VITAMIN C AND THE AGING EYE

AN EXPERIMENTAL CLINICAL STUDY

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DETROIT

In the course of routine refraction tests on a number of patients at the Hastings State Hospital during the late summer months of 1937, clouding of the optic media associated with more or less impaired vision was noted in an undetermined percentage of cases; apparently this was a precursor of senile cataract, a concomitant feature of early cataract or a morbid condition per se. The patients ranged in age from 41 to 73 years, represented both sexes and included workers and nonworkers. None was a newcomer to the institution. Only a small percentage of this group could be classed as actually senile. In view of references in the literature within the past few years to changes in the vitamin C content of the lens and of other structures of the eye in cataractous conditions (to be discussed later in this paper) and in view also of the combination of circumstances which conceivably might lead to vitamin C deficiency at this institution (geographic location, nature of diet and other factors), it was thought that an investigation into the status of the hospital population in this regard might prove enlightening.

Such an investigation seemed further indicated by the rather frequent occurrence of minor infections of the upper respiratory passages among the patients at this institution during the winter months, the occasionally extremely poor progress in the healing of decubitus ulcers and other lesions involving loss of skin, despite apparently insufficient clinical grounds for such delay, and the observation that some of these decubitus ulcers improved promptly and markedly after the administration of large quantities of tomato juice.

Attention is called to the work of Wolbach,[1] von Jeney and Törö [2] and Lanman and Ingalls [3] concerning the role of vitamin C in the forma-

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1. Wolbach, S. B.: Controlled Formation of Collagen and Reticulum: A Study of the Source of Intercellular Substance in Recovery from Experimental Scorbutus, Am. J. Path. (supp.) **9**:689, 1933; Vitamin C and the Formation of Intercellular Material, New England J. Med. **215**:1158 (Dec. 17) 1936; The Pathologic Changes Resulting from Vitamin Deficiency, J. A. M. A. **108**:7 (Jan. 2) 1937.

(Footnotes continued on next page)

tion of intercellular material and thus in repair of wounds, and to the observations of Perla and Marmorston,[4] Jusatz,[5] Hetler,[6] Cady,[7] McCullough[8] and Takahashi[9] on the role of vitamin C in the maintenance of resistance to infection and in the prevention of disturbances of the respiratory passages in cases of scurvy.

In the optic media of the eye, which represent various types of tissue, any change in character, specifically any impairment of metabolism and nutrition, is readily manifested in decreased transparency and thus in measurable impairment of vision. It would seem logical, therefore, to search for a correlation between the degree of vitamin C saturation of the body and the presence of visual disturbances. The work here reported represents an attempt to determine the relation between the blood level of vitamin C, its excretion in the urine and the condition of the optic media, as well as the reaction of the latter to treatment with this substance.

No general review of the literature on vitamin C will be attempted in this report, but attention is called to the various comprehensive reviews at present available.[10]

The minimum daily intake of ascorbic acid required by a normal adult in order to maintain an adequate blood level is, according to

2. von Jeney, A., and Törö, E.: Die Wirkung der Ascorbinsäure auf die Faserbildung in Fibroblastkulturen, Virchows Arch. f. path. Anat. **298**:87, 1936; abstracted, Arch. Path. **24**:670 (Nov.) 1937.

3. Lanman, T. H., and Ingalls, T. H.: Vitamin C Deficiency and Wound Healing, Ann. Surg. **105**:616 (April) 1937.

4. Perla, D., and Marmorston, J.: Role of Vitamin C in Resistance, Arch. Path. **23**:543 (April); 683 (May) 1937.

5. Cevitamic Acid Stimulation of Specific Antibody Production, editorial, J. A. M. A. **109**:714 (Aug. 28) 1937.

6. Hetler, R. A.: Nutrition and Infections of Respiratory Mucous Membranes, Ann. Otol., Rhin. & Laryng. **46**:629 (Sept.) 1937.

7. Cady, F. C.: Association of Scurvy with Oral Diseases, Pub. Health Rep. **52**:1526 (Oct. 29) 1937.

8. McCullough, N. B.: Vitamin C and Resistance of the Guinea Pig to Infection with Bacterium Necrophorum, Arch. Path. **25**:139 (Jan.) 1938.

9. Takahashi, cited by Wachsmuth, W., and Heinrich, G.: Hypovitaminose und Osteomyelitis, Klin. Wchnschr. **17**:269 (Feb. 19) 1938; abstracted, J. A. M. A. **110**:1529 (April 30) 1938.

