

*Conclusions.* The gas gangrene group of anaerobes grow luxuriantly in a medium consisting of a buffered salt-mixture with dextrose and gelatin. Highly purified gelatin is not suitable. In this medium all the toxigenic gas gangrene species produce a high and consistent yield of hemotoxin and lethal toxin. The toxins are actively antigenic and make effective toxoids.

13382

### Effect of Quinine on Metabolism in Fasting Dogs and in Patients with Creatinuria.\*

A. T. MILHORAT, W. E. BARTELS AND V. TOSCANI.

*From the Russell Sage Institute of Pathology in Affiliation with the New York Hospital and the Departments of Medicine and Psychiatry, Cornell University Medical College, New York.*

The observation that quinine diminishes the output of certain urinary substances has been confirmed by several investigators; however, practically all of the experiments heretofore reported were made on animals or human subjects receiving an adequate diet. Prior<sup>1</sup> appears to have been the only investigator who studied these effects of quinine during fasting and in his studies, which were made on only one dog, urea was the only urinary substance that was determined. Aoki<sup>2</sup> found a diminution in the output of creatine and creatinine when quinine was given to patients with hyperthyroidism and animals which had received desiccated thyroid gland. Since quinine is now used in the management of certain muscular disorders, *e. g.*, *myotonia congenita* and muscular rigidity of paralysis agitans, it seemed of interest to further investigate the metabolic effects in an attempt to elucidate the action of the drug in these muscular syndromes.

*Methods.* There were two series of experiments, one on fasting dogs, the other on patients with muscular wasting and creatinuria. Female dogs were fasted for a preliminary period of at least 10 days and throughout the experiments but were allowed free access to drinking water. The animals were kept in metabolism cages

---

\* Aided by a grant from the National Foundation for Infantile Paralysis, Inc.

<sup>1</sup> Prior, *Arch. f. d. ges. Physiol.*, 1884, **84**, 237.

<sup>2</sup> Aoki, K., *Folia endocrin. Jap.*, 1928, **3**, 1331 (abstr. *Jap. J. Med. Sci.*, 1931, **4**, 13).

which permitted quantitative collection of all voided urine specimens. At the end of each 24-hour period the animals were catheterized and the bladder rinsed with sterile distilled water.

After a control period of several days during which the urinary output of the various substances was constant, each animal was given quinine by mouth in doses of from 0.2 to 0.4 g. In some experiments a single dose was given; in others the drug was administered on successive days for periods up to 6 days. Twelve complete experiments on 4 dogs were made.

The patients were 2 boys, aged 10 and 13 years, with progressive muscular dystrophy of several years' duration. Both patients showed considerable wasting and weakness of most of the muscles of the trunk and extremities. The subjects were maintained in a special metabolism ward where the diet could be rigidly supervised, and where quantitative collections of urine and feces could be made.

For a preliminary period of a few weeks and during the periods of observation the diet was kept constant from day to day. Both patients were given amounts of quinine which appeared to be as much as they were able to tolerate without significant side-effects.

*Observations and Discussion.* In fasting dogs the administration of quinine produced significant decreases in the excretion of total nitrogen, urea nitrogen, phosphorus and inorganic sulfur, whereas the elimination of creatine, creatinine, vitamin C, ammonia, amino-acid nitrogen and organic sulfur were unaffected. The output of chlorides which was determined in only one experiment was definitely lowered after quinine administration. The effect of quinine was variable during the first day after the drug had been given. In the main, there was but little effect on the elimination of the urinary constituents during the first day in most experiments, but on the second and third day following the administration of quinine the decrease in nitrogen excretion amounted to as much as 30% in some experiments. The effect of quinine appeared to be more definite when a single dose of the drug was given than in the experiments in which quinine was given on several successive days. The greatest effect of quinine was observed when the urine no longer gave a positive test for the drug with Mayer's reagent. Since the urinary elimination of nitrogen and other substances often was increased on the first day after the drug had been given it would appear that quinine first increases the elimination of nitrogen, urea, and phosphorus and then later decreases the output of these substances. This would explain why the effect of the drug on nitrogen output is more apparent when a single dose of quinine is given than when the drug is

given on successive days. In other words, the late effect of the drug in decreasing the urinary nitrogen often is partially offset by the subsequent doses, the early effects of which would be to increase the output. In experiments in which the drug was given for 6 consecutive days no increase in the effect was noted after the second day. When the administration of the drug was stopped no subsequent change in the nitrogen output was observed, suggesting that the level of nitrogen elimination on the sixth day of quinine administration was no lower than that induced by continuance of fasting alone.

