Vitamin C


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The report by Hagelescu, of Bucharest, that ascorbic acid was deficient or absent in the urine of his asthmatic patients, and that clinical improvement usually followed the intravenous administration of ascorbic acid, has led to a considerable amount of investigation into the role of ascorbic acid in allergic disease, particularly in asthma and hay fever.

Several theories have been advanced in attempting to account for the reduced amounts of ascorbic acid in the urine and blood plasma of allergies and to provide a rational explanation for the clinical improvement noted by many observers when ascorbic acid therapy was employed.

Hochwald reported that he was able to reduce the incidence of anaphylactic shock in sensitized animals by the intravenous administration of ascorbic acid before reinjection of the sensitizing protein. He attributed this effect to the reduction potential of ascorbic acid. In an attempt to repeat the work of Hochwald and to evaluate his theory, Schaefer1 found the reduction in the incidence of shock to be 14%, a figure which he claimed to be within the limit of experimental error. Upon administering oxidized ascorbic acid (20% unoxidized), he found no significant difference in results from those obtained with unoxidized ascorbic acid. He concluded that the reduction potential of ascorbic acid could not be the carrier of any protective effect in anaphylaxis.

Over a period of four years, Holmes and Alexander10 made occasional observations indicating a lowering of the body level of ascorbic acid during hay fever attacks. On the assumption that histamine may be inactivated by ascorbic acid and that an additional supply of it may be necessary to react with histamine during allergic states, they administered ascorbic acid to 25 hay fever patients. When a daily dose of 200 mg. or more was administered, about two-thirds of those reporting were clinically improved.

The antihistamine effect of ascorbic acid on isolated bronchiolar lumen was investigated by Ruskin.19 The results indicated conclusively, he reported, that it is an effective histamine antagonist.

In another article, Ruskin16 advanced the theory that there is a definite relationship between histamine sensitivity and adrenal cortical insufficiency, with accompanying depletion of the sodium ion and of ascorbic acid. On the hypothesis that nasal allergy and asthma may be precipitated by an imbalance of the triad cortical hormone-sodium-ascorbic acid, he made a study of the effect of sodium ascorbate,

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particularly in those allergic states that were somewhat refractory to high dosages of ascorbic acid. The results of the study indicated that sodium ascorbate was much more effective than ascorbic acid in relieving the symptoms of nasal allergy and of asthma.

Maynadier reviewed the difference of opinion concerning the antianaphylactic powers of ascorbic acid. He pointed out that, since anaphylaxis does not account for all of the symptoms of asthma, suprarenal insufficiency undoubtedly being a factor, and since suprarenal insufficiency and ascorbic acid insufficiency are parallel, it is possible that the clinical improvement observed following ascorbic acid therapy might be due to its ability to overcome suprarenal insufficiency.

In the light of present knowledge, it is not possible to evaluate these and other theories that have been offered to explain the action of ascorbic acid in allergic disease. It is to be hoped, however, that the parallelism between ascorbic acid deficiency and adrenal insufficiency will be thoroughly explored. Since the adrenal is the body tissue richest, by far, in ascorbic acid, it may be that allergic response is due to malfunction of the adrenal, such malfunction being caused by depletion of its ascorbic acid.

Study of the literature reveals sharp differences of opinion regarding the therapeutic value of ascorbic acid, among clinicians who have employed it in the treatment of allergic disease. Some report nearly all subjects improved, some to the point of complete remission of symptoms. Others report no improvement, or so little that the treatment is not justified. The brief summaries that follow by no means include all of those published, but they may be taken as typical.

Maynadier, reported 11 cases, children from 5 to 13 years of age, all of whom had a history of severe asthma of long duration, not amenable to the usual methods of treatment. Ascorbic acid was administered daily by intravenous route, the usual dose being 100 mg. Treatment was continued for 20 days, in a few instances, 30 days. In most of the cases, the series was repeated after a rest of from two weeks to a month. In nine of the cases, considerable alleviation or complete remission of symptoms was secured. In the other two cases, treatment was not completed.