10. (*a*) Wilder, R. M., and Wilbur, D. L.: Diseases of Metabolism and Nutrition: Review of Certain Recent Contributions, Arch. Int. Med. **61**:297 (Feb.) 1938. (*b*) Booth, M., and Hansen, A. E.: The Present Day Status of the Vitamins: A Review, Journal-Lancet **57**:530 (Dec.) 1937. (*c*) Wright, I. S., and Lilienfeld, A.: Pharmacologic and Therapeutic Properties of Crystalline Vitamin C (Cevitamic Acid), with Especial Reference to Its Effects on Capillary Fragility, Arch. Int. Med. **57**:241 (Feb.) 1936. (*d*) Perla and Marmorston.[4]

Göthlin [11] and Abbasy and his co-workers,[12] about 25 mg. Schultzer's [13] recent work confirmed this. Apparently no symptoms are known to be associated with excessive intake. Determinations of the ascorbic acid level of the blood by various investigators have given roughly comparable results, so that it is possible at present to determine at least approximately what may be considered a normal level and what a minimum level, below which one may presume a deficient intake. According to Mirsky, Swadesh and Soskin,[14] the total ascorbic acid content of whole blood ranges between 1.11 and 2.88 mg. per hundred cubic centimeters. Farmer and Abt [15] found values of from 0.69 to 2.36 mg. per hundred cubic centimeters for reduced ascorbic acid content of blood plasma. Bellows,[16] in a comparison of the ascorbic acid levels in the blood plasma of normal and of cataractous persons, found average values of 1.02 and 0.605 mg. per hundred cubic centimeters, respectively. In another report by Farmer and Abt,[17] these authors stated that an ascorbic acid content of the blood plasma reduced to less than 0.50 mg. indicates "marked insufficiency of vitamin C intake," while Ingalls and Warren [18] stated that they considered levels below 0.30 mg. indicative of asymptomatic scurvy. Later references to the level of this substance in the blood [19] specified 0.70 mg. per hundred cubic centimeters as an

11. Göthlin, G. F.: Method of Establishing a Vitamin C Standard and the Requirements of Physically Healthy Individuals by Testing the Strength of the Cutaneous Capillaries, Skandinav. Arch. f. Physiol. **61**:225 (May) 1931; cited in Human Requirement for Vitamin C, editorial, J. A. M. A. **110**:1928 (June 4) 1938.

12. Abbasy, M. A.; Harris, L. J.; Ray, S. N., and Marrack, J. R.: Diagnosis of Vitamin C Subnutrition by Urine Analysis, Lancet **2**:1399 (Dec. 21) 1935.

13. Schultzer, P.: On Saturation of Scurvy Patient with Small Doses of Ascorbic Acid: Consideration of Daily Human Requirement, Biochem. J. **31**: 1934 (Nov.) 1937.

14. Mirsky, Swadesh and Soskin, cited by Stephens, D. J., and Hawley, E. E.: The Partition of Reduced Ascorbic Acid in Blood, J. Biol. Chem. **115**:653 (Oct.) 1936.

15. Farmer, C. J., and Abt, A. F., cited by Stephens, D. J., and Hawley, E. E.: The Partition of Reduced Ascorbic Acid in the Blood, J. Biol. Chem. **115**:653 (Oct.) 1936.

16. Bellows, J.: Biochemistry of the Lens: V. Cevitamic Acid Content of the Blood and Urine of Subjects with Senile Cataract, Arch. Ophth. **15**:78 (Jan.) 1936.

17. Farmer, C. J., and Abt, A. F.: Determination of Reduced Ascorbic Acid in Small Amounts of Blood, Proc. Soc. Exper. Biol. & Med. **34**:146 (March) 1936.

18. Ingalls, T. H., and Warren, M.: Frequency of Asymptomatic Scurvy in Patients on Bland Diets, New England J. Med. **217**:443 (Sept. 9) 1937.

19. Perla and Marmorston.[4] Wilder and Wilbur.[10a]

approximate (or minimum) average [20] value in normally nourished persons.

Among reports in the literature on values for urinary excretion, it will suffice to refer to Youmans and his associates,[21] who stated that "a daily urinary excretion of . . . 20 mg. . . . is suggested as the lower limit of normal daily excretion," and to Abbasy and his co-workers,[12] who asserted that "about 20 mg." is the average daily excretion of a normal adult receiving an adequate diet in England and stated that 10 to 15 mg. should be considered a minimum level, below which a substandard diet may be presumed.

In view of the fact, however, that ascorbic acid is excreted in some amount in the urine of every person not actually bedfast with scurvy, determinations of the presence of this substance in single specimens of urine occasionally give a far from adequate picture of the actual state of deprivation. The administration of accurately measured test doses, either intravenously or by mouth, with subsequent determination of the amount of the vitamin excreted during a measured period, has therefore been introduced as of value in establishing a diagnosis of subclinical scurvy and vitamin subnutrition of all degrees. The dose given perorally differs according to different investigators, ranging from 200 to 600 mg. or more. Abbasy and his co-workers [12] stated that the diet may be presumed to be "unduly low in vitamin C content" if there is no response to a single test dose of 700 mg. on the second day after administration. Youmans and his associates [21] stated that "for the present" excretion of 30 per cent of a test dose of about 600 mg. by adults may be taken to indicate the lower limit of "saturation."

