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.

* Aided by grants from the Beaumont Trust Fund and the Dazian Foundation for Medical Research.

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

phenolic substance was considered to be altered by the injected enzyme to account for the lowered blood pressures observed.

The present experiments were carried out with mushroom tyrosinase preparations made by modifications of the purification procedures of Keilin and Mann.[3] The valuation of the enzymic activity was made upon a catechol-hydroquinone substrate in terms of "catecholase" units as defined by Adams and Nelson.[4] The final preparations were made up to contain 500 "catecholase" units per ml and contained about 2 mg per ml of non-dialyzable total solids. By heating such preparations for 40 minutes to 60°C, about 95% of the "catecholase" activity was destroyed, and such preparations are referred to as heat-inactivated.

Four patients with malignant or premalignant hypertension were hospitalized and observed before treatment for 7 to 10 days, with blood pressures taken twice or more daily. In the first patient studied, the marked local reactions from injections of the unheated enzyme preparations suggested that the hypotensive response might be due to non-enzymic substances in the preparation. Treatment was then continued with heat-inactivated preparations and it was observed that, while the enzymic activity was almost completely absent and the local reactions were somewhat less, these preparations were still very effective in lowering blood pressure. The 3 subsequent patients were consequently only treated with the heat-inactivated preparations, and there also resulted marked falls in their blood pressures. Two of the patients showed falls in blood pressure from control levels of 210/160 and 210/150 to 170/130 and 135/90 respectively, when 5 ml intramuscularly was being injected daily during the following treatment period. In these 2 patients the T-waves of their electrocardiograms became upright and their cardiac size decreased. Papilledema and hemorrhages of the eye grounds regressed or disappeared and the patients felt better subjectively. The subject whose record is shown in Fig. 1 was almost blinded by hypertensive retinopathy, but after the tenth injection could read a newspaper. On Fig. 1 are charted the blood pressure and temperature observations made on this patient. In the other 2 patients the dosage was not uniform throughout the treatment period, but dosages of from 3 to 8 ml were given with resultant lowering of blood pressure from control levels of 220/150 and 200/110 to 178/128 and 150/90 respectively.

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[2] Schroeder, *Science*, 1941, **93**, 116.

[3] Keilin and Mann, *Proc. Roy. Soc. London* B, 1938, **125**, 187.

[4] Adams and Nelson, *J. Am. Chem. Soc.*, 1938, **60**, 2474.

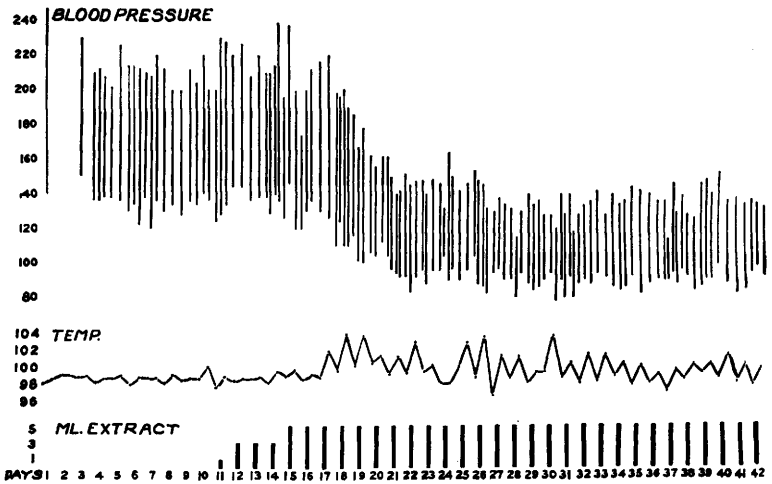

FIG. 1.

Effects of intramuscular injections of from 1 to 5 ml of heat-inactivated tyrosinase preparations 54K and 58K on arterial blood pressure and temperature of patient with arterial hypertension.

Effects other than upon the symptoms of arterial hypertension are notable. Local inflammatory response and systemic reactions such as chills and fever of varying degree, perspiration, with general malaise and rarely, nausea, are observed. Such effects have also been notable in the therapeutic experiments with kidney extracts that have been reported by Page and coworkers.[5] These other effects, noted both with mushroom and kidney extracts, resemble those which may be expected after injection of a non-specific protein material, and it seems possible that such effects and the therapeutic results so far observed are closely related.

The observations demonstrate that heat-inactivated tyrosinase preparations can produce significant lowering of blood pressure and remission of other symptoms of arterial hypertension in man. Such effects as have been observed are as marked as those which have been reported by others following injections of active tyrosinase preparations, and therefore show the effects upon the symptoms of arterial hypertension to be unrelated to the enzyme content of the preparations.

[5] Page, Helmer, Kohlstaedt, Kempf, Gambill and Taylor, *Ann. Int. Med.*, 1941, **15**, 347.