TABLE III. Hog Vasopressin and ACTH-Release.

Preparation	l-Arterenol .0002M	Dose vasopressin per flask, μg	Ratio, exp. to control	95% limits
Benfey	Present	.5	1.5	.9→2.6
"	"	.5	1.4	.8→2.6
m-cresol purified	Absent	.2	1.3	.9→1.7
Idem	"	.5	.9	.8→1.2

terior pituitary tissue. The results reported here indicate that free histamine is not the neurohumour responsible for the release of ACTH. If histamine in pitressin is bound in a peptide linkage, as Swingle *et al.*(4) suggest, then it should have been liberated by their extraction procedure. In our hands posterior pituitary preparations lose their CRF activity when subjected to overnight hydrolysis in 6N HCl at 110°C(15), a procedure which would not destroy histamine. Similarly, we cannot support the claims of Martini *et al.*(5) that vasopressin may stimulate the anterior lobe to release ACTH. Their results were obtained with impure preparations which could contain CRF(7). The same conclusion, with respect to the absence of CRF activity in histamine, was reached independently by Guillemin(16).

Summary. Histamine and purified lysine (hog) vasopressin did not accelerate the release of ACTH by isolated rat pituitaries. In contrast, purified CRF preparations in minute doses significantly increased the release of ACTH.

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Sulfamethoxypyridazine: Preliminary Observations on Absorption and Excretion of a New, Long-Acting Antibacterial Sulfonamide.* (22569)

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Antimicrobial agents that have a prolonged action have potential advantages, particularly if they are effective in prophylaxis, or in the prolonged treatment of chronic or subacute infections, or in the suppression of chronic infections that are difficult to eradicate. A new antibacterial sulfonamide, sulfamethoxypyridazine (3-sulfonamido-6-methoxypyridazine)† was found to have the following properties, judged from experiments in dogs, rabbits and mice: high solubility in urine, good absorp-

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† Generously provided by Lederle Laboratories Division, American Cyanamid Co. under the trademark Kynex (Lederle).

tion from the gastrointestinal tract, very slow urinary excretion, poor acetylation, good penetration into the brain, and antibacterial activity equivalent to sulfadiazine(1). These properties were of sufficient interest to warrant exploration of this agent in humans. Preliminary observations on absorption and excretion of this compound after a single oral dose in normal subjects are here presented.

Materials and methods. Each of 6 normal, young adult males was given 4.0 g (8 tablets of 0.5 g each) orally with a glass of water before breakfast. Oxalated venous samples of blood were obtained just before and 1, 3, 5, 8, 12, 24 and 105 hours after the dose. Each subject emptied his bladder just prior to the dose and complete collections of urine were made during the following 72 hours in 2, for 48 hours in 2 others and for 24 hours in a fifth subject. Food and fluids were taken *ad libitum*. A voided specimen of urine was also obtained from each subject at the time of the last blood. The concentrations of free and total sulfonamide, calculated as sulfamethoxypyridazine, were determined by the method of Bratton and Marshall(2). Part of some of the specimens of blood was also used to determine the hematocrit and the concentration of the drug in the plasma in order to calculate the concentration in the blood cells and the rate of renal clearance of the drug from the plasma.‡

Results. Blood levels. The concentration of total sulfamethoxypyridazine in the whole blood of each of the subjects is shown in Fig. 1; the averages of these values and of those for the free drug in all of the subjects are also shown. The maximum concentrations (average about 15 mg per 100 ml total and 13 mg per 100 ml free) were achieved 5 hours after the dose was taken and maintained for the next 3 hours; after that time the levels fell rather slowly, although the rate of fall was somewhat faster between 8 and 12 hours than it was later. At 24 hours the average concentrations of total and free drug were 12.1 and

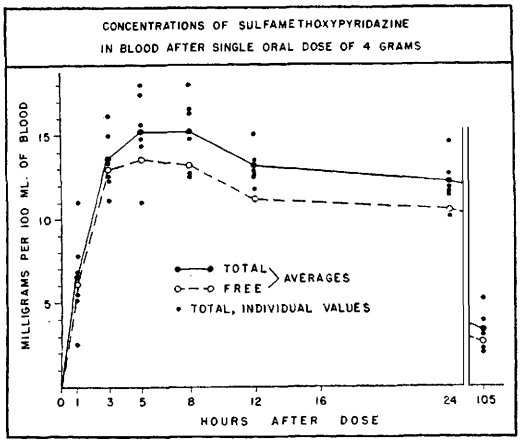

FIG. 1.

