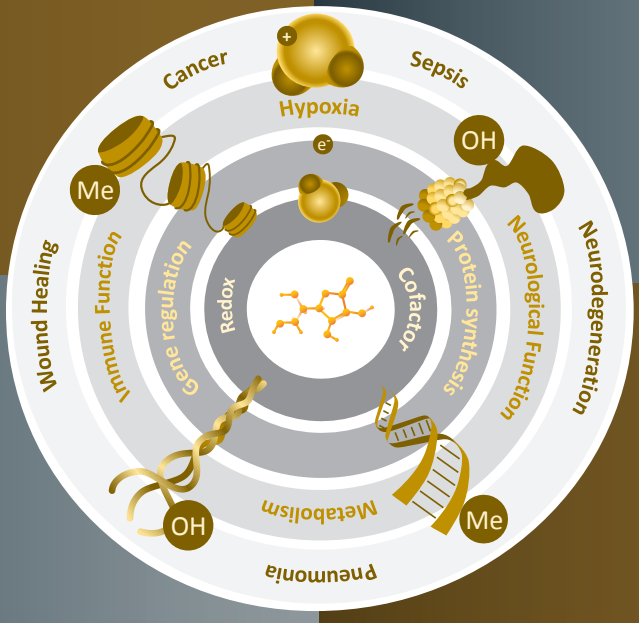
VITAMIN C

NEW BIOCHEMICAL AND FUNCTIONAL INSIGHTS



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Vitamin C

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Chapter 11

Vitamin C and the Brain

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CHAPTER ELEVEN

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INTRODUCTION

Vitamin C plays essential roles in brain metabolism and neurotransmission, and it protects neural tissue from the adverse effects of oxidative stress. This review analyzes the clinical evidence that vitamin C deficiency affects mental function, explains the role of vitamin C deficiency and vitamin C therapy in diseases of the brain, including mental illness, and considers the possibility that, when administered in pharmacologic doses, vitamin C improves mood and cognitive function. Recommendations are offered for rational clinical practice and future clinical research.

VITAMIN C: BRAIN PHYSIOLOGY AND HOMEOSTASIS

Physiology

The brain requires vitamin C to metabolize substrates and synthesize neurotransmitters, regulate their

release, and modify their actions [1–12]. Vitamin C also protects the brain from oxidative damage [2–4,6,9,11–20]. In rodent models, severe vitamin C deficiency impairs monoamine synthesis and neurotransmission and impairs memory, cognition, and behavior [21–23], but does not seem to induce anxiety [21]. Moderate vitamin C deficiency diminishes muscular strength and impairs agility without affecting memory or cognition [23].

Homeostasis

Any analysis of the clinical consequences of vitamin C deficiency and vitamin C therapy must start by defining normal and deficient vitamin C status. Hypovitaminosis C is defined as a plasma vitamin C concentration <28.4 μmol/L; marginal vitamin C deficiency as a plasma vitamin C concentration <28.4 μmol/L but >11.4 μmol/L, and definite biochemical deficiency as a concentration <11.4 μmol/L. Hypovitaminosis C occurs in 10% of the general populations of healthy societies, in 30% of cigarette smokers, and in 60% of acutely ill hospitalized patients [24–27]. The disease of terminal vitamin C deficiency, scurvy, is uncommon but not rare in socially equitable and economically stable societies. Scurvy typically develops when the plasma vitamin C concentration falls and remains below 11.4 μmol/L. (The values in these widely used reference ranges were originally intended as convenient benchmarks expressed in milligrams per liter [mg/L]. Thus, the lower limit of the normal reference range, 28.4 μmol/L, is 5 mg/L; the lower limit of the marginal range, 11.4 μmol/L, is 2 mg/L.)

Vitamin C's concentration in cerebrospinal fluid (CSF) is approximately three times higher than in the bloodstream. Intraneuronal and glial concentrations are approximately five times higher yet [8,26,28]. Thus, a normal human plasma vitamin C concentration of 50 μmol/L corresponds to ~200 μmol/L in the CSF and 1 mmol/L in the brain. The brain conserves its vitamin C store more effectively than the other tissues of the body [28–30]. This protective mechanism may allow the brain to function more effectively than other tissues in the presence of vitamin C deficiency.

