

## SPECIAL ARTICLE

# The Administration of Large Doses of Ascorbic Acid in the Prevention and Treatment of the Common Cold

## Part II

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Beginning at about the age of seven and following a tonsillectomy I began to be plagued with otitis media of which I suffered from 50 to 60 bouts over the next 20 years. These recurrent infections were treated by a series of different methods including Cubeb cigarette smoke blown into the ear by my mother, the local application of heat, sulfadiazine in nasal sprays and the earlier and later forms of injected penicillin which was useful as soon as I suffered from a sore throat if taken at the first signs of infection, but only for the secondary bacterial component of my double infection which began with a vims which appeared to pass the sentence which was executed by the bacteria. I stumbled upon the employment of ascorbic acid because of the advertisements for the bioflavonoids and vitamin C as beneficial in the prevention and treatment of the common cold. It was apparent that the mixture diminished the symptoms of the common cold for me and for my wife, but not enough for us to continue with its employment. Would larger doses perhaps be more effective?

The doses were increased as each increment proved itself as giving better results until I reached a maximum and satisfactory effect. I did not permit myself to be dissuaded by the gloomy conclusions of others, whose work I

continued to recognize had shown only that vitamin C had not been helpful against colds *at the dosage used in their studies*, and not the unmeasured generality that this drug had been proven utterly useless against colds.

I was then able to suppress colds, at will, in five subjects. There is no doubt that we really suffered from colds during these suppressed versions of the disease, because we continued to be aware—but just aware—of whatever symptoms had been characteristic of our formerly unmodified colds. Although running of the nose would be practically non-existent, on rare occasions a single drop might appear at the nares; however, not a trace of "itchiness" had accompanied it in its roll down the turbinates. The thickened stage of nasal discharge was never reached. Sneezing and coughing were quite unusual. A throat did not proceed to "soreness" but, in some cases, there was a slight sensation of its presence. Hoarseness was uncommon. Headache was inconsequential. Malaise, if at all recognizable was usually so minor as to be undeserving of the name. Secondary bacterial invasions did not occur.

I learned that the treatment had to be initiated early enough and needed to be continued at a high level for some time and then withdrawn or diminished

only gradually. It was noted that the infection so treated although suppressed appeared to last longer. When not treated the duration was usually from five to seven days, but when treated all evidence of the viral infection was not gone until eight to eleven days had passed. It was as though the suppression of the inflammatory response was at the expense of some delay in the development of a completed immunity to the causative viruses. It seemed also that despite the delay of immediate immunity the development of the usual several weeks' of resistance was in no way retarded.

There were two objections to the treatment, It was expensive in that the cost of the drugs was more than \$25,00 for each cold; and there were two variables, the bioflavonoids and the ascorbic acid, Was it possible that the vitamin C alone was responsible for the obvious effects, or was there a synergistic action of the so-called vitamin P? The texts suggested that the latter substance demonstrated little pharmacological activity, although a deficiency was thought to cause an increase in the permeability of capillary walls, It did not seem to me that the flavone factor in lemon juice (citrin) and in Hungarian red pepper and consisting of a mixture of flavones, eriodictyol and hesperidin could be of any great importance,

Nevertheless, I initiated a double-blind study using ascorbic acid alone, ascorbic acid plus bioflavonoids, flavonoids only and, fourthly, a lactose placebo with the two "vitamins" present either alone or together in 200 mg quantities, It was shortly obvious that there was no need to continue double-blind techniques. The continued studies were done by the single blind method, As noted in the introductory remarks, a cold is a tenuous entity. Its treatment required -a high degree of informality with much use of the telephone to encourage the subjects to

continue to discipline themselves as regards the use of the ascorbic acid. Attention was intensive and supervision essential. At no time was any subject requested to take a dosage of ascorbic acid which had not been exceeded by members of my family and by me without ill effects.

