synergistic effect of TB1 and Teracycline in acid, neutral and alkaline media.

In Table 2 this combined effect is also recognized on *M. tuberculosis* resistant to SM, PAS or INH.

Then we studied the efficacy of these drugs by the animal experiment. Table 3

Table 2. Combined effect of Tetracycline (TC) and TB1 on *M. tuberculosis* H 37 Rv resistant to SM, PAS, or INH (γ/ml).

Deqree of resistance	resistant to 100 γ/ml SM		resistant to 100 γ/ml PAS		resistant to 100 γ/ml INH	
Drugs	TC	TBI	TC	TBI	TC	TBI
TC alone	12.5	—	18.7	—	4.7	—
TB1 alone	—	50.0	—	50.0	—	9.3
TC+TB1	4.7	4.7	6.25	6.25	3.13	3.13
TC+1/10 TB1	9.3	0.93	12.5	1.25	3.13	0.31

Table 3. Survival time of animals (in days).

	Control animals (not treated)	TB1 20 γ/g	TC 100 γ/g	TB1 20 γ/g + TC 100 γ/g
Survival time (mean value)	13.5	17.5	16.1	19.2

shows the survival time of tuberculous mice treated daily with 20γ/body weight (gram) of TB1, 100γ/g. TC, and 20γ/g. TB1 with 100γ/g. TC, as compared with that of control animals.

Here we can again find a combined effect of TB1 and Tetracycline.

In our laboratory we usually use a particular experimental method for the study of antituberculous chemotherapy. After the medication we draw out the blood from humans at one hour interval, and each time we put the serum from the blood thus obtained into the Kirchner's liquid medium at the concentration

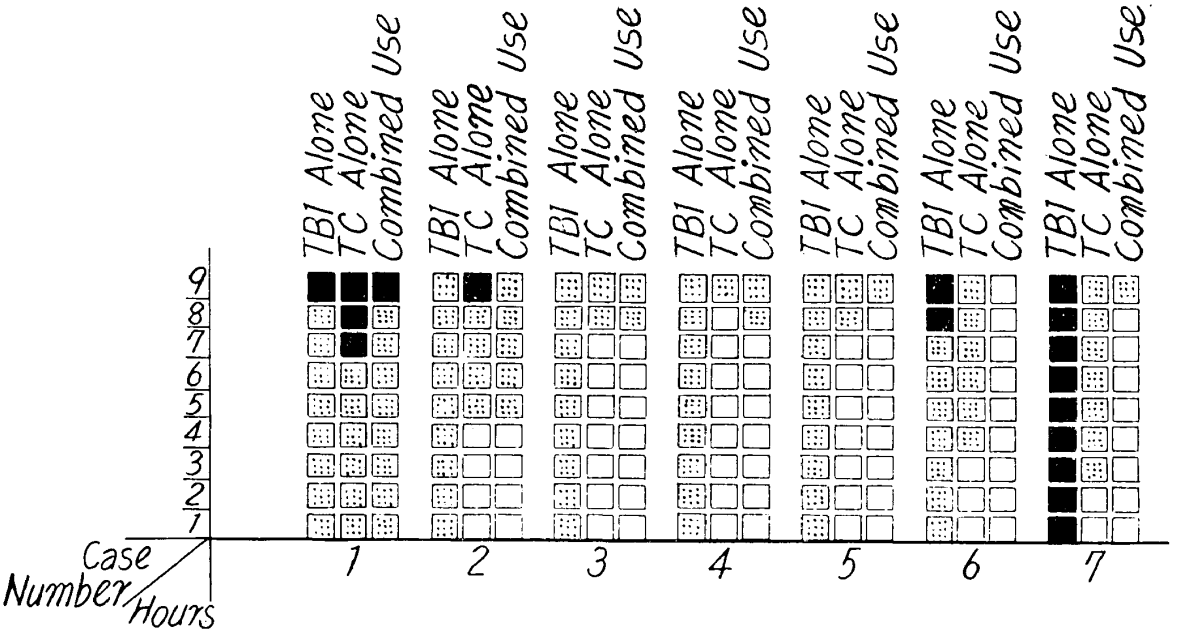

Figure 1. Bacteriostatic Activity in Blood.

of 90%. Then *M. tuberculosis* is cultured in these media. By this method we can determine how many hours the bacteriostatic activity of the blood lasts. Figure 1 shows the results. The ordinate in the graph indicates the number of the cases. Black squares indicate no inhibition of the growth of cultures; dotted squares, partial inhibition, and white ones complete inhibition.

We know from the figure that 6 to 7 hours after the medication, the combined use of 100 mg. TB1 and 1.5 g Tetracycline has a definite effect, compared with the use of each drug alone.

Finally we would like to present the clinical results. The treatment was applied to 21 pulmonary tuberculosis patients with fibrotic and serious lesions, who had not converted the tubercle bacilli in sputa to negative in spite of a long term chemotherapy with SM, PAS and INH.

We gave them daily both 0.1 g. TB1 and 1.0 g. Tetracycline or Oxytetracycline.

Table 4 shows the results of the bacillus findings in sputa. Here we can see that the conversion rate to negative nears 50% after 3 or 4 months of treatment.

Table 4. Culture readings in sputa.
(0.1 g TB1 + 1.0 g TC or OTC daily)

Months	1	2	3	4
Number of cases with positive culture before treatment	21	21	21	15
Conversion to negative	8	12	10	7

Now we have to know the side effects of this treatment. We have experienced 26 cases including a few with negative culture before treatment. Among them we found four cases whose appetite decreased, two of them recovered by methionine treatment and in the other two we had to stop the medication. There was no case with leucopenia. In urines we found no abnormal findings. In 5 cases, by the bromsulphalein test, we found that their hepatic function worsened, but we could not find any serious hepatic damage. And we experienced only one case with black tongue which disappeared however after a Vitamin B_2 treatment. We suppose that with this regimen we must especially pay attention to the hepatic function.

In summary we wish to recommend a new regimen, TB1 and Tetracycline, for the chemotherapy of pulmonary tuberculosis patients who are not converted the tubercle bacilli to negative in spite of a long term chemotherapy with any other drugs.