10.3 mg %, respectively. After 105 hours there were still appreciable concentrations in the blood, averaging 3.3 and 2.8 mg % total and free drug, respectively. The proportion of the drug in conjugated—presumably acetylated—form was very small in the first 3 hours and subsequently averaged less than 15% (range 5-22%). *Diffusion into blood cells.* The concentrations of total sulfamethoxypyridazine observed in whole blood and plasma and the concentrations in the cells calculated from these values and the hematocrit are shown for a few random specimens in Table I. These crude values indicate little or no diffusion of the drug into the blood cells. *Renal clearance.* The rates at which sulfamethoxypyridazine is cleared from the plasma

TABLE I. Diffusion of Sulfamethoxypyridazine into Erythrocytes.

Subject	Hr after dose	Hematocrit	Conc.,* mg/100 ml — Whole blood	Plasma	Erythrocytes, calculated
W.J.	5	48.3	11.1	25.4	0
	8	46.3	12.6	22.6	1.1
	12	47.0	11.8	24.4	0
	24	47.5	12.6	21.0	3.5
	105	47.5	4.1	8.9	0
R.N.	5	42.5	14.8	25.2	0.7
	8	42.6	12.6	22.4	0
	12	41.6	12.7	25.2	0
C.P.	8	44.7	16.4	28.2	1.8
R.C.	3	46.9	15.0	23.6	5.3
	5	44.7	15.6	29.6	0
	8	43.6	16.4	26.2	3.7

* Total drug.

‡ The authors are indebted to Miss Ellen J. Doyle and Miss Mary I. Kendrick for carrying out the chemical determinations.

TABLE II. Renal Clearance of Sulfamethoxypyridazine.

Subject	Period of study: Hr after dose	No. of min.	Avg concentration in plasma, mg/100 ml: Free	Acetyl	Amt excreted in urine during period, mg: Free	Acetyl	Plasma cleared, ml/min.: Free	Acetyl	Clearance ratio: Acetyl/Free
W.J.	5- 8	180	22.2	1.8	49	34	1.2	10.5	8.6
	8-12	240	21.8	1.7	64	52	1.2	12.8	10.7
R.N.	5- 8	180	22.8	1.0	79	49	1.9	27.0	14.2
	8-12	240	22.8	1.0	147	79	2.7	33.0	12.2
C.P.	5- 8	180	23.0	5.2	78	146	1.9	15.6	8.2

by the kidney were calculated in 3 subjects for periods when the blood levels were at or near maximal (Table II). The free drug was cleared at a very slow rate, averaging 1.8 ml of plasma per minute; the acetylated drug was cleared at an average rate of 19.8 ml per minute or 11 times that of the free drug. *Urinary excretion.* Since the fluid intake was not controlled in this study, the rate of urine flow varied considerably among the subjects and at different times in the same subject. As a result, the concentrations of drug in the urine varied widely (Fig. 2). In the subject with the largest volume of urine concentrations of total drug in the individual specimens of urine collected between 5 and 24 hours after the dose varied between 29 and

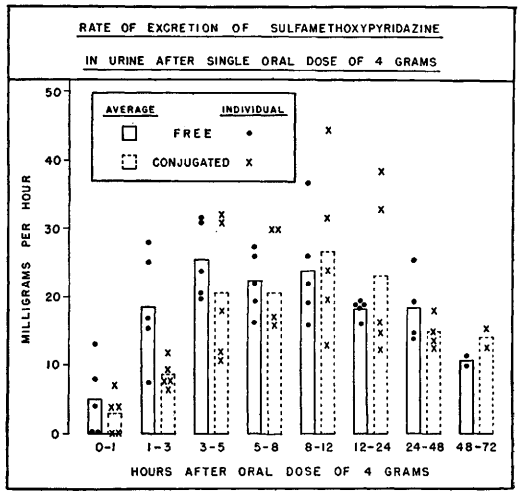

FIG. 3.