The data on patients are given in Tables I and II and are in essential agreement with those on fasting dogs. Both patients had a slightly increased output of urinary nitrogen on the days when quinine was administered. In one subject (Case 2), in whom the excretion of fecal nitrogen was determined, the retention of nitrogen was reduced during the period when the drug was given, and increased in the subsequent period of observation. Since the elimination of nitrogen in the stool was essentially unchanged, the alterations in urinary output could not have been the result of changes in the intestinal absorption of the nitrogen.

TABLE I.  
Effect of Quinine on Urinary Creatinine and Creatine.

Patient	Nitrogen intake, g	Daily urinary output			Quinine sulfate per os, g
		Nitrogen, g	Creatinine, g	Creatine, g	
1	8.00	4.73	.200	.382	
	8.16	5.43	.200	.376	
	8.16	5.02	.200	.437	
	8.80	5.93	.198	.376	0.4
	8.16	6.02	.200	.437	0.4
	8.16	5.88	.195	.367	
	8.00	6.06	.193	.407	1.0
	8.00	5.55	.198	.440	
	8.16	6.08	.171	.404	1.4
	8.16	5.12	.184	.451	
	8.00	6.18	.184	.423	1.6
	8.00	4.58	.180	.378	
	2	Data in Table II		.178	.497
		.167	.565		
		.178	.490		
		.149	.469	0.6	
		.162	.486	0.6	
		.203	.474	0.6	
		.180	.510	1.0	
		.151	.462	1.0	
		.178	.480		
		.180	.503		
		.186	.529		

TABLE II.  
Effect of Quinine on Daily Retention of Nitrogen, Calcium, Phosphorus and Inorganic Sulfur in Case 2.

Daily output												Quinine sulfate, <i>per os</i> , g
Nitrogen		Calcium		Phosphorus		Inorg. sulfur		Daily retention				
Urine, g	Stool, g	Urine, g	Stool, g	Urine, g	Stool, g	Urine, g	Stool, g	N, g	Ca, g	P, g	S, g	
5.53	1.03	.043	.743	.557	.390	.295	.013	1.62	.343	.281	.238	
5.47	1.03	.046	.743	.568	.390	.282	.013	1.68	.340	.270	.251	
5.40	1.03	.051	.743	.545	.390	.264	.013	1.75	.333	.293	.269	
5.25	1.12	.042	.822	.520	.464	.292	.013	1.81	.265	.284	.287	.6
5.78	1.12	.031	.822	.593	.464	.340	.013	1.28	.275	.171	.239	.6
5.60	1.12	.032	.822	.483	.464	.329	.013	1.46	.275	.281	.250	.6
6.22	1.12	.032	.822	.502	.464	.395	.013	0.84	.275	.262	.234	1.0
5.78	1.12	.026	.822	.450	.464	.329	.013	1.28	.281	.314	.295	1.2
5.40	1.36	.025	.967	.440	.483	.258	.021	1.42	.137	.295	.267	
4.98	1.36	.034	.967	.500	.483	.214	.021	1.84	.128	.245	.311	
4.83	1.36	.042	.967	.566	.483	.197	.021	1.99	.120	.179	.328	

The daily intakes of nitrogen, calcium and phosphorus were constant and were 8.18 g, 1.129 g and 1.228 g, respectively. The intake of sulfur was 0.546 g daily except on days of quinine administration when the intake was 0.592 g for first three days, 0.622 g on fourth day and 0.637 g on fifth day.

The urinary elimination of calcium was unchanged, but the amounts in the feces were increased during both the period when quinine was given and in the subsequent period, so that the retention of calcium was reduced during both these periods. Likewise, the fecal elimination of phosphorus was increased during these two periods, with the result that the retention was slightly diminished during the period of drug administration and during the subsequent period, although the urinary output was decreased.

Of interest are the findings on the urinary outputs of preformed creatinine and creatine. In contrast with the observations of Aoki<sup>2</sup> no significant change in the output of these substances was observed in the present investigations. These findings offer support to the interpretation that the effect of quinine on muscular function in certain disorders is not due to a direct metabolic action on the muscles. In a previous report<sup>3</sup> it was postulated that the effect of quinine in muscular disorders is due to an antagonistic action on cholinergic nerve stimulation.

<sup>3</sup> Milhorat, A. T., *Arch. Neurol. and Psychiat.*, 1941, **45**, 74.