VITAMIN C AND ITS RELATION TO CATARACT

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The excellent experimental work and reviews which have appeared, especially in the last two years, from the department of ophthalmology of Northwestern University Medical School have increased the interest in the possible relation between the onset of cataract and the body stores of vitamin C (cevitamic acid). Delay in the development of cataract, possibly through dietary means, is a matter of such practical importance that a study of patients available in the Strong Memorial Hospital and the Rochester Municipal Hospital seemed worth while.

A brief summary of the literature may well precede a report of our laboratory findings. Bourne,[1] in her recent discussion of metabolic factors in the production of cataract, stated that "the physical and metabolic integrity of the lens is to some extent dependent upon the maintenance of a normal metabolism of the whole organism. General metabolic disturbance may affect the lens by creating a deficiency of some substance essential to lens metabolism by producing toxic substances, by altering the composition of the aqueous in respect to the water, salt or hydrogen ion concentration or by other metabolic disorders as yet unknown." Bourne considered all possible factors which might alter the normal metabolic function of the lens. We here confine ourselves to but one phase—the possible relation of cevitamic acid.

Glick and Biskind [2] stated: "The lens of the eye, having no blood supply, is especially dependent on those intracellular substances which form oxidation-reduction systems for the maintenance of many of its metabolic processes." They tabulated the concentration of cevitamic acid in the lenses of a number of animals as reported by various workers and found a range from 2 mg. per hundred grams of tissue in the rat

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1. Bourne, M. C.: Metabolic Factors in Cataract Production, Physiol. Rev. **17**:1 (Jan.) 1937.

2. Glick, D., and Biskind, G. R.: Studies in Histochemistry: X. Distribution of Vitamin C in the Lens of the Eye, Arch. Ophth. **16**:990 (Dec.) 1936.

to 104 mg. in fish. The value for the lens in man is given as 31 mg.[3] This agrees with the work of Müller and Buschke,[4] who found the normal human lens to contain 30 mg. of cevitamic acid per hundred grams of tissue. This high percentage of vitamin C in the lens of the human eye naturally raises the question as to its origin and function. Why should vitamin C be found in much lower concentrations in the cataractous lens? Bellows[5] has reported that subjects with cataract have a lower concentration of cevitamic acid in the blood than do normal subjects, an average of 0.605 mg. per hundred cubic centimeters for the group with cataract against 1.02 mg. for the group of normal subjects. Single morning specimens of urine showed a lower excretion of vitamin C for his six patients with cataract than for six normal persons of a corresponding age, the amount excreted being expressed as milligrams of vitamin C per cubic centimeter of urine.

Glick and Biskind[2] have demonstrated that age in itself is a factor in establishing the level of cevitamic acid in lens as well as in other tissues. They found the level of vitamin C in the lens of a cow to be from 10 to 15 per cent lower than that in the lens of a calf. Such a difference has been found by various writers for all other tissues. Those tissues which have the highest metabolic activity or those taken from the growing young are always higher in vitamin content than the tissues of mature animals. The vitamin C content of mature and immature cataract,[6] however, is much too low to be accounted for by the factor of age alone.

The ability to produce cataract in the albino rat through poisoning with naphthalene,[7] or with excessive amounts of galactose, as first employed by Mitchell and Dodge,[8] has made possible studies of the effect of the administration of vitamin C on the onset of cataract. Bellows[9] was able to show that the administration of cystine and, to

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3. von Euler, H., and Malmberg, M.: Neue Versuche über Askorbinsäure (C-Vitamin) in tierischen Augenlinsen, Arch. f. Augenh. **109**:225, 1935.

4. Müller, H. K., and Buschke, W.: Vitamin C in Linse, Kammerwasser und Blut bei normalem und pathologischem Linsenstoffwechsel, Arch. f. Augenh. **108**:368, 1934.

5. 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.

6. Bellows, J.: Biochemistry of the Lens: VII. Some Studies in Vitamin C and the Lens, Arch. Ophth. **16**:58 (July) 1936.

7. Müller, H. K.; Buschke, W.; Gurewitsch, A., and Brühl, F.: Vitamin C in Kammerwasser und Linse: Seine Bedeutung für Physiologie und Pathologie des Linsenstoffwechsels, Klin. Wchnschr. **13**:20 (Jan. 6) 1934.

