For instance, it is well known that combing the hair, shaving, and similar acts definitely transplant the virus, causing new lesions. However, the spread of lesions from one individual to another is a little more difficult to establish. Undoubtedly it does occur. Whether any precautions should be taken in institutions or schools to isolate individuals with warts is another matter. The consensus seems to be that this is not necessary. It may be, however, that, in institutions such as the seminary or orphanage, individuals with warts should observe some precautions. How strict these should be is difficult to say. Certainly a great deal more work must be done on the transmissibility of these lesions before one can establish such standards. It is not my purpose here to try to set up these requirements but merely to point out the possible communicability of this virus infection of the skin that, while similar to the average virus infection in many respects, also has some interesting differences.

Vaccines of wart tissue are ineffective in the therapy of warts. I tried this therapy in a series of cases, some years ago, using both human wart tissue extracts and wart vaccine prepared from the cow. The results were unsuccessful and never published. Veterinarians employ a wart vaccine in the treatment of lesions on cows that I understand is quite successful. Warts on cows apparently are an entirely different virus, with immune reactions equally as different. This merely helps point out the complexity of the problem as well as the lack of knowledge about the spread of one of the commonest of all diseases. There are probably a number of strains of the virus, some of which may be more communicable than others. This has been pointed out by Blank,[6a] and it may well be the explanation of the variability in apparent communicability of these lesions.

Summary and Conclusions

In two groups of institutional residents the incidence of warts was about the same. Of children in a certain orphanage, 25% developed warts over a one and one-half year period. About 20% of the inmates of a small seminary group did the same over a much shorter period. It is felt that some strains of wart virus are more communicable than others, although this has not been proved. Simple precautions may help to prevent the spread of warts.

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BLOOD ASCORBIC ACID LEVEL IN BIOFLAVONOID AND ASCORBIC ACID THERAPY OF COMMON COLD

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During the past year treatment with the bioflavonoids has been widely publicized as a means of preventing or modifying the common cold. One of the reasons given for the effect has been that they potentiated ascorbic acid (vitamin C) in alleviating cold symptoms. Since there was no convincing proof available, either in support or in denial, we undertook a pilot study to explore the validity of these statements. Within the limits of this study, the bioflavonoid tested showed effect neither on the incidence or cure of colds nor on the ascorbic acid content of the blood. In the course of the study, interesting data were developed regarding the relationship of blood ascorbic acid levels to the incidence and cure of colds. These are reported in detail.

Method

The study was made on 89 volunteer medical students and student nurses for the three-month period from February to May, 1956. Four groups were established and given capsules (three times daily,

From the Dartmouth Medical School and the Hitchcock Foundation.

• The incidence and course of common colds were followed in 89 medical students and nurses who volunteered in a study of the efficacy of naringin, a bioflavonoid extracted from grapefruit peel and used in remedies for colds. One group of 22 subjects received 333 mg. of naringin and 65 mg. of ascorbic acid three times daily for three months; a second group received naringin only, another ascorbic acid only, and the fourth a placebo. These substances were administered in capsules as nearly alike as possible. Symptoms of colds were systematically recorded, and the levels of ascorbic acid in the blood were determined periodically. The average level of ascorbic acid in 22 men who were to receive ascorbic acid by mouth was initially 0.96 mg. per 100 cc. of blood; after 12 weeks of taking only ascorbic acid the average for this group was 1.41 mg. per 100 cc. of blood. In all groups and at all stages, the blood ascorbic acid levels for males were significantly lower than those for females. There was no evidence that the naringin affected the ascorbic acid level of the blood, prevented colds, or cured them.

orally) made up as follows: group 1, bland placebo; group 2, naringin (bioflavonoid), 333 mg., and ascorbic acid, 65 mg.; group 3, ascorbic acid, 65 mg.; and group 4, naringin (bioflavonoid), 333 mg. (Naringin is an extract of grapefruit peel.) Every effort was made to disguise the contents of the capsules. All looked

