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Effects of Clinical Doses of Phenobarbital on Blood and Urine Ascorbic Acid in Human Subjects.

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(Introduced by W. H. Olmsted.)

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That barbituric acid derivatives were effective in stimulating ascorbic acid excretion in rats was demonstrated by Longenecker and his co-workers.[1] Within 5 days the administration of sodium phenobarbital caused an increase of 15 times in the urinary excretion of ascorbic acid.

This experiment records the effects of clinical doses of phenobarbital on the plasma, whole blood, and urinary values of ascorbic acid in human subjects. Although some other drugs are equally effective in stimulating ascorbic acid excretion in animals, phenobarbital was chosen because it is so commonly used in clinical medicine. It should be recalled that a daily dose of 20 mg of sodium phenobarbital was given by King and his co-workers to a 250 g rat, whereas we administered 180 mg to a 70K subject.

In rats, it was shown that 5 days were required to stimulate the maximum excretion of ascorbic acid, so a 5-day period of phenobarbital administration was chosen for the human subjects. The 180 mg daily dose did affect the subjects in so much that dizziness and diplopia were notable on the 5th day.

Plan of Experiment. Three subjects were used. Subject A was a well developed male weighing 170 pounds, subject B a well developed male weighing 185 pounds, and subject C a normal adult female weighing 125 pounds. The following diet was consumed each day during the entire experiment:

Food	g	Food	g	Food	g
Am. cheese	20	Figs, dried	30	Pork	75
Bacon	10	Flour	3	Puffed wheat	15
Beef	75	Grape jelly	30	Ripe olives	30
Butter	45	Grape juice	100	Soda crackers	12
Cream	170	Jello	16	Sugar	13
Dates	20	Limas, dried	20	Walnuts	15
Eggs	2	Macaroni	10	W. W. bread	120
Evap. milk	200	Peas, dried	20	Total calories	3021

Total calories in individual diets were adjusted by varying the amount of bread, milk, cream, butter, and flour according to the

[1] Longenecker, H. E., Fricke, H. H., and King, C. G., *J. Biol. Chem.*, 1940, **135**, 497.

individual preferences of the 3 subjects. During the month of the experiment the weights of the subjects did not change.

The vitamin C free diet was supplemented with 25 mg of pure ascorbic acid administered with the morning meal. The constancy of the diet ruled out variations in ascorbic acid excretion due to changes in pH of urine. Ascorbic acid and phenobarbital were taken at approximately the same time each day. It was hoped to arrange the ascorbic acid intake so that blood, and urinary changes would be evident. The subjects voided frequently enough so that urine remained in the bladders of the subjects for only a short period of time.[2] The urine volumes were quite constant, that of subjects A and B averaged 1250 cc daily, while that of subject C averaged 889 cc daily. The subjects performed the same work daily either in the hospital or laboratory. Following a 10-day control period, phenobarbital was taken for a period of 5 days. A second control period followed the drug period.

Chemical Methods. Fasting daily specimens of blood were taken. The plasma and whole blood methods of Mindlin and Butler[3] and Butler and Cushman[4] were used to determine the ascorbic acid values.

The urine ascorbic acid was determined on 24 hour specimens by the method of Roe and Hall[5] adapted to the Evelyn photoelectric colorimeter. Recovery experiments on this method gave 90% to 99% recovery of added ascorbic acid.

Results are recorded in Table I.

It is evident that there was a very slight but definitely steady decline in whole blood, plasma, and urinary excretion of ascorbic acid during the 3 weeks of observation in all 3 subjects. In both male subjects, no significant change took place in the ascorbic acid metabolism during the administration of phenobarbital. In the one female subject, there appeared a slight but significant rise in ascorbic acid excretion and decrease in the whole blood values during administration of phenobarbital. We cannot explain this observation.

If ascorbic acid were used by the human being in detoxifying phenobarbital as Longenecker, *et al.,* believe occurs in the rat, we would expect a decrease in the blood value for ascorbic acid and a decrease in urinary output during phenobarbital administration to man. It is possible that if on the basis of weight the dosage to

[2] Sherry, S., and Friedman, G. J., PROC. SOC. EXP. BIOL. AND MED., 1939, **42**, 707.