8. Mitchell, H. S., and Dodge, W. M.: Cataract in Rats Fed on High Lactose Rations, J. Nutrition **9**:37 (Jan.) 1935.

9. Bellows, J.: Biochemistry of the Lens: IX. Influence of Vitamin C and Sulfhydryls on the Production of Galactose Cataract, Arch. Ophth. **16**:762 (Nov.) 1936.

a lesser extent, of vitamin C delayed the onset of the cataracts in the experimental groups. He wrote: "Galactose in some way causes a loss of the sulfhydryl content of the crystalline lens. . . . If it could be shown that they diminish in amount before the opacities in the lens appear, this, coupled with the fact that an excess of these substances in the diet delays the onset of opacities, would make it reasonably certain that the loss of these substances is responsible for cataract formation." Von Euler and Malmberg [3] found the vitamin C content of the lens of normal rabbits and guinea pigs to be 16 mg. per hundred grams, while the value for the lens of such animals rendered scorbutic by dietary restriction was diminished to 10 and 0.5 mg., respectively. The administration of large doses of vitamin C raised the level as high as 26 mg. They further reported that the value of 31 mg. for the normal human lens is diminished to 5 mg. by the presence of cataract.

A further experiment by Bellows [9] showed a diminished quantity of sulfhydryls (glutathione and cysteine) but little change in the vitamin C content before there was any visible change in the lens. Since, however, vitamin C to some extent delayed the onset of cataract, "one is led to believe that the sulfhydryls and vitamin C are partially interchangeable in carrying out oxidation and reduction in the crystalline lens. Thus, as the sulfhydryl content diminishes, vitamin C, if available, will take over more and more of this function and will keep the lens more or less viable for some time. One may theorize that senile cataract in man may arise in a similar way . . ."

The question as to whether the absence of cevitamic acid precedes the formation of cataract or is a result of it cannot yet be answered. The possibility of a low vitamin C content predisposing to the formation of cataract suggests itself.

A question arises here, as with other determinations of cevitamic acid by titration with 2, 6-dichlorophenolindophenol: Is the method specific for cevitamic acid, especially when it is so closely associated with large amounts of glutathione and cysteine? Conflicting reports appear, but again one turns to the experiments of Bellows and Rosner,[10] who by the use of the enzyme from the Hubbard squash found that at p_H 2 the reduction of the dye is due to vitamin C. This confirms the experiments of Demole and Müller,[11] who found the vitamin C content, as indicated by the biologic test, to be in good agreement with that indicated by the chemical test, if loss of vitamin C during handling were

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10. Bellows, J., and Rosner, L.: Biochemistry of the Lens: VIII. New Proof of the Presence of Vitamin C in the Crystalline Lens, Arch. Ophth. **16**:248 (Aug.) 1936.

11. Demole, V., and Müller, H. K.: Ueber das Vorkommen von Ascorbinsäure in Linse und Kammerwasser, Biochem. Ztschr. **281**:80, 1935.

prevented. This also further confirms the observations on the chemical method for the estimation of vitamin C by Ahmad.[12]

In the present study patients admitted to the ophthalmologic service of the Strong Memorial Hospital were followed. It is unfortunate that complete data are not available for all. The vitamin C content of the blood was determined for 43 patients; of the urine, for 48 patients, and of the lens, for 36 patients, but complete studies were made on only 16. The data are tabulated for convenience and presented in the tables, the average values for the entire group being used in all tables except table 4, which contains the complete data on 16 patients.

The values for the lens are expressed as milligrams of cevitamic acid per hundred grams of moist lens; for the blood, as milligrams per hundred cubic centimeters of whole blood, and for the urine, as total milligrams in a twenty-four hour specimen. The values for the blood were obtained on patients during fasting. No source of vitamin C was given during the collection of the "basal" specimens of urine, since it was desired to ascertain the saturation level at the time of the patients' admission to the hospital in order to obtain the full effect of the previous dietary habits on the stores of the vitamin C in the body tissues.

