better up to 8 weeks in the supplemented group, but the mortality during the 24 weeks of the study followed the initial and not the achieved ascorbic acid levels and was actually higher (not significant) in the treated group. Clearly, any work on the effects of ascorbic acid deficiency and immunity should distinguish between primary ascorbate deficiency and secondary folinic acid deficiency effects. Even so, folinic acid deficiency resulting from such a disturbance of folic acid metabolism can and does occur in vitamin C-deficient humans, monkeys, and guinea pigs on what would otherwise be an adequate folic acid intake, and in such cases it is treatable with ascorbic acid alone; so impairment of immunity due to this disturbance of folate metabolism may properly be considered as a result of ascorbic acid deficiency.

XXIV. PROLONGED UPPER RESPIRATORY INFECTIONS

An extensive literature has accumulated concerning *Vitamin C and the Common Cold,* which is the title of a book by Pauling (1970). Many attempts have been made to answer two questions — one is whether vitamin C deficiency is associated with an increased incidence, severity, or duration of colds and the other is whether large doses of ascorbic acid can decrease the incidence, severity, or duration of colds. In this section, we are concerned only with the first question, which relates to vitamin C-deficient individuals. Thus, we are limited to a consideration of studies where the subjects were known to be vitamin C deficient.

Glazebrook and Thomson (1942) reported a study of 15- to 20-year-old cadets at a naval academy in Scotland, which provided a diet containing only 10 to 15 mg of ascorbic acid per student per day, because the food was cooked and then kept hot too long before it was served. Moreover, many of the cadets came from poor homes where the diet had been deficient in ascorbic acid. Indeed, many of them had severe gingivostomatitis which was known to respond to treatment with vitamin C, as a result of earlier work by Roff and Glazebrook (1939).

A total of 335 cadets were given ascorbic acid supplements, 200 mg daily, for 6 months, and 1100 cadets served as controls. The incidence of colds and tonsillitis was 30.1% in the ascorbic acid-treated group and 34.5% in the control subjects. This is only a 13% reduction in the incidence of colds and tonsillitis and is not statistically significant because there is a 12% probability of such a difference occurring by chance. However, as pointed out by Pauling, 23.0% of the cadets in the ascorbic acid group and 30.5% of the controls were admitted to sick quarters for severe colds and tonsillitis. This is a 25% reduction of admissions in the ascorbic acid-treated group and the probability of it having been due to chance is only 1%, which is a highly significant finding. The average number of days in sick quarters because of infection (corysa, tonsillitis, rheumatic fever, or pneumonia) was 2.5 for the cadets receiving ascorbic acid and 5 for the controls. The most important finding was that there were 17 cases of pneumonia and 16 cases of rheumatic fever among the 1100 controls and no case of either disease among 335 cadets given ascorbic acid supplements. Such a result does not require statistical analysis, but in fact, the probability of its being due to chance is about 0.3%.

In a study of experimental scurvy in man, Bartley et al. (1953) observed just as many colds in the control as in the deprived subjects, but the mean duration of the colds in the deprived subjects was 6.4 d as compared with 3.3 d in nondeprived subjects. This clearly suggests that colds last longer in ascorbic acid-deficient subjects. On its own, it would not prove this, as the results did not quite reach the 5% level of significance, but since it is confirmatory of the earlier findings of Glazebrook and Thomson (1942), it is valuable evidence.

A study of ascorbic acid supplementation, 1 g daily vs. placebo, was carried out on 90

of the students and staff at the University of Strathclyde in Glasgow and was reported by Charleston and Clegg (1972). They observed dramatic results, for there was a 49% reduction in the incidence of colds in the vitamin group, and this was highly significant ($p < 0.002$). The average duration of the colds in the ascorbate group was 3.5 d, as compared with 4.2 d, but this was less significant ($p < 0.05$). However, a subsequent double-blind controlled study by Clegg and MacDonald (1975) showed 34% fewer colds in students taking 1 g a day of D-isoascorbic acid, an isomer of vitamin C, but no benefit to those taking L-ascorbic acid.

Anderson et al. (1972) reported a much larger Canadian study of 1000 volunteers who took part in a very well-controlled double-blind study, of ascorbic acid, 1 g daily, vs. placebo, at the University of Toronto during the winter months. In this study, the incidence of colds was only 9% less in the ascorbate group, and this was not significant. However, there was a statistically significant difference ($p < 0.05$) between the two groups in the number of subjects who remained free of illness throughout the study period. Furthermore, the subjects receiving the vitamin experienced approximately 30% fewer total days of disability (confined to the house or off work) than those receiving the placebo, and this was statistically highly significant ($p < 0.001$). The reduction in disability appeared to be due to a lower incidence of constitutional symptoms such as chills and severe malaise.

