CCXXXVI. ON THE SATURATION OF A SCURVY PATIENT WITH SMALL DOSES OF ASCORBIC ACID. CONSIDERATION OF THE DAILY HUMAN REQUIREMENT¹

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EARLY experience in the British navy went to show that 1 oz. lemon juice, corresponding to 15 mg. ascorbic acid, was the daily dose required to protect adults from scurvy. Göthlin [1931], using the capillary resistance test as criterion, found 20–30 mg. daily necessary to protect from latent scurvy. Recent work on the metabolism of ascorbic acid, made possible by Tillmans's method of titration with dichlorophenolindophenol, has indicated much higher figures. Van Eekelen [1936] estimated the necessary daily dose for an adult of 70 kg. as high as 60 mg. under normal conditions. This quantity, however, corresponding to the vitamin C content of 120 ml. lemon juice, would appear to be excessive, and therapeutic observations of the writer are in support of this conclusion.

A patient suffering from moderately severe scurvy was treated with intravenous injections of 40 mg. daily of ascorbic acid in hospital while receiving a diet practically free of vitamin C. During a control period prior to treatment his symptoms progressed; but they diminished as soon as treatment began. In the course of 5 days there was a great improvement in the patient's condition; after 2 weeks the symptoms had almost disappeared, and the lowered capillary resistance had become normal [Schultzer, 1933].

The question of the saturation point with ascorbic acid was determined in three patients, also suffering from moderately severe scurvy [Schultzer, 1936]. The word "saturation" is employed in the sense defined by Johnson & Zilva [1934], saturation being attained when with ingestion of a constant amount of ascorbic acid the daily excretion in the urine becomes roughly constant. Large daily doses of ascorbic acid, 300–600 mg., were given, the times taken to produce saturation in the 3 patients were 5, 2 and 3 weeks and the total quantities of ascorbic acid administered prior to saturation were 9.5, 7.0 and 14.4 g., respectively. The patient who required the largest quantity received the acid orally, whereas the other two received it intravenously.

In these cases although saturation was only reached after some weeks, the symptoms began to subside and the capillary resistance became normal in a few days. The clinical histories of these three patients were thus similar to that of the earlier case which was cured by the relatively small dose.

From the above observations two questions suggest themselves: (1) Is the quantity of ascorbic acid needed for saturation a measure of the quantity required to satisfy the body's reserves? (2) Is saturation any criterion for the clinical treatment for scurvy? The following observations on a scurvy patient treated at the Kommunehospitalet in Copenhagen are an attempt to answer these two questions.

PRESENT INVESTIGATION

The technique employed was the same as in the earlier investigations [Schultzer, 1936]. The patient was immediately put on a vitamin C-free diet which had previously been shown to promote the development of scurvy. The

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urine was titrated for vitamin C by Tillmans's method as modified by Harris & Ray [1935]. The capillary resistance was tested before and after treatment by Göthlin's method.

The patient was an unmarried man, 65 years of age, of body wt. 63 kg. and previously of good health. Inquiries elicited the fact that his daily diet had been extremely deficient in vitamin C.

He complained of pains in the gums and tiredness and presented a typical picture of scurvy, of about the same degree of severity as the patients previously investigated by the writer. There were marginal gingivitis, suffusions and petechiae in the skin, oedema especially on the legs, an exudate in the right knee accompanied by pain and greatly reduced mobility. The capillary resistance was lowered to 18 petechiae. The blood examination revealed a slight simple anaemia (Hb, 77%, Sahli). There was no thrombopenia. Ewald's test meal was given twice and indicated achlorhydria. The temperature was slightly raised, not exceeding 38°. The systolic blood pressure was 110 mm.

Control pre-experimental period. After the patient had been put on the vitamin C-free diet in hospital the daily excretion of ascorbic acid was determined over a control period of 1 week. In this period, during which he was kept in bed, the oedema of the right leg subsided to some extent but the pain increased, and the knee became so tender that it could not be moved. The gingivitis was unchanged. At the end of the control period the capillary resistance was still low: 22 petechiae. The temperature was still slightly raised.

Experimental period. A daily dose of 40 mg. ascorbic acid was given intravenously. It was dissolved in 8 ml. water just before use and the solution was brought just to boiling-point and quickly cooled before injection. A loss of about 10% activity is allowed for this boiling.

The progress of this man was exactly the same as that of the patient described in 1933, who received similar treatment. The scurvy symptoms began to subside immediately, and in the course of about a week the patient was clinically cured. The day after the first injection he stated that the pains were greatly diminished, and 2 days later the petechiae were gone and the suffusions had decreased in extent. The temperature was normal after 3 days. There was improvement in the gingivitis in 4 days and entire disappearance in a week. The mobility of the right knee improved rapidly. Table I shows the capillary resistance and the

Table I. *Capillary resistance and passive flexion of right knee under treatment*

Day of treatment	No. of petechiae (Göthlin)	Maximum passive flexion of right knee
1	22	0
5	15	90
7	—	110
9	—	125
11	8	150
15	7	180
18	7	—

increase in the maximum passive flexion of the knee under the treatment. On the eleventh day the capillary resistance was normal and remained so. The temperature, which during the control period was slightly raised, became normal. The haemoglobin percentage (Sahli) rose from 77 to 90 during the treatment, without other medication.

The urinary excretion of ascorbic acid

The pre-experimental period. In the 7 days of the pre-experimental period the patient had an average output of 11 mg. ascorbic acid per 24 hr., about the same as the patient showing the lowest output in the 1936 observations. The results of these are included in Table II for purposes of comparison. The day-to-day variations were not great and the weekly average can be taken as trustworthy evidence of the excretion.

