not establish the existence of scurvy. The practically uniform finding of sharply lowered levels in initial determinations in a series of 21 cases is, however, considered significant. With the exception of the 5 cases noted these individuals were on their usual dietary regime.

Summary. The blood plasma ascorbic acid (reduced form) in active cases of rheumatoid arthritis is regularly low if the individuals have not been maintained on a *high* vitamin C supplement. Unadvised cases were found to show uniformly lowered levels. The reduction is striking. Such levels rise in response to extra supplements of vitamin C. In many this rise is refractory. Our studies indicate that in some cases the intake required to maintain adequate vitamin C levels in the plasma are much above the average requirement for normal individuals. The mechanism involved is unexplained.

8971 P

Reduced Ascorbic Acid Content of Blood Plasma in Rheumatic Fever.*

J. F. RINEHART, L. D. GREENBERG, AND A. U. CHRISTIE.

From the Departments of Pathology and Pediatrics, University of California Medical School.

The thesis was advanced that vitamin C deficiency may be an important factor in the etiology of rheumatic fever.[1] This concept was based upon the experimental production of a disease state with manifold similarities to rheumatic fever, by subjecting guinea pigs to the combined influence of vitamin C deficiency and infection. Epidemiologic and clinical considerations were noted which afforded confirmatory evidence for the validity of the concept. In studies reported by Schultz, Sendroy and Swift,[2] and Perry[3], the clinical significance of this concept was questioned or denied.

* Aided by a donation from the California Fruit Growers Exchange and by the Christine Breon Fund for Medical Research. We are also indebted to Hoffmann-LaRoche, Inc., for supplies of ascorbic acid.

1 Rinehart, J. F., and Mettier, S. R., *Am. J. Path.*, 1934, **10**, 61; Rinehart, J. F., Connor, C. L., and Mettier, S. R., *J. Exp. Med.*, 1934, **59**, 97; Rinehart, J. F., *Ann. Int. Med.*, 1935, **9**, 586; Rinehart, J. F., *J. Lab. and Clin. Med.*, 1936, **21**, 597.

2 Schultz, M. P., Sendroy, J., and Swift, H. F., *J. Clin. Invest.*, 1935, **14**, 698.

3 Perry, C. B., *The Lancet*, 1935, **229**, 426.

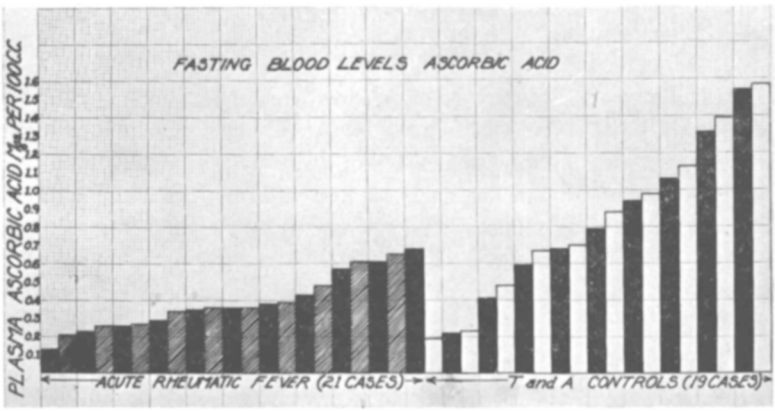

FIG. 1.

The present communication is based upon the study of the fasting blood plasma levels of reduced ascorbic acid in cases of rheumatic fever and chorea along with control groups. This and current studies[4] indicate that the plasma level of reduced ascorbic acid is an accurate index of the vitamin C intake as recently reported by Farmer and Abt.[5] The ascorbic acid plasma levels in our control groups are somewhat lower than those of Farmer and Abt, whose method we employed, probably because our study is based on fasting blood specimens. This, we feel, is an essential precaution for adequate comparative data.

In 21 cases of acute rheumatic fever the reduced ascorbic acid content of the blood ranged from 0.13 to 0.68 mg. per 100 cc., with an average of 0.39 mg.† The distribution is shown in the accompanying diagram (Fig. 1). A control series of cases, composed of children admitted to the University of California Hospital for tonsillectomy, is shown for comparison. In this group of 19 cases the range was 0.22 mg. % to 1.57 mg. % with an average of 0.81 mg. %. This series represent a comparable social and age group.‡

[4] Greenberg, L. D., Rinehart, J. F., and Phatak, N. M., PROC. SOC. EXP. BIOL. AND MED., 1936, **35**, 135.

[5] Farmer, C. J., and Abt, A. F., PROC. SOC. EXP. BIOL. AND MED., 1935, **32**, 1625.

† Three of the 5 cases with levels above 0.5 mg. % were not seen before the vitamin C content of the diet had been materially increased.

‡ At the time this study was reported data on a significant number of cases with infections, other than rheumatic fever, were not available. At present ascorbic acid determinations have been made on 19 cases of miscellaneous non-rheumatic infections in children. In this group, plasma values range from 0.16 to 1.61 mg. per 100 cc. with an average of 0.78 mg. 74% of the cases gave values above 0.5 mg. per 100 cc.