In the field of ophthalmology, the most fruitful work is that dealing with the general role of the vitamins in the normal and abnormal metabolism of the eye,[22] as there appears to exist a close interrelation between the effects of several vitamins, notably A, C and G (riboflavin), on the oxidation-reduction processes of the various structures of the eye. Buschke [22a] pointed out that the crystalline lens, because of its eminent suitability for research of this kind, was one of the first organs in which the water-soluble oxidation-reduction systems, vitamins C and G, glutathione and the "oxidation catalyzer," vitamin A, could be demonstrated as coexistent. A considerable amount of work has been done in connection with the presence of vitamin C in the anterior chamber

20. Wortis, H.; Wortis, S. B., and Marsh, F. I.: Rôle of Vitamin C in Metabolism of Nerve Tissue, Arch. Neurol. & Psychiat. **39**:1055 (May) 1938.

21. Youmans, J. B.; Corlette, M. B.; Akeroyd, J. H., and Frank, H.: Studies of Vitamin C Excretion and Saturation, Am. J. M. Sc. **191**:319 (March) 1936.

22. (*a*) Buschke, W.: Die Vitamine in der Ophthalmologie, Ztschr. f. Vitaminforsch. **5**:37 (Jan.) 1936. (*b*) Pavía, J. L., and Diez, M.: Las vitaminas A y C en oftalmologia, Rev. oto-neuro-oftal. **12**:13 (Jan.) 1937.

and in the lens with normal and with pathologic conditions. Of special interest in connection with the work here reported are repeated determinations of the concentration of the vitamin in eyes with cataractous conditions and with aphakia,[22] all results pointing to a definite reduction of the vitamin with these conditions, especially the latter, and in the amount of the reduction in the presence of cataract more or less corresponding with the degree of opacity of the lens.

Reports on attempts to apply this information clinically, however, are difficult to find. One reference to such work among American clinicians is that of treatment with vitamin C and a diet rich in glutathione of a group of patients suffering from cataracts caused by dinitrophenol,[23] in which "rapid improvement" was noted. One report from England [24] described the "very favorable reaction" of a patient with congenital cataract to administration of vitamins A and C, as measured both by reading tests and by ophthalmoscopic examination.

Since ascorbic acid therapy was begun at this institution, reprints were received of work performed in Buenos Aires, by Pavía,[25] on cataractous persons of advanced age. Ascorbic acid was administered both intravenously and directly into the anterior chamber of the eye, and the effects were checked by biomicrographic study of the lens. Despite the fact that some of the patients treated had suffered impairment of vision for a number of years, the percentage of improvement was gratifying (70 per cent in 10 cases). The results were much poorer in a series of 7 patients treated with subcutaneous injections only. The amounts of ascorbic acid administered in the latter instance were, however, not especially large. Of special interest is the finding that the improvement in the condition of the optic media and consequently in the visual acuity of 1 patient persisted during two months of observation after institution of treatment, despite a gradual drop of the urinary excretion values of ascorbic acid. The author concluded that this phenomenon tends to bear out other investigative work which indicates that the ascorbic acid content of the anterior chamber can remain high regardless of the level in the blood plasma.

Pavía determined the amount of ascorbic acid to be administered by titrating the amount excreted in the urine; he came to the conclusion that when this figure goes below 3 mg. per hundred cubic centimeters with excretion of a normal twenty-four hour volume of urine, it is necessary to administer 300 mg. of ascorbic acid daily and that when the

23. Josephson, E. M.: Ascorbic (Cevitamic) Acid in Cataract with Special Reference to Dinitrophenol Cataracts, Science **82**:222 (Sept. 6) 1935.

24. Koepcke, G. M.: Vitamins and Infections of Eye, Nose, Throat and Sinuses, Journal-Lancet **57**:460 (Oct.) 1937.

25. Pavía, J. L.: Catarata senil: Un nuevo tratamiento medico, Rev. oto-neuro-oftal. **12**:182 (July) 1937.

content exceeds 3 mg., it is necessary to give only 100 mg. every other day. In Pavía's cases the duration of treatment was apparently determined entirely by the degree of improvement obtained. The author, however, did not specify the length of treatment he considered adequate definitely to determine whether any beneficial effect is to be expected.

Other references to dosage include a statement by Ingalls [26] to the effect that Johnson and Zilva and Hawley and his associates noted "no significant increase" in the excretion of ascorbic acid by unsaturated persons after daily administration of 200 mg. for several days. He also cited van Eekelen, who required 1,800 mg. for resaturation after abstaining for one month from foods containing vitamin C. There is, however, no reference to the manner in which this amount was taken nor to the time required. Youmans and others [21] stated that a daily dose of 25 to 100 mg., has little effect on the excretion value of unsaturated persons, and Wood [26a] described a patient who had frank scurvy with no ascorbic acid in the urine, who excreted 1 to 7 mg. after taking a dose of 600 mg. but none after that, despite a daily dose of 80 mg. for one week, with clinical improvement.

