in which chronic hypertension had been produced by renal ischemia. This observation corresponds to the findings of Prinzmetal, Friedman and Oppenheimer,[2] who could not find increased pressor properties in the extracts of blood from patients with hypertension or from dogs with experimental renal hypertension.

10103

Sulfanilamide and Diaminodiphenylsulfone and Their Diacetyl Derivatives in the Treatment of Experimental Intradermal Streptococcus Infections of Rabbits.

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The therapeutic effectiveness of sulfanilamide in experimental beta hemolytic streptococcus infections has usually been determined by the subcutaneous and oral administration of the compound to mice inoculated intraperitoneally.

Upon administration by either route the compound is rapidly absorbed and eliminated. A portion is conjugated into the acetyl derivatives but its therapeutic effects are unknown. It is commonly stated that in human beings the blood should carry from 10 to 12 mg of free sulfanilamide per 100 cc for therapeutic effectiveness.

As shown by Kolmer and Rule[1] the intradermal (shaven abdominal skin) injection of *virulent* beta hemolytic streptococcus in rabbits produces a large severe local lesion of hyperemia and edema followed by necrosis and abscess formation admirably suited for chemotherapeutic investigations since the influence of chemical agents may be determined clinically as well as, and very importantly, by lesion cultures. Septicemia rarely develops but by the simultaneous injection of streptococcus intravenously, septicemia is produced followed by suppurative arthritis in a large percentage of animals.

As shown by Kolmer, Brown, Rule and Werner[2] sulfanilamide in doses of 0.1 to 0.5 g per kilo orally twice daily (6 hours apart) for 5 days in succession usually produced clinical regression of the local

[2] Prinzmetal, M., Friedman, B., and Oppenheimer, E. T., PROC. SOC. EXP. BIOL. AND MED., 1938, **38**, 493.

[1] Kolmer, J. A., and Rule, A. M., *J. Lab. and Clin. Med.*, 1937, **22**, 1097.

[2] Kolmer, J. A., Brown, H., Rule, A. M., and Werner, M. L., *J. Lab. and Clin. Med.*, in press.

TABLE I.

Sulfanilamide and Derivatives in the Treatment of Intradermal Streptococcus Infections of Rabbits.*

Compounds	Dose per kilo,† g	Before Treatment		First Day		Second Day		Third Day		Fourth Day		Fifth Day		Seventh Day		Tenth Day	
		Clin.	Cult.	Clin.	Cult.	Clin.	Cult.	Clin.	Cult.	Clin.	Cult.	Clin.	Cult.	Clin.	Cult.	Clin.	Cult.
Sulfanilamide	0.05	4‡	+	4	+	3	+	3	+	3	+	2	+	abs.	+	abs.	+
	0.1	4	+	4	+	3	+	2	+	2	+	2	+	abs.	+	abs.	+
	0.25	4	+	4	+	2	+	2	+	2	+	abs.	+	abs.	+	abs.	+
	0.4	4	+	3	+	3	+	2	+	2	+	1	+	1	+	abs.	+
	0.5	4	+	3	+	2	+	2	+	2	+	1	+	abs.	+	abs.	+
Acetyl Deriv. Sulfanilamide	0.1	4	+	4	+	4	+	4	+	4	+	abs.	+	abs.	+	abs.	+
	0.25	4	+	4	+	4	+	4	+	4	+	4	+	abs.	+	abs.	+
	0.5	4	+	4	+	4	+	4	+	4	+	3	+	abs.	+	abs.	+
	0.8	4	+	4	+	4	+	4	+	4	+	2	+	D	+		
	1.0	4	+	4	+	4	+	4	+	4	+	3	+	D	+		
4,4'-diaminodiphenylsulfone	0.05	4	+	4	+	4	+	3	+	2	+	2	+	abs.	+	abs.	+
	0.1	4	+	4	+	4	+	3	+	2	+	1	+	abs.	+	abs.	+
	0.25	4	+	4	+	4	+	4	+	2	+	1	+	abs.	+	abs.	+
	0.4	4	+	4	+	2	+	2	+	1	+	1	—	1	—	1	—
	0.5	4	+	4	+	2	+	2	+	1	+	1	+	1	—	1	—
Diacetyl deriv. 4,4'-diamino-diphenylsulfone	0.1	4	+	4	+	4	+	4	+	4	+	4	+	abs.	+	abs.	+
	0.25	4	+	4	+	4	+	4	+	4	+	4	+	abs.	+	abs.	+
	0.5	4	+	4	+	4	+	4	+	4	+	4	+	abs.	+	abs.	+
	0.8	4	+	4	+	4	+	4	+	4	+	3	+	2	+	1	—
	1.0	4	+	4	+	4	+	4	+	3	+	2	+	1	+	1	—
Controls	—	4	+	4	+	4	+	4	+	4	+	4	+	abs.	+	abs.	+
	—	4	+	4	+	4	+	4	+	4	+	abs.	+	abs.	+	abs.	+
	—	4	+	4	+	4	+	4	+	4	+	abs.	+	abs.	+	abs.	+
	—	4	+	4	+	4	+	4	+	4	+	4	+	abs.	+	abs.	+
	—	4	+	4	+	4	+	2	+	2	+	2	+	abs.	+	abs.	+

* Inoculated intradermally with 0.6 cc of 18-hour broth culture (room temperature).

