plastic acini were more regular and rounded in shape than those in the unchanged tumor zones.

The treatment exerted no measurable effect upon the amount of milk secreted by the mamma, nor did histologic examination disclose any departure from the manifestations normally occurring in lactating mammary tissue.

As for the non-suckling and the male animals, pituitary lactogenic hormone in 4 daily doses of 40 units each, administered to 2 females and 2 males bearing transplanted tumors of 42 days, produced no changes in the neoplasms. Likewise similar treatment of 6 spayed females and an equal number of castrated males following 15 injections of 0.25 mg each of progesterone dissolved in sesame oil, or of 2 intact females and 2 males that had received 17 injections of progesterone, exerted no influence on the transplanted cancers. The progesterone, given 3 times weekly, was begun 10 days after transplantation, the lactogenic factor 3 days following the final treatment with the former. Tumors of animals that received only progesterone failed to show changes.

While the administration to 3 normal females and 5 males of 17 injections, given 3 times weekly, of 0.25 mg of progesterone and 0.025 mg of estradiol dipropionate resulted in extensive secretion in the tumors, the alterations did not differ from those induced by this quantity of estradiol alone. Treatment of 2 normal females and an equal number of males with 4 daily doses of 40 units each of pituitary lactogenic hormone, begun 3 days following the completion of the previously described course of progesterone and estradiol, did not enhance the effects of the latter combination of hormones.

Summary. The daily injection of 40 to 80 crop gland units of pituitary lactogenic hormone for 4 to 6 days into rats suckling their young induced secretory changes in a transplanted mammary adenocarcinoma. The hormone produced no effect on the tumors of non-nursing females or normal males. Progesterone also exerted no influence, nor did it affect, when given simultaneously with estradiol dipropionate, the secretory phenomena induced in the neoplastic cells by the latter substance alone. Pituitary lactogenic hormone failed to induce secretion in the tumor cells of animals previously treated with progesterone, and did not enhance the alterations produced by the combined administration of progesterone and estradiol.

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Absorption and Excretion of Sulfamethyldiazine (2-Sulfanilamido-4-methyl-pyrimidine) in Human Subjects.

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Sulfamethyldiazine (2 - sulfanilamido - 4-methyl-pyrimidine) was prepared and characterized by Roblin *et al.*[1] at the same time that they reported on sulfadiazine. Both these drugs were found to be active in mice against experimental pneumococcal and streptococcal infections in mice. The former was found to be 2½ times as soluble as the latter in water at 37°C and its N4-acetyl derivative was also reported to be twice as soluble as that of sulfadiazine. Maximum blood levels in mice of sulfamethyldiazine were found to be slightly higher than those obtained on the same dose of sulfadiazine. The 4-6-dimethyl derivative[2] is considerably

[1] Roblin, R. O., Jr., Williams, J. H., Winnek, P. S., and English, J. P., *J. Am. Chem. Soc.*, 1940, **62**, 2002.

[2] Roblin, R. O., Jr., Winnek, P. S., and English, J. P., *Ibid.*, 1942, **64**, 567.

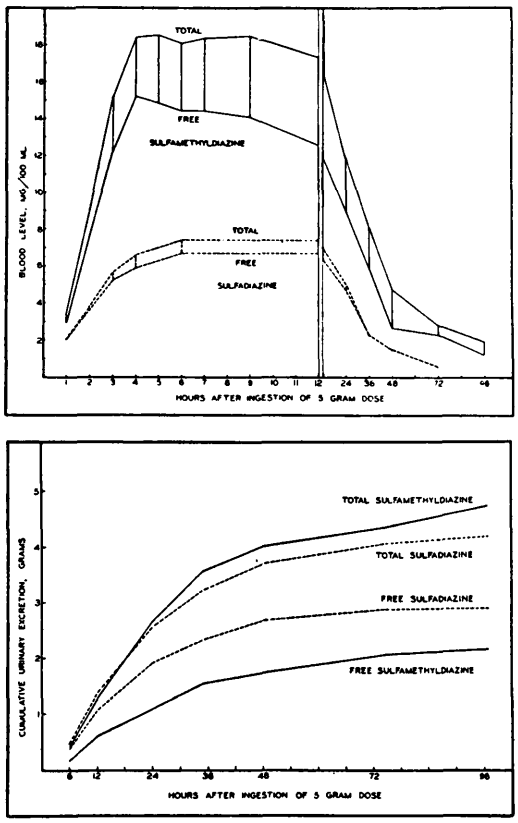

FIG. 1.