EXPERIMENTAL STUDY

In regard to the procedure to be followed at this institution, it seemed desirable to complete all tests within one season, in view of the fact that seasonal variations in the degree of ascorbic acid saturation may be assumed with a fair degree of certainty.[27]

It was decided to establish as many fairly large groups of approximate values as possible before investigation of the special group of patients who presented visual disturbances. Tests on the vitamin C level in the blood were carried out also on a small group of subjects not connected with this institution but living under similar conditions. They represent a part of the nursing staff of the general hospital at Hastings, Neb. Tests on this group were performed in April and May 1938.

It proved preferable, in the interests of cooperation and because of the fact that we were dealing with patients with mental disease, to run tests on several persons simultaneously for short periods, rather than long individual tests in the determinations of urinary excretion of the vitamin. No subject was tested without a preliminary complete analysis of urine, and all persons with definitely pathologic findings were rejected. Other requisites for inclusion in the test were subjective well-being, freedom, as far as determinable, from syphilis and active tuberculosis and absence of special treatment, such as metrazol or insulin shocks or therapy with the hypertherm.

26. Ingalls, T. H.: Studies on the Urinary Excretion and Blood Concentrations of Ascorbic Acid in Infantile Scurvy, J. Pediat. **10**:577 (May) 1937.

26a. Wood, P.: A Case of Adult Scurvy, Lancet **2**:1405 (Dec. 21) 1935.

27. Corlette, M.; Youmans, J. B.; Akeroyd, J., and Frank, H.: A Clinical Study of Vitamin C Excretion, South. M. J. **29**:37 (Jan.) 1937.

Participants in the tests included the members of the medical staff and their wives, the members of the nursing staff, the day and the night attendants, confined patients and patients on parole as well as various employees of other types. All of these subjects ate all meals at the institution. As far as possible, men and women were chosen in equal numbers, with the exception of the outside group, which consisted entirely of women. The tests were begun in January 1938 and continued without interruption throughout February, March, April and May. All tests on the vitamin level in the blood and in the urine preparatory to controlled administration of ascorbic acid were completed by the end of March, i. e., at a time when the values would presumably be lowest.

The urine was collected in dark brown bottles; it was acidified to contain approximately 5 per cent glacial acetic acid and was kept at or near ice box temperature. Titrations were carried out at 8 a. m., 3 p. m. and 8 p. m. The urine was examined by titration of duplicate samples with 2,6-dichlorobenzenone-indophenol; the blood plasma was tested by the method of Farmer and Abt.[17] Blood was obtained by venipuncture, as a duplicate test, and occasionally other tests were made on each sample.

The first step in this series was a test on the twenty-four hour urinary excretion, carried out without any preparatory procedures and involving the largest number of subjects examined in any group. Some time later, twenty-four hour collections of urine were again undertaken, after the ingestion of 600 mg. of pure ascorbic acid in tablet form. The test dose was taken with breakfast, and collection of urine was started immediately; fresh fruits and fruit juices were eliminated from the diet during the period of collection, with no other change in the daily routine. In addition, the level of ascorbic acid in the blood plasma was determined, specimens of blood being taken in the morning during fasting.

The patients suspected of visual disturbances due to clouding of the media were first segregated by preliminary examination; they were then examined and grouped by a consulting ophthalmologist and were finally subjected to the tests on vitamin excretion and level in the blood just described. Before administration of ascorbic acid was begun as treatment, the series was narrowed to 12 patients, 8 women and 4 men. This number obviously represented only a fraction of the group of patients in whom difficulties of the same sort were encountered in refraction tests and in other tests at this institution. It was necessary, however, to pick subjects who could be counted on to describe their subjective impressions more or less accurately and consistently and whose mental conditions were not likely to change in the course of this investigation.

Homogeneity in every respect is not claimed for this group. All 12 persons, however, had in common subjective visual difficulties, especially in performing skilled tasks or in reading, and refraction could not be satisfactorily determined. If glasses were satisfactory when first fitted, they soon ceased to give good service. Three of the subjects, women 56, 64 and 73 years old, respectively, had well developed unilateral cataracts. One other, a woman aged 63, showed bilateral opacities of the lens; another woman, aged 47, had beginning bilateral cataracts.

For four weeks only 6 of the 12 subjects, 4 women and 2 men, received ascorbic acid. The remaining 6 served as controls in order that changes in the levels in the blood might be evaluated more accurately, as the oncoming change in seasons and the consequent change in the general diet were expected to bring about a general rise in the ascorbic acid reserves of the institutional population as a whole. Determinations of the vitamin level in the blood were carried out once a week on the subjects under treatment, except on the first subgroup for the fourth week, and on both subgroups after the fourth week. From the fourth week on, both

subgroups received ascorbic acid daily in addition to the regular diet. Small amounts of tomato juice were included as a regular fortifying feature of the diet five weeks after treatment was first begun (after one week for the second subgroup).

Treatment was begun with the administration of between 300 and 350 mg. of ascorbic acid daily. This dose was reduced for short periods in some cases, depending on the level in the blood, but at the conclusion of treatment (eight weeks for the first subgroup, four weeks for the second) 11 of the 12 subjects were receiving approximately 350 mg. daily. One patient did not receive any ascorbic acid during the last week of treatment. Determinations of levels in his blood plasma made during this week and those made subsequently are considered separately.