TABLE 1.—*Blood Ascorbic Acid Level Determinations in Group 1: Patients Given Placebo*

Patient No.	Sex	Level, Mg./100 Cc. Initial Wk.	6th Wk.	12th Wk.	During Cold	Wk. of Cold	Results of Treatment
1	M	1.02	0.60	1.50	0.80	5th	No change
5	M	1.04	1.32	1.60	1.36	5th	Improved
9	M	1.12	1.08	1.52			
13	M	0.72	1.08	1.80	1.24	7th	No change
					1.84	4th	Cured
17	M	1.12	1.12	1.10	1.32	4th	Improved
21	M	0.80	0.76	1.30			
25	M	1.00	1.28	0.88			
29	M	0.40	0.44	0.40			
33	M	1.12	1.16	0.44			
37	F	1.60	1.40	1.28			
41	M	1.16	1.52	1.44			
45	M	1.08	1.12	0.96			
49	M	1.08	1.28	1.10			
53	F	1.60	1.80	...			
57	F	1.20	1.20	...			
61	M	0.76	0.88	1.12			
65	F	1.60	1.16	1.08			
69	F	1.12	1.32	...			
73	F	1.44	1.40	1.40			
77	M	0.44	0.28	0.50	0.40	5th	Worse
81	F	0.52	0.70	1.54	0.80	6th	No change
85	F	1.48	1.64	1.12			
89	M	1.36	...	...			

and tasted alike. Even the doctors conducting the study did not know the key to the code numbers used. Groups were assigned in rotation. Thus the first volunteer in line received bland placebo, the second naringin (bioflavonoid) and ascorbic acid, and the fifth bland placebo, as the rotation started over again.

TABLE 2.—*Blood Ascorbic Acid Level Determinations in Group 2: Patients Given Bioflavonoid and Ascorbic Acid*

Patient No.	Sex	Level, Mg./100 Cc. Initial Wk.	6th Wk.	12th Wk.	During Cold	Wk. of Cold	Results of Treatment
2	M	1.12	1.48	2.00			
6	M	1.08	1.12	1.48	1.08	2nd	Cured
10	M	0.80	1.16	1.28	0.96	2nd	Cured
					1.16	6th	Worse
14	M	0.96	1.36	1.30			
18	M	1.12	1.60	1.38	1.12	1st	Improved
					1.20	4th	Improved
22	M	0.56	1.52	1.10			
26	M	0.72	1.28	1.20			
30	M	0.72	1.52	...			
34	M	0.96	1.60	1.30			
38	F	1.48	2.00	1.72			
42	M	1.12	1.48	1.30	1.60	4th	Cured
46	M	0.92	1.08	1.04			
50	M	1.08	1.44	1.50			
54	F	1.40	1.84	...			
58	F	1.76	1.84	1.28			
62	F	1.84	1.64	...			
66	F	1.40	1.56	1.72			
70	F	1.88	1.76	1.56			
74	F	1.48	1.44	1.84			
78	M	1.32	1.40	1.84			
82	M	0.96	1.48	...			
86	F	1.28	1.92	1.68			

Each subject received a regional physical examination and had blood taken for a determination of ascorbic acid level the day he started the study. All the volunteers were started on the regimen within a single week. Thereafter they continued taking their particular capsule for the three months of the study. At the 6-week and 12-week points in the study, determinations of blood ascorbic acid level were made on all 89 participants. The subject was instructed to report cold symptoms (such as coryza, headache, malaise, fever, or sore throat) the day of onset. At this time the physical examination and determination of blood ascorbic acid level were repeated. He was asked to take no specific cold remedies, not even aspirin or nasal sprays, during the course of the infection. He continued taking the same dosage of the capsule assigned to his group. No antibiotics were used. During the infection the same physician made a record (daily when possible) of the cold's progress or regression. On the fifth day the cold was evaluated as cured, improved, unchanged, or worse.

