

follows a die-away curve with the slow elimination of isomannide and continued diuresis. In the dog, after the intravenous injection of isomannide solution the concentration of the compound in the urine was found as high as 10%. At this time the concentration in the blood was approximately 0.2%, which indicates the capacity of the kidneys of some dogs to concentrate this compound 50 fold. The great solubility of isomannide in water permits ready absorption from the alimentary tract in man, dogs and rats, producing diuresis rather than catharsis as does mannitol.

Summary. Isomannide when administered orally to man or by vein to dogs is excreted unchanged in the urine in large quantities producing an increase in urine volume. Isomannide when ingested in large quantities or administered intravenously produced no toxic symptoms. Like urea, isomannide permeates the red blood cells eliciting the characteristic osmotic phenomena. The diuretic activity of isomannide is likely due to its lack of tubular absorption, thus increasing the osmotic pressure of the fluid upon which the water-absorbing cells are acting and thereby increasing the volume of urine excreted.

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Sulfanilamide and Derivatives in the Treatment of Experimental Tuberculosis of Guinea Pigs.

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Sulfanilamide has been found by Rich and Follis¹ to exert a markedly inhibitory effect upon experimental tuberculosis of guinea pigs when given in 2 daily doses of 0.1 g and 0.5 g divided into 4 doses. Treatment was started 3 days before the subcutaneous injection of human tubercle bacilli. Smithburn,² however, failed to observe any beneficial effects from the daily administration of 0.2 g to guinea pigs by intraperitoneal injection 24 hours before the intracerebral inoculation of virulent human bacilli. Greey, Campbell and Culley³ have reported that sulfanilamide (Prontylin powder) in 3

¹ Rich, A. R., and Follis, B. H., Jr., *Bull. Johns Hopkins Hosp.*, 1938, **62**, 77.

² Smithburn, K. C., *PROC. SOC. EXP. BIOL. AND MED.*, 1938, **38**, 574.

³ Greey, P. H., Campbell, H. H., and Culley, A. W., *PROC. SOC. EXP. BIOL. AND MED.*, 1938, **39**, 22.

daily doses of 0.1 g each *per os* started 3 days before subcutaneous inoculation with virulent human bacilli had an inhibitory effect upon the development of lesions; when the infection had been present 17 to 24 days, treatment did not alter the macroscopic appearance of the lesions. The development of sensitivity to tuberculin was unaltered by sulfanilamide therapy.

Sixteen guinea pigs were inoculated subcutaneously in the region of the inguinal lymph nodes with 0.00002 g of virulent tubercle bacilli; 4 were kept as untreated controls. Treatment of the remaining 12 was begun 2 hours after inoculation; 4 were given 0.2 g sulfanilamide per kilo divided into 2 doses 6 hours apart by intramuscular injection daily for 8 days (16 doses); 4 were given 0.3 g and 4 were given 0.5 g per kilo divided into 2 doses 6 hours apart daily for the same period. Three of the untreated controls died in 39 to 63 days after inoculation with well developed tuberculous lesions in the lymph nodes, spleen, liver and lungs, showing tubercle bacilli in smears and confirmed by microscopical examination of the tissues; the fourth was killed on the 66th day for autopsy purposes. Of the 12 treated animals 10 died in 23 to 65 days after inoculation and the remaining 2 were killed on the 65th day for autopsy purposes. All showed tuberculous adenitis and splenitis of a degree comparable to the untreated controls; 10 showed tuberculous infection of the liver and 8 of the lungs, confirmed by positive smears for tubercle bacilli and by microscopical examination of the tissues (Table I). In general terms we have interpreted the results as indicating that sulfanilamide had no curative activity under the conditions of the experiment.

Thirty-seven guinea pigs were inoculated with 0.00002 g virulent human tubercle bacilli by subcutaneous injection in the region of the inguinal lymph nodes; 7 were kept as untreated controls. Treatment was started 9 days later, at a time when the glands showed first evidences of infection, with the following 6 derivatives of sulfanilamide in the form of sodium salts:

No. 2219	p-sulfonamide benzene azo	(1'-naphthylamine-4'-sulfonic acid).
No. 2247	" "	" (1-naphthol-5 " ").
No. 2251	" "	" (1-naphthol-4 " ").
No. 2253	" "	" (2-naphthol-6 " ").
No. 2274	" "	" (chloro-resorcinol).
No. 2306	Sodium sulfanilamide.	

Each of these compounds was tolerated by mice and rabbits in an average dose of 1.5 g per kilo administered subcutaneously and *per os*.