Goldsmith, Ogaard, and Gow determined the blood plasma level of ascorbic acid in the general clinic population, excluding those with allergies and those with deficiency diseases. They found it to vary from 0.07 to 2.40 mg.% with a mean value of 0.60 mg.% (approx.). Thirty-two patients with allergies were chosen for study. Of 29 with bronchial asthma, 17 also had hay fever, and 4 had urticaria. Of the remaining three cases, two had hay fever alone and one had urticaria alone. All were adults, 28 white females, 2 white males, 2 Negro females. The ascorbic acid mean level for the 29 asthmatics was 0.41 mg.% (approx.). The difference between this and the mean level for the general clinic population was 2.7 times the probable error, which might or might not be significant. The test cases were given oral doses of 200 mg. daily for several days, and were then placed on a daily dose of 100 mg. Treatment was continued for several months. Seven members completed the treatment. Six of the 7 were unable to maintain a level of 1.0 mg.%, while all of the members of a control group were able to maintain that level. This may be interpreted as indicating an increased requirement of ascorbic acid in patients with asthma. In 2 of the 7 who completed treatment, there appeared to be some relationship between the blood level of ascorbic acid and the frequency and severity of attacks of asthma. In the 5 other patients, there was no appreciable improvement.

Diehl treated an unspecified number of bronchial asthmatics with 300 mg. of
ascorbic acid daily via the intravenous route. The duration of treatment was not disclosed. A few of the cases were completely refractory. Several were unmistakably benefited, in most instances after protracted treatment. It was found that no improvement resulted in those cases where a deficiency of ascorbic acid did not exist. One patient who had a long-standing refractory vasomotor rhinitis was completely relieved at once when treatment began.

Hunt selected 25 subjects with bronchial asthma, all out-patients, 16 females, 9 males, 5 children. No determinations of urinary ascorbic acid were made. The subjects were given 50 mg. tablets of ascorbic acid, one tablet to be taken each morning and one each night. No marked improvement in any of the cases was noted. Five patients were given "massive" doses of ascorbic acid by injection. One was given one intramuscular dose of 500 mg.; 3 were given one intravenous dose each of 400 mg.; and one was given one intravenous dose of 800 mg. None received benefit "within 25 to 30 minutes."

Shaw and Thelander advanced the hypothesis that ascorbic acid deficiency may be responsible for allergic states in children. They suggested that the human infant offers the best subject for study of the problem. No cases were cited but the authors stated that they had been giving 25 mg. routinely after the first few days of life and had noted a reduction in the incidence of colic.

Wagner noted ascorbic acid deficiency in the urine of the mother of an infant with eczema. Ascorbic acid was administered to the mother and the infant's eczema was relieved. There was a relapse when the mother discontinued therapy. Six other cases were treated successfully, but in these, the ascorbic acid was administered to the infants. The author reports other cases: several itching exanthemas in older children, one of seborrhea of the scalp in an adult male, another of fissured hands. All were relieved by the administration of ascorbic acid.

Kogan and Bogdanova determined the urinary ascorbic acid in 20 patients with bronchial asthma and in 3 control persons. All of the asthmatics had low excretion of ascorbic acid. It was particularly low during attacks, even to the point of parallelism with the gravity of the attack. Up to 600 mg. were administered daily but the saturation point was not reached in the asthmatic patients. The authors believe that, although a disturbance in the metabolism of ascorbic acid is not specific for bronchial asthma, there are pathogenic relationships between such disturbances and the allergic nature of the disease.

Holmes and Alexander administered ascorbic acid to 25 hay fever patients, 13 of whom were deficient in urinary ascorbic acid. When 100 mg. were given daily for one week, 5 were improved of 16 reporting. When 200 mg. were given on the same schedule, 12 were improved of 14 reporting. The dosage was increased to 500 mg. and 8 out of 12 were improved. One subject was given one dose of 1000 mg. and experienced immediate relief.

Hebald administered ascorbic acid to 10 patients with ragweed hay fever during the 1943 season. Nine received no other treatment, one also was given ragweed extract. The daily dose was 500 mg., half being given in the morning and half in the evening. Five of the patients received this treatment for 3 weeks, the other 5 for 4 weeks. Eight of the subjects apparently received no benefit, two seemed to be improved. The author concluded that ascorbic acid is not an effective form of treatment for hay fever.

Engelsher treated 48 hay fever patients with a divided dose of 500 mg. of ascorbic acid, for a period of two weeks. It was the opinion of the author that the treatment was of little, if any, benefit.

In a paper reporting no case histories, Korbsch claimed that ascorbic acid in doses of up to 1 Gm. daily will alleviate
the symptoms of acute and secondary rhinitis. He further asserted that he has obtained complete remission of symptoms of the common cold after one intravenous injection of ascorbic acid in high dosage.