I limited myself to 22 subjects, a number I could carefully supervise. Almost all were of professional stature. The majority were adults whose ages ranged from 30 to 50, with the extremes being five children younger than 12 (whose treatments were supervised by -adults) and the oldest subject was 73 years of age.

My observations suggested that it might be best to spare children colds completely where possible by quick control of the upper respiratory infections of the adults of the family and ordinarily to permit the cold to run its unmodified course if a child did catch one, even though the children are the most likely patients to develop secondary bacterial infections, In any case, even for adults, the suppression of colds by ascorbic acid—at least as it stands at present—is not a form of treatment ideally suited to the capacities of every last patient. The patient must persist in taking his medicine as ordered and for the prescribed time.

Surely I am aware of the possible danger of interfering with the development of naturally occurring antibodies or immune responses. Although there has not been a single serious consequence to the suppression of colds by ascorbic acid in more than 400 such trials, I still hesitate to state that prolongation of the activity of the virus may not give the organisms time and opportunity to modify their nature so that an attack on another organ or system might occur. In actual practice there has been what probably amounts to a small increased incidence of transient muscle involvement, or soreness of -the back or stiffness of the neck,

both of which, of course, may occur with untreated infections with viruses of the upper part of the respiratory tract.

The 22 subjects mentioned have been studied systematically and under conditions which were as controlled as is possible in a clinical investigation of an affection such as the common cold. Some acted as what are commonly termed their own controls in that they were sometimes permitted to suffer from untreated colds and at other times were treated by one or the other of the four trial "drugs" used successively in new colds. Equally valuable for comparative purposes were the clinical courses of several individuals each treated differently at one and the same time during the course of a specific upper respiratory infection which affected several or all of the members of one household.

None of the subjects was studied for less than three years, and for almost all, the duration of observation was four or five years. In the past all had experienced from one to four colds each year with the usual number being three. While it was taken for granted -that the memory of the incidence of past infections may have been exaggerated, the minimal expected number of colds of the group overall was estimated to be approximately 225. But during the five-year period of observation there were -actually only 160 upper respiratory tract infections. The validity of the treatment employed cannot be based on the reduction of expected colds, but if this is true it would certainly suggest that the program had some sort of value as a prophylactic measure too.

Of the 160 "cold incidents" there were 23 which could not be included in the results, because for the particular cold the subjects did not correctly follow the particular treatment prescribed for them. Some of these occurred at the beginning of the study

when the discipline involved in the taking of the drug according to schedule was being established and some at the end when some of the subjects were able to recognize the fact that they were being treated with a placebo and refused to proceed with a useless type of therapy.

#### **The Method of Treatment**

Within the first 24 hours of a typical infection which the patient recognizes as his usual early symptoms of a cold, and the sooner the better, the beginning dose of ascorbic acid of 600 or 625 mg is taken every three hours. Ascorbic acid is available in various tablet strengths and the patient may take, for example, three of the 200 mg tablets or two and one-half of the 250 mg tablets. The medication will work equally well when a single 200 mg tablet is taken every hour or when two tablets are administered every two hours, but this more frequent ingestion only makes for unnecessarily complicated treatment schedules. On the other hand, experience has taught me that four of the tablets taken every four hours are not as satisfactory, for the reason that during the earlier and more violent stages of the infection, the patient often becomes aware somewhere near the end of a three-hour period that symptoms are recurring or are imminent. It is actually sometimes pleasant to look forward to the next dose to be taken. The need for a three-hour schedule of doses parallels laboratory observations and data that the levels of ascorbic acid in the plasma have returned to normal after the ingestion of quite large quantities in this time (E. N. Todhunter, R. C. Rabbins and J. A. McIntosh. *J Nutrition* 23:309 1942). If the amount of ascorbic acid taken at bedtime is increased to 750 mg, there is no need to awaken the patient at night for the "missed" dose provided that the first dose of the next day is also raised to 750 mg. Experience has

shown that a sustained release capsule for overnight effect is thus not needed, but its eventual availability would seem to have an obvious application in the treatment schedule.