As plasma vitamin C concentrations increase within the normal range, CSF concentrations also increase, but less than proportionately. As plasma vitamin C concentrations decrease, CSF concentrations remain approximately stable until the plasma concentration falls below ~28.4 μmol/L. As plasma concentrations drop further below normal, CSF concentrations decrease increasingly severely [1,8,31–37].

In summary, a level of vitamin C consumption that is sufficient to maintain normal plasma vitamin C concentrations is associated with normal (approximately threefold higher) vitamin C concentrations in the CSF and much higher concentrations in neurons. Insufficient or deficient plasma vitamin C concentrations are associated with subnormal CSF concentrations. We don't know if subnormal CSF concentrations reduce brain concentrations, or reduce them enough to impair human brain metabolism, neurotransmitter synthesis or function, or weaken the brain's antioxidant defenses.

To make matters more complicated, animal models of vitamin C deficiency do not necessarily apply to the human condition [38]. As Levine and Padayatty have pointed out, the signs and symptoms of scurvy can be traced to impaired activities of specific vitamin C–requiring enzymes [26]. Does human scurvy deplete neurons of vitamin C enough to impair neurotransmitter synthesis, release, and regulation? States of vitamin C deficiency that impair neurotransmitter synthesis, action, and behavior in animal models may not occur in humans, if they succumb to its hemorrhagic complications before their brain becomes severely depleted of the vitamin.

The homeostatic mechanisms that stabilize CSF and brain vitamin C concentrations in vitamin C deficiency also buffer them against large increases in plasma concentration [8,10]. Using a novel nuclear magnetic resonance (NMR) imaging technique [39], Terpstra et al. infused a bolus of 3.4 g sodium ascorbate into the veins of normal volunteers [40]. Plasma vitamin C concentrations increased from 80 to 600 μmol/L, but brain vitamin C content did not change 2, 6, 10, and 24 hours after the vitamin injection. Notwithstanding this important evidence, a case report of a child with untreatable optic glioma who responded to high-dose intravenous vitamin C [41] sounds a note of caution about drawing firm conclusions from this limited evidence.

Vitamin C Deficiency and the Mind–Body Problem

The brain normally maintains an even keel of vitamin C content as it navigates the choppy seas of

variable dietary supply. How severe does vitamin C deficiency have to be to disrupt brain function? When vitamin C deficiency disease occurs, does it primarily affect the brain—a sensitive, discerning organ—or primarily disrupt and damage the other tissues of the body, which send distress signals to the brain that disturb cognition and mood? Formal assessment of nutritional influences on human cognition presents many challenges [10,42]. For example, marginal vitamin C deficiency could subtly impair physical performance [43–46] or immunity [47,48] in ways that create anxiety or distress in some, predisposed people but not others. High-dose intravenous vitamin C could reduce fatigue and improve quality of life in people with cancer by improving their overall physical well-being without exerting any direct effect on brain metabolism or neurotransmission [49,50]. The clinical evidence bearing on this question is considered next.

MENTAL EFFECTS OF VITAMIN C DEFICIENCY

The disease of terminal vitamin C deficiency, scurvy, manifests in various ways. The commonest and most specific signs of scurvy are follicular hyperkeratosis, corkscrew hairs, and hemorrhagic phenomena such as perifollicular hemorrhage, petechiae, purpura, and bruising in the skin, gums, and occasionally in joint spaces and elsewhere. The diagnosis of scurvy is confirmed by documenting a history of vitamin C deficiency and observing prompt clinical improvement after appropriate vitamin C provision. It is helpful (but usually unnecessary) to document a plasma vitamin C concentration <11.4 μmol/L.

