TREATMENT OF TUBERCUROSIS WITH METHYL-PROMIZOLE

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Inhibition of the growth of tubercle bacilli in vitro and in vivo was attempted using Methylpromizole (Mp).* MP was used alone or with Streptomycin (SM) for 16 patients with acute miliary tuberculosis, tuberculous meningitis and pulmonary tuberculosis unsuitable for collapse therapy or cases which had become worse after Lucite Ball Plombage. The following clinical experiments were made: measurement of content of MP in blood by the modified method of Bratton Marshall, Slide Cell Culture of tubercle bacilli, and phagocytosis.

A series of Sauton's culture fluid (P. H. 7. 2) was set up to include MP diluted to various concentrations of 1:1,000~1:2,048,000. Into each tube was put exactly 1mgm of tubercle bacilli (Frankfurt strain). These were cultured for 5 weeks at 37°.C. The growth of the tubercle bacilli was completely inhibited in concentrations of 1:1,000~1:32,000 (1:32000 contains MP 3.125mgm per 100c.c.). The growth was fair in dilutions 62,000×~2,480,000×. (Table I and II)

Table 1

Inhibition of growth of Tubercle bacilli in Vitro

MP. content	Interval cultured			
	1Week	2Ws	3Ws	4Ws
1000×	−	−	−	−
2000×	−	−	−	−
4000×	−	−	−	−
8000×	−	−	−	−
16000×	−	−	−	−
** 32000×	−	−	−	−

* Supplied by the courtesy of Chugai pharmaceutical Company.

** $\frac{1}{32000}$ gm Per c.c. =3.125mgm Per 100c.c.

MP. Content	Intenval cultured			
	1Week	2Ws	3Ws	4Ws
64000×	−	−	±	++
128000×	−	−	±	++
256000×	−	±	±	++
512000×	−	±	±	++
1024000×	−	±	+	++
2048000×	−	±	+	++
Contrast	−	±	±	++

Table Ⅱ

Inhibition of growth of T. B. in Vitro

MP. content	Interval cultured					
	1Week	2Ws	3Ws	4Ws	5Ws	6Ws
15000×	−	−	−	−	−	−
20000×	−	−	−	−	−	−
25000×	−	−	−	−	−	−
30000×	−	−	−	−	−	−
35000×	−	−	+	+	+	+
40000×	−	−	+	+	+	+
45000×	−	−	+	+	+	+
50000×	−	−	+	+	+	+
55000×	−	−	+	+	+	+
60000×	−	−	+	+	+	+
65000×	−	−	+	+	+	+
Contrast	−	−	+	++	++	++

Animal Experiment:

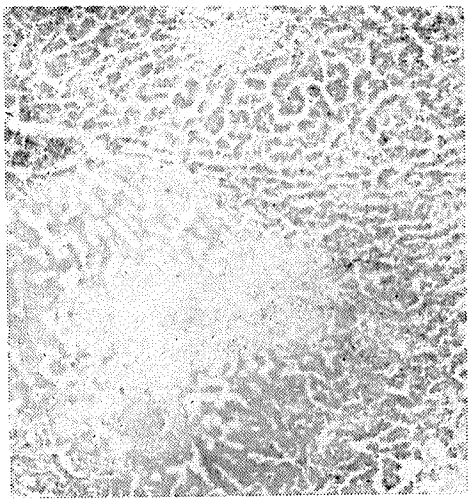
In this experiment guinea pigs were infected subcutaneously in the groin with tubercle bacilli. These animals died of miliary tuberculosis in the usual time.

Other animals infected at this same time were given MP in their diet 4 weeks after infection. These animals of the treated group which had survived 5 weeks were sacrificed and the tissues were compared histologically with

those of the control group. Marked differences were noted between the two groups, the disease process had been obviously inhibited in the treated group. (Fig. I)

Fig. I.

Liver of guinea pig infected with T. B. (contrast)



Liver of guinea pig treated with methyl-Promizole

Clinical Experiments.