Comparison of average values obtained in 3 subjects receiving 5 g of sulfamethyldiazine orally 1 hour after breakfast with those obtained in 11 subjects receiving 5 g of sulfadiazine in the same manner. Each dose was given with 500 ml of water and the daily fluid intake was maintained at about 3 liters.

Above. Average blood levels.

Below. Average cumulative urinary excretion.

more soluble than the monomethyl compound. Numerous reports are available on the use of sulfadiazine and recently reports have appeared in England concerning clinical trials of the dimethyl derivative.[3,4] The present report deals with preliminary studies on the pharmacology of sulfamethyldiazine* in humans and some observations on the antipneumococcal action of this compound. The methods used were the same as those employed in similar studies reported from this laboratory.[5-7]

Blood levels. A single 5 g dose of sulfamethyldiazine was administered to each subject with about 500 ml of water about an hour after breakfast and blood and urine samples were tested as in previous studies[7] except that more frequent blood samples were taken during the first 12 hr. The average blood levels in 3 subjects are shown in Fig. 1 which also shows the average blood levels in 11 subjects who received sulfadiazine in the same manner. The concentration of sulfamethyldiazine in the blood rose more rapidly, attained levels about twice as high, and were sustained for much longer periods than sulfadiazine. Both the total amount and the proportion of the former compound that was found in the conjugated form were greater than for sulfadiazine. The maximum blood levels (Table I) averaged over 20 mg per 100 ml and occurred in from 4 to 9 hr; of this amount about 20% was determined as the conjugated (? acetylated) compounds. After 24 hr, the blood levels of sulfamethyldiazine were from 10 to 14 mg per 100 ml, of which from 2 to 3 mg were conjugated. This compares with an average of 5 mg per 100 ml 24 hr after the sulfadiazine dose, with only small amounts found in the conjugated form. After 72 hr there was still from 1 to 3.5 mg per 100 ml of sulfamethyldiazine in the blood. Most of the drug found in the blood, and sometimes all of it, was shown to be in the plasma (Table II).

Urinary excretion (Fig. 1, lower portion, and Table I). Almost all of the ingested sulfamethyldiazine (84-100%) was recovered from the urine. From 40 to 70% (average 53%) was recovered in the first 24 hr and from 80 to almost 100% (average 89%) was recovered in the first 72 hr. Of the drug excreted during the first 24 hr, from 51 to 61% was recovered as conjugated (? acetyl-

[3] McCartney, D. W., Smith, G. S., Luxton, R. W., Ramsay, W. A., and Goldman, J., *Lancet*, 1942, **1**, 639.

[4] Jennings, P. A., and Patterson, W. D., *Ibid.*, 1942, **2**, 308.

* The sulfonamide drugs used in these studies were supplied by the Lederle Laboratories, Inc.

[5] Strauss, E., Lowell, F. C., Taylor, F. H. L., and Finland, M., *Ann. Int. Med.*, 1941, **14**, 1360.

[6] Peterson, O. L., Strauss, E., Taylor, F. H. L., and Finland, M., *Am. J. Med. Sc.*, 1941, **201**, 357.

[7] Peterson, O. L., and Finland, M., *Ibid.*, 1942, **204**, 581.

TABLE I.
Maximum Blood and Urine Concentrations and Urinary Excretion After a Single 5 g Dose of Sulfamethyldiazine (2-sulfanilamido-4-methylpyrimidine).

Subject	Wt, kg	Max. blood conc., mg/100 ml			Max. urine conc., mg/100 ml			% administered drug recovered in urine		% recovered drug conjugated	
		Free	Total	Hr*	Free	Total	Period*	In 24 hr	In 72 hr	First 24 hr	24-72 hr
1	70	15.1	18.6	5	66	167	24-36	40.0	78.9	51.9	56.7
2	63	17.4	22.4	9	61	135	12-24	49.2	99.2	51.3	56.2
3	65	17.8	21.7	4	46	115	9-12	70.6	93.8	61.5	68.7

*Hours after ingestion of the dose.

TABLE II.
Distribution of Sulfamethyldiazine Between Plasma and Red Blood Cells.