Methods of ascertaining the cevitamic acid content of the blood, urine and tissue are reported elsewhere.[13]

From the data presented in the tables it can be seen that in our series there is no correlation between the vitamin C content of the lens and the age of the patient or between the age or the vitamin C content of the urine and the vitamin C content of the lens, but that there is a correlation between the vitamin C content of the urine and that of the blood.

There is a possible correlation between age and the vitamin C content of the blood, as indicated in table 1. If one calculates the average age of the cataractous and normal patients studied by Bellows,[5] one finds that with the difference in the vitamin C content of the blood in the two groups there is correspondingly an age difference. The group of cataractous patients, with an average vitamin C content of the blood of 0.605 mg. per hundred cubic centimeters, have an average age of

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12. Ahmad, B.: Observations on the Chemical Method for the Estimation of Vitamin C, Biochem. J. **29**:275, 1935.

13. (*a*) Hawley, E. E.; Stephens, D. J., and Anderson, G. K.: The Excretion of Vitamin C in Normal Individuals Following a Comparable Quantitative Administration in the Form of Orange Juice, Cevitamic Acid by Mouth and Cevitamic Acid Intravenously, J. Nutrition **11**:135 (Feb.) 1936. (*b*) Stephens, D. J., and Hawley, E. E.: Partition of Reduced Ascorbic Acid in the Blood, J. Biol. Chem. **115**:653 (Oct.) 1936. (*c*) Hawley, E. E.; Daggs, R. G., and Stephens, D. J.: Effect of the Administration of Acid and Alkaline Salts upon the Ascorbic Acid Content of Guinea Pig Tissues, J. Nutrition **14**:1 (July) 1937.

66, while the group of normal subjects, with an average vitamin C content of the blood of 1.02 mg. per hundred cubic centimeters, average 14 years younger.

Specimens of urine obtained under basal conditions with one exception showed a vitamin C content below normal (average, 9 mg. for a twenty-four hour specimen). Specimens of blood obtained under basal conditions with one exception showed vitamin C contents in the lower

TABLE 1.—*Average Values for Vitamin C Tabulated on the Basis of Age*

Age	Vitamin C Content of Blood, Mg. per 100 Cc.	Number of Patients	Vitamin C Content of Lens, Mg. per 100 Gm.	Number of Patients	Vitamin C Content of Urine, Mg. per 24 Hr. Specimen	Number of Patients
Under 20	1.03	10	..	..	13	15
21-30	1.12	5	13	1	12	4
31-40	1.02	1	16	2	12	2
41-50	0.94	1	11	1	7	1
51-60	0.98	7	23	9	10	5
61-70	0.91	12	21	9	12	13
71-80	0.88	5	16	11	6	6
Over 80	0.96	2	10	1	7	2

TABLE 2.—*Data Tabulated on Basis of Vitamin C Content of Urine*

Vitamin C Content of Urine, Mg. per 24 Hr. Specimen	Vitamin C Content of Blood, Mg. per 100 Cc.	Number of Patients	Vitamin C Content of Lens, Mg. per 100 Gm.	Number of Patients	Average Age	Number of Patients
Under 5	0.85	8	24	5	66	9
6-10	0.89	12	15	4	59	12
11-15	1.08	11	25	2	43	10
16-20	0.86	1	..	..	51	2
21-25	1.01	3	14	2	54	4
26 and over	0.92	1	..	..	65	1

TABLE 3.—*Data Tabulated on Basis of Vitamin C Content of Lens*

Vitamin C Content of Lens, Mg. per 100 Gm.	Average Age	Number of Patients	Average Vitamin C Content of Lens, Mg. per 100 Gm.
Under 10 mg.....	37.0*	1	9.4
10-15 inclusive.....	64.5	16	13.23
16-20.....	67.6	5	18.20
21-25.....	61.5	6	23.26
26-30.....	66.0	2	29.75
31-35.....	65.0	4	34.20
36 mg. and over.....	58.0	2	42.50 and 66.00†

* The patient had a traumatic cataract.
† The patient had leukemia; the vitamin C content of the blood was 5.9 mg. per hundred cubic centimeters (footnote 13b).

normal range (average, 0.97 mg. per hundred cubic centimeters). The values for the vitamin C contents of the lens were distributed as follows: 1 above normal (30 mg. per hundred grams), 2 normal, 5 from 20 to 25 per cent low, 3 from 30 to 40 per cent low and 5 from 50 to 60 per cent low.