† Divided into two parts and given *orally* twice a day (10 A.M. and 3 P.M.) for 5 days in succession (10 doses). First dose 24 hours after intradermal inoculation.

‡ 4 = severe lesion; 3 = less severe, etc.; + abs. = abscess; D = died (positive heart blood cultures).

skin lesions but complete bactericidal effects (negative lesion cultures) were only occasionally and irregularly produceed.

As shown by Bauer and Rosenthal[3] 4,4'-diaminodiphenylsulfone first reported on by Buttle, Stephenson, Smith and Foster,[4] is approximately 30 times as active against streptococci as sulfanilamide in experimental infections of mice. The diacetyl derivative of this compound, introduced by Fourneau, Trefouel, Nitti and Bovet[5] was found to have a therapeutic index 6 times as high as sulfanilamide.

Twenty-five rabbits were inoculated intradermally (shaven abdominal skin) with 0.6 cc (several punctures) of 18-hour broth culture (room temperature) of a *virulent* strain of beta hemolytic streptococcus. Large local lesions of hyperemia and edema with positive cultures resulted in 24 hours.

Five animals were kept as untreated controls and over a period of 10 days all resulted in the production of abscesses with positive lesion cultures at daily intervals (Table I).

Five were given sulfanilamide orally in dose of 0.05 to 0.5 g per kilo per day (divided into 2 doses at 10 a.m. and 3 p.m.) for 5 days in succession, the first dose being administered 24 hours after intradermal inoculation. Clinical improvement began on the second to fifth days of treatment which was well marked by the seventh day, but all animals developed small abscesses with positive daily lesion cultures over the period of 10 days' observation (Table I).

Five were given 0.1 to 1.0 g of the acetyl derivative of sulfanilamide orally per day (divided into 2 doses at 10 a.m. and 3 p.m.) for 5 days in succession, but with practically no clinical evidences of therapeutic effectiveness; all lesion cultures remained positive throughout the period of 10 days. The rabbits receiving 0.8 and 1.0 g per day died after the fifth day of treatment due to toxicity of the compound (Table I).

Five animals were given 0.05 to 0.5 g 4,4'-diaminodiphenylsulfone per kilo per day (divided into 2 doses at 10 a.m. and 3 p.m.) for 5 days in succession. Clinical improvement began on the second to third days of treatment but rabbits receiving 0.05 to 0.25 g daily continued to show positive lesion cultures over the 10 days of observation. Two receiving 0.4 and 0.5 g daily showed practically complete healing on the fifth day of treatment with negative lesion cultures (Table I).

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[3] Bauer, H., and Rosenthal, S. M., *Public Health Reports*, 1938, **53**, 40.

[4] Buttle, G. A., Stephenson, D., Smith, S., and Foster, G. E., *Lancet*, 1937, **1**, 1331.

[5] Fourneau, E., Trefouel, J., Nitti, F., and Bovet, D., *Compt. rend. Acad. d. Sci.*, 1937, **204**, 1763; *ibid.*, 1937, **205**, 299.

Five were given the diacetyl derivative of 4,4′-diaminodiphenylsulfone orally in doses of 0.1 to 1.0 g per kilo daily (divided into 2 doses at 10 a.m. and 3 p.m.). Doses of 0.1 to 0.5 g per kilo produced no clinical effects and lesion cultures were positive throughout; doses of 0.8 and 1.0 g per kilo produced some healing on the fourth to fifth days of treatment which resulted in sterile lesion cultures on the tenth day.

Summary. (1) Sulfanilamide by oral administration to rabbits showed curative effects upon local intradermal streptococcus lesions but did not result in complete bactericidal effects in the dosage employed. (2) The acetyl derivative of sulfanilamide was practically without curative effects. (3) 4,4′-diaminodiphenylsulfone was more curative than sulfanilamide and produced complete bactericidal effects in the larger doses. (4) The diacetyl derivative of 4,4′-diaminodiphenylsulfone was without curative effects in the same dosage as sulfanilamide but produced some curative effects in higher dosage. (5) The results with sulfanilamide, 4,4′-diaminodiphenylsulfone and its diacetyl derivative by oral administration to rabbits with experimental intradermal streptococcus infections have not been as good as reported in the treatment of experimental streptococcus infections of mice by parenteral administration; the differences in results may be due to the difference in the species of animals employed and partly to the routes of administration.

10104

Ineffectiveness of Sulfanilamide in the Treatment of Canine Filariasis.

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Recent reports indicate that sulfanilamide is ineffective in the treatment of several animal parasites.[1, 2] However, as helminths vary so greatly in habitat, morphology and physiology, it appears possible that sulfanilamide may have a selective action upon certain species just as it appears to have on the coccal group of bacteria.

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1 McCoy, O. R., PROC. SOC. EXP. BIOL. AND MED., 1938, **38**, 461.

2 Keil, E., *Arch. f. Schiffs. u. Trop. Hyg.*, 1936, **40**, 400.