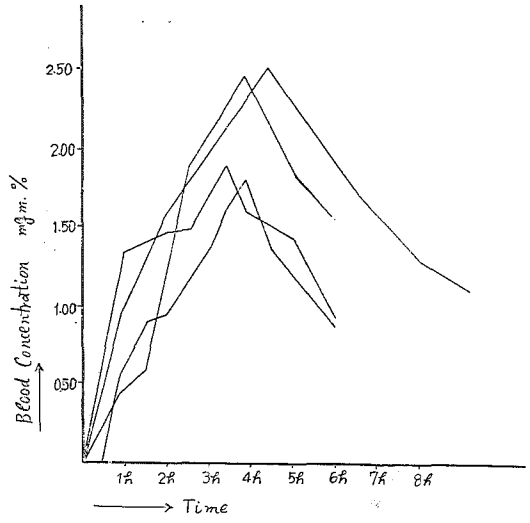
These were begun by giving 1.5 gms. MP. daily, but had to be discontinued owing to toxicity. Dosage was reduced to 0.3 gms daily, and increased gradually until patients were receiving 1.2 gms to 1.5 gms a day over long periods. Some patients tolerated 2.0 gms daily.

In 4 cases given 1.0 gm of MP, the blood concentration reached a maximum value of 2.45 mgm percent and 1.74 mgm percent in 3 and 3.5 hours respectively. Concentration after 6 hours was 1.6 mgm percent and

0.95 mgm per cent. Even after 8 hours, the concentration was still considerable. (Fig Ⅱ)

Fig. Ⅱ

Blood concentration after Administration of 1.0 gm of MP.



As a result MP is now given routinely at 6 or 8 hour intervals.

A comparison of blood concentrations in cases of medication at 8 and 6 hour intervals is shown in table Ⅲ. Both maximum and minimum values were higher in the 6 hourly administration.

Table Ⅲ

Comparison of blood concentration

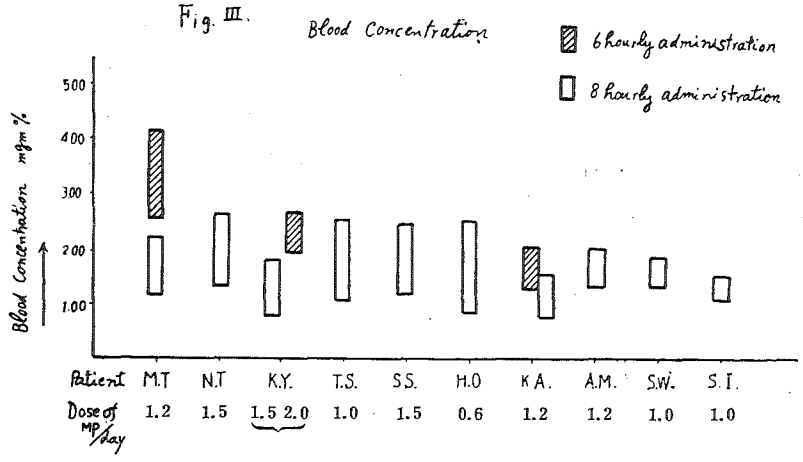
Medication at 8 and 6 hour intervals.

Patient	Dose of MP. gms/day	8 hourly mgm%		6 hourly mgm%	
		min.	max.	min.	max.
M. T.	1.2	1.108	2.296	2.684	4.074
K. A.	1.2	0.637	1.200	1.068	1.582

The maximum doses which could be continued without toxic effects were found to be 1.2 to 1.5 gms. per day.

It was found that, regardless of the total daily dose, the higher blood concentration was obtained by the exhibition of MP at 6 hourly intervals (max. values 4.07~2.68 mgm%; min. 1.58~1.07 mgm%) rather than at 8 hours (max. values 2.67~1.47 mgm%; min. 1.20~0.64 mgm%). (Fig. Ⅲ.)

