agent depending on the experimental conditions. The number of organisms decreases at a constant rate until 99% of the organisms have been destroyed. The rate of killing varies with different organisms. The action of penicillin on hemolytic streptococci is not accompanied by lysis of the organisms. No detectable amount of penicillin is destroyed or absorbed from solution by the organisms. It appears to be effective only when active multiplication takes place.

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Chemotherapeutic Activity of Penicillin.*

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The activity of penicillin *in vitro* has been discussed in detail in previous communications.[1] Its *in vivo* activity was first reported by Chain, *et al.*,[2] and by Florey, *et al.*[3]

In vivo Activity. Mice infected intraperitoneally with varying amounts of a highly virulent strain of hemolytic streptococci (C203 Mv) were treated subcutaneously with small amounts of penicillin.

TABLE I.
Effect of Subcutaneous Injection of Penicillin on Group A Hemolytic Streptococcus Infections (C203 Mv).

Dilu. of culture	No. of orgs. inj. ×1000	No. of mice	Amt. of penicillin,* cc	No. of days treated	No. dead (<48 hrs)	No. prolonged life (2-7 days)	No. survived (>7 days)
2.0cc	180,000	9	.4-.65	<6	3	1	5
1.0cc	90,000	10	.4-.60	<6	1	2	7
10^{-1}	9,000	15	.2-.58	<6	2	4	9
10^{-2}	900	13	.2-.57	<6	0	4	9
10^{-3}	90	11	.2-.57	<6	0	3	8
Controls							
10^{-5}	0.9	15	0	0	15	0	0

*Alcoholic solution: Total dosage per mouse calculated to be <7 mg dry weight.

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We are indebted to Dr. Martin H. Dawson for his valuable help and suggestions throughout this work.

1 Hobby, G. L., Meyer, K., Chaffee, E., PROC. SOC. EXP. BIOL. AND MED., 1942, **50**, 277, 281.

2 Chain, E., *et al.*, *Lancet*, 1940, **2**, 226.

3 Florey, H. W., *et al.*, *Lancet*, 1941, **2**, 177.

TABLE II.
Titration of Activity of Penicillin* Against Hemolytic Streptococci *in Vivo*.

Dilution of culture	Penicillin (mg)	No. mice	No. survived
10^{-2}	1.5	3	3
	1.0	3	3
	0.75	3	3
10^{-1}	1.5	3	3
	1.0	3	3
	0.75	3	0†
Undiluted	1.5	4	4
	1.0	4	2†
Controls			
10^{-6}	0	10	d. < 2 days
10^{-7}	0	10	d. < 2 days

*Ammonium salt containing 150-200 Oxford Units per mg.
†Two mice showed prolonged survival time in each instance.

Table I shows the results of treatment with crude preparations, and Table II shows the results with highly purified material. It is apparent that 1.5 mg of penicillin is sufficient to protect mice against 1 cc of whole culture containing at least 1,000,000 lethal doses. Amounts as small as 0.75 mg protected against 10^{-3} dilutions of culture containing at least 1000 lethal doses. Treatment was effective if started as long as 8 hours after infection. (Table III.)

Mice were infected similarly with varying amounts of a highly virulent strain of pneumococcus type II. The subcutaneous injection of similar amounts of penicillin again gave adequate protection.

Further experiments showed penicillin to be effective intraperitoneally and intravenously as well as subcutaneously.

Penicillin is rapidly excreted when injected in solution and frequent injections are therefore necessary. This difficulty was eliminated by the use of suspensions in oil or dry pellets.

Oil Suspensions. Penicillin, prepared in the form of the sodium salt,† was dissolved in a drop of water and the solution mixed with

TABLE III.
Subcutaneous Injection of Penicillin Started 8 Hours after Intraperitoneal Injection with Hemolytic Streptococci: Strain C203Mv.