Five children who had suffered rheumatic fever in the past and had been maintained on a controlled high vitamin C intake for months prior to the examination, showed ascorbic acid levels ranging from 0.84 mg. % to 1.15 mg. %, with an average of 1.02 mg. %. This probably approaches an optimal post absorptive level. Seven cases, quiescent at the time of examination but with a history of recent or old rheumatic activity, gave values which ranged from 0.44 mg. % to 0.71 mg. %: averaging 0.53 mg. %. Three other cases of chronic rheumatic heart disease for whom a high vitamin C intake had been advised gave levels of 0.37, 0.45, and 0.67 mg. %. Poverty precluded satisfactory cooperation in this group. These data indicate that "rheumatic" children (although not suffering from active disease), unless maintained on a controlled high vitamin C intake, are likely to lie in a sub-optimal metabolic range with respect to vitamin C.

In the majority of cases of acute rheumatic fever, after basal observations, vitamin C was supplied in generous amounts and subsequent determinations made. The vitamin C was given as orange juice or as ascorbic acid. The dosage, in terms of ascorbic acid, ranged from 100 mg. to 500 mg. daily. In cases that could be followed for adequate periods the plasma levels of ascorbic acid rose following this regime. In some instances this occurred rather

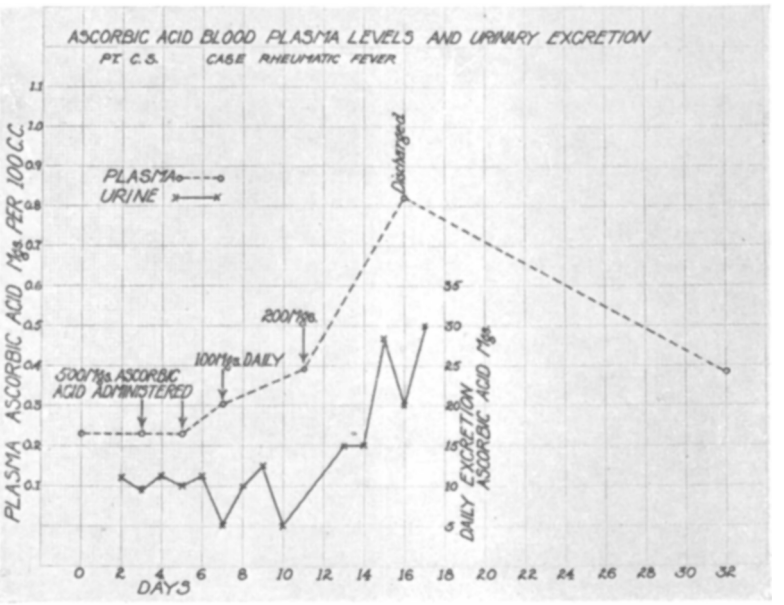

FIG. 2.

promptly; in others the rise was delayed. A particularly refractory case, in which we had the opportunity to study both blood plasma levels and urinary excretion, is shown in Fig. 2. The failure of increased urinary excretion and the slight elevation of the plasma ascorbic acid after 2 massive doses of vitamin C is shown. The fall of the plasma level after the patient was discharged from the hospital is significant. Another case of unusual interest was that of an 11-year-old child who suffered from a very severe acute rheumatic carditis. In spite of massive doses of vitamin C, ranging from 200 to 400 mg. daily, the plasma ascorbic acid remained depressed for a period of 40 days. This case terminated fatally.

It is worthy of note that cases of uncomplicated chorea did not show the uniformly depressed plasma ascorbic acid levels that occurred in rheumatic fever. Four cases gave initial fasting blood levels of 0.27, 0.94, 1.0 and 1.18 mg. ascorbic acid per 100 cc.

A concurrent study[4] leads us to believe that fasting plasma ascorbic acid levels below 0.7 mg. per 100 cc. lie in a sub-optimal range. This is in essential agreement with the findings of Abt, Farmer, and Epstein.[6] They found ascorbic acid levels ranging from 0.8 to 2.0 in a group of infants and children on adequate diets. A group on low vitamin C intake ranged from 0.51 to 0.77 mg. per 100 cc.

Summary. In acute rheumatic fever the reduced ascorbic acid level of the blood plasma is found to be almost uniformly lowered. Our data further indicates that at least some and perhaps a high percentage of "rheumatic" children, although the disease process is clinically quiescent, tend to lie in less low but distinctly sub-optimal ranges. It has not been determined that this is due to inadequate intake or to what extent it may have resulted from anorexia, digestive disorders or depletion by the disease itself. The data presented indicates that the plasma ascorbic acid levels usually parallel the vitamin C intake. However, some cases are quite refractory in their responses to oral administration of the vitamin even in large doses.

[6] Abt, A. F., Farmer, C. J., and Epstein, I. M., *J. Pediat.*, 1936, **8**, 1.