RESULTS

In a consideration of the findings, attention is first called to the difference in the average urinary excretion of ascorbic acid among the three large institutional groups. Only the values for the "officer" group (physicians and their wives, heads of the nursing departments, etc.) actually exceeded the minimum figures considered as indicative of

TABLE 1.—*Average Twenty-Four Hour Urinary Excretion of Ascorbic Acid* **

Subjects	Men and Women	Men	Women
25 officers	32.22	31.13	33.32
96 employees	14.06	16.65	14.03
Day workers	15.41	.....	.....
Night workers	13.70	.....	.....
31 patients†	10.94	10.64	11.22

* Values indicate milligrams.
† Excluding those treated with ascorbic acid.

normal vitamin C nutrition, while the values for the employee group (night and day attendants, clerical employees, etc.) hovered in the main around the minimum values cited in the literature, and the excretion levels of the patient group were, with only two or three exceptions, well below these values. The exceptions in the latter group, moreover, in no case exceeded the minimum normal values (table 1).

The levels in the blood plasma represented a parallel to the findings just cited—on the whole, however, with less marked differences between the three institutional groups (table 2).

The outside group of graduate and student nurses showed levels in the blood plasma closely approximating the averages given by Bellows and others, both in March and in May, with a slightly higher average in the later determinations (table 2).

The most striking and illuminating differences were obtained in determinations of excretion after a test dose (table 3). The practically complete failure on the part of the patients to eliminate any of the test dose within twenty-four hours is the outstanding finding for these sub-

jects. One woman, who lived in the same ward as other patients included in these tabulations, reflected the fact that she was receiving a high vitamin diet in the values for vitamin C after the test dose as well as, to a less complete degree, in the level in the blood plasma, but not at all in the regular urinary excretion of ascorbic acid. The latter was 11.58 mg. in twenty-four hours (highest value for a female patient taking the regular diet, 17.02 mg.; average for both sexes, 10.94 mg.). The level in the blood plasma was 1.00 mg. per hundred cubic centimeters (highest value for a female patient taking the regular diet, 0.50 mg.; average for both sexes, 0.49 mg.). The excretion of this

TABLE 2.—*Level of Ascorbic Acid* in Blood Plasma*

Subjects	Men and Women, Average	Men, Average	Women, Average	Highest Value
13 employees	1.12	0.97	1.24	1.90
16 patients†	0.49	0.51	0.47	0.65
15 members of outside group, March 9, 1938	0.70	....	....	1.20
6 members of outside group, May 24, 1938	0.76	....	....	1.30

* Values indicate milligrams per hundred cubic centimeters.
† Excluding those treated with ascorbic acid and a patient given a special diet (see text).

TABLE 3.—*Twenty-Four Hour Urinary Excretion of Ascorbic Acid* After Test Dose*

Subjects	Men and Women, Average	Men, Average	Women, Average	Highest Value
11 employees	122.82	101.80	165.98	205.60
18 patients†	11.62	15.26	9.80	24.28

* Values indicate milligrams.
† Excluding those treated with ascorbic acid and a patient given a special diet (see text).

woman after a test dose was 226.11 mg. in twenty-four hours (highest value for a female patient taking the regular diet, 16.04 mg.; average for both sexes, 11.62 mg.).

The lowest values throughout were obtained for the 12 patients segregated for special treatment because of visual disturbance. (This grouping of patients, as of all subjects tested, was done before any tests on excretion or on level in the blood had been carried out.) The second subgroup of these 12 treated subjects, however, indicated a slight general rise in the blood plasma values, apparently coincidental with the seasonal changes in diet, when tested one month later, before treatment was started (table 4).

Studies of the excretion values obtained for all groups without test doses at various times of the day indicated that the ascorbic acid appeared

to be excreted in amounts roughly corresponding to the number of hours during which individual samples were collected. A comparison of the fractional excretion values after the administration of test doses, however, revealed group differences in that the patients, who showed an apparently complete lack of saturation or of vitamin C reserves, maintained about the same ratio of excretion as without the test dose, whereas the employees as a whole excreted more ascorbic acid during the seven hours from 8 a. m. to 3 p. m., i. e., immediately after ingestion of the test dose, than during the next seventeen hours, from 3 p. m. to 8 a. m. the following morning, despite a rather poor response to the test dose as compared with data given in the literature.[28]

The fact that the accuracy of the excretion tests, especially, depended much on the cooperation both of the subjects tested and of

TABLE 4.—*Average Twenty-Four Hour Urinary Excretion of Ascorbic Acid, Level in Blood Plasma and Response to Test Dose for Patients Before Treatment*

Observation	Subjects	Men and Women	Men	Women
Urinary excretion*	Subgroups 1 and 2 (12 patients)	6.35	8.02	5.50
Level in blood plasma, March 16-21, 1938†	Subgroups 1 and 2 (12 patients)	0.45	0.47	0.44
Level in blood plasma, April 23, 1938†	Subgroup 2 (6 patients)	0.55	....	....
Response to test dose‡	Subgroups 1 and 2 (12 patients)	7.11	9.31	5.85

* Values indicate milligrams per twenty-four hours.
† Values indicate milligrams per hundred cubic centimeters.
‡ Values indicate milligrams.

the employees aiding in the collection of specimens was considered; as a rough means of control, the amounts of urine excreted by the various groups in twenty-four hours were measured together with the amounts of ascorbic acid. The general average for all types of employees and patients, comprising about 150 subjects, was thus found to be 1,278 cc.