The lack of correlation between the values for the blood, urine and lens might be explained on the basis of the duration of the vitamin deficiency. The more recent dietary would be reflected in the vitamin C content of the blood and urine, while that of the lens might be decreased owing to a prolonged inadequacy. Accurate dietary histories

TABLE 4.—*Data on Group of Sixteen Patients for Whom Records Are Complete*

Patient	Vitamin C Content of Lens, Mg. per 100 Gm.	Age	Vitamin C Content of Blood, Mg. per 100 Cc.	Vitamin C Content of Urine, Mg. per 24 Hr. Specimen	Diagnosis
M. O.	10.40	81	1.08	6	Cataract; diabetes; blind for several years
C. D.	10.50	43	0.94	7	Posterior polar cataract, complicated
L. D.	12.50	66	0.64	13	Retinitis pigmentosa; bilateral senile cataract
G. H.	12.70	68	1.10*	22*	Subcapsular cataract
H. S.	13.20	26	0.95	12	Gonococcic vaginitis; posterior polar cataract
M. C.	17.80	73	0.89	10	Hypertensive cardiac disease
F. C.	19.50	57	0.89	15	Hypertensive cardiac disease; senile mature cataract
B. G.	20.50	57	1.14	11	Bilateral cataract, cortical and immature
T. D.	22.20	39	1.02	4	Traumatic cataract
J. L.	22.20	72	0.79	5	Arteriosclerotic cardiac disease; senile mature cataract; hypertension
E. G.	23.15	59	1.14	7	Intra-ocular hemorrhage; senile mature cataract
A. L.	24.00	66	0.61	3	Glaucoma; old iritis
J. G.	25.50	76	1.00	2	Glaucoma at 69 years; cortical cataract
W. H.	29.30*	66	0.84	4	Mature senile cataract
P. H.	30.20*	66	1.35*	12	Mature senile cataract, 8 years standing
L. J.	42.50	53	1.07	11	Glaucoma; dislocated lens

* The values are within the expected normal range. We regret that to date we have not been able to obtain a normal lens for analysis but must accept the value of 30 mg. (footnotes 3 and 4).

TABLE 5.—*Correlation of Average Values for Vitamin C in the Lens with Those in the Blood and Urine and with Age*

Lens, mg. per 100 Gm.....	10-15	16-20	21-25	26-30	31-36
Average age, years.....	57 (5)*	62 (3)	62 (5)	62 (2)	53
Blood, mg. per 100 cc.....	0.94 (5)	0.97 (3)	0.91 (5)	1.10 (2)	1.07 (1)
Urine, mg. per 24 hr. specimen	12 (5)	12 (3)	4 (5)	8 (2)	11 (1)

* The numbers of patients included in the average are given in the parentheses.

TABLE 6.—*Correlation of Average Values for Vitamin C in the Urine with Those in the Blood and with Age*

Urine, mg. per 24 hr. specimen	Under 5 mg.	6-10	11-15	16-20	21-25
Age, years.....	64 (5)*	64 (4)	54 (6)	.....	68 (1)
Blood, mg. per 100 cc.....	0.85 (5)	1.01 (4)	1.01 (6)	.....	1.10 (1)

* The numbers of patients included in the average are given in the parentheses.

are difficult to obtain and not too satisfactory. As to a possible correlation between the cevitamic acid content and the cause of cataract, none is found. Analysis of the mature cataract of eight years' standing which was removed from subject P. H. and determination of the vitamin C

content of the blood indicated that both were in the normal average range. The vitamin C content of the urine was slightly lower than the average, but, as has been pointed out, the immediate preceding diet is a definite factor in determining the level. The mature cataract of E. G. was higher in vitamin content than the traumatic cataract of T. D. or the immature cataract of B. G. A larger series of patients might, of course, alter the data.

Since the average of the values for the vitamin C content of the urine was so definitely low, the question arose as to whether old age in itself with its almost universal dietary change might not, at least in part, account for the low levels.