Subject	Hr after dose	Concentration of Sulfamethyldiazine (mg/100 ml)						Hematocrit, %
		Whole blood		Plasma		Cells (calculated)		
		Free	Total	Free	Total	Free	Total	
2	36	8.0	10.2	15.5	19.0	0	0	44.0
	72	2.9	3.2	4.9	5.6	0.4 (?)	0.2	
3	4	12.1	14.7	17.8	21.7	4.3	5.3	43.0
	24	5.1	6.4	7.1	10.0	2.3 (?)	1.6	

ated) sulfamethyldiazine, and from 56 to 69% of the drug recovered during the next 48 hr were in the conjugated form. With sulfadiazine the average urinary recoveries were 52 and 81% during the first 24 and 72 hr respectively; and the proportion of conjugated drug averaged 26% and 35% during the first 24 hr and the next 48 hr, respectively. The maximum concentrations of sulfamethyldiazine in the urine varied from 115 mg per 100 ml in the nine to 12-hr sample in one subject to 167 mg per 100 ml in the 24 to 36-hr specimen in another. Only 44 mg of the former and 66 mg of the latter were determined as the free compound. Examination of the urinary sediments revealed no abnormal elements in any of the specimens except for rare red blood cells in one sample and occasional white blood cells in 3 samples, all obtained from the same patient who received sulfamethyldiazine.

Antipneumococcal activity of sulfamethyldiazine in human blood. This was studied with type III pneumococci by a method similar to that previously used in this laboratory.[8] The tests were carried out with defibrinated blood obtained 1 hr and 18 hr after ingestion of a 4 g dose. The blood levels were from 1.7 to 5.5 mg of free drug per 100 ml. The results are shown in Table III. At these low levels, 0.5 ml of the drug-containing blood exerted a marked bacteriostatic action on from 100 to 100,000 pneumococci.

Discussion. The higher blood levels obtained with sulfamethyldiazine suggest that therapeutic levels might be obtainable in human cases with much smaller doses than have been found necessary with sulfadiazine. The greater solubility also offers the possibility of less urinary tract irritation from precipitated crystals. In these respects the monomethyl compound should prove to be superior to the dimethyl derivative since the doses found necessary to maintain levels of the latter which are comparable to those obtained with sulfadiazine are usually twice those ordinarily employed.[3,4] However, the possibility of a deleterious action of sulfamethyldiazine on kidney structures, which is different from that which is attributable to the deposit of crystals of the drug, is suggested from chronic toxicity experiments in animals, and was not observed with sulfa-

[8] Spring, W. C., Jr., Lowell, F. C., and Finland, M., *J. Clin. Invest.*, 1940, **19**, 163.

TABLE III.

Antipneumococcal Action of Fresh Defibrinated Human Blood Obtained After Ingestion of a 4 g Dose of Sulfamethyldiazine.

Subject	Hr after dose	Blood level in mg/100 ml (free)	Hr. of incubation	Pneumococci added					
				10^6	10^5	10^4	10^3	10^2	10
H	0*	0	24	++	++	++	++	++	++
	1	1.7	24	++	++	++	+	—	—
			48	++	++	++	++	±	±
	19	3.8	24	++	—	—	—	—	—
			48	++	++	±	±	±	0
T	0	0	24	++	++	++	++	++	++
	1½	4.5	24	++	++	++	++	++	—
			48	++	++	++	++	++	±
	18	4.9	24	++	++	—	—	—	—
			48	++	±	±	±	±	0
M	0	0	24	++	++	++	++	++	0
	1	5.5	24	++	++	—	—	—	—
			48	++	++	±	±	±	±
	18	3.0	24	++	++	—	—	—	—
			48	++	++	±	±	±	0

0.5 cc defibrinated blood; type III pneumococcus in active growth phase; inoculum contained in 0.1 cc of broth; growth in sealed pyrex tubes rotated in incubator.

++ equals full growth with color change; + equals partial growth with slight color change; — equals no color change; ± equals no color change, few colonies in subcultures on blood agar.
*Control.

diazine.[9] The acute toxicities of sulfadiazine and sulfamethyldiazine, however, were approximately the same. Any clinical trial must, therefore, be undertaken with caution, particularly with respect to its use in patients requiring prolonged therapy. The possibility of neurological complications such as those encountered with sulfamethylthiazole must also be kept in mind.

Summary and conclusions. After a single 5 g oral dose of sulfamethyldiazine, the blood levels rise much more rapidly, higher levels are attained, and these are sustained longer than after a similar amount of sulfadiazine. The monomethyl compound was excreted more completely in the urine than sulfadiazine, but a larger proportion of the former was found in the conjugated (? acetylated) form. Sulfamethyldiazine warrants a clinical trial with doses that are smaller than those customarily used. Particular attention, however, should be paid to the possibility of renal or nerve damage in cases in which prolonged treatment with the drug is contemplated.

[9] Feinstone, W. H., Follis, R. H., Jr., and Williams, R. D., Sulfamethyldiazine (1 Sulfanilamido-4-methylpyrimine) as a chemotherapeutic agent. To be published.