Fig. III. Blood Concentration



In 4 cases of acute miliary tuberculosis and tuberculous meningitis, MP alone was used in one case with no effect, of the other, for whom MP and SM were used, one showed no effect, the rest showed some improvement: one case of tuberculous meningitis survived 12 months, and one case of acute miliary tuberculosis survived more than 15 months to recover completely. (Table Ⅳ, Fig. Ⅳ)

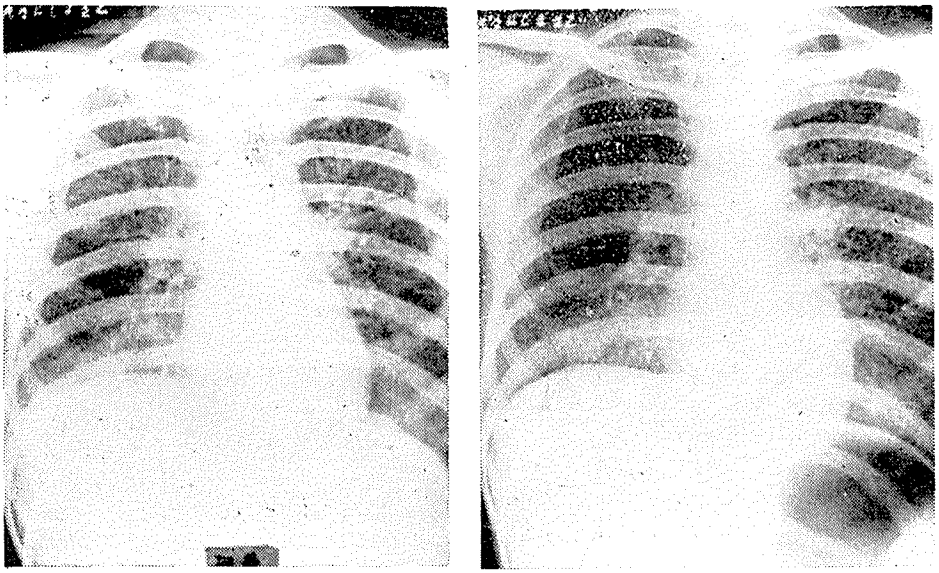
Table Ⅳ. MP. Treatment of Tuberculous meningitis and acute miliary tuberculosis

Patient	Diagnosis	Date	Dose of MP. or SM. gm	Cerebrospinal fluid						Judgement
				Eirst Pressure	Xantho chromie	Cells	Albumine	Saccharide	Tbc. B.	
K. I. 39. F	Miliary Tuberculosis Combined with Tuberculous meningitis	On Admission 10/Ⅸ'49		300	+	543/3	Demarcation 1	0.040	−	no effect (Survived 132days)
		20/Ⅹ'49	54gms SM.	350	++	189/3	20	0.043	−	
		12/Ⅻ'49	6gms SM. 11.8gms MP. (17days)	220	+	878/3	10	0.043	−	
A. K. 33. F.	Tuberculous Meningitis	On Admission 7/Ⅰ'50		300	++	431/3	6	0.040	+	improvement (Survived 347days)
		26/Ⅱ'50	46gms SM.	260	+	748/3	10	0.035	+	
		10/Ⅵ'50	60gms SM. 144.3gms MP. (164days)	200	+	350/3	7	0.060	−	
		26/Ⅷ'50	24.0gms MP. (16days)	150	±	22/3	2	0.066	−	