Two variables were accepted as calculated risks to the accuracy of the study: diet and individual reliability. Although the majority of the subjects ate in the same hospital cafeteria, precise control of their diet was felt to be beyond the scope of this essentially pilot study. We recognized, of course, the varying degrees of reliability with which 89 persons would take 3 capsules a day for three months; we believe, however, that close supervision and the medical orientation of the participants kept this factor of error at a minimum.

TABLE 3.—*Blood Ascorbic Acid Level Determinations in Group 3: Patients Given Ascorbic Acid*

Patient No.	Sex	Level, Mg./100 Cc. Initial Wk.	6th Wk.	12th Wk.	During Cold	Wk. of Cold	Results of Treatment
3	M	1.08	1.32	1.50	1.40	3rd	Improved
7	M	1.28	1.52	2.00	1.92	3rd	Cured
11	M	1.12	1.36	2.00	1.32	3rd	Cured
15	M	0.96	1.68	1.24	1.60	3rd	Improved
19	M	1.12	1.08	0.80	1.08	3rd	Cured
23	M	1.08	1.52	1.10			
27	M	0.72	1.28	1.40			
31	M	1.08	1.16	1.70			
35	M	0.72	0.96	...			
39	F	0.96	...	...			
43	M	1.12	1.48	1.20			
47	M	0.76	1.44	1.50			
51	F	1.16	1.28	...			
55	F	2.04	2.08	1.32			
59	F	1.32	1.28	1.20	1.68	1st	Cured
63	F	1.40	1.52	1.84	1.52	4th	Cured
67	F	1.28	1.72	...			
71	F	1.28	1.40	1.52			
75	F	1.12	1.56	2.72			
79	M	0.88	1.36	1.08	1.52	4th	Improved
83	M	0.96	...	...			
87	M	0.52	...	...			

Tables 1, 2, 3, and 4 give the detailed blood ascorbic acid levels accumulated during this study. They are included in their complete form, partly because they are the basis for the conclusions of this pilot study and partly because comparable records of blood ascorbic acid levels in normal young adults are relatively rare. (Ascorbic acid blood levels were determined according to the technique of Roe and Kuether [1] under the supervision of John P. Davison, Ph.D., assistant professor of the physiological sciences in the Dartmouth Medical School.)

Results

Table 5 summarizes the effectiveness of bioflavonoid with and without ascorbic acid. When used alone, it produced the same results as a placebo. When used with ascorbic acid, the results were comparable to

those with ascorbic acid alone. Table 6 indicates that the prolonged administration of bioflavonoid had no effect on the blood ascorbic acid level. Females consistently showed a higher blood ascorbic acid level than males (table 6—statistically significant at the 0.01 level). Most of those receiving ascorbic acid showed an increased blood ascorbic acid level. Those receiving ascorbic acid developed just as many colds as those not receiving it (table 5). In this small series, those receiving ascorbic acid showed more rapid improvement in their colds than those not receiving it (tables 1 to 5 inclusive—statistically significant at the 0.05 level).

Comment

Ascorbic acid deficiencies have been noted not only in classic scurvy but in other infectious and metabolic disorders, such as rheumatoid arthritis, rheumatic fever, tuberculosis, and certain virus infections. The importance of ascorbic acid in maintaining capillary integrity has long been recognized. We will discuss neither the related background nor the literature.