It was also learned that when the three-hour interval was exceeded and larger individual doses were thus needed, -there was the disadvantage that they caused pyrosis (heartburn). This was easily relieved by a small quantity of bicarbonate of soda in water.

When ascorbic acid is used at the dosages described and for only short periods of time, gastrointestinal disturbances are the only side effects commonly noticed. After several days of these high dosage levels, there may be an excess of abdominal gas, which most patients infinitely prefer to the symptoms of the cold which they are aware would distress them were they not taking their ascorbic acid. It should be noted that other common methods of treating cold symptoms are not free of side effects, especially those of a sympathomimetic type,

After the patient has taken the large doses prescribed for the initial stages of the cold for some three to four days, it is possible for him to diminish the quantity of ascorbic acid. The three-hour schedule is still adhered to, but the dose of the vitamin is reduced to 375 to 400 mg. If (the reduction of the dose has been premature, typical cold symptoms will reassert themselves within a period of 12 hours or less. Should this occur, it is necessary to return to the initial size doses as soon as possible; and despite them the symptoms may not be re-aborted for as long as 12 to 18 hours (laboratory data, Todhunter, et al, op. cit).

Should there be no recurrence of the typical symptoms when the dose has been reduced and maintained -at the lower level for two or three days, then a further reduction in the quantity of ascorbic acid taken may be attempted •with the new doses taken at the three-

hour intervals but consisting of only 200 or 250 mg. After several days of this dosage level the interval may be increased to four and six hours between the tablets of 200-250 mg dosage, and if there is no evidence of any recurrence of the typical symptoms the use of the ascorbic acid may cease by the tenth to twelfth day of -treatment.

It is interesting and should be remembered that as the ascorbic acid doses are reduced there *may* occur—only rarely—one or two atypical symptoms which may not be recognized as accompaniments of a viral infection. There may be painful twinges of the muscles in unusual locations or "odd" headaches. These call for immediate increase in the dosage of the ascorbic acid as well as for a prolongation of the treatment period. If these complications—if so they may be termed—are recognized for what -they are, then the patient learns by practice to watch his own progress more carefully and to reduce the doses of the vitamin less quickly, in which case, with subsequent respiratory tract viral infections, such complications will appear less and less often. There are no practical objections to the continuation of the high initial doses entirely throughout the period of treatment. I felt that it is only judicious to employ as little of the drug as may be necessary. I was also interested in the determination of what the lowest effective dose might be.

On one occasion I kept a cold active for approximately 27 days, alternately suppressing it and permitting it to recur by altering the amounts of ascorbic acid I took. It was interesting -that each time I attempted to re-suppress the infection it became more difficult for me to do so. And finally I was forced to resort to penicillin to prevent the old "spin-off" of a viral infection into a bacterial invasion affecting my ears.

To repeat, I have learned that it is advisable (and still safe) to err on the side of prescribing too large a dose of

ascorbic acid in the later stages of a viral infection rather than too small a one. It seems to me that if one takes it upon himself to exercise a pharmacological authority which may actually extend the duration of an infection beyond the limits which would naturally occur if the infection were permitted to run its natural course, then modified as that infection may now be, one must also assume full responsibility for seeing to it -that the ailment is thoroughly restrained until it is finally vanquished by the normally developed immunological response.

### Results

In the treatment of 137 observed colds the prescribed doses were properly -taken. In 34 of these the treatment consisted of commercial duo-CVP, and the cold was satisfactorily suppressed in 31 instances. In another 50 colds the treatment consisted of ascorbic acid alone either as supplied by the U. S. Vitamin and Pharmaceutical Corporation, New York, or later, of other brands purchased locally and at random. Of these 50, the colds were nicely suppressed in 45. Of the eight failures in these two "successful" trials, six can be accounted for and will be recalled in the Discussion below.

There was no overt clinical difference between the colds suppressed by the ascorbic acid employed alone and those where it was combined with flavonoids. It made no difference what brand of vitamin C was taken as long as it was fresh. Among 29 medications with bioflavonoids alone, the cold was in no way visibly modified from what would have been ordinarily expected in 28 of the instances.