With the permission of Dr. Eric Green and the active cooperation of Mr. George K. Anderson, studies were made on the urine of twelve patients in the Monroe County Home. Subjects were carefully selected as to age to be controls for the group of patients with ocular conditions; that is, cataractous changes could not be detected in any of the patients. The average urinary excretion of cevitamic acid for this group was 11.71 mg. in a twenty-four hour specimen, obtained under basal conditions, with extreme values of from 5.91 to 18.20 mg. As in our subjects from the hospital, the response to a daily dose of 200 mg. of vitamin C was followed. The response to the first 200 mg. of the vitamin raised the output for the group to an average of 13.07 mg. The large retention of the vitamin (intake minus urinary content) indicated a state of tissue unsaturation. A dietary survey of previous intake indicated that the ingestion of vitamin C was low. The average vitamin C content of the urine for the entire group of patients with ocular conditions (including those on whom complete data were not obtained) was 10.60 mg. in a twenty-four hour specimen, obtained under basal conditions, with extreme values of from 2 to 24 mg. The response, to the first 200 mg. of vitamin C in this group was 13 mg. The two groups, therefore, were not unlike in tissue saturation, as evidenced by initial level and response. The patients with ocular conditions were not more depleted of their stores of vitamin C than the patients from the county home. The urinary excretion in response to successive constant doses of vitamin C continued approximately the same over a period of a week for both groups. From these two sets of data it could not be seen "that in a cataractous subject much larger quantities of vitamin C are required to raise the value in the blood plasma than in a normal person" (Bellows [5]). However, the values for persons in the same age groups whose normal diet was consistently higher in vitamin C than was that of the patients at the county home might be the same as those reported by Bellows. It is hoped to obtain some patients in the same age group who have orthopedic conditions and whose dietary

intake can be controlled for a long period to ascertain whether or not the normal response to vitamin C is lower in the elderly person than it is in the younger person irrespective of ocular abnormalities.

SUMMARY

While from our data there is a definitely decreased amount of cevitamic acid in the cataractous lens, from a normal of 30 mg. to 10 mg. per hundred grams of lens tissue, and while there is a definitely lowered vitamin content in the urine, the values for the blood are in general within a low normal range.

No correlation could be found between age and the content of vitamin C in the lens, urine and blood, except the blood-urine relation, which is physiologic, and a possible age-blood correlation.

No correlation was found between the type of abnormality in the lens and the level of vitamin C.

Dietary histories in general indicate a lowered intake of foods rich in vitamin C in the old age group, probably due to several factors:

(*a*) The comparatively recent realization of the need of vitamin C and, for its adequate intake, the inclusion of citrus fruits or uncooked fruits and vegetables in the diet. The food habits of the older generation, which are so frequently continued through life, did not include these foods.

(*b*) The decreased use of fresh fruits and vegetables due to economic stress. Many of our patients are in the "low income" group.

(*c*) The voluntary decrease of acid foods or foods hard to chew or of high roughage content which so commonly occurs with advancing years.

To quote Bellows:[5] "The absence or diminution of cevitamic acid in the aqueous and in the lens of the cataractous eyes brings forth the question of the relationship of vitamin C and cataract. Is the loss of vitamin C secondary to the changes in the lens, as Bietti has suggested, or does its diminution or deficiency precede the development of opacities in the lens?" Though adequate diet cannot fail to be more effective in the preservation of normal function than one deficient in any respect and the inclusion of sufficient amounts of food rich in vitamin C advantageous, and in spite of the contrary evidence of other investigators, one is forced to conclude from the data here presented that the low content of vitamin C in the lens may be a result of cataractous changes rather than the underlying cause and that tissue saturation as measured by the vitamin C content of the urine and blood suggests that it is probably not responsible for the onset of the cataract.

Since this paper was accepted for publication it has been the privilege of one of us to read and discuss the manuscript of a paper on the use of the Evelyn photoelectric colorimeter as a means of measuring the reducing substances in urine. Dr. Evelyn's excellent discussion indicates that undoubtedly values for cevitamic acid as heretofore determined are too high. In urine certainly other reducing substances besides cevitamic acid may enter into the reaction and increase the titration value.