

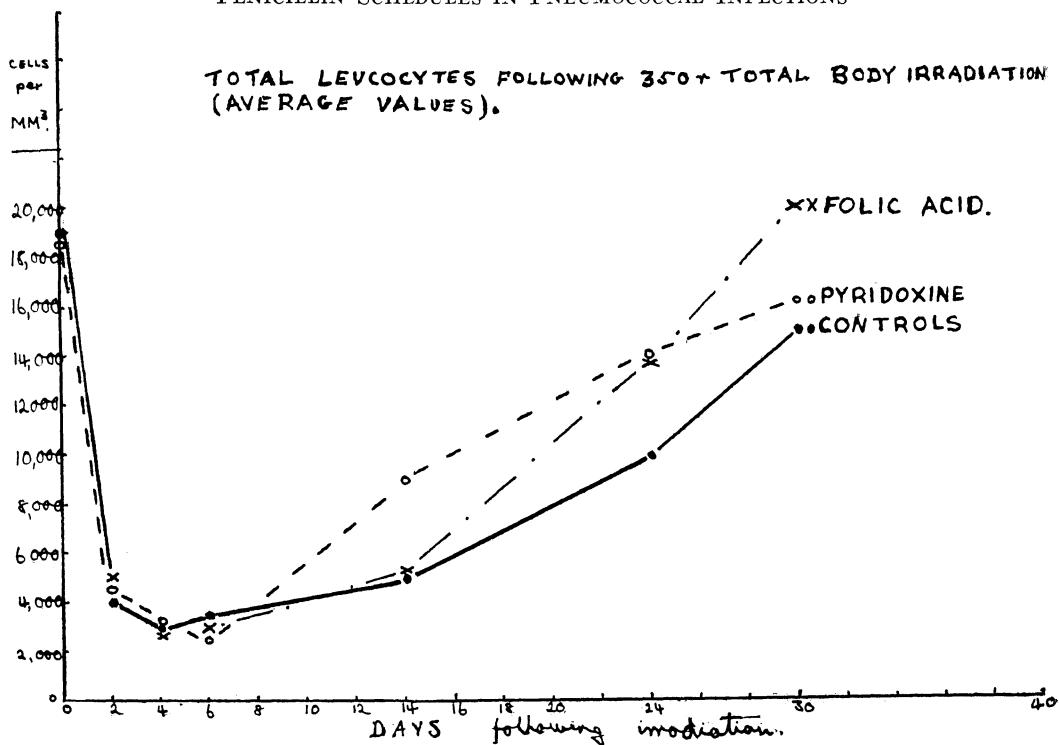


FIG. 4.

Curves showing average total W.B.C. counts plotted against days following irradiation with 350 r of control mice, and mice medicated with folic acid, and with pyridoxine.

15 γ of folic acid injected daily during a period of 7 days prior to radiation and 15 days after radiation prolonged significantly the survival time of the irradiated mice. Similar observations were made with pyridoxine hydrochloride. Thus, irradiated mice injected with 50 γ of pyridoxine hydrochloride intramuscularly daily 7 days prior to radiation and 13 days post-radiation, ex-

tended significantly the life span of the irradiated mice, as compared with the irradiated, unmedicated mice.

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Comparative Effectiveness of Two Penicillin Treatment Schedules in Pneumococcal Infections of Mice.

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The methods currently employed for penicillin therapy are based largely on the principle that adequate blood levels of the antibiotic must be constantly maintained through-

out the period of treatment. Consequently, since penicillin is rapidly excreted after its injection in aqueous solution, repeated doses at 3-hourly intervals are usually given to re-

plenish the blood concentration. The demands of this therapeutic program impose a heavy burden on the nursing staffs of hospitals and create difficult problems for the practitioner who is treating patients at home, while the repeated injections are painful to the patient and disturb his rest. For these reasons attention lately has been turned to the question whether there is an essential need for constantly elevated blood levels of penicillin and whether injections at less frequent intervals may be successfully employed.

The observations of Tillett, Cambier and McCormack¹ were the first to suggest that the antibacterial effect of penicillin might persist for longer periods of time than was indicated by measurements of penicillin concentration in the blood, and that the wider spacing of injections might be safely attempted in the treatment of lobar pneumonia. These results were confirmed experimentally by Jawetz,² who treated hemolytic streptococcal infections in mice and demonstrated that the antibacterial effect of penicillin persisted for as long as 8 hours, while the blood concentration was measurable for only one hour. In addition, White, Lee, and Alverson³ showed that mice infected with hemolytic streptococci could be cured with a single large dose of penicillin given orally. More recently Zubrod⁴ determined the effect of different dosage schedules of penicillin upon hemolytic streptococcal infections in mice and showed that the controlling factor in survival rate was the total dosage of penicillin and not the interval at which it was administered.

The present report deals with the effect of penicillin on pneumococcal infections in mice, in which the same daily doses of the antibiotic were administered by 2 different treatment schedules. The work was carried out as a controlled laboratory experiment to complement clinical studies on the penicillin

therapy of pneumococcal pneumonia in human subjects.