Ruskin reported 8 cases of allergy treated with sodium ascorbate. Five of the subjects had hay fever, two had asthma and one had a nasal allergy of unknown origin. All of the subjects were improved, some to almost complete remission. Two of the subjects had proved refractory to previous therapy with ascorbic acid. The author expressed the opinion that sodium ascorbate was more effective than ascorbic acid in allergic states.

Newbold selected 8 hay fever patients, all of whom were skin sensitive to extract of short ragweed. He injected the extract intradermally into each and measured the diameters of the wheals. Ascorbic acid was administered for three days and the test was repeated. No significant differences in the diameters of the wheals were noted. The author concluded that ascorbic acid therapy has little effect on the skin sensitivity of hay fever sufferers.

Friedlaender and Feinberg determined the ascorbic acid blood levels of 48 hay fever subjects and found all levels to be within the normal range. A daily dose of 500 mg. of ascorbic acid was administered for periods varying from one to 6 weeks. All ascorbic acid blood levels were increased, but only 3 subjects reported clinical improvement. The authors discussed the difficulty in evaluating the results of hay fever therapy because of variation in the concentration of pollen geographically, seasonally, and daily, plus the response of the individual, aggravation of symptoms by cold and rain, and the influence of psychic suggestion.

Ruskin called attention to the changing ideas concerning the dosage of ascorbic acid, doses of 1000 mg. now being rather common, contrasting with the much smaller doses employed in the early days of ascorbic acid therapy. He reported the therapeutic trials of tablets containing ascorbic acid and thiamin hydrochloride. These tablets, in a number providing 750 mg. of ascorbic acid and 3 mg. of thiamin hydrochloride daily, were given to 27 hay fever patients. The patients were divided into two groups: group A, numbering 16, received tablets only; group B, numbering 11, received the tablets plus desensitization. Twenty-four patients reported definite improvement. Of 12 of the 27 who were also asthmatic, 8 were improved. Of 14 who had food allergies, 11 were improved.

Pelner pointed out that food allergy may produce clinical syndromes other than those gastro-intestinal in nature, e.g., migraine, asthma, and eczema. In discussing the treatment of gastro-intestinal allergy, which is largely unsatisfactory, he noted that ascorbic acid in large doses, 500 mg. or more per day, may detoxify a minor allergen, but could not be expected to detoxify a food to which the subject is overwhelmingly allergic. Eliminating the food and giving ascorbic acid seemed to produce the best results in this form of allergy.

Ruskin reported the results of sodium ascorbate treatment in 13 hay fever patients, 7 of whom also had asthma. The dosage ranged from 1 Gm. to 2 Gms. daily. All of the patients were improved, several to the point of complete remission of clinical symptoms.

A careful study of these and other reports of therapeutic trials of ascorbic acid in allergic disease reveals several circumstances that might explain the differences of opinion as to its worth. One of these is the apparent influence of the dosage employed. Although there are exceptions, most of the favorable reports are those of trials in which the higher dosages of ascorbic acid were employed. The dramatic results obtained when dosages of from 750 mg. to 2 Gm. per day were employed indicate that some of the earlier
failures may be attributable to inadequate dosage.

The results of those investigations in which the urinary, or blood levels of ascorbic acid were determined indicate, in general, that the greatest benefit may be expected from ascorbic acid therapy in those patients whose levels are considerably below normal. It is possible that some of the therapeutic failures reported were due to the inclusion of subjects who were not deficient in ascorbic acid. A third possible explanatory circumstance is the failure of most of the reporting clinicians to employ other therapeutic measures in support of the ascorbic acid therapy. In any scientific investigation, it is proper to reduce the variables to a minimum. It might well be, however, that ascorbic acid therapy alone could be inadequate in an allergic syndrome but adequate if supported by the concurrent administration of other substances of proved value in the treatment of allergic disease.

On the basis of the latter possibility the author undertook the study of the effectiveness of combinations of ascorbic acid with agents that have been found useful in mitigating the symptoms of allergy.

One hundred and thirty-one patients with a variety of allergic diseases, excepting allergic asthmatic bronchitis, and who had secured a measure of relief from the symptoms of their allergy through administration of antihistamines, were given combinations of an antihistamine and ascorbic acid. Seventy-four members of the group received tablets containing 25 mg. of Thephorin* and 200 mg. of ascorbic acid. Fifty-seven received tablets containing 2 mg. of Chlor-Trimeton** and 250 mg. of ascorbic acid. A subsequent paper will elaborate on the results of this therapy. For the purposes of this paper, however, it may be said that the ascorbic acid appeared to have a potentiating effect on the antihistamines. Almost without exception the subjects reported better and longer lasting relief from symptoms when a combination of antihistamine and ascorbic acid was used. In most instances it was possible to increase the interval between doses, thus reducing the incidence of side effects.

