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Experimental Studies on Blood Sulfanilamide Levels Attained After Powdered Drug Administration by Inhalation.

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The possibilities of therapeutic effect and the dangers of overabsorption which might be produced by sulfanilamide administered by inhalation led to the following experiments. Harris, Sommer and Chapple[1] reported on the inhalation of sulfathiazole microcrystals (Smith, Kline and French) whereas our own experiments utilized ordinary dry sulfanilamide powder (Merck). In Harris, Sommer and Chapple's experiments white mice and guinea pigs were used as test animals. Blood levels of as high as 16.57 mg sulfathiazole/100 cc were observed in the mice which were kept for varying intervals of time up to 4 hours in a box containing the sulfathiazole "smoke." To test whether the absorption actually occurred in the lungs, tracheotomy and ligation of the esophagus was performed in 2 guinea pigs and the spray of microcrystals put into the trachea. Blood sulfathiazole levels attained were 3.46 and 1.93 mg/100 cc.

Harris *et al.*, also made therapeutic observations, finding that their inhalation procedure caused a great reduction in mortality due to inhalation of pneumococcus in mice suffering from influenza. Boissard and Fry[2] administered sulfanilamide powder by nasal insufflation to 26 children with a chronic mixed *C. diphtheriae* and hemolytic streptococcus infection of the nose. Good therapeutic results were obtained, but no blood sulfanilamide levels were reported nor was any attempt made to cause the sulfanilamide to go into the deeper portions of the respiratory tract.

Experiments. Bag method. Two dogs weighing 13.4 and 9.8 kg respectively were anesthetized with nembutal and a flannelette bag tied tightly around the snout of each of them. The flannelette was porous enough so that they could breathe through it. One end of the bag was attached to a blow bottle containing sulfanilamide powder through which was blown a current of air from an electric air pump. During the blowing of the air the blow bottle was continually shaken. The amount of sulfanilamide introduced into the animal was calculated approximately by estimating the amount blown out of the bottle and subtracting from this the amount caught in the interstices of the flannelette. This represents a maximum value and the true weight of drug inhaled is probably much less due to loss on the animal's hair and through the bag. The maximum

TABLE I.
Blood Sulfanilamide Levels Attained After Inhalation by the Bag Method in Two Dogs.

Dog	1			2		
Wt, kg	13.4			9.8		
Max. amt of Sulfanilamide, g	16			42		
Inhalation time	3:11-3:18; 3:21-3:33; 3:36-3:55 P.M., 12-11-42 Total = 38 min.			2:43-2:49; 2:51-2:58; 3:00-3:07; 3:18-3:22 P.M., 12-14-42. Total = 24 min.		
	Date	Time	Level	Date	Time	Level
Blood Sulfanilamide mg/100 cc	12-11	3:22 P.M.	1.0	12-14	3:30 P.M.	2.2
	"	4:00 "	2.3	"	4:50 "	2.4
	"	11:50 "	1.3	"	10:55 "	2.1
	12	10:15 A.M.	1.2	17	3:30 "	2.0
	21	11:00 "	neg.			

[1] Harris, T. N., Sommer, H. E., and Chapple, C. C., *Am. J. Med. Sci.*, 1943, **205**, 1.

[2] Boissard, J. M., and Fry, R. M., *Lancet*, 1942, **1**, 610.

TABLE II.
Urine Sulfanilamide Levels Attained After Inhalation by the Bag Method in Dog 2.

Date	Time	Vol. urine specimen, cc	Urine sulfanilamide, mg/100 cc
12-14	5:30 P.M.	50	50
"	11:05 "	30	250
15	5:00 "	90	60
17	3:30 "	10	trace

blood sulfanilamide levels attained were 2.3 and 2.4 mg/100 cc as shown in Table I. The blood levels showed a prompter rise than did the urinary drug levels as shown in Table II. These 2 dogs lived and were observed for some time following the inhalation and showed no ill effects.

Intratracheal method. In 3 additional dogs under nembutal anesthesia a catheter attached to the sulfanilamide powder blow bottle was inserted into the trachea through the larynx about as far as the bifurcation. Blood sulfanilamide levels attained by this method were considerably higher than by the other, the maximum levels reached being 33.2, 33.2, and 12.2 mg/100 cc in the 3 experiments as shown in Fig. 1. Brief protocols follow:

Experiment 3. Dog weight, 11.0 kg, less than 13 g sulfanilamide powder inhaled. Initial blood level of 12.2 mg/100 cc at 3:10 p.m. on 12-18-42, 8 minutes after cessation of 34 minutes of inhalation. Two days later the animal was very groggy, ate and drank little and coughed up considerable loose phlegm. At this time the high blood level shown in Fig. 1 of 20 mg/100 cc may have been due to swallowing coughed-up sputum. The early development of a high level of 12.2 mg almost immediately after the inhalation would, however, argue for a respiratory tract absorption. On December 21 the dog appeared normal except for a frequent

