of Elberfeld, Germany. It is only fair to admit, however, that the question of the significance of what have been regarded as exoerythrocytic stages by others, and are so regarded by the authors in the *Plasmodium circumflexum* infections mentioned here, will not be altogether conclusively settled until typical malaria infections are transferred to clean birds by inoculation of these stages alone. It is of interest that these stages have so far been observed only in acute cases, and not in all of these. Fatal cases are most likely to exhibit them.

10227

Failure of Ascorbic Acid to Influence Albuminuria and Hematuria in Nephritis.*

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Following the isolation and identification of Vitamin "C" in 1932, several reports on the effectiveness of ascorbic acid on hematuria of acute nephritis and from other causes appeared in the European literature. Szent-György[1] reported favorable results in cases of hemorrhagic nephritis following 150-200 mg of ascorbic acid on alternate days. Koranyi and Bentsath[2] also noted a hemostatic effect in nephritic hematuria. Engelkes[3] described 2 cases of hematuria and albuminuria in which the red blood cells in the urine disappeared in 10 and 6 days, respectively, after administration of 100-200 mg daily. Ceruti and Costanzo[4] stated that in 2 patients suffering from nephritis and essential forms of hematuria, 50 mg were given daily for 10 days with satisfactory results verified by microscopic studies of the urine. These favorable reports prompted Murphy[5] to advocate routine administration of ascorbic acid in cases of acute nephritis with hematuria. On the other hand, Parsons,[6] Wilbur,[7] and Abt and Farmer[8] in reviewing the subject of Vitamin

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1 Quoted in Wright, I. S., and Lilienfeld, A., *Arch. Int. Med.*, 1936, **57**, 241.

2 Koranyi, A., and Bentsath, A., *Orvosi hetilap.*, 1935, **79**, 378.

3 Engelkes, H., *Lancet*, 1935, **2**, 1285.

4 Ceruti, G., and Costanzo, F., *Riforma Medica*, 1937, **53**, 1770.

5 Murphy, F. D., *International Clinics*, 1938, **2**, 231.

6 Parsons, L. G., *Lancet*, 1938, **1**, 123.

7 Wilbur, D. L., *Arch. Int. Med.*, 1937, **59**, 512.

8 Abt, A. F., and Farmer, C. J., *J. A. M. A.*, 1938, **111**, 1555.

"C", have stated that there is no real evidence that Vitamin "C" is of any value in any other condition than scurvy.

In order to determine definitely whether ascorbic acid did or did not have any therapeutic value in controlling hematuria in nephritis, 6 patients with acute and subacute nephritis were studied. Ascorbic acid excretion was determined by titration with 2,6-dichlorophenol-indophenol after standardization with known solutions of crystallin ascorbic acid. Hematuria was estimated by daily Addis counts on the 12-hour night urine or by hemoglobin determinations when there was gross hematuria. Dr. R. F. Hanzel kindly made the hemoglobin determinations using a modification of Bing and Baker's benzidine method. Protein was determined by Shevky and Stafford's method. In order to minimize oxidation of the ascorbic acid, urine voided during the day was collected in bottles containing glacial acetic acid. Since this would hemolyze red cells and prevent counting, the night urine was preserved with toluol. All specimens were kept in the dark in the ice box and analyzed early the next morning. After a control period of 3 to 6 days, Merck's "cebione"† was given daily for a week or 10 days. One patient received 100 mg intravenously and the others 1 gm by mouth daily.

TABLE I.
Effect of Ascorbic Acid on Hematuria and Albuminuria in Nephritis.

		Control Period			Ascorbic Acid Period			After Period	
Name	Age Sex	Prot. g 12 hr	RBC 10^6 12 hr	Ascorbic Acid mg 24 hr	Prot. g 12 hr	RBC 10^6 12 hr	Ascorbic Acid mg 24 hr	Prot. g 12 hr	RBC 10^6 12 hr
MB	27F	.05	1.9	19.1	.06	1.1	536.7	.13	1.0
AR*	20F	.98	5.9	6.4	1.43	4.0	52.3	1.06	4.2
MW	28F	1.95	*500	22.2	.81	249	238.2	.45	106
TK	16M	3.11	3.3	24.7	3.46	3.6	394.9	2.37	6.5
EB	26F	.08	2.9	14.5	—	—	541.5	1.86	2.4
AB	15M	7.83	†.34	12.6	11.77	†1.01	245.1	10.85	†.76

*100 mg intravenously.
†g hemoglobin per 12 hr.

The results are presented in summary form. Table I shows the average values obtained during the control period, during the administration of ascorbic acid and for the first 2 to 4 days after its withdrawal. In one case the daily excretion of ascorbic acid was below 10 mg, a point below the level said by Harris[9] to indicate deficiency; 3 were below 20 mg, indicating low intake. In all cases, however, administration of large doses of ascorbic acid resulted in greatly

† Kindly furnished by Merck & Co.

[9] Harris, L. J., and Ray, S. N., *Lancet*, 1935, **1**, 71.

augmented excretion within the first 2 days, which would indicate that there was no marked unsaturation of the body. No hemorrhagic skin manifestations were present. In 3 cases, the amount of hematuria remained the same or increased; in 2 cases there was a slight but not significant decrease, and in one case (M.W.) there was definite improvement, although the urine did not clear up by any means. This, however, may well have been coincidental since subsidence of hematuria in acute nephritis is the rule rather than the exception. Subsequent follow-up of these 6 cases showed that 3 of the 6, including this last one, finally cleared the hematuria. The amount of albuminuria was not altered during administration of ascorbic acid, except in M.W.

Our studies have been unable to confirm the benefits of ascorbic acid on nephritic hematuria reported in the literature. While this study was in progress, Walther[10] reported negative results similar to ours in 3 cases of hematuria and glomerulo-nephritis. It is our opinion that the administration of Vitamin "C" is not indicated for the hematuria of nephritis unless there is clear-cut evidence of Vitamin "C" deficiency.

Summary. In 5 patients with hematuria due to acute or subacute nephritis, the administration of ascorbic acid in massive doses over a period of 6 to 10 days sufficient to saturate the body stores had no significant effect on the amount of hematuria or albuminuria. In one case there was a definite decrease but coincidental spontaneous improvement could not be excluded.

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Diluted and Undiluted Diphtheria Toxoid as Immunizing Agents in Man.

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Hartley[1] observed that guinea pigs injected with diluted toxoid attained a higher immunity to diphtheria toxin than those receiving an equivalent amount of undiluted toxoid. These results were confirmed by Timmerman and Brandwijk.[2] The present study was

10 Walther, G., *Med. Klin.* 1938, **8**, 260.

1 Hartley, P., *Brit. J. Exp. Path.*, 1935, **16**, 468.

2 Timmerman, W. A., and Brandwijk, A. C., *Brit. J. Exp. Path.*, 1936, **17**, 252.