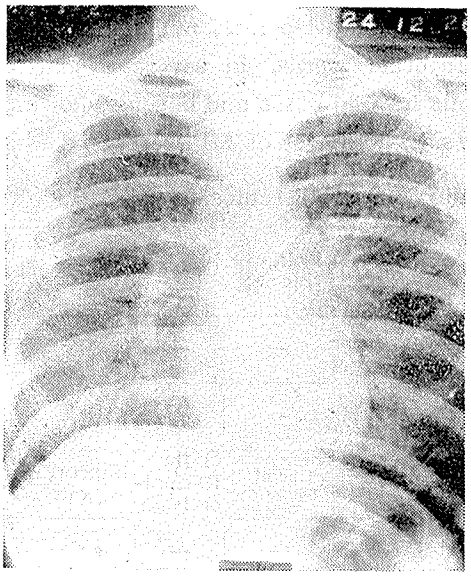
Patient	Diagnosis	Date	Dose of MP. or SM.	Clinical Symptoms				Judgement
				Fever Type	X-Ray	Tbc. B in urine	Cerebr-ospin. fluid	
T. H. 24. F.	Miliary Tubercul-osis	On Admission 17/Ⅰ'50		Fever -heat	miliar	−	normal	no effect (Survived 127 days)
		6/Ⅱ '50	3.1gms MP. (7days)	〃	〃	−	〃	
		14/Ⅲ'50	40gms SM.	〃	〃	+	〃	
M. T. 34. F.	〃	On Admission 22/Ⅷ'49		〃	〃	+	〃	improvement
		2/Ⅹ '49	40gms SM.	Slight -fever	〃	+	〃	
		11/Ⅰ '50	45.7gms MP. (40days)	Feverheat after slight fever	〃	−	〃	
		23/Ⅱ '50	40gms SM.	Slight -fever	〃	−	〃	
		6/Ⅵ '50	48.0gms MP. (40days)	〃	〃	−	〃	
		26/Ⅵ '50		Feverlos	fibrous	−	〃	
				RECOVERY				

Fig. Ⅳ. Patient M. T. 34. F. Miliary Tuberculosis

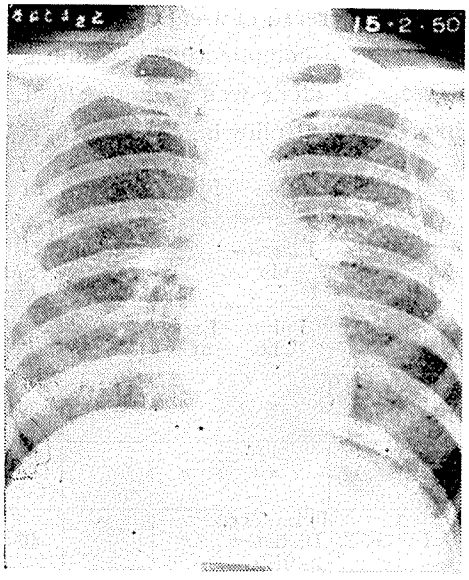
1. 22/Ⅷ'49 On Admission, 2. 2/Ⅹ'49 after SM therapy.



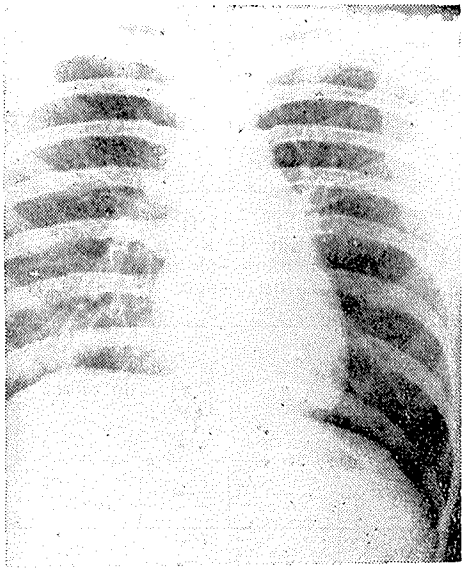
3. 26/XII '49 after MP therapy.



4. 15/II '50 after SM therapy.



5. 26/VI '50 after MP therapy.



6. 3/X '50 complete recovery.