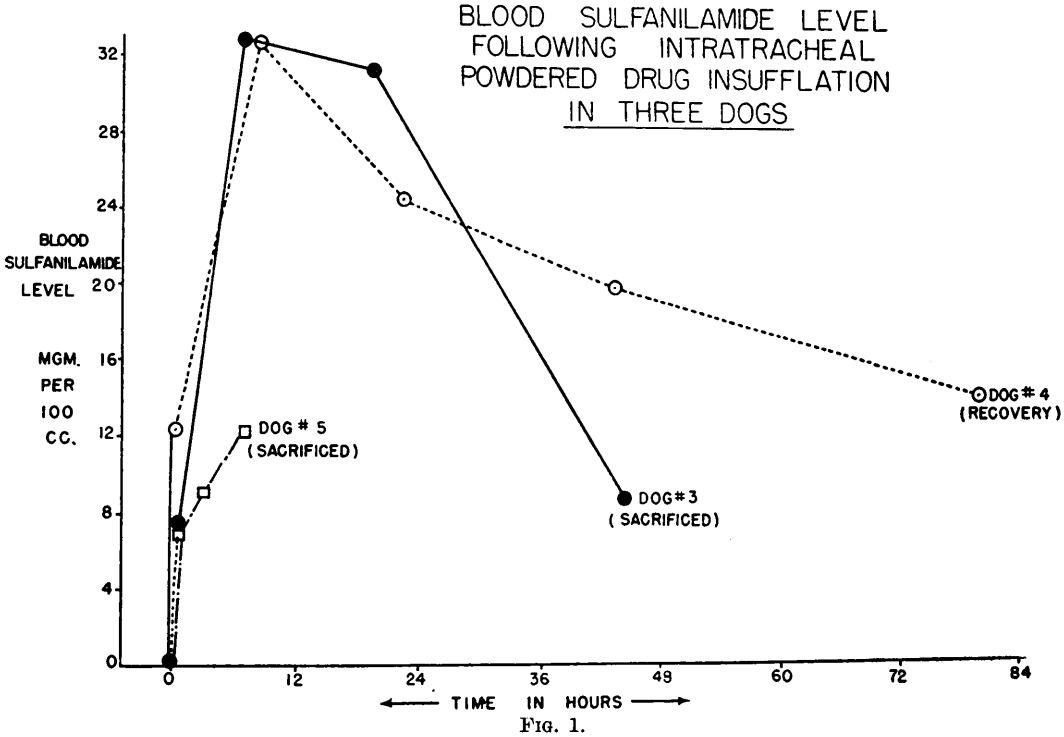

FIG. 1.

The rise in blood sulfanilamide concentration occurring after intratracheal powdered drug insufflation.

raspy, non-productive cough. It was killed with sodium cyanide and necropsy revealed nothing abnormal in any organs except the lungs, where long reddish yellow membranous strands of fibrinous material protruded from and partially plugged the main bronchi and some smaller bronchioles. Otherwise the lungs appeared normal and there was no evidence of sulfanilamide powder in the lungs or trachea.

Experiment 4. Dog weight, 18.4 kg, less than 17 g sulfanilamide powder inhaled. Initial blood level of 7.7 mg/100 cc at 4:40 p.m. on 12-18-42, 6 minutes after cessation of 50 minutes of inhalation. The animal had a harsh cough with practically no sputum during the first few days after inhalation. The dog was groggy on December 19 but was apparently normal the next day. The urine sulfanilamide level at noon the day after the inhalation was 1660 mg/100 cc. Large feathery crystals were seen in the test tube of urine. Recovery.

Experiment 5. Dog weight, 12.6 kg, less than 7 g sulfanilamide powder inhaled. Initial blood level of 7.1 mg/100 cc at 3:50 p.m. on 12-21-42, 3 minutes after cessation of 54 minutes of inhalation. The animal was killed with sodium cyanide 6 hours after the inhalation. Necropsy revealed nothing unusual in the kidneys, liver, heart, spleen, adrenals, or other organs except the trachea and bronchi. In the trachea and larger bronchi there were probably several grams of mucoid coated sulfanilamide while the smaller bronchioles showed only a small fleck of this material.

Summary and conclusions. The intratracheal insufflation of sulfanilamide powder in dogs will produce high blood levels of the drug (up to 33.2 mg/100 cc) associated with high urinary levels (up to 1660 mg/100 cc) and accompanied by general symptoms of depression and intoxication. A local accumulation of the powder persists during at least the first 6 hours and is followed by cough and signs of irritation of the lining of the trachea and bronchi which may last for several days.

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Attempts to Acclimate Poliomyelitis Virus to Tomato Plants.*

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It is now generally believed that the gastrointestinal tract of the human from the stomadeum to the hind gut is probably the main portal of entry of poliomyelitis virus.[1,2,3]

Because the gastrointestinal tract has been implicated, it has been thought by us that the virus might be found on and ingested with food. The common edible plants present no ostensible signs of infection, but it is possible that they may become infected without external or internal evidence of disease. We were not able, however, to demonstrate the presence of poliomyelitis virus in or on fruits, etc.,[4] although our failure to find it does not mean that it was absent. It was decided to see if poliomyelitis virus could be acclimated to some common plant.

The tomato was chosen for this work. Forty-eight tomato plants were planted in the university greenhouse and allowed to grow to an age where 4 separate shoots had appeared along the main stalk. They were then divided into sets of 6 and tested with one of the following materials: (a) "enteric"

* Sponsored by the National Foundation for Infantile Paralysis, Inc.

1 Toomey, John A., *J. Ped.*, 1941, **19**, 103.

2 Toomey, John A., *Ann. Int. Med.*, 1935, **8**, 7.

3 Toomey, John A., *J. Ped.*, 1936, **8**, 664.

4 Toomey, John A., Takacs, W. S., and Tischer, Linda A., *J. Ped.*, 1943, **23**, 168.