In 22 of 24 instances in which the lactose-filled capsules alone were taken the colds were seemingly untempered and ordinary.

All medications were issued in the orange duo-CVP capsules, except that during the later studies white tablets

of ascorbic acid were sometimes used. Not only were the capsules identical, no matter what they contained, but the schedules were identical as described herein; and any drugs which had not been taken were returned to me before the next cold appeared and needed to be treated.

In this small group of subjects there was not one who failed to obtain successful results as regards his symptomatic response if his intake of ascorbic acid was both sufficient and well-timed. Judgment as to the successful suppression of the symptoms of a cold must, at some point, be subjective and cannot be a quantitative and therefore measurable value, but as far as the subjects themselves were concerned there was no question on -this point because the suppression of .the symptoms was so gratifying.

In contradistinction to the studies of others, no attempt was made to identify the specific virus or viruses responsible for any infection. Clinically, the colds showed a considerable, though characteristic variety and were, as noted previously, spread through a period of five years or more. The majority of the subjects resided in Massachusetts, but some lived in Pennsylvania and several in Hawaii. It seems reasonable to assume that -there was in this sample -a fair representation of the many viruses known to cause "colds." It should be noted that when treated the clinical courses of the patients, no matter where they resided, were very similar indeed, allowing for minor differences of no importance. I do not wish to imply that ascorbic acid should be thought of as a general anti-viral agent. I only asseverate that it may be employed to suppress the symptoms of a cold quite effectively. Now that we know how widely organisms which do not synthesize it vary in their needs for it, only additional studies can tell us how far its usefulness can be extended.

### Some Theoretical Considerations on the Role of Ascorbic Acid

I have dutifully listed the textbook descriptions of the functions of ascorbic acid and have added to those some of the more modern concepts of its actions and the variations in its requirements in human beings, I saw no point in expressing my personal opinions until the body of this communication had been written. I do have some ideas of my own which are based on what I have observed and have developed along the lines of logic. Studies may prove them to be true, at least in part, but I must disclaim any certainty if only because overconfidence in similar speculations made in the past and later shown to be inaccurate acted only as obstacles to the use of higher doses of the vitamin than had customarily been administered.

Two possibilities suggest themselves, and it may be that neither is justifiable. If we limit our speculations to one aspect, the method of action, it is obvious that ascorbic acid suppresses the symptoms of the viral infection which is known as the common cold. The most obvious causes of these discomforts are those associated with inflammation. As an example, there is the hoarseness which results from an exudation of plasma and cells into the vocal cords and the surrounding mucous membranes. If it is true that ascorbic acid decreases the permeability of capillary vessels, then there would be less than the normal inflammatory response when it is taken. It may also be true that despite *in vitro* studies to the contrary, ascorbic acid may render individual tissue cell membranes less permeable to the viruses, in which case there might be what might be termed a double-barreled action. Here there would be a lessened cell penetration, and therefore fewer replications of the viruses, as well as the decreased permeability of the capillary walls which is itself another aspect of

cell-wall effect. The first of these, diminished respiratory cell penetrability, might explain the prophylactic success of ascorbic acid administration, and the second, decreased permeability of capillary walls, its symptom-suppressive action.

If these suppositions have any validity, they make for reasonable explanations of some of the failures and partial failures in this method of treatment of colds. Too small a quantity of ascorbic acid would not do what was intended or, what amounts to the same thing, if the ascorbic acid has been oxidized or has otherwise deteriorated, the doses taken are not what they appear to be. It is too much to demand of the vitamin to expect it to be effective when the humidity of the ambient air is so low (Lubart, J. *New York J Med* 62:816 1962) that we have damaged mucous membranes, or when there is a secondary inflammation caused by exposure to fumes or high levels of smog, or if there is a swelling occasioned by an allergic response. Consideration must always be given to the possibility that all of the ascorbic acid administered is not absorbed when there is an abnormality of the contents of the intestinal tract as there might be if a food such as yoghurt has been ingested in any large quantity recently. And we would have no right to expect ascorbic acid to be effective in the presence of a mixed viral-bacterial infection or when the infection is chiefly or only bacterial in type.

