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Aluminum Penicillin in Mouse Protection Tests.

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In searching for a preparation of slowly absorbed penicillin that would give satisfactory results, the amorphous aluminum salt of penicillin was prepared in our laboratories. As expected, this penicillin was found to be highly insoluble in water. It was therefore thought that if it could be suspended in a suitable non-aqueous medium a single daily parenteral injection would give prolonged therapeutic activity. Peanut oil was selected as the vehicle for suspension.

It is the purpose of this report to show the protective effect of aluminum penicillin in peanut oil on mice infected with *Diplococcus pneumoniae*. Clinical reports to be published elsewhere will describe blood level determinations and therapeutic efficacy of aluminum penicillin in human subjects. However, when 300,000 units of aluminum penicillin in peanut oil is given intramuscularly to human subjects, blood levels of 0.03 units per ml of serum were found to persist from 12 to 24 hours. The concentration of penicillin in body fluid of treated mice has not been determined.

Procedure. 18 to 22 g mice were infected intraperitoneally with 0.5 ml of a 10^{-5} dilution of an 18-hour broth culture of *Diplococcus pneumoniae* Type I (SVi strain) containing 1000 MLD. Two hours later treatment was begun as indicated in Table I by injecting 0.1 ml of the suspension of penicillin in peanut oil intramuscularly. The suspensions were made by diluting penicillin in oil and mixing in a Waring blender to the proper unitage. All dilutions were assayed before use. Treatment was repeated daily for 4 days and mice were held until the eighth day when the results were finally determined.

Under the conditions of these experiments, the effectiveness of aluminum penicillin was compared with calcium penicillin in peanut oil and sodium crystalline penicillin in peanut oil and beeswax (4.8 W/V). Untreated, in-

fectured controls died within 36 hours. The results are shown in Table I.

From the above data it is determined that the PD_{50} for each of the compounds tested is:

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|---------------------------------------|----------|
| (1) Aluminum penicillin in peanut oil | 34 units |
| (2) Sodium penicillin in oil and wax | 40 units |
| (3) Calcium penicillin in oil | 95 units |

This suggests that under the conditions described, aluminum penicillin is superior in protective ability to either of the other compounds tested. This may be considered surprising in view of the reference to human blood levels in which aluminum penicillin does not appear to remain in the blood stream as long as peanut oil and beeswax preparations. Further studies are in progress to explain this seeming inconsistency, however, it seems appropriate at this time to propose an explanation. Aluminum penicillin being very insoluble in water must, for purposes of assay or utilization by the animal body, be converted into a soluble salt, *e.g.* sodium penicillin. This process takes place *in vivo* slowly and at a rate proportional to the amount of aluminum penicillin present in tissues. For this reason blood serum levels run a curve having a peak about one hour after injection, slowly diminishing in several hours to a level below an amount that can be measured by present methods for determining its concentration. This lower concentration, though at present not considered therapeutic, may be adequate to hold the invading organisms in check until the body defenses can overcome the infection.

To further study the prolonged action of aluminum penicillin in oil against pneumococcal infections in mice, infected animals were treated with a single intramuscular injection. Results of these protection tests are given in Table II.

Conclusion. Aluminum penicillin in oil ef-

TABLE I.
Protection with Multiple Doses of Penicillin.

Preparation	Units of penicillin		No. of mice	Survivors 8 days	% protection
	Daily	Total 4 days			
Aluminum penicillin in oil	200	800	80	80	100
	150	600	50	50	100
	100	400	90	89	99.0
	75	300	90	88	98.0
	50	200	90	73	81.0
	25	100	90	30	33.2
Sodium crystalline penicillin in oil and beeswax (4.8 W/V)	200	800	50	48	96.0
	100	400	50	48	96.0
	75	300	50	46	92.0
	50	200	50	34	68.0
	25	100	50	11	22.0
Calcium penicillin in oil	200	800	50	37	74.0
	150	600	50	32	64.0
	100	400	50	26	52.0
	75	300	50	21	42.0
	50	200	50	2	4.0
	25	100	30	0	0.0
Controls	No treatment		60	0	0.0

TABLE II.
Protection with a Single Dose of Aluminum Penicillin in Oil.

Preparation	Units of penicillin	No. of mice	Survivors	
			8 days	% protection
Aluminum penicillin in oil	400	50	50	100
	200	50	50	100
	150	50	46	92
	100	50	47	94
	75	50	45	90
Control	None	30	All dead 36 hrs	

fectively combats induced pneumococcus infection in mice. Compared with calcium penicillin in oil or sodium penicillin in peanut oil

and beeswax preparation, the aluminum penicillin in oil is more effective on a unit for unit basis.