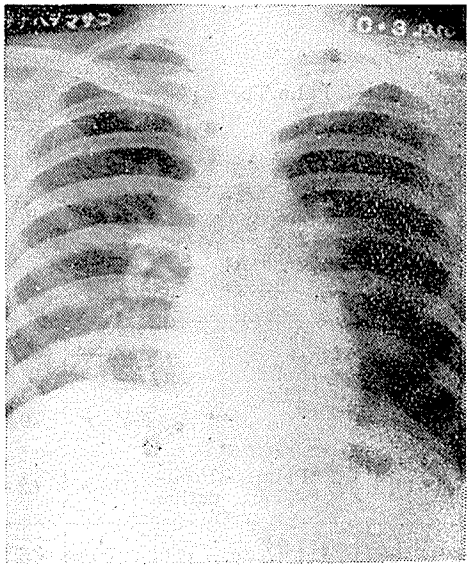


Table V deals with 12 cases either unsuitable for collapse therapy, or worse after surgical intervention. In two cases no more than 5 gms could be given owing to toxicity, and these do not appear in the final figures.

In 6 cases with exudative disease, 3 were somewhat improved by MP only, 2 by MP and SM, while in another treatment was without effect. In 4 cases

of productive disease, there were little effect, but two showed the following results: increase of weight, decrease in sedimentation rate, and the disappearance of a complicating peritonitis. In other words, in severe exudative cases, MP alone was without effect, but in mild cases and in some showing improvement following SM therapy, results with use of MP were good.

Table V. MP. Therapy of pulmonary Tuberculosis

Patient	Age and Sex.	Diagnosis	Form		Dose of MP. (SM.) gm.	Density of MP. in Blood mg%	Collapse-therapy	Surgical Operation	Judgement
T. H.	34. F.	Pulm. Tbc.	Exudative	MP. therapy	2. 9		—	—	discontinuance of therapy, owing to toxicity
H. O.	37. F.	〃	〃		4. 5	0. 51～2. 50	—	—	〃
A. M.	24. M.	〃	〃		96. 1	1. 04～1. 75	(right) artificial Pneumothorax	(left) Resinplombage	improvement
S. I.	46. F.	Pulm. Tbc. Diabetes mellitus	〃		40. 2	0. 87～1. 15	—	—	〃
K. Y.	32. F.	Pulm. Tbc.	〃		112. 0	2. 04～2. 61	—	—	〃
N. T.	24. M.	Pulm. Tbc.	〃	SM. therapy	(8)	1. 47～2. 67	—	—	no effect by MP.
				MP. 〃	16. 0				
				SMand MP	(20) 35. 4				improvement by MP. and SM.
				MP. therapy	378. 3				
S. W.	40. F.	Pulm. Tbc. Laryngeal Tbc.	〃	SM. 〃	(40)	1. 00～1. 56	(right) artificial Pneumothrax	(left) Resin-plombage	improvement by MP. and SM.
				MP. 〃	58. 9				
Mo. S.	24. M.	Pulm. Tbc.	〃	SM. 〃	(40)		〃	〃	no effect
				MP. 〃	70. 0				
T. S.	31. F.	Pulm. Tbc.	Productive	MP. 〃	63. 5	1. 15～2. 32	—	—	no effect by MP.
Mi. S.	17. F.	Pulm. Tbc.	〃	〃	46. 3		—	—	no effect by MP.
S. S.	21. F.	Pulm. Tbc. with Peritonitis	〃	〃	135. 4	1. 20～2. 35	(left) artificial Pneumo. thorax	—	improvement (disappearance of peritonitis)
K. A.	25. M.	Pulm. Tbc. with Peritonitis	〃	〃	97. 2	1. 07～1. 58	—	—	improvement (disappearance of peritonitis)

Sedimentation rate: in 10 cases, 7 decreased obviously, and 3 were unchanged. (Table Ⅵ.)