It is a fair question to ask why ascorbic acid administration is not effective when begun only during the third or fourth days or later in the viral infection. The answer is that it may be possible to diminish the extent of additional exudation, but many cell changes and much edema have already occurred and are not reversible, and there has been an opportunity for a maximum replication of the viruses.

It might also be asked whether there

is not something of a risk in electing to limit the amplitude of the natural inflammatory response and perhaps suffer a diminution of the immunity which might otherwise have been acquired. It must be remembered that the viruses in question are not, in the ordinary sense of the word, lethal; and the consequences of their presence are more often annoying rather than disabling except in special cases and epidemics where virulent organisms are widespread. In such circumstances are we not wise in doing what we can to hinder the evolution of the inflammatory reaction which serves as a base for more serious effects and secondary infections even if this has been accomplished at the cost of a temporary delay of some immunity. In any case, such immunity or lack of it can be shown to apply only to the one virus under consideration and to its several related viruses, and not to any of the others with which the patient can subsequently become infected.

#### Discussion

As the reader will have noted, it was not possible to write the usual type of exposition paper on the use of ascorbic acid in the treatment of the symptoms of colds, because at every step along the road some discussion was necessary. What follows is also discussion but in terms of the work of other investigators and of some of my own observations which have not been touched upon, and which I think need emphasis.

If I am correct in the interpretation of my studies and a daily dose of five grams of ascorbic acid, at least at the beginning, is needed to suppress the symptoms of the common cold satisfactorily, and if the schedule described must be scrupulously followed- then it is not at all astonishing that the results here reported differ from those of other investigators. These were studies concerned with the employment of one

gram or less daily and one investigation in which three grams were used and discovered to be ineffective, from which data it was perhaps too generally concluded that vitamin C was without any useful effect upon colds.

I must insist that the exact quantity of the drug administered is critical, as is the schedule critical; smaller doses of ascorbic acid or longer intervals between doses may actually prolong the overall duration of symptoms of the cold itself. In other words, if the required amount of the vitamin is not going to be taken, it is much better not to take any ascorbic acid at all.

Mention has been made of the pyrosis and production of intestinal gas which may be associated with high ascorbic level intake. The texts suggest that all excess amounts of vitamin C are rather casually excreted in the urine, but they rarely deal with any such dosage quantities as are required for the alleviation or suppression of the symptoms of colds. Because I was not able to find many references to the use of doses as large as those I found necessary, I needed to do some studying of the gastrointestinal effects of ascorbic acid for myself.

I have personally taken five grams or more of ascorbic acid daily for several periods of as much as six months. Another member of my family took the same quantities but for not quite as long a time. There seems to be no doubt that the normal intestinal flora may be converted into a predominantly anaerobic type which produces an excess of intestinal tract gases that are both annoying and persistent (Lorraine Gall, IBM Space Systems Laboratory, Washington, D. C., personal communication).

It has been known that ascorbic acid taken in a daily range of three to four grams may alter serum electrolytes as well as lead to a decrease in the motility of the intestinal tract (Danhof, I. E., University of Texas, personal com-

munication), This effect of the vitamin may well account for the flatulence which, while only occasional, occurs too often to be thought of as coincidental. It was especially prominent in two subjects who persevered in taking large doses of ascorbic acid for much more than the recommended limit of 12 days. Excess gas is never more than transient if one sticks only to the recommended no-more-than-12-day courses.

The dangers in interpretation of the prophylactic use of any drug are well known, because there is no method of being certain that the disease in question would necessarily have afflicted the subject. It is, however, known that the so-called immunity to viral infections of the upper respiratory tract is short-lived and, in fact, that some only confer immunity against themselves and perhaps for closely related viruses which have not changed antigenically.