Experimental. Swiss mice of both sexes weighing from 15 to 18 g were inoculated intraperitoneally with 1,000 LD₅₀ doses of a standard laboratory strain of Type I pneumococcus. Two hours after infection treatment was begun with crystalline sodium penicillin G* dissolved in a physiological solution of sodium chloride and injected subcutaneously in volumes of 0.2 to 0.5 cc, depending upon the dose employed. Groups of 20 mice were treated for 4 days with total daily doses of penicillin ranging from 20 to 140 units. Ten mice of each group received half of the daily dose at 12 hour intervals while the remaining 10 mice received one-eighth of the daily dose every 3 hours. One group of 10 mice was left untreated to serve as controls. As an additional control on the possible effect of the larger initial doses of penicillin in the animals treated twice daily, groups of 5 mice were given a single injection of penicillin ranging from 10 to 70 units. Finally, in order to ascertain whether a cure could be effected with a single massive dose of the drug, additional groups of 5 mice were given one injection of 100, 200 or 1,000 units of penicillin. The animals were observed for a period of 2 weeks following treatment at the end of which time the final mortality rates were recorded.

The results are shown in Table I and may be summarized as follows:

1. The minimal 100% curative dose of penicillin was 140 units daily regardless of whether this was administered in 2 equal parts at 12-hourly intervals or in 8 equal parts at 3-hourly intervals.

2. There were no apparently significant differences in the mortality rates among mice treated twice daily and 8 times daily with equivalent doses of penicillin less than 140 units.

3. It was possible to effect a 100% cure with a single injection of 1,000 units of penicillin.

The comparative PD₅₀ doses of penicillin

* Throughout the remainder of this paper the word "penicillin" refers only to crystalline penicillin G.

¹ Tillett, W. S., Cambier, M. J., and McCormack, J. E., *Bull. N. Y. Acad. Med.*, 1944, **20**, 142.

² Jawetz, E., *Arch. Int. Med.*, 1946, **77**, 1.

³ White, H. J., Lee, M. E., and Alverson, C., *Proc. Soc. Exp. Biol. and Med.*, 1946, **62**, 35.

⁴ Zubrod, C. G., *Bull. Johns Hopkins Hosp.*, 1947, **81**, 400.

TABLE I.
Comparison of Penicillin Treatment Schedules in
Pneumococcal Infection of Mice.

Penicillin units per day	Frequency of penicillin injections		
	Single inj.	Every 12 hr	Every 3 hr
1000	5/5*		
200	4/5		
140		9/9	10/10
120		7/10	9/10
100	2/5	9/10	6/9
80		9/10	8/10
70	3/5		
60	2/5	5/10	4/10
50	0/5		
40	0/5	2/10	1/10
30	0/5		
20	0/5	2/10	0/10
None		0/10	

* Numerator indicates number of mice surviving, denominator indicates total number of mice.

administered twice daily and every 8 hours were calculated according to the method of Reed and Muench.⁵ The PD50 dose of penicillin was 60 units daily when given every 12 hours and 72 units daily when given every 3 hours. Although this would seem to indicate some advantage when the drug was administered twice a day in larger individual doses, the difference is not statistically significant.

Discussion. It must be pointed out that this experiment determined the minimal curative and PD50 doses of penicillin only for an arbitrarily selected treatment period of 4 days. What constitutes the absolute minimal effective dose of penicillin would appear, however, to depend mainly on 2 factors—the size of the daily dose and the duration of treatment—which bear some reciprocal relationship to one another. In other words, the larger the daily dose the shorter the time required for effective treatment. This is borne out by the fact that a single injection of penicillin may be curative, provided that the dose is large enough.

The outstanding feature of the results obtained under the conditions of this experiment is that the effectiveness of penicillin

therapy appeared to depend more upon the total daily dose of the drug than upon the intervals at which it was administered. Our findings in the treatment of pneumococcal infections in mice are therefore entirely in accord with those of Jawetz² and Zubrod⁴ for streptococcal infections in the same animal. It thus becomes evident, as suggested by Bigger,⁶ that the mode of action of penicillin in controlling bacterial infection is a complex mechanism which cannot be explained simply on the basis of a constant effective concentration of the antibiotic. As one part of this mechanism the enhanced antibacterial effect of a sudden large increase in the level of penicillin may possibly counterbalance its virtual disappearance from the blood during prolonged intervals after administration, but how this is brought about and what other factors may be involved, especially with regard to the defensive reactions of the infected host, cannot be stated at present. Nevertheless it is clear that the antibacterial effect of penicillin persists long after measurable quantities are known to have disappeared from the blood^{2,7} and that, under certain conditions, daily doses given in 2 injections have a therapeutic action equivalent to the same daily doses divided into 8 injections. These findings illustrate that within limits one may depart from the therapeutic principle of a constantly maintained level of penicillin and suggest a clinical application in the treatment of human infections.

Summary. The therapeutic effects of penicillin injected every 12 hours into mice infected with pneumococci were compared with the effects of similar daily doses divided into 8 injections at intervals of 3 hours.

With both treatment schedules the 100% curative daily dose and the PD50 daily dose were found to be similar.

The significance of these findings is discussed.

⁶ Bigger, J. W., *Lancet*, 1944, **2**, 497.

⁷ Rammelkamp, C. H., and Keefer, C. S., *J. Clin. Invest.*, 1943, **22**, 425.

⁵ Reed, L. J., and Muench, H., *Am. J. Hyg.*, 1938, **27**, 493.