TABLE 4.—*Blood Ascorbic Acid Level Determinations in Group 4: Patients Given Bioflavonoid*

Patient No.	Sex	Level, Mg./100 Cc. Initial Wk.	6th Wk.	12th Wk.	During Cold	Wk. of Cold	Results of Treatment
4	M	1.20	1.28	1.70	1.28	5th	Cured
8	M	1.08	0.88	1.20			
12	M	0.72	1.20	1.20			
16	M	0.96	0.72	1.00	1.00	5th	Improved
					0.96	1st	Worse
20	M	1.08	1.08	1.00			
24	M	1.00	1.20	0.86			
28	M	1.12	1.08	0.80			
32	M	1.28	1.40	1.00			
36	M	0.88	1.08	1.20	1.00	3rd	Worse
40	M	1.40	0.88	1.30			
44	M	1.08	0.96	1.52	1.08	1st	Improved
48	M	1.28	0.76	1.20			
52	F	1.08	1.20	1.28	1.12	7th	Improved
56	F	1.75	1.64	...			
60	F	1.56	1.48	1.32	1.08	3rd	Improved
					1.20	5th	Worse
64	F	1.36	1.40	1.44			
68	F	1.80	1.84	1.60			
72	F	1.48	...	...			
76	F	1.72	1.84	...			
80	M	0.64	0.96	0.60			
84	F	1.24	...	...			
88	F	1.36	1.48	1.50			

Recently certain naturally occurring substances have been found to have a related function in maintaining the integrity of the intercellular cement substance. The materials as a group have been classified as flavone glycosides and include such substances as hesperidin, rutin, and naringin. We are particularly concerned with those substances derived from citrus fruit peels, grouped together under the title of bioflavonoids. The significant literature on this subject was summarized at a meeting of the New York Academy of Sciences in 1955, which is reported in the annals of that organization.[2] Various articles in this monograph suggest a relationship between ascorbic acid and the bioflavonoids, with particular reference to their effects on capillary fragility. The monograph also reports the clinical use of the bioflavonoids and ascorbic acid in the treatment of disorders related to decreased capillary permeability. These include poliomyelitis, rheumatic fever, and bleeding related to pregnancy. The hypothesis that the bioflavonoids may prevent or modify colds is apparently based on this same property.

With this possibility in view, a number of drug compounds appeared on the market during the winter of 1955-1956 featuring a bioflavonoid content. Most of these compounds also contained such old cold treatment stand-bys as aspirin, caffeine, and ascorbic acid. The limited statements regarding this treatment of colds reported the use of the whole compound, without reference to specific studies based on the effect of the bioflavonoid alone.

We are reporting a pilot study on the effectiveness of one bioflavonoid per se. It is, of course, not definitive. But, in the absence of any comparable evaluation of a material whose commercial distribution is already widespread, we feel that even this limited study may be helpful to the medical profession. The approximately 300 determinations of blood ascorbic acid level were a by-product of the bioflavonoid study. The series is far too small to warrant conclusive interpretations, but the data raise several points of interest that may serve as points of departure in more definitive studies.

TABLE 5.—*Incidence and Cure of Colds with Bioflavonoid and Ascorbic Acid*

Group	No. in Group	No. Colds in Group	Colds Cured or Improved in 5 Days
Placebo	23	7	3
Bioflavonoid plus ascorbic acid	22	6	5
Ascorbic acid	22	8	8
Bioflavonoid	22	8	4

TABLE 6.—*Average Blood Ascorbic Acid Level in Males and Females*

	Level, Mg./100 Cc. Placebo		Bioflavonoid Only		Ascorbic Acid Only		Bioflavonoid and Ascorbic Acid	
	M	F	M	F	M	F	M	F
Initial	0.95	1.32	1.06	1.48	0.96	1.32	0.96	1.56
6th wk.	0.99	1.33	1.04	1.55	1.35	1.55	1.39	1.76
12th wk.	1.12	1.28	1.12	1.43	1.41	1.72	1.39	1.63

Summary

We are reporting a controlled pilot study of the clinical effect of bioflavonoids and ascorbic acid (vitamin C) on the incidence and cure of the common cold, correlated with serial determinations of blood ascorbic acid level on the 89 medical students and student nurses comprising the test group. The administration of a bioflavonoid had effect neither on the incidence or cure of colds nor on the ascorbic acid level of the blood.

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Statistical analyses were done by J. Laurie Snell, assistant professor of mathematics, Dartmouth College.

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