From observations made over a span of a number of years it appears to me that when one is exposed to an obvious source of infection, as when a patient sneezes in one's face, a dose of 600-750 mg of vitamin C will prevent a possible cold, especially when a second dose of the same magnitude- is taken three hours later, Should this simple prophylactic program be followed faithfully, colds will occur less frequently and there is often no need to go on to the treatment schedule which has been outlined, As noted, it is difficult, if not impossible, to validate statistically a program of prophylaxis unless the population studied as treated and as controls is immensely large. It is with some hesitation, then, -that I mention the experience of three nurses who have taken the drug under my supervision at a rate of 250 mg of ascorbic acid daily for four consecutive seasons, In an environment where upper respiratory tract infections are common, especially that of a general hospital (J. B. Thomas Hospital, Peabody,

Massachusetts), each has been completely free of colds while most other nurses working in the same milieu have been afflicted on one or more occasions, necessitating absence from duty\* Each of the three was formerly subject to frequent colds. Before going to the theater where one may be exposed to many people suffering from colds, a prophylactic dose may be taken before leaving home and another 750 mg dose upon returning, with a gratifying absence of the usual possible infections.

As evidence of the harmlessness of such a program, it should be mentioned that one of the three nurses has taken vitamin C daily for 12 years, during the first eight on her own initiative and for the remaining four under my supervision. During the former period the dose was usually 100-200 mg daily. Proof that she had not developed an immunity from any visible subclinical infections was demonstrated when, at my request, she ceased taking the ascorbic acid for one season during which she was afflicted with two colds. Of these, one was treated successfully by the suppression method as outlined, and the other was permitted to run its course, which proved to be typical. Of course, a "series" of one patient does not establish a hypothesis, but this patient's history is mentioned because of the long use of the vitamin with no obvious harm.

When the physician-patient finds himself the unwilling host to one or more symptoms which may or may not be evidence of an upper respiratory tract invasion by a virus such as an unexplained gastroenteritis or otherwise inexplicable headache or an erratic muscle ache, it may be wise to begin ascorbic acid therapy. If a disease not restrainable by the vitamin develops, this "insurance" has at least been inexpensive and safe. And if the symptoms *are* suppressed then one may or may not choose to presume that the method of treatment was successful.



Since he can never exactly repeat the circumstances and thus make a scientific and controlled experiment of the procedure. But he may elect to continue with the ascorbic acid therapy too.

It must be remembered that vitamin C is easily oxidized and therefore may lose its potency. A bottle of tablets obtained from the hospital pharmacy may have been opened months before being dispensed. It is therefore wise to purchase the smallest quantity of tablets, usually 100, in a paper-sealed bottle from a drug outlet or large pharmacy which sells a large volume of this and similar products. For the treatment of each new cold it is best to begin with tablets from a new bottle.

Mention has been made of the special susceptibility of some women to colds at certain times in the menstrual cycle. There seems to be a compensatory interval of about three days, pre-menstrual, when there is a natural cold-suppressive state during which it is not necessary to use ascorbic acid should a cold occur.

### Summary

What is usually referred to as the common cold has been reviewed in general terms, and the signs, symptoms

and the clinical course of viral infections have been described.

The epidemiology of viral infections has been surveyed. The predisposition of human beings to viral infections has been commented upon. The magnitude of the problem of the common cold has been given consideration.

The traditional treatment of the infections in question has been examined and criticized.

The problem of scurvy has been canvassed and the many roles of ascorbic acid explored. The requirements of human beings for ascorbic acid have been discussed. My personal experiences with the use of ascorbic acid in the treatment of viral and the prevention of subsequent bacterial infections have been delineated.

The method of treatment and prophylaxis of the common cold has been outlined and the results of both prophylaxis and treatment are analyzed.

Theoretical considerations of the method of treatment and of some possible drawbacks have been listed. A discussion of the roles of ascorbic acid in the prophylaxis and treatment of the common cold ends this review of the subject.

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