Table Ⅵ. Sedimentation rate

Patient	Before MP. therapy	2Weeks after	4W	6W	8W	10W	3 Months	6 M	9 M	11M	1 Year	Judgement
S. S.	42	20	28	15	2	2						decreased
K. Y.	23	19	15	19	12							〃
N. T.	80		58		65		43	80 Haemoptysis	70	50	54	〃
S. I.	128	97	88		81							〃
A. M.	44	42	40		9	12						〃
T. S.	66	75	64	12	8		14					〃
K. A.	25	25	24	24	16	16	9					〃
M. T.	107	60	118	101	100	102	88					unchanged
S. W.	90	112		80		92						〃
A. K.	12	24		5	18		3					〃

Gaffky count: in 10 cases, 7 were unchanged, 1 increased, 2 decreased (Table Ⅶ.)

Table Ⅶ. Gaffky count

Patient	Diagnosis	Before Treatment	Afer Administration	Judgement
M. T. 31. F.	Miliary Tbc.	O, Culture (+)	O, Culture (+)	Unchanged
S. S. 21. F.	Pulm. Tbc. (Peritonitis)	O, 〃 (−)	O, 〃 (−)	〃
A. K. 33. F.	Tbc. Meningitis	O, 〃 (−)	O, 〃 (−)	〃
K. A. 25. M.	Pulm. Tbc. (Peritonitis)	O, 〃 (−)	O, 〃 (−)	〃
N. T. 24. M.	Pulm. Tbc.	1 ～ 3	0 ～ 1 ～ 4	〃
S. I. 46. F.	Pulm. Tbc. Diabetes Mellitus	1 ～ 3	1 ～ 2	〃
S. W. 40. F.	Pulm. Tbc. Laryngeal Tbc.	2 ～ 3	2 ～ 3	〃
K. Y. 32. F.	Pulm. Tbc.	3 ～ 6	2	Decreased
A. M. 24. M.	〃	7 ～ 9	2 ～ 6	〃
T. S. 31. F.	〃	2 ～ 3	5 ～ 8	Increased

In all cases, phagocytosis of living tubercle bacilli was unchanged during these experiments with MP. (Table Ⅷ)

Table Ⅷ Phagocytosis

Patient	Strain	Percentage of Leucocytes Phagocyting T. B.					
		Before Treatment	1Week after	2 W	3 W	4 W	5 W
S. I.	Frankfurt	82	80				
H. O.	〃	77	75				
T. S.	〃	70	77		76		72
K. A.	〃	84		85		85	
K. Y.	〃	88		86		90	

Using leucocytes from healthy subjects, the phagocytosis of tubercle bacilli from patients receiving SM or MP therapy was measured and the resisting power of this strain of T.B. determind. The resistance of tubercle bacilli (to phagocytosis) increased markedly after the SM therapy (probably with the development of resistance to Streptomycin). No change in phagocytosis was noted using MP. (Table Ⅸ.)

Table Ⅸ. Resistance of T.B. to phagocytosis

	Strain of Bacilli		Percentage of Leucocytes phagocyting T. B.	Resistance of T. B. to Phagocytosis
Contrast	Frankfurt		79.7	100
Methyl-promizole	Ⅰ	Before MP. treatment	78.4	102
		After giving 168.0 gms MP.	78.3	102
	Ⅱ (after SM. therapy)	Before MP. treatment	51.1	156
		After giving 270.0 gms MP.	48.2	165
	Ⅲ (after SM. therapy)	Before MP. treatment	51.2	156
		After giving 108.0 gms MP.	50.8	157
Strepto-mycin	Ⅳ	Before SM. therapy	74.8	107
		After giving 80.0 gms SM.	37.2	214

MP in the blood of patients, when used for Slide Cell Culture had a definitely inhibitory action. (Table Ⅹ.)

Table X. Slide Cell Culture of T.B.