The values for the vitamin C content of blood plasma obtained before, during and after treatment of the special group of 12 patients are compiled in table 5. It will be noted that, apart from the initial fluctuations encountered when an attempt was made to achieve a maxi-

28. Wright, I. S.; Lilienfeld, A., and MacLenathen, E.: Determination of Vitamin C Saturation: A Five Hour Test After an Intravenous Test Dose, Arch. Int. Med. **60**:264 (Aug.) 1937. Wortis, H.; Liebmann, J., and Wortis, E.: Vitamin C in the Blood, Spinal Fluid and Urine, J. A. M. A. **110**:1896 (June 4) 1938. Abbasy and others.[12] Youmans and others.[21]

mum rise in level in subgroup 1, the values of the blood plasma dropped to a fairly constant high level below that of the initial rise in 10 of the 12 patients, despite the fact that the daily amounts of ascorbic acid administered far exceeded the amounts required to maintain a normal

TABLE 5.—*Level of Ascorbic Acid in Blood for Patients Before, During and After Treatment*

				Subgroup 1 Week of Treatment									
Case No.	Patient	Sex	Age, Yr.	Before Treatment	First	Second	Third	Fourth	Fifth	Sixth	Seventh	Eighth	First Week After Treatment
1	M. B.	F	73	0.45	1.90	1.90	1.75	....	2.30	2.20	1.80	1.80	1.50
2	E. Ba.	F	64	0.44	2.80	1.90	2.20	....	2.50	2.55	2.25	1.80	1.55
3	M. Ho.	F	42	0.43	2.40	2.25	2.20	....	2.75	2.00	2.35	2.20	1.65
4	M. Ha.	F	56	0.40	2.40	2.20	2.15	....	2.60	2.15	2.10	1.75	1.55
5	R. J.	M	38	0.41	1.40	1.45	1.60	....	2.00	1.55	1.75	1.75	1.20
6	G. B.	M	54	0.60	2.00	0.75	1.80	....	1.15	1.85	1.80	1.70	1.40
	Average			0.46	2.15	1.74	1.95	....	2.22	2.05	2.01	1.83	1.47

				Subgroup 2 Week of Treatment									
Case No.	Patient	Sex	Age, Yr.					Before Treatment	First	Second	Third	Fourth	First Week After Treatment
7	E. Bo.	F	41	0.40	....	....	....	0.55	2.55	2.35	1.85	2.00	1.55
8	I. H.	F	47	....	....	....	....	0.50	....	2.20	1.75	1.40	0.80
9	H. M.	F	63	0.48	....	....	....	0.60	2.50	2.10	1.75	1.95	1.70
10	S. B.	F	56	0.46	....	....	....	0.54	1.90	1.80	1.75	1.50	(1.30)*
11	H. J.	M	64	0.47	....	....	....	0.58	2.40	2.20	1.70	(1.20)†	(0.90)†
12	J. C.	M	55	0.40	....	....	....	....	0.95	1.85	1.70	1.50	1.40
	Average			0.44	....	....	....	0.55	2.06	2.08	1.75	1.67	1.36
	General Average			0.45	....	....	....	....	2.15	2.07	1.88	1.76	1.43

* Treatment continued during fifth week; not included in average.
† No treatment during fourth week; not included in average.

level in the blood and in the urine. That this apparent inability to maintain the maximum attainable level in the blood for more than a short period was, moreover, not due to decreased absorption in the gastrointestinal tract is indicated by the values for urinary excretion obtained for 11 of the 12 patients at the end of the eighth (fourth) week of treatment (table 6), which show a tremendous spilling over of ascorbic acid, practically equivalent, in fact, to the daily dose administered in tablet form.

The twenty-four hour urinary excretion of ascorbic acid was again tested immediately after the final manifest readings of visual acuity for this group, or about eleven days after termination of treatment. The values obtained are included in table 6. It will be noted that the patients differed little from one another in their excretion as tested at any one time, either toward the end of treatment or a fortnight later, but it may be seen also that the values obtained at the latter time are throughout equivalent only to the lower limit of normal daily excretion during a well balanced dietary regimen. That is to say, within eleven days of administration of excessive amounts of the vitamin, with evidence of high values in the blood plasma, the urine failed to show any evidence of an excess of the substance in the body. This indicates the presence of reserve depots in the body; Wortis, Wortis and Marsh [20] have most recently stressed the fact that certain parts of the central nervous system, as well as related structures (pituitary gland, crystalline lens and aqueous humor of the eye and adrenal glands), have been definitely found to contain relatively large amounts of ascorbic acid independent of the level in the blood.