Dilu. of culture	No. of mice	Amt. penicillin,* cc	No. of days treated	No. died† (<48 hrs)	No. prolonged life (2-7 days)	No. survived (>7 days)
10^{-5}	3	.48	4			3
10^{-6}	3	.51	4	1	1‡	1
10^{-7}	3	.48	4		1‡	2

*Alcoholic solution: Total dosage per mouse calculated to be <7 mg dry weight.
†5 untreated control mice died in <30 hours.
‡Hearts' blood cultures taken at autopsy showed no organisms.

† For part of the sodium salt used we are indebted to Chas. Pfizer and Co., Brooklyn, N.Y.

TABLE IV.
Effect of Subcutaneous Injection of Oil Suspensions of Penicillin on Hemolytic Streptococcus Infections in Mice.

Dilution of culture	No. of mice	Penicillin, mg	No. died (<48 hrs)	No. prolonged life (2-7 days)	No. survived (>7 days)
10-1	6	3.0		3	3
10-3	24	3.0-4.0	7	3	14
Controls					
10-6	9		9		
10-7	9		9		

sesame oil. A single subcutaneous injection of approximately 3.0 mg of penicillin in such a suspension was adequate to protect 66% of mice against the intraperitoneal inoculation of over 1000 lethal doses of hemolytic streptococci. (Table IV.)

Dry Pellets. Penicillin was mixed with 4 parts of pure cholesterol and ground to form a homogeneous mixture. Pellets of the mixture containing 1.5 to 3 mg of penicillin each were prepared in a pill press.

The implantation of a single pellet subcutaneously, 1 to 4 hours after infection, protected 66% of mice against over 1000 lethal doses of hemolytic streptococci (C203 Mv). (Table V.)

Toxicity. Mice were injected intravenously with varying amounts of penicillin in solution. The LD_{50} for an 18 g mouse was found to be 32 mg of the sodium salt or 12 mg of the ammonium salt—equivalent to 1.8 g and 0.67 g respectively per kg body weight.

With lethal doses no abnormal pathology was observed other than congestion of the lungs. Immediate choking and gasping followed the injection and death occurred within 1 to 3 minutes. With sub-lethal doses, respiration was extremely rapid, followed by complete prostration lasting for a variable length of time. Recovery followed after a period of between 15 minutes and several hours.

Guinea pigs were inoculated intravenously with 320 mg of the sodium salt of penicillin or the equivalent of 1.3 g per kg of body

TABLE V.
Effect of Subcutaneous Implantation of Dry Penicillin on Hemolytic Streptococcal Infections in Mice.

Dilution of culture	No. of mice	Penicillin, mg	No. died (<48 hrs)	No. prolonged life (2-7 days)	No. survived (>7 days)
10-3	29	1.5-3.0		8	21
Controls					
10-6	6	0	6		
10-7	6	0	6		

weight. No pyrogenic or other toxic symptoms were observed.

The toxicity of the ammonium salt was tested by Dr. Phillips Thygeson in tissue culture, in the chorioallantoic membrane, and when applied directly to the human eye.[4] No toxicity was observed.

Sodium and ammonium salts of penicillin were administered to humans. The daily injection of 170 mg of purified penicillin, having an activity of 240 Oxford units per mg, for a period of 6 days produced no untoward effect.

Summary. Penicillin is highly effective against hemolytic streptococcus and pneumococcus infections in mice when given subcutaneously, intravenously or intraperitoneally. When given in the form of oil suspensions or dry pellets, a single subcutaneous injection confers a high degree of protection. Penicillin is apparently non-toxic within the range of therapeutic dosage.

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Effects on Arterial Hypertension of Heat-inactivated Tyrosinase Preparations.*

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Recent studies of the mechanisms involved in the production of experimental renal hypertension show that several humoral agents may be involved. Following the hypothesis that phenolic amines may be involved in renal hypertension, Schroeder and Adams[1] found tyrosinase preparations from mushrooms to be effective in lowering the blood pressures of hypertensive animals. Their studies were extended to the effects of tyrosinase preparations on arterial hypertension in man and reported results in 17 patients, with significant falls in blood pressures in 13 of these following daily administration of unspecified amounts of their tyrosinase preparations. Some

[4] Thygeson, P., personal communication.

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[1] Schroeder and Adams, *J. Exp. Med.*, 1941, **73**, 531.