Patient	Before MP. Treatment	1Week after MP. Treatment	2 W.	3 W.	4 W.	5 W.	6 W.	7 W.	8 W.
M. T.	++	++	++	±	±	±	±	±	
A. M.	+	+	±	±	±	±			
S. W.	±	±	−	+	+				
K. A.	++	++	+	++	±	+	+		
H. O.	+	+	±	+*					
K. Y.	+	+	±	+	+	−	+		
S. S.	+++	++	+	+	±	+	±	+	+
S. I.	+	±	±	±					

Toxic effects from MP occured in many cases. These were: cyanosis, anorexia, nausea, vomiting. and headache. By giving a small dose at the start, the amount could usually be increased gradually, but in 2 cases out of 16, not more than 5.0 gms daily could be attained owing to nausea and vomiting. In some cases the dose could not be increased sufficiently to provide the desired blood level. In many cases, number of erythrocytes and haemoglobin decreased slightly, but the number of leucocytes rather tended to increase. (Table XI). Increase of eosinophiles was not observed. In another case, icterus appeared 4 days after the start of treatment, and disappeared 10 days after its discontinuance. There was little change in urine, no influence on thyroid gland or gonads: no exanthem.

Table XI. Influence on blood

Patient	Hæmoglobin (by Sahli) and Red cells									Leucocytes	
	Before MP.	2Weeks after	4Ws	6Ws	8Ws	10Ws	3 Months	6Ms	9Ms	Before MP.	Course during treatment
S. S	(92) 403	(82) 372	(72) 378	(65) 334	(64) 330	(70) 331				9000	8400~11400
N. T.	(68) 504	(85) 480	(90) 509		(74) 545	(76) 548		(56) 377	(59) 339	8800	11400~16200
S. W.	(62) 357	(65) 366	(55) 264	(60) 246						8700	9200~10600
A. K.	(91) 382	(72) 330		(72) 318		(72) 304	(79) 311	(75) 262		5900	5500~ 7800
M. T.	(62) 330	(65) 320		(57) 238		(50) 290	(58) 282			11100	12680~16000
A. M.	(72) 491	(61) 424	(62) 360	(66) 350	(60) 320					11300	12000~16900
T. S	(65) 436	(68) 310	(60) 288	(58) 262	(50) 257					9800	8100~16000

* after discontinuance of MP therapy, owing to vomiting

Summary

1. Methylpromizole inhibited the growth of tubercle bacilli in vitro, in dilutions up to 1:32000.

2. MP included in the diet of guinea pigs from 4 weeks after infection with tubercle bacilli, resulted in definite evidences of healing.

3. In cases with acute miliary tubeculosis and tuberculous meningitis, MP alone was used with no effect. When MP was used with Streptomycin there appeared to be some favourable effect: one case of tuberculous meningitis survived 12 months, and one case of acute miliary tuberculosis survived more than 15 months to recover completely.

4. In severe exudative cases of pulmonary tuberculosis, MP alone was without effect, but in mild cases and in some cases showing improvement following SM therapy, results with use of MP were good.

5. MP in the blood of patients, when used for Slide Cell Culture had a definitely inhibitory action.

6. Tubercle bacilli did not develop resistance to MP.

7. Side effects: cyanosis, anorexia, nausea, headache, anaemia, to indicate the chief symptoms. In some these were sufficient to require discontinuance of the therapy.

BIBLIOGRAPHY

(1) Feldman, W.H, Hinshaw, H.C., and Mann, F.C.
Am. Rev. Tuberc., 50:418 (1944)

(2) Milgram, L., Levitt, I., and Unna, M.
Am. Rev. Tuberc., 55:144 (1947)

(3) Lincoln, E.M., T.W. Kirmse, and De Vito, E.
J.A.M.A., 136:593 (1948)

(4) Lincoln, E.M., and Kirmse, T.W.
Lancet, 1:767 (1949)

(5) Morizo Ishidate:
NISSHIN-IGAKU 36:No.12 (1949)

(6) Tetsumaro Sasaki:
SAISHIN-IGAKU 5:No.2 (1950)

(7) E.M. Lincoln, and T.W. Kirmse.
Am. Rev. Tuberc., 61:159 (1950)

(8) T. Anderson and S.J. Strachan.
Lancet. 2:135 (1948)

(9) D.G. Madigan
Lancet, 2:169 (1948)