Since asthmatic bronchitis, both the allergic type and the chronic variety of obscure etiology, is relatively unresponsive to antihistamine therapy, the author attempted to determine if ascorbic acid in the form of the sodium salt would also increase the effectiveness of antiasthmatic drugs. Sodium ascorbate was used because it does not cause gastric distress as ascorbic acid often does and the reports of Ruskin and others indicate that the sodium ion may be essential to the utilization of ascorbic acid by the adrenal. Ninety-nine asthmatics, most of whom were chronic sufferers from the disease, were used in the study. Previous to commencement of the experimental therapy, all had used with variable control of symptoms a combination of theophylline, ephedrine and a barbiturate. Each member of the group was given a supply of T-Bardrin† Capsules and was instructed to take one capsule at the onset of symptoms and to repeat at intervals of four hours until the symptoms were controlled. Each of the capsules contained 195 mg. theophylline, 8 mg. ephedrine, 8 mg. sodium pentobarbital, 8 mg. sodium phenobarbital and 300 mg. sodium ascorbate.

A detailed analysis of the results of the experiment will be presented in a later paper. For the purposes of this preliminary report it may be said that this form of antiasthmatic therapy far surpasses any other within the author's experience. No member of the experimental group

* Clinical material furnished by Hoffmann-La Roche Inc., Nutley, New Jersey.
** Clinical material furnished by Schering Corporation, Bloomfield, New Jersey.
† Clinical material furnished by Angier Chemical Company, Inc., Boston, Mass.
to receive a considerable measure of relief, and in many cases the remission of symptoms was apparently complete. Perhaps the most striking result was the reduction in the quantity of medicament necessary to control symptoms. Some patients had previously ingested such large amounts of antiasthmatic drugs that the side effects had forced the discontinuance of therapy. Most of these were able to remain symptom-free by taking one of the experimental capsules per day. In addition to providing more prompt relief than the other types of therapy ordinarily employed in bronchial asthma, the combination of drugs represented by T-Bardrin usually evokes a pronounced sense of euphoria in the patient, a most important factor in the management of this type of disease.

Summary and Conclusions

A review of the literature on the use of ascorbic acid in the treatment of allergic disease revealed conflicting opinions regarding its value, although the weight of evidence seemed to be in its favor. Careful study of the data submitted indicated that the lack of success reported by some clinicians may have been the result of inadequate dosage and the failure to use adjunctive therapy in support of the ascorbic acid.

On the basis of these possibilities, the author undertook the study of the effect of combinations of ascorbic acid and antihistamines in the treatment of a variety of allergic diseases other than allergic asthmatic bronchitis. One group of subjects received tablets containing 200 mg. of ascorbic acid and 25 mg. of Thephorin. Another group received tablets containing 250 mg. of ascorbic acid and 2 mg. of Chlor-Trimeton. The results indicate that the combination of ascorbic acid and antihistamine is much more effective than antihistamine alone. Relief is more prompt and the duration of effect is prolonged. Through the reduction in the quantity of medicament necessary for the control of symptoms, the incidence and the severity of side effects are lessened.

Because the antihistamines are relatively ineffective in the treatment of asthmatic bronchitis, whether of the chronic or the allergic type, it was decided to investigate the usefulness of a combination of ascorbic acid with drugs that had been found of value in this disease. A number of subjects were given capsules of T-Bardrin containing 195 mg. theophylline, 8 mg. ephedrine, 8 mg. sodium pentobarbital, 8 mg. sodium phenobarbital and 300 mg. sodium ascorbate. The latter was used instead of ascorbic acid in order to avoid gastric distress and because the sodium ion may be necessary for utilization of ascorbic acid by the adrenal.

This combination gave much more prompt and longer lasting relief than had been obtained using similar combinations but without sodium ascorbate. Smaller and less frequent doses were required, thus minimizing the incidence and severity of side effects. A pronounced sense of euphoria was experienced by many of the subjects, probably because of the diminished quantity of medicament, particularly the barbiturates, required for the control of symptoms.

Bibliography

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