such as the appearance of abnormal mitosis and "nuclear explosions" in normoblasts, alteration of the nuclear pattern of mature and primitive erythroid cells and formation of cells resembling megaloblasts, and production of bizarre, giant metamyelocytes.[2] Similar pathological cells have not been observed in dogs receiving diaminopurine. Therefore, it cannot be inferred that the agent acts as an antagonist of PGA in the metabolism of hematopoietic tissues.

Summary. The administration of large doses of 2,6-diaminopurine in mice and rats can result in death within a few hours. In dogs, large doses caused protracted vomiting, hemorrhagic diarrhea, dehydration and death within 48 hours. Doses permitting survival of rats and dogs for 24 hours or longer produced depletion of bone marrow and damage to epithelium of colon and ileum. The course of intoxication and changes in bone marrow permit a differentiation between the actions of 2,6-diaminopurine and a folic acid-antagonist like 4-aminopteroylglutamic acid.

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Effect of Mercury on Renal Tubular Transfer of p-Aminohippurate and Glucose in Man. (17449)

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The depressant effect of intravenously administered salyrgan (mersalyl) on the maximum renal tubular secretion of p-aminohippurate (Tm_{PAH}) in man has been demonstrated.[1,2] The inability of the mercurials, salyrgan and meralluride (mercuhydrin), to depress the Tm_{PAH} in the dog has also been shown.[2,3] That the maximum tubular reabsorption of glucose (Tm_G) in the dog is unaffected by mercury chloride or meralluride in dosages of 4 mg of bound mercury per kilogram of body weight has been established recently.[3] With regard to the Tm_G in man, Weston *et al.*[4] have reported that the intravenous administration of 2 cc of mercuzanthin or thiomerin, "immediately after several ten minute control periods generally resulted in a 40-80% decrease."

Thus the current concept is that intravenously administered mercurials depress the renal tubular transfer systems for PAH and glucose in man but leave unaffected these systems in the dog. It is the purpose of this study to re-examine the effect of a mercurial, mercuzanthin, on the Tm_{PAH} and Tm_G in man.

Method. Ten fasting male subjects were used in the Tm_G observations. Five of the 10 subjects used for the Tm_G observations plus an additional subject were used in the Tm_{PAH} determinations. All of the subjects were free of demonstrable renal dysfunction. The study pattern was the same for all of the subjects. Using the saturation methods outlined by Goldring and Chaisis[5] 3 control urine collection periods, each of 12 minutes duration, were obtained. Two cc of mercuzanthin* were injected intravenously at the end of the third control period. Immediately following the third period, 5 consecutive 20

1 Brun, C., Hilden, T., and Raaschow, F., *Acta Pharm. Toxicol.*, 1947, **3**, 1.

2 Berliner, R. W., Kennedy, T. J., and Hilton, J. G., *Am. J. Physiol.*, 1948, **154**, 537.

3 Handley, C. A., Telford, J., and LaForge, M., PROC. SOC. EXP. BIOL. AND MED., 1949, **71**, 187.

4 Weston, R. E., Grossman, J., Edelman, I. S., Escher, D. J. W., Leiter, L., and Hellman, L., *Fed. Proc.*, 1949, **8**, 164.

5 Goldring, W., and Chasis, H., *Hypertension and Hypertensive Disease*, The Commonwealth Fund, New York, 1944.

* One cc of mercuzanthin represents 135 mg of the sodium salt of b-methoxy-hydroxy-mercuri-propylamide of cyclopentane dicarboxylic acid equivalent to 39 mg of mercury and 35 mg of anhydrous theophylline.

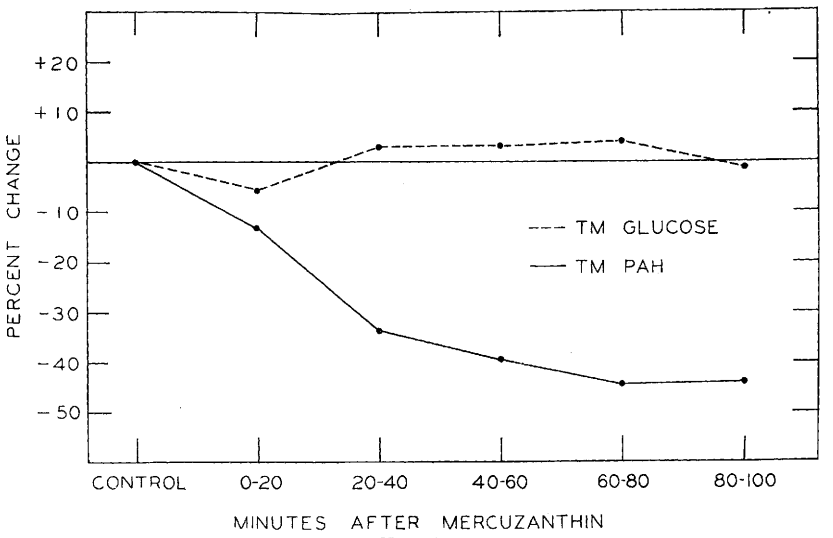

FIG. 1.

