as much as 8°C, while little change is observed in patients with advanced peripheral disease. Digital blood flow in normal individuals shows a marked increase, while it rises only slightly in patients with moderate or advanced peripheral arterial disease. In all groups the fall in systolic pressure is greater than that in diastolic pressure. From these observations it may be concluded that SC 1950 is an effective spasmolytic agent, capable of increasing the blood flow to the periphery, but beset by a number of side reactions upon intravenous as well as rectal administration.

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Adsorption, Distribution and Excretion of Tripelennamine (Pyribenzamine). (17702)

E. LEONG WAY* AND ROBERT E. DAILEY.†

From the Department of Pharmacology, George Washington University, School of Medicine, Washington, D.C., the College of Pharmacy and the Division of Pharmacology, School of Medicine of the University of California, San Francisco.

Despite the wide therapeutic usage of tripelennamine (Pyribenzamine), little is known in regard to the physiological disposition of this antihistaminic agent. The urinary excretion of tripelennamine after oral administration has been reported to be about 10%(1), 15.8-25.5%(2), and greater than 85%(3). So far as we have been able to ascertain, the tissue distribution of this compound has not been reported. Our interest in general in the metabolism of basic amines of therapeutic interest led us to investigate the absorption, distribution, and excretion of tripelennamine.

Procedure and results. Estimation of tripelennamine. This was accomplished by applying a general procedure for organic bases described by Brodie and Udenfriend(4,5). The method is based upon the extraction of the base from tissue brei with an organic solvent and then reacting the compound with methyl orange to form a colored complex which is soluble in the solvent and can be measured photometrically. Technical grade benzene was found to be a suitable solvent for quantitatively extracting tripelennamine from tissues. Low blanks (optical density less than 0.015) were obtained for most tissues.‡ A high degree of specificity for the method was attained by washing the benzene extract of tissue with 0.5 M phosphate buffer pH 7. This procedure resulted in the removal of a small amount of interfering material, presumably metabolic products of tripelennamine, which reacted as the parent compound.

To illustrate the specificity of the procedure the distribution ratios of tripelennamine between benzene and water at various pH values were compared with those of apparent tripelennamine recovered from tissue minces of rats given the compound. The results, as shown in Table I, indicate that the method is highly specific since the distribution ratios of the recovered drug are in good agreement with those of a known sample of tripelennamine.

* Present address: University of California, Medical Center, San Francisco, Calif.

† Present address: Smith, Kline, and French Laboratories, Philadelphia, Pa.

1. Perlman, E., *J. Pharmacol.*, 1949, v95, 465.

2. McGavack, T. H., Drekter, I. J., Schutzer, S., and Heisler, A., *J. Allergy*, 1948, v19, 251.

3. Jones, H. M., and Brody, E. S., *J. Am. Pharm. Assn.*, 1949, v38, 579.

4. Brodie, B. B., and Udenfriend, S., *J. Biol. Chem.*, 1945, v158, 705.

5. Brodie, B. B., Udenfriend, S., and Dill, W., *J. Biol. Chem.*, 1947, v168, 335.

‡ Technical benzene on standing may give higher brain blanks and must be checked at frequent intervals for such changes. Also, brain blanks vary with different samples of technical benzene.

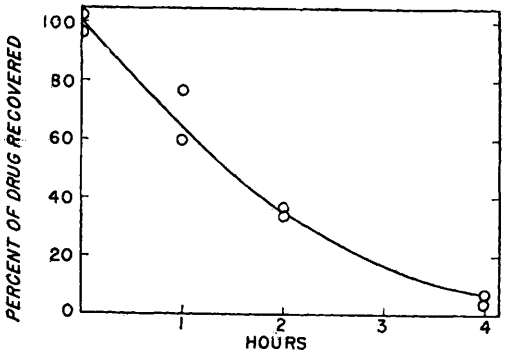
TABLE I.
Distribution Ratios of Tripelennamine Remaining in Benzene to Total Drug (Added or Recovered) After Equilibration with Various Buffers.