TABLE I.
Sulfanilamide in the Treatment of Experimental Tuberculosis of Guinea Pigs.*

Pig No.	Dose per kilo† g	Death (Days after Inoc.)	Autopsy Findings			
			Lymph Nodes	Spleen	Liver	Lungs
1	.2	39	†+	+	—	—
2	"	56	+	+	—	+
3	"	23	++	++	++	+
4	"	47	+	++	+	+
5	.3	60	++	++	+	++
6	"	61	++	++	+	++
7	"	65§	+	++	+	—
8	"	58	+	++	+	+
9	.5	64	+	++	++	+
10	"	65§	+	++	+	—
11	"	65	+	++	+	—
12	"	62	+	++	+	+
13	Control	39	+	++	++	++
14	"	58	+	++	+	—
15	"	63	+	++	++	+
16	"	66§	+	+	+	+

*Animals inoculated with 0.00002 g human tubercle bacilli by subcutaneous injection in inguinal region.

†Divided into 2 doses given daily 6 hours apart for a total of 8 days (16 doses) by intramuscular injection. First dose given 2 hours after inoculation.

‡+ = slight tuberculous infection with few tubercle bacilli in smears of lesions; ++ = heavy infection.

§Killed for autopsy purposes.

The doses given per kilo of weight are shown in Table II. Each was divided into 2 parts given 6 hours apart by intramuscular injection daily for 6 days; then every other day for 4 days, followed by treatment every 3 days for 4 days, totalling 28 doses.

Five of the 7 untreated controls died in 23 to 50 days after inoculation and the remaining 2 were killed on the 43rd day for autopsy purposes. All showed severe tuberculous adenitis and splenitis, confirmed by direct smears of the lesions for tubercle bacilli and by microscopical examination of the tissues; all showed infection of the liver and 6 showed macroscopic infection of the lungs.

Twenty-five of the 30 treated animals died in 25 to 46 days after inoculation and the remaining 5 were killed on the 46th day for autopsy purposes. All showed tuberculous adenitis, confirmed by positive smears and microscopical examination of the tissues; 29 showed confirmed macroscopic lesions of the spleen, liver and lungs. Our interpretation of the results indicated that the 6 derivatives of sulfanilamide employed were without beneficial effects under the conditions of the experiment.

Conclusions. (1) Sulfanilamide by intramuscular administration was without demonstrable beneficial effect in the treatment of experimental tuberculosis of guinea pigs when begun 2 hours after inocu-

TABLE II.
Derivatives of Sulfanilamide in the Treatment of Experimental Tuberculosis of Guinea Pigs.*

Compound No.	Dose per kilo† g	Death (Days after Inoc.)	Autopsy Findings			
			Lymph Nodes	Spleen	Liver	Lungs
2219	1.0	40	‡++	+	+	++
"	"	37	++	+	+	++
"	2.0	38	+	—	—	—
"	"	34	++	++	+	+
"	"	46§	+	+	+	+
2247	1.0	31	++	++	+	+
"	"	40	++	+	++	+
"	2.0	38	++	++	++	+
"	"	37	++	++	+	+
"	"	36	++	+	+	++
2251	0.1	46§	++	++	++	++
"	"	41	++	+	+	+
"	0.2	39	++	++	++	+
"	"	35	+	++	+	+
"	"	34	++	++	++	++
2253	0.1	46§	++	+	++	+
"	"	25	+	++	+	+
"	0.2	46§	+	+	+	+
"	"	45	++	+	+	+
"	"	46	++	+	+	+
2274	0.1	33	+	+	+	+
"	"	27	++	++	++	+
"	0.2	32	++	++	++	++
"	"	26	++	++	++	++
"	"	26	++	+	+	++
2306	1.0	46§	++	+	+	+
"	"	36	+	+	+	+
"	2.0	36	+	+	+	++
"	"	40	+	+	+	+
"	"	39	+	+	+	+
Control	—	32	++	++	+	+
"	—	43§	++	++	++	++
"	—	25	++	++	++	+
"	—	31	++	+	++	+
"	—	43§	++	++	++	+
"	—	50	++	++	+	—
"	—	23	++	+	+	+

*Animals inoculated with 0.00002 g human tubercle bacilli by subcutaneous injection in inguinal region.

†Divided into 2 doses given daily 6 hours apart for 6 days; then every other day for 4 days, followed by treatment every 3 days for 4 days of treatment (total 28 doses). Treatment started 9 days after inoculation.

‡+ = slight tuberculous infection with positive smears for tubercle bacilli; ++ = heavy infection.

§Killed for autopsy purposes.

lation. (2) Six derivatives of sulfanilamide in the form of their sodium salts, by intramuscular injection, were without demonstrable curative effects in the treatment of experimental tuberculosis of guinea pigs when treatment was started 9 days after inoculation.