The individual points represent the mean per cent change in Tm_G of 10 subjects and in Tm_{PAH} of 6 subjects for 5 consecutive 20 minute urine collection periods following the intravenous administration of 78 mg of organically bound mercury. The control value is based on the mean of three 12 minute urine collection periods for each subject.

minute urine collection periods were obtained. The total time following injection of the mercury to the end of the last urine collection period was 100 minutes. Inulin, used in measuring the glomerular filtration rate, was determined using Harrison's modification of the method of Alving.[6] PAH determinations, using diluted urine and cadmium sulfate filtrates of plasma, were made by the method of Bratton and Marshall.[7] Glucose determinations were made according to the method of Nelson.[8]

Results. When the values for the group were averaged for each period, the maximum depression of Tm_{PAH} was 44.5% of the control value and occurred during the urine collection period from 60-80 minutes following the administration of mercuzanthin (Fig. 1). The mean Tm_{PAH} values decreased from 73.3 mg/min to 44.9 mg/min following the administration of mercury (Table I). This difference is significant ($N = 6$, $t = 11.05$, $P < .01$). In the case of the Tm_G observations, no significant difference was noted between the mean values of the pre- and post-mercurial observations ($N = 10$, $t = .275$, $P > .70$, Table I). The first postmercurial urine collection period (0-20 minutes) was not used in calculation of the mean for either Tm_G or Tm_{PAH} because of the possible effect of the theophylline base on the renal tubular function. The apparent decrease in Tm_G for the first post-mercurial urine collection period (0-20 minutes) is not significant.

Comment. The renal tubular reabsorption of glucose is generally believed to be effected through a phosphorylation mechanism.[9] Assuming that this is the mechanism operative in glucose reabsorption by the renal tubules, mercury must have been ineffective, at least in the amounts used in this study, in blocking the activity of this system. This belief finds an interesting parallel in the studies of Hepler and Simonds.[10] Using mercury chloride, these investigators demonstrated that glycosuria could not be induced in dogs unless the animals showed a 4 + albuminuria and marked renal tubular necrosis. The observa-

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[7] Bratton, A. C., and Marshall, E. K., Jr., *J. Biol. Chem.*, 1939, **128**, 537.

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TABLE I.
Changes in Tm_G and Tm_{PAH} Following Mercury Administration.

	Tm_G, mg glucose/1.73 sq. m/min.			Tm_{PAH}, mg PAH/1.73 sq. m/min.		
Age, yr	Control	Post-mercury	% change	Control	Post-mercury	% change
53	296	316	+ 6.8	98.3	58.3	—40.7
57	206	191	— 7.3	—	—	—
44	254	270	+ 6.3	52.3	23.3	—55.4
59	198	200	+ 1.0	—	—	—
65	248	248	± 0.0	50.6	24.9	—50.8
67	271	312	+15.1	—	—	—
53	377	361	— 4.2	83.2	54.3	—34.7
62	252	221	—12.3	—	—	—
61	224	267	+19.2	83.4	61.5	—26.3
48	246	238	— 3.3	—	—	—
69	—	—	—	71.9	47.2	—34.4
			Mean			
58	257.2	262.5	+ 2.1	73.3	44.9	—40.4

Control values represent the mean of 3 twelve minute urine collection periods. Post-mercury values represent the mean of 4 twenty minute urine collection periods, extending from 20 to 100 minutes following the injection of mercuzanthin.

tion that the Tm_{PAH} is diminished while the Tm_G is unchanged following the administration of mercury strongly implies that the mechanisms involved in PAH and glucose transfer are different. However, in conjunction with this belief, it is interesting to note that the simultaneous measurement of Tm_{PAH} and Tm_G in the dog results frequently in a depression of the former and occasionally in a depression of the latter.[11,12] In man the simultaneous determination of Tm_{PAH} and Tm_G may result in a depression of the former and an apparent increase in the latter.[13] At present the observed depressions are presumed to be a result of competition for available energy between the PAH and glucose transfer systems with the latter being favored.[11]

Summary. The intravenous administration of 78 mg of organically bound mercury (2 cc mercuzanthin) causes a significant decrease in the Tm_{PAH} but no significant change in the Tm_G in man. It is concluded that under the conditions of this study mercury had no effect on the renal tubular glucose transfer system in man.

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