Regardless of the date of the last tests for visual acuity all patients in the treated group were examined at the same time for reading ability and with the ophthalmoscope shortly before beginning treatment; those in subgroup 1 were reexamined after four weeks of treatment; those in subgroups 1 and 2 were examined two weeks later, again at the conclusion of the treatment and finally about eleven days after treatment had been discontinued.

Of the 12 patients thus studied, 1 man and 1 woman could not be included in a final consideration of the effects of treatment because of their psychotic condition. All of the remaining 10 showed some degree of opacity in the vitreous, and 5 showed beginning, moderately advanced or mature cataracts. Other findings were, in some instances, unusually pale disks and narrowed, somewhat tortuous retinal arteries.

Of the 5 patients primarily showing changes of the lens, 4 showed no improvement whatsoever, either of the ophthalmoscopic picture or of visual acuity as determined by manifest readings. The fifth, patient 10 (S. B., table 5), a 56 year old woman, had already undergone an operation for removal of the left lens and showed beginning cataract of the right lens. The left vitreous in particular, however, showed opacities also. Treatment apparently produced no change in the condition of the remaining lens but did affect the opacities of the vitreous, with improvement of vision in both eyes (table 7).

The remaining 5 patients showed improvement of vision (table 7), but it is worthy of note that before treatment the outstanding ophthal-

moscopic findings in these cases were changes in the fundus and in the vitreous and that the latter changes regressed under treatment to a remarkable extent, with complete clearing in some instances.

Associated with these objectively determinable changes under treatment was subjective improvement of vision, expressed by such statements as these: "My eyes are stronger"; "I can do my needle work without my glasses now"; "I can read much easier"; "Things seem so much clearer than they did." Moreover, both objective and subjective improvement set in rapidly when it occurred at all and in most cases did

TABLE 6.—*Twenty-Four Hour Urinary Excretion of Ascorbic Acid* for Patients During and After Treatment*

Time of Determination	Average	Highest Value
Last week of treatment	323.21	356.13
11 days after treatment	16.30	28.88

* Values indicate milligrams.

TABLE 7.—*Manifest Readings of Visual Acuity for Patients Treated Before, During and After Treatment**

Case No.†	Patient	Sex	Age, Yr.	March 15	April 19 or Later	May 31
4	M. Ha.	F	56	O. D. 20/70 O. S. 20/70	O. D. 20/40 O. S. 20/40	O. D. 20/40+2 O. S. 20/40
6	G. B.	M	54	O. D. 20/00 O. S. 20/70	O. D. 20/00 O. S. 20/50	O. D. 20/200 O. S. 20/50
7	E. Bo.	F	41	O. D. 20/70 O. S. 20/50—1	O. D.‡ 20/40—1 O. S. 20/40—2	O. D. 20/30—2 O. S. 20/30—2
10	S. B.	F	56	O. D. 20/70+2 O. S. 20/00	O. D.‡ 20/40—2 O. S. 20/200+1	O. D. 20/50+1 O. S. 20/100+1
11	H. J.	M	64	O. D. 20/200 O. S. 20/200	O. D.† 20/100+1 O. S. 20/200+2	O. D. 20/70 O. S. 20/70—1
12	J. C.	M	55	O. D. ? O. S. ?	O. D.§ 20/40+2 O. S. 20/30—2	O. D. 20/30—1 O. S. 20/30

* One test not included.
† Numbers same as in table 5.
‡ Tested May 7.
§ Tested May 15.

not progress much after two weeks of daily treatment. The last examination, made about eleven days after completion of several weeks of treatment, showed only occasional further changes of note.

As the 2 patients eliminated from this series were originally included in subgroup 1, only 4 subjects in this subgroup were actually considered in these comparisons. Of these, 2, or 50 per cent, reacted favorably to treatment. In subgroup 2, 4 of 6, or 66 per cent, reacted favorably to treatment. This subgroup received only half as much ascorbic acid as subgroup 1; the patients were distributed within the two subgroups as evenly as possible in regard to both age and ophthalmologic findings.

A comparison of the average ages of the patients whose vision improved with those in whom it was unimproved indicates that the older the person, the less favorable the reaction, as the subjects whose condition improved showed an average age of 54.3 years, as against 61.8 years for those whose status remained unimproved. It should be noted, however, that among the most strikingly benefited persons was a patient 64 years old.