Originally 527 dental practitioners and their wives were studied by Cheraskin et al. (1973) using questionnaires concerning their daily vitamin C consumption and the incidence of respiratory symptoms. In subsequent years, 171, 116, 64, and 12 of these subjects completed new questionnaires and attended group seminars on nutrition. A highly significant relationship was found between increasing ascorbic acid intakes and a decreasing incidence of respiratory symptoms, which was very encouraging. Unfortunately, the attrition rate may have caused a bias, even in the first 3 years, for those who appreciated benefit from their diet would be more likely to return than would those who felt no such benefit. Studies concerning the use of ascorbic acid supplements for the prevention or treatment of the common cold have been the subject of reviews by Chalmers (1975), Thomas and Holt (1978), and Editorials (1976, 1979).

Most authors have concluded that ascorbic acid supplementation does not reduce the incidence of the common cold in well-nourished individuals, but many well-controlled studies have shown beneficial effects in reducing the severity and/or duration of cold symptoms; other studies have not, so the literature is said to be contradictory. Another, more reasonable interpretation might be that some studies included an appreciable number of ascorbic acid-deficient subjects and thus showed benefit, while other studies included mostly subjects who were not in need of ascorbic acid supplements.

Not only dietary intake of ascorbic acid, but all of the factors discussed in Volume I affect the blood and tissue levels of ascorbic acid. So ascorbic acid needs vary from person to person, from time to time, and from place to place. Clearly, males, aged persons, smokers, and those with achlorhydria, hemolysis, infection, hemosiderosis, or hypercupremia, and many other conditions need more ascorbic acid than others. For this reason, some, like Pauling, having advocated very large doses of ascorbic acid, 1 g a day for prevention and 4 g a day for treatment of colds, so as to be sure of providing for those with very high needs. In the opinion of the writer, these very high doses will probably not be necessary if sufficient chelating fiber (flavonoid or catechin) is given with ascorbic acid to prevent wastage of the vitamin by oxidation and hydrolysis (see Chapter 11, Volume I).

Indeed, some studies of dietary supplementation with vitamin C in moderate doses, with or without bioflavonoids, have shown just as much benefit as the megadose ascorbic acid studies have done. Franz et al. (1956), studying four groups receiving the bioflavonoid naringin, or ascorbic acid, 195 mg daily, or a combination of naringin and ascorbic acid, or placebo, observed significantly more rapid recovery from corysa in the two ascorbic acid-

treated groups ($p < 0.05$). Similarly, Baird et al. (1979) observed that subjects receiving 80 mg of ascorbic acid a day as orange juice, or 80 mg of ascorbic acid in an orange-flavored drink, had 14 to 21% fewer respiratory symptoms than a control group receiving the orange-flavored drink without ascorbic acid ($p < 0.05$). Incidentally, these two studies involved the nonchelating flavonoids naringin from grapefruit and hesperidin from oranges. Only the smaller amounts of eriodictyol in orange juice would provide chelation and preservation of ascorbic acid to some extent. However, the acidity of the juice undoubtedly retards losses of ascorbic acid oxidation and subsequent hydrolysis.

It is interesting to note that Tebrock et al. (1956), providing ascorbic acid, 50 mg, with and without lemon bioflavonoid complex (or orange bioflavonoid complex), 250 mg four times a day, or a placebo, to patients with corysa, who also received a cold remedy containing an antihistamine, a decongestant, and two analgesics, observed no benefit from ascorbic acid. Were the antihistamine effects of the vitamin concealed by the antihistamine effects of the cold remedy?

XXV. INCREASED BLOOD HISTAMINE LEVELS

Human ascorbic acid deficiency, even of mild degree, is associated with an increased blood histamine level, which is promptly reduced by the administration of ascorbic acid, as shown by Clemetson (1980). The effects of ascorbic acid on histamine metabolism will be discussed more fully in Chapter 1, Volume III, but it is pertinent here to observe that ascorbate-responsive histaminemia is by no means rare, being present in perhaps one tenth or even one third of an apparently healthy active working population. Even if ascorbic acid did not increase resistance to infection, which it does in ascorbate-deficient people, it should be no surprise that decreasing the blood histamine level makes us feel better.

Histamine levels are always increased locally in an area of inflammation and histamine is responsible for much of the vasodilation and congestion of inflamed tissues. Indeed, acute inflammation is in many ways like local scurvy. Ascorbic acid, in addition to its many other virtues, is an effective antihistamine. The fact that ascorbic acid decreases whole blood histamine levels undoubtedly explains the findings of Zuskin et al. (1973) that ascorbic acid reduces the airway constriction induced by the inhalation of histamine in human adults. It also explains the practical findings of Valik and Zuskin (1973), who carried out ventilatory function tests before and at the end of the work shift on workers in a textile factory, who were exposed to flax dust. Ascorbic acid (500 mg daily), given daily before the shift for a week, caused a significant reduction in measured airway constrictor effects of the dust. It also provided subjective improvement in 12 out of 13 byssinotic workers as compared with 2 out of 13 who felt some improvement after receiving placebo tablets.

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