Sample description	Buffer pH					
	4	5	6	7	9	14
Added to water	8	40	90	101	104	—
Recovered from liver	11	42	85	101	99	103
" " kidneys	12	43	83	95	96	—
" " brain	9	36	90	108	101	—
" " lungs	6	34	91	104	100	—
" " spleen	10	41	91	102	101	—
" " heart	10*	34	88	103	107	—
" " muscle	22*	41	88	98	106	—

* Levels too low for accurate determination.

The likelihood of two substances having the same distribution ratios under such rigidly defined physical conditions is rather remote(4).

Rate of absorption. The rate of oral absorption of tripelennamine was studied on 8 rats. After administering 100 mg/kg of the compound by stomach tube, 2 rats were sacrificed at 0, 1, 2 and 4 hours later. Their entire gastro-intestinal tracts were removed, diluted to 500 cc, thoroughly minced, and 1 cc aliquots analyzed for tripelennamine. The results as shown in Fig. 1 suggest that tripelennamine is rapidly and completely absorbed. Excretion of the unchanged compound by the gastro-intestinal tract appears to be relatively minor. To rule out that the rapid disappearance of the compound may be due in part to its destruction in the enteric tract, 2 rats were given a known amount of the compound by stomach tube and sacrificed shortly thereafter. Their entire gastro-intestinal tracts plus contents were removed, suspended in Ringer and incubated for 2 hours.



RATE OF DISAPPEARNCE OF PYRIBENZAMINE FROM THE GASTRO-INTESTINAL TRACT AFTER ORAL ADMINISTRATION.

FIG. 1.

On analyzing for tripelennamine in the usual manner, no alteration in its concentration was noted.

Tissue Distribution of Tripelennamine. Studies were made chiefly on rats. The first group of animals were given 50 mg/kg of tripelennamine hydrochloride intraperitoneally and were sacrificed at various time intervals. Various organs were removed, minced and analyzed for tripelennamine. The results in Table II indicate that tripelennamine rapidly leaves the blood and localizes in tissues. Considerable variation in tissue levels after intraperitoneal administration of the compound is apparent from the results. It is of interest to note that highest concentrations were found in the lungs. High levels of the agent were also present in the liver, kidneys and the spleen. Brain also contained appreciable quantities of tripelennamine and low levels of the compound were detected in the blood, muscle and heart. That extensive accumulation of tripelennamine does not occur is shown by the fact that the drug was not detectable in tissue 24 hours after its repeated administration for several days. Oral administration resulted in elevated levels in the liver (Table III). Studies made on a guinea pig, gave a distribution pattern similar to that obtained with rats and the localization of tripelennamine in the lungs appeared even greater.

It should be pointed out that in order to increase the accuracy of measuring tripelennamine in tissues, the dose of the drug administered was larger than that usually necessary to induce pharmacologic effects. However, the results resemble somewhat those re-

TABLE II.
Distribution of Tripelennamine in Animals after Intraperitoneal Administration.

Dose schedule	Time sacrificed, hr	mg/kg fresh tissue							
		Brain	Lungs	Liver	Kidneys	Spleen	Heart	Muscle	Blood
Rats									
50 mg/kg	1	27	43	37	31	83	7	6	3
	1	18	38	25	29	11	5	3	2
	1	15	63	33	30	14	5	4	2
50 mg/kg	2	5	24	8	12	5	5	4	—
20 mg/kg 2 × daily 4 days	24	<2	<2	<2	<2	<2	<2	<2	<2
	24	<2	<2	<2	<2	<2	<2	<2	<2
30 mg/kg 3 × daily 4 days	24	<2	2	<2	<2	4	<2	<2	<2
	24	2	<2	<2	<2	<2	<2	<2	<2
50 mg/kg 2 × within 60 min.*	all dead 10′ after 2nd inj.	66	75	187	187	187	27	22	9
Same	all dead 30′ after 2nd inj.	—	78	105	75	123	—	—	5
60 mg/kg single inj.	died within 60′	35	39	—	—	—	—	—	25
Guinea pigs									
50 mg/kg	1	16	130	14	27	32	10	—	2
100 mg/kg	died within 20′	57	81	270	69	71	54	—	12
”	died within 20′	60	146	270	88	128	37	—	23

* Pooled organs of 6 rats.