Table II. *24-hr. urinary excretion of ascorbic acid, in mg. The figures are the averages for the period (1 week)*

	Patient No. 1 (1936)	Patient No. 2 (1936)	Patient No. 3 (1936)	Patient (1937)
(1) Before treatment	13	19	25	11
Daily dose of ascorbic acid ...	300 mg. intravenous	300 + 300 mg. intravenous	600 mg. oral	40 mg. intravenous
(2) After treatment:				
1st week	15	24	27	11
2nd week	13	157	89	16
3rd week	32	302	188	17
4th week	54	321	229	26
5th week	70*	—	—	28

* In the last 24 hr. of this period the output was 199 mg.

In the present patient saturation was reached after three weeks' treatment, during which the 24 hr. output rose from 11 to 17 mg. After this it was constant at 26–28 mg. in the fourth and fifth weeks.

Thus the clinical cure was complete in about 1 week, whereas saturation did not occur till the fourth week. There was a similar relation between clinical cure and saturation in the earlier observations when large doses of ascorbic acid were given (Table II).

Subsequent high dosing with ascorbic acid. When the point of saturation had arrived it was not feasible to keep the patient in hospital, but as it was possible to rely on his intelligent co-operation, it was arranged for him to receive high doses after discharge. He attended the hospital every afternoon, bringing his 24 hr. urine specimen, and received an intravenous injection of 600 mg. ascorbic acid. The result of this subsequent high dosing is illustrated in Table III.

Table III. *Subsequent high dosing with daily intravenous injection of 600 mg. ascorbic acid after attaining saturation on a dose of 40 mg. daily*

Day of treatment	Excretion of ascorbic acid in 24 hr. in mg.
1	52
2	110
3	149
4	123
5	169
6	233
7	268

There was an immediate reaction with a higher output of ascorbic acid, and saturation was reached after 5 days (see Table III). This confirmed an earlier observation of the writer on six young men receiving adequate amounts of vitamin C [Schultzer, 1936].

DISCUSSION

The experience of the British navy was that 30 ml. lemon juice daily (=15 mg. ascorbic acid) was an adequate preventive dose against scurvy for an adult. Göthlin [1931] recommended a higher figure, 40–60 ml. lemon juice (=20–30 mg. ascorbic acid) to protect the organism from latent scurvy as shown by lowered capillary resistance. It is clear from the observations of Göthlin [1931] and of the writer [1934, 1, 2] that lowered capillary resistance occurs in individuals living on a diet deficient in vitamin C.

Recently, however, the excretion of ascorbic acid in the urine has been employed as a means of determining the minimum daily requirement. Van Eekelen determined the daily human requirement by giving large doses of ascorbic acid, 250 or 500 mg. daily with periods of no addition, until saturation was attained. The total quantity of ascorbic acid necessary before saturation was reached, divided by the number of days required, was taken as the daily requirement. This calculation, which is of doubtful validity, gave the daily requirement of a man of 70 kg. as 60 mg. ascorbic acid. The writer's experiments show the basis of this calculation to be untenable, seeing that the total quantity of ascorbic acid necessary to reach saturation depends upon the size of the daily dose given. On larger daily doses of ascorbic acid scurvy patients studied by the writer [Schultzer, 1936] took from 7.0 to 14.4 g. before they were saturated; the time taken varied from 3 to 5 weeks. The patient described in the present paper received the relatively small dose of 40 mg. per day, became saturated in 23 days after ingestion of a total quantity calculated at only 0.83 g. That this patient was actually saturated is clear from his record during a subsequent period of high-dosing with 600 mg. daily (Table III), when there was an immediate increase of output with saturation after 5 days. This result showed the reaction of a normal individual [Johnson & Zilva, 1934; Guldager & Poulsen, 1935; Schultzer, 1936]. It is evident that such experiments with large doses of ascorbic acid give no trustworthy information as to the reserves or requirements of the organism or any evidence as to the fate of the ingested ascorbic acid.

Strictly speaking, these conclusions apply only when the ascorbic acid is administered parenterally. When the ascorbic acid is given by the mouth, there are other complications, as for example the loss in the gastro-intestinal tract, and the greater disposition of patients with achlorhydria to develop vitamin C deficiency may be significant [Schultzer & Griis, 1935].

SUMMARY

1. The urinary excretion of ascorbic acid has been studied in a patient with scurvy of moderate severity.
2. In a pre-experimental period in which a vitamin C-free diet was given, the average daily excretion of ascorbic acid was found to be 11 mg.
3. In an experimental period on the same diet with administration of 40 mg. ascorbic acid daily intravenously, there was a rise to 16 mg. in the urinary output of ascorbic acid in the second week; saturation, in the sense of Johnson & Zilva, occurred in the fourth week, with a 24-hourly excretion of 26 mg.
4. These findings are compared with previous findings of the author on other patients with scurvy of similar degree, who received ascorbic acid in much larger quantities, from 300 to 600 mg. daily.
5. No difference was found in the time required for obtaining saturation, whether the dose of ascorbic acid was large or small.

6. It is concluded that saturation tests of this kind offer no means of estimating the reserve stores of ascorbic acid in the organism or of estimating the daily requirement of ascorbic acid.

7. 40 mg. ascorbic acid daily were found to be an adequate curative dose if injected intravenously. It is therefore suggested that the daily human requirement may be less than this dose.

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