[3] Mindlin, R. L., and Butler, A. M., *J. Biol. Chem.*, 1938, **122**, 673.

[4] Butler, A. M., and Cushman, M., *J. Clin. Invest.*, 1940, **19**, 459.

[5] Roe, J. H., and Hall, J. M., *J. Biol. Chem.*, 1939, **128**, 329.

TABLE I.
Ascorbic Acid Concentration of Whole Blood, of Plasma and of Urine.

Date 1941	A				B				C			
	Whole blood mg%	Plasma mg%	Urine mg%	Urine 24 hr mg	Whole blood mg%	Plasma mg%	Urine mg%	Urine 24 hr mg	Whole blood mg%	Plasma mg%	Urine mg%	Urine 24 hr mg
2-5	.84	.40	.61	5.20	.63	.22	.38	4.40				
2-6	1.22	.46	.45	5.48	1.12	.31	.32	4.13				
2-7	1.27	.43	.46	4.80	.86	.33	.28	3.47				
2-8	.99	.43	.39	4.84	1.20	.40	.34	2.43				
2-9	1.12	.58	.35	3.94	.89	.55	.20	1.86	1.12	.58	.34	2.90
2-10	.96	.40	.69	7.54	1.07	.34	.58	6.84	1.20	.54	.89	6.30
2-11	1.37	.42	.48	6.73	.63	.39	.31	3.91	1.37	.60	.66	2.15
2-12	1.36	.40	.48	4.90	1.04	.37	.27	4.90	1.25	.55	.43	3.30
2-13	.79	.34	.46	2.59	.71	.36	.44	5.20	1.22	.50	.45	4.50
2-14	.76	.30	.43	4.18	.73	.30	.31	3.85	.92	.51	.40	3.89
2-15	.77	.32	.50	5.76	.64	.21	.35	3.89	1.00	.47	.43	4.65
Phenobarbital gr iii h.s.												
2-16	.56	.32	.19	2.31	.62	.23	.12	2.18	.68	.52	.28	3.43
2-17	.86	.26	.25	3.53	.76	.14	.27	2.50	.95	.39	.47	3.60
2-18	.80	.31	.49	6.32	.66	.19	.42	5.75	.80	.38	.68	5.60
2-19	.63	.16	.41	5.27	.57	.14	.28	5.34	.70	.32	.53	5.68
2-20	.73	.25	.31	4.30	.52	.16	.27	3.70	.56	.35	.56	4.92
Drug discontinued												
2-21	1.10	.24	.24	2.64	.72	.23	.22	2.92	1.03	.33	.38	3.40
2-22	.60	.20	.32	5.51	.65	.20	.25	3.40	.73	.38	.54	3.80
2-23	.64	.27	.25	3.47	.53	.23	.20	5.30	.74	.32	.36	3.97
2-24	.67	.25	.35	3.50	.67	.15	.34	3.59	.81	.32	.52	3.30
2-25	1.05	.20	.33	4.95	1.11	.15	.24	2.40				
2-26	.50	.16	.24	3.66	.46	.16	.24	2.40				
2-27	.64	.16	.13	1.15	.64	.13	.24	2.40				
Avg												
1st control	1.04	.41	.48	5.09	.87	.34	.34	4.08	1.15	.54	.52	3.96
Drug	.72	.26	.33	4.35	.63	.17	.27	3.89	.74	.39	.50	4.65
2nd control	.74	.21	.27	4.55	.68	.18	.25	3.20	.83	.34	.45	3.62

humans had been comparable to that given by Longenecker to rats some effect would have been noted. It is possible the drug was conjugated with ascorbic acid in the urine, but this does not occur in rats and one would expect in this case some reduction in ascorbic acid values in whole blood or plasma.

Summary. There was no significant change in whole blood, plasma, or urinary excretion of ascorbic acid following administration of 180 mg of phenobarbital daily to human subjects. Twenty-five mg of crystalline ascorbic acid daily is insufficient to maintain whole blood or plasma values when the subjects take an ascorbic acid-free diet.