TABLE III.
Distribution of Tripelennamine in Rats 1 Hr after 100 mg/kg Orally.

mg/kg fresh tissue								% total dose recovered in gastrointestinal tract + contents
Brain	Lungs	Liver	Kidney	Spleen	Heart	Muscle	Blood	
7	8	18	7	<2	<2	<2	<2	77
—	4	34	9	6	<2	<2	<2	61

ported for another antihistamine agent, diphenhydramine (Benadryl) by Glazko and Dill(6) and our previous findings(7,8) on other basic amines (Demerol, and d,l methadone).

Further evidence that tripelennamine rapidly leaves the blood and concentrates in tissue is indicated in experiments following single and repeated intravenous injections of the drug into the saphenous vein of unanesthetized rats. Although the intravenous LD_{50} of tripelennamine in rats is reported to be 12 mg/kg(9), it was found possible to inject

6. Glazko, A. J., and Dill, W. A., *J. Biol. Chem.*, 1949, v179, 403.

7. Leong Way, E., Gimble, A. I., McKelway, W. P., Ross, H., Sung, C. Y., and Ellworth, H., *J. Pharmacol.*, 1949, v96, 477.

8. Leong Way, E., Sung, C. Y., and McKelway, W. P., *J. Pharmacol.*, 1949, v97, 222.

9. Mayer, R. L., Hays, H. W., Brousseau, D., Rennick, B., and Yonkman, P. P., *J. Lab. Clin. Med.*, 1946, v31, 749.

TABLE IV.
Distribution of Tripelennamine in Rats after Intravenous Administration.

Dose, mg/kg	Schedule	Time sacrificed	mg/kg fresh tissues							
			Brain	Lungs	Liver	Kidneys	Spleen	Heart	Muscle	Blood
15	Single inj.	Died 3′	152	91	6	5	5	122	20	6
15	″	Died 3′	85	66	—	—	—	—	—	16
7.5	″	*3′	36	51	<2	2	6	15	2	3
5	″	3′	20	61	—	—	—	10	—	<2
40	Repeated inj.† in 80′	30′	15	16	8	18	18	2	3	<2
40	40′	30′	26	36	12	25	22	6	9	11
35	30′	30′	38	67	21	49	24	9	9	—
20	45′	15′	24	27	10	20	14	3	3	2
30	25′	Died	38	62	—	—	—	—	—	3
20	15′	″	49	73	10	—	—	—	—	14
50	35′	″	55	88	17	92	37	23	14	10

* Convulsing when sacrificed.
† 5-10 mg fractions at 5-10′ intervals.

the animal with as much as 40 mg/kg by this route when the dosage was administered over a 30-40 minute period in 5-10 mg/kg fractions. On sacrificing these animals 30 minutes after the last injection and analyzing their tissues for tripelennamine, lung levels were again found to be highest. Brain, kidneys and spleen levels were almost as high, and liver concentration, somewhat lower (Table IV). The reversal in order of brain and liver as to the amount of tripelennamine present was the chief difference in tissue distribution found between intravenous and intraperitoneal administration of the compound.

Animals which did not survive a given tripelennamine dosage were analyzed immediately upon cessation of respiration for tissue levels of the compound. The lung and brain levels in the animals which died from intravenous administration were high and liver levels low. In contrast animals which died after intraperitoneal administration of tripelennamine had exceedingly high concentrations of the drug in the liver, spleen and kidneys, but the levels in the brain, lung and heart were approximately comparable to the figures obtained after intravenous administration.

The concentration of tripelennamine in the brain appears to be related to its toxic effects. Four animals which were sacrificed during or shortly after having convulsive seizures had tripelennamine brain levels ranging from 24-38 mg/kg. Of the 4 animals having a brain level between 35-38 mg/kg, 2 died and the other 2 experienced severe convulsions before they were sacrificed. The brain levels of 5 other rats which died were over 40 mg/kg (range 45-152 mg/kg). Also the level from the pooled brains of 6 rats which died from intraperitoneal administration was 66 mg/kg.