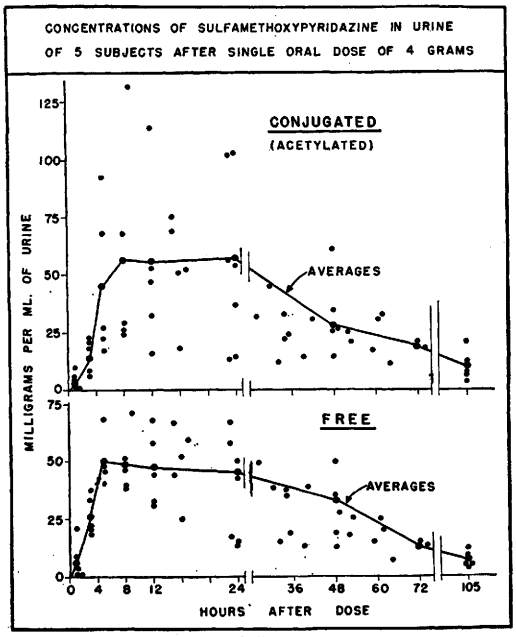

FIG. 2.

66 mg %, in contrast to values ranging from 136 to 204 mg % in the subject who put out the smallest amount of urine. The *rate* of excretion of the drug, particularly in the free form, showed much less variation (Fig. 3). The volume of urine in any given period did not seem to have any marked effect on the rate of excretion of the drug. Average curves for the cumulative excretion of the drug over 72 hours are shown in Fig. 4. In the first 24 hours the average amount excreted was 24.6% (range 18.8 to 31.0%) of the administered dose; an additional 20.2% (range 17.7 to 26.3%) was excreted from 24-48 hours and, of the 2 subjects whose urine was collected during the third 24-hour period, one excreted 13.6% and the other 12.6% of the dose in that time. Of the amount excreted, the proportion determined to be in the conjugated form at different times varied from 35 to 60%, similar fluctuations being noted in each of the sub-

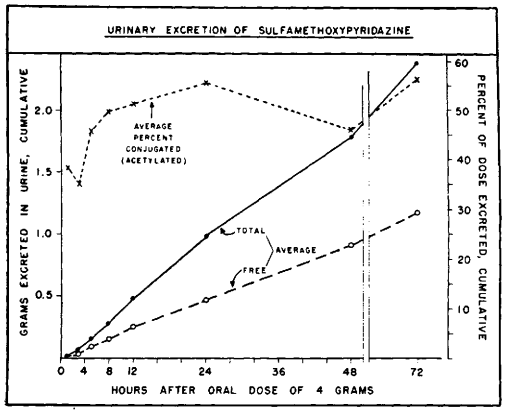

FIG. 4.

jects. Specimens of urine collected 105 hours after the dose still contained concentrations of drug averaging 19.3 mg % total and 7.8 mg % free.

Untoward effects. The urinary sediment was examined microscopically in specimens collected between 8 and 24 hours and revealed no abnormalities. The only untoward effect experienced by 3 of the 6 subjects was some lassitude followed by frontal headache that began between 3 and 5 hours after the dose and lasted 4 or 5 hours; the headache was aggravated by sudden motions of the head but this did not interfere with normal activity.

Summary and conclusions. Concentrations of sulfamethoxypyridazine in blood and urine of 6 normal adult males were determined after a single oral dose of 4 g. The drug was well absorbed, yielding high levels of free drug and only small amounts in acetylated form in the plasma. Little if any of the drug diffuses into the blood cells. The drug is cleared slowly from the plasma, the acetylated form being cleared by the kidney about 11 times as fast as the free drug. Urine concentrations varied up to about 200 mg %, between 35 and 60% being in the conjugated form. Significant levels were still present in the blood and urine 105 hours after the dose. This prolonged action should be of clinical interest and suggests that further exploration of the potentialities of this new sulfonamide drug is warranted.

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Morphological Transformation of *Candida albicans* in Tissues of Mice.* (22570)

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Organisms of the genus *Candida* exhibiting filamentous morphology are commonly seen in smears prepared from the oral and vaginal cavities of infected persons. Cells of *C. albicans* with filamentous morphology have also been observed in deeper tissues including nervous tissue, kidneys, adrenals, cardiac and skeletal muscle and various portions of the gastrointestinal tract(1-5).

In rabbits experimentaly infected by the intravenous injection of *C. albicans,* large numbers of filamentous cells are found especially in kidneys(6,7). On the basis of morphology in tissue Baker(8) has classified *C. albicans* with those fungi which are found in tissue as "filaments and round bodies." Scherr and Weaver(9) have speculated that "when the mycelial phase of the fungus becomes evident in the later stages of an infection, it would appear that some factor which normally favors the Y (yeast) forms has diminished in function."

While studying the host tissue reaction to washed yeast-phase cells of pathogenic fungi, it was observed that cells of *C. albicans* rap-

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