

'Intermittent Chemotherapy' in Intracardially Infected Tuberculous Guinea-Pigs¹

'Intermittent chemotherapy' with isonicotinic acid hydrazide (INH) and streptomycin sulphate (SM) is a standard method of tuberculosis chemotherapy in humans^{2,3} due to painstaking experimental work⁴⁻⁸. Great risks are involved if 'intermittent chemotherapy' is attempted in miliary tuberculosis or tubercular meningitis. Data regarding intermittent chemotherapy in acute fulminating guinea-pig tuberculosis is fragmentary. An acute progressive infection was produced in guinea-pigs by intracardiac injection of *Mycobacterium tuberculosis*. Control guinea-pigs died of tuberculous pneumonia between the 8th and the 19th day of infection. There was no initial period of daily therapy in our experiments as given by others⁴.

Materials and methods. In the first experiment, 40 female guinea-pigs, weighing c. 450 g each, were injected intracardially with 0.5 mg (moist weight) of a 21-day-old culture of *Mycobacterium tuberculosis* strain H37Rv by

livers and spleens only. The guinea-pig treated for 6 days a week showed no lesions in the lung, liver and spleen. It was evident that 'intermittent triple drug therapy' for 6 days a week was the best regimen.

In the second experiment with intermittent dual drug therapy with INH and SM the difference in the mean survival time between drugs given 6 days a week or twice or thrice a week was not marked (Table II).

In our experiments triple drug therapy for 6 days a week was superior to the other forms of treatment (Table I) but with dual drug therapy this superiority is less apparent (Table II).

More experimental work is necessary in monkeys, rabbits, hamsters, guinea-pigs and mice before 'intermittent chemotherapy' can be given in miliary tuberculosis or tuberculous meningitis in humans. An initial period of daily chemotherapy may be necessary as showed in the model of GRUMBACH⁴.

Table I. Effect of combined intermittent triple drug therapy (INH + SM + 1314TH) in intracardially infected tuberculous guinea-pigs

Group	No. of guinea-pigs	Days treatment per week	No. of doses of INH 25 + SM 50 + 1314TH 50 (mg/kg)	Mean survival time \pm S.E. (days)
1	7	6	18	38.1 \pm 5.0 ^a
2	7	3	9	25.0 \pm 3.3 ^a
3	7	2	6	30.7 \pm 7.7 ^a
4	7	1	3	25.1 \pm 3.7 ^a
5	7	--	--	13.1 \pm 1.3

^a Significantly different from control at $P < 0.05$.

the method of GUPTA and MATHUR⁹. They were then divided into 5 equal groups and INH, SM and 2-ethylisothionicotinamide (Thioamid, 1314TH) administered (Table I). INH and 1314TH were given orally whereas SM was given i.m.

On the 14th day of infection one guinea-pig was necropsied from each group and the lung, liver and spleen were subjected to routine histopathology.

In the second experiment 54 female guinea-pigs, weighing c. 425 g each, were intracardially injected with 0.25 mg (moist weight) of a 14-day-old culture of *M. tuberculosis* strain H37Rv, as in the previous experiment. The guinea-pigs were divided as shown in Table II.

Results. Table I shows that the best therapeutic effect was noted in the group given these drugs (INH, SM and 1314TH) 6 days a week.

Histopathology. On the 14th day of infection the control guinea-pig showed pneumonic consolidation of the lung with thickened pleura, fatty degeneration of the liver with large tracts of epithelioid cells and lymphocytic infiltrations, and complete disorganization of the normal follicular pattern of the spleen with areas of epithelioid cell collections. Guinea-pigs given drugs once, twice or thrice weekly showed minimal epithelioid tubercles in the

Table II. Effect of combined intermittent dual drug therapy (INH + SM) in intracardially infected tuberculous guinea-pigs

Group	No. of guinea-pigs	Days treatment per week	No. of doses of INH 50 + SM 100 (mg/kg)	Mean survival time \pm S.E. (days)
1	9	6	18	36.0 \pm 3.5 ^a
2	9	3	10	31.6 \pm 5.7 ^a
3	9	2	7	33.1 \pm 4.7 ^a
4	9	1	4	21.7 \pm 4.6 ^a
5	9	1/2	2	19.1 \pm 2.8 ^a
6	9	--	--	12.5 \pm 1.1

^a Significantly different from control at $P < 0.05$.

Zusammenfassung. Es wurde eine stark progressive Tuberkulose bei Meerschweinchen durch eine intrakardiale Injektion von *M. tuberculosis* bewirkt, worauf die Wirkung einer befristeten Chemotherapie mit Isoniazid, Streptomycin und Thiomid untersucht wurde.

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Lucknow (India), 24 March 1969.

- 1 Communication No. 1364 from the Central Drug Research Institute, Lucknow (India).
- 2 N. K. MENON, Int. Union Tuberc. Q. Rev. 77, 3 (1966).
- 3 K. N. RAO, Antiseptic 65, 157 (1958).
- 4 F. GRUMBACH, G. CANETTI, G. GROSSET and M. LE LIRZIN, Tubercle, Lond. 48, 11 (1967).
- 5 J. M. DICKINSON and D. A. MITCHISON, Tubercle, Lond. 47, 381 (1966).
- 6 H. BLOCH, Am. Rev. resp. Dis. 84, 824 (1961).
- 7 C. E. PALMER, S. M. FEREBEE and L. HOPWOOD, Am. Rev. Tuberc. pulm. Dis. 74, 917 (1966).
- 8 H. J. CORPER and M. L. COHN, Science 106, 446 (1947).
- 9 S. K. GUPTA and I. S. MATHUR, Indian J. med. Res. 52, 973 (1964).