Urinary Excretion of Tripelennamine. In 4 humans (3 males and 1 female) after 50-100 mg of tripelennamine orally, less than 1% was recoverable in the urine after 15-24 hours. This is considerably less than the values (15.8-22.5%) reported by McGavack, *et al.* who also used the methyl orange technic and is probably attributable to the fact that they used much higher doses of tripelennamine (400 mg). Perlman(1) reported results similar to ours and indicated also that about 10% is excreted in the urine in a conjugated form which can by hydrolyzed in alkali to tripelennamine. In partial confirmation of his findings, we found that on subjecting the urine of individuals receiving tripelennamine to alkaline hydrolysis, the amount of methyl orange reactants recovered was increased about 8 fold. The high urinary excretion values (86-91%) reported by Jones and Brady(3) may be attributed to the fact that they were measuring essentially the metabolic products of tripelennamine.

In 4 rats which were given 50 mg/kg of tripelennamine intraperitoneally, less than 0.5% was present in the urine after 5 hours and less than 2% after 24 hours. Since our earlier studies established that storage of the

compound was not prolonged and its excretion via gastro-intestinal tract was negligible, it is concluded that the compound is to all practical purposes completely metabolized in the body.

The low urinary excretion of tripelennamine is not unlike results we have found with other antihistamines, diphenhydramine (Benadryl), phenindamine (Thephorin) and pyranisamine (Neo-antergan), which are excreted in the urine only to a minor extent after oral administration(10,11).

Role of the liver in the metabolism of tripelennamine. Preliminary studies *in vitro* and *in vivo* indicate that the liver is important for metabolizing tripelennamine. In studies with tissue slices of various organs, the liver was found to be by far most active for altering tripelennamine. Less than 10% of tripelennamine was recovered after aerobic incubation of 20 μg of the compound for 2 hours at 38° with 200 mg of liver slices suspended in Krebs-Ringer solution. In 2 rats which were partially hepatectomized, severe convulsions were noted and one animal died after the administration of 40 mg/kg of tripelennamine intraperitoneally, whereas this did not occur when 2 laparotomized rats were given the same dose. Also, in our distribution studies with normal animals, convulsions were not noted after 50 mg/kg of tripelennamine.

Summary. Tripelennamine (Pyribenzamine) was estimated by the Brodie methyl orange technic which was modified to give a high degree of specificity. The compound is rapidly and completely absorbed by rats following oral administration. It rapidly leaves the blood and localizes in all tissues especially lungs. Brain, kidneys, spleen, liver and heart all may concentrate appreciable amounts, the level of tripelennamine present in each organ being somewhat dependent upon its mode of administration. High brain levels of tripelennamine were consistently noted with lethal doses of the compound. Prolonged storage of the compound does not occur and only small amounts are excreted via the urine and feces. It is concluded that the compound is almost completely metabolized in the body. The liver subsequently was found to be the most active organ for metabolizing tripelennamine.

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10. Leong Way, E., Overman, J. R., and Howie, D. L., *Fed. Proc.*, 1947, v6, 382.

11. Unpublished findings.

Effect of Feeding Polyoxyethylene Monostearates on Growth Rate and Gross Pathology of Weanling Hamsters.* (17703)

B. S. SCHWEIGERT, B. H. MCBRIDE, AND A. J. CARLSON.

From the Division of Biochemistry and Nutrition, American Meat Institute Foundation, Departments of Biochemistry and Physiology, University of Chicago.

Considerable interest has developed in studying the effects of ingesting emulsifying agents such as polyoxyethylene derivatives of fatty acids on the assimilation of various lipoidal materials(1). The present study was undertaken to determine the effect of feeding polyoxyethylene monostearate preparations on the growth rate, food efficiency and gross pathology of weanling hamsters.

Experimental. Weanling hamsters† (4-6 weeks of age) of mixed sexes were placed in individual cages in an air-conditioned room

* We are indebted to Mr. Donald Kraybill and Mr. Roy Ring for their assistance in the care of the animals.

1. Anon., *Nutrition Rev.*, 1949, v7, 205.

† Obtained from the Haskins Rabbitry, St. Louis, Mo.