All patients were questioned at regular intervals concerning the general state of appetite, sleep, elimination, etc. In the majority of cases the responses were favorable, in some cases remarkably so, especially in regard to mood and appetite. One patient in particular (patient 11, H. J., table 5), a 64 year old man, suffered severely from pains in all large joints and in the spine, with marked initial stiffness on arising from bed or after sitting in one position for any length of time. After the first week of treatment this patient spontaneously offered the information that the initial stiffness had diminished considerably and that the pains in the joints were definitely less troublesome. Throughout the remainder of the treatment and subsequently he has repeatedly made the statement that he feels "better in every way than for the past two years." This feeling of general well-being can probably be ascribed in great part simply to the relief from the constant articular pains. This effect of the administration of ascorbic acid seems, moreover, to be in accordance with recent reports on the manifestations of various degrees of vitamin C deficiency.[29]

It was observed also that in determination of the vitamin levels in the blood plasma the punctured veins, which had, especially in the older members of the group, shown a tendency to bleed rather profusely after venipuncture, gradually improved in this respect to a remarkable degree.

Four of the 12 patients comprising the treated group were inmates of epileptic wards and were receiving either phenobarbital or phenobarbital and bromides at the time this investigation was carried out. The medication apparently had no effect on the reaction to ascorbic acid, for the number and character of the seizures experienced by these patients in the course of the year revealed no demonstrable change during ascorbic acid therapy.

SUMMARY

Various groups of the employee and patient population of the Hastings State Hospital were tested for the twenty-four hour urinary excretion of ascorbic acid, the level of the substance in the blood

29. Rinehart, J. F.; Greenberg, L. D.; Baker, F.; Mettier, S. R.; Bruckman, F., and Choy, F.: Metabolism of Vitamin C in Rheumatoid Arthritis, Arch. Int. Med. **61**:537 (April) 1938. Booth and Hansen.[10b]

plasma and the twenty-four hour excretion after a peroral test dose of 600 mg. of pure ascorbic acid in tablet form. The tests were all carried out during the late winter months of 1938. The findings differed among the different groups; they indicated definite vitamin C deficiency for the patients in general.

For a control group of persons not connected with the institution the levels in the blood plasma were determined in March and May 1938, the test at the latter time coinciding with termination of treatment at this institution. The findings corresponded in the main with those given in the literature for normally nourished subjects.

All the described tests were performed also on a special group of patients who presented visual disturbances due apparently to changes in the tissues associated with aging of the eye. These patients were subjected, in addition, to ophthalmoscopic examination and to reading tests. The findings indicated an even more marked vitamin C deficiency in this group than among the other institutional patients.

The special group was divided into two subgroups, one of which received massive daily doses of ascorbic acid by mouth for eight weeks, while the other received the same medication for four weeks.

Determinations of the levels of reduced ascorbic acid in the blood plasma were carried out at regular intervals during treatment and one week after it, in addition to ophthalmoscopic and reading tests. The twenty-four hour urinary excretion was determined during the last week of treatment and again two weeks later, immediately after the final examination for visual acuity. The findings indicated improvement of eyesight in all patients not suffering primarily from senile cataract. The general well-being of the patients under treatment appeared to be beneficially affected as well.

All findings are recorded in tabular form and briefly discussed, with mention of incidental observations not directly related to the problem under consideration. Sixty per cent of the treated group as a whole showed improvement, as measured by reading test, ophthalmoscopic examination and the subjective reactions of the patients. The results indicated, moreover, that marked improvement sets in within the first two weeks of treatment, if it occurs at all, with slow progression or no further change from then on. Cataracts were apparently not affected by this method of treatment, all improvements being due to clearing of the other optic media and apparently even to some degree to a beneficial effect on the retinal vessels and the head of the optic nerve (or the optic nerve as a whole?). Whether the latter findings represented a direct or an indirect action of ascorbic acid is still a matter of conjecture, although reports of recent work indicate that a direct effect is probable.[20]

CONCLUSIONS

From a comparison of the excretion values and the levels in the blood during and after treatment as well as from the results of ophthalmoscopic and reading tests, it appears that ascorbic acid deficiency can be held at least partly responsible for impairment of vision associated with senescence of the human eye and that the administration of ascorbic acid by mouth in adequate doses can counteract this process, so far as the crystalline lens is not primarily involved.

The lens, although showing a definitely subnormal ascorbic acid content with cataractous conditions, apparently cannot be favorably affected by the administration of ascorbic acid by mouth, even in excessive amounts, after senile changes have set in.

The findings here reported also indicated that little is gained by continuing the administration of large amounts of ascorbic acid if there is no measurable improvement after daily treatment for two weeks. This time limit is liberal.

The fact has not been lost sight of that a method of treatment properly combining more than one of the vitamins known to be specifically associated with the metabolic functioning of the eye may prove successful when ascorbic acid alone ceases to be of benefit.

The Henry Ford Hospital.

All manifest readings of visual acuity were carried out by Dr. D. M. Judkins-Davies, of the medical staff of Hastings State Hospital, who first suggested a possible connection between vitamin deficiency and the condition of the optic media of the patients at this institution and who was in close cooperation with me during the testing of the various groups.

Dr. E. C. Foote, of the Foote Clinic, Hastings, Neb., was ophthalmologic consultant.

The ascorbic acid used in these tests was furnished by the Department of Clinical Research of the Abbott Laboratories, North Chicago, Ill.