Historical accounts, case reports, and clinical reviews commonly describe fatigue, lassitude, subjective weakness, apathy or emotional irritability, and anorexia as cardinal symptoms of scurvy. Indeed, apathy, irritability, and psychomotor retardation have been described for centuries as heralding the onset of scurvy [51]. A classic report of 19 cases of scurvy stated that "all patients complained of fatigue, weakness and anorexia for months or years and had noted bruises usually related to slight trauma for a few weeks or several years" [52]. A clinical review prepared for the World Health Organization claims that in adults, full-blown scurvy "is preceded by a period of latent subclinical scurvy the early symptoms of which include lassitude, weakness and irritability; vague, dull aching pains in the muscles or joints of the legs and feet and weight loss" [53]. One reviewer asserts that the psychological symptoms of scurvy stem from impaired brain function [51]. It is therefore plausible that fatigue could be a symptom of latent or subclinical vitamin C deficiency [54] when it is considered that nonspecific mental symptoms are harbingers of many metabolic and endocrine diseases.

But where do mental symptoms like fatigue and mood disturbance fit into the symptom spectrum of human vitamin C deficiency? Do they indicate dysfunction of a vitamin C–deficient brain, or a normal brain's emotional responses to the metabolic dysfunction, damage, and inflammation caused by vitamin C deficiency elsewhere in the body, or a combination of these effects? This question is pertinent for two reasons. First, the evidence that the brain sequesters vitamin C more effectively than other organs increases the likelihood that vitamin C deficiency has little direct effect on it. Second, it bears on the scientific plausibility of the popular claim that vitamin C administration to people with normal or nearly normal vitamin C status relieves fatigue by improving brain function.

Case Reports

One way to evaluate the relationship between vitamin C deficiency and brain function is to determine how frequently fatigue, lassitude, subjective weakness, or mood disturbance occur in people with scurvy, and the relationship of these mental symptoms with its somatic manifestations.

I searched MEDLINE from 1946 to August 2019 for obtainable and interpretable case reports of adult scurvy published in English or French, using the Medical Subject Headings (MeSH) terms *ascorbic acid deficiency* or *scurvy* (MeSH or key word) or by pairing *ascorbic acid* (MeSH) or *vitamin C* (key word) with *fatigue*. Many more articles were identified by scanning the reference citations in these articles. Articles were deemed interpretable when they contained enough information to judge the presence or absence of fatigue, lassitude, subjective weakness or mood disturbance, the typical skin or mouth lesions of scurvy, musculoskeletal abnormalities (leg or joint pain or effusion), anemia, and dyspnea. The search identified 132 case reports that described 267 patients (198 men and 69 women; 74% men) [52,54–183].

Characteristic skin or mouth lesions were present in every case of scurvy, because they were its identifying features. Fatigue or a related symptom was noted in 107 patients (40%), anemia in 200 patients (75%), and signs of joint or musculoskeletal disease in 75 patients (28%).

Of the 200 patients with anemia, 76 had noteworthy fatigue and 124 did not. Of the 67 patients without anemia, 35 had fatigue and 32 did not. Of the 108 patients with fatigue, 73 had anemia and 35 did not.

The predominance of scorbutic men over women is consistent with the greater frequency of hypovitaminosis C in men [184], a phenomenon that has been attributed to sex differences in lifestyle and self-care and to differences in body composition [185].

The main conclusion of this analysis is that while noteworthy fatigue and related subjective symptoms, including anorexia, occur often in scurvy, they are far from universal. Fully 60% of patients with scurvy either did not experience fatigue or failed to complain of it, or the authors of the case reports did not deem it sufficiently striking or disproportionate to the clinical setting and the patient's physical disability to merit mention or comment. Failure to note fatigue does not necessarily mean it is absent, and the case reports varied in the amount of detail they provided; fatigue could have been underreported. But it is important to avoid the logical error of circular reasoning by asserting that because a patient has scurvy the patient must experience fatigue, and because the patient experiences fatigue, it must be a necessary feature of scurvy. Going by the text of the case reports, more than half of people with scurvy do not experience unusual or noteworthy fatigue, even though most of them also suffer from anemia, a well-known cause of fatigue. (The 75% prevalence of anemia in these case reports is in line with previous conclusions based on smaller numbers of cases [52,56,57,60,76,186].) It should be noted that many, if not most of the patients described in the case reports suffered from starvation disease and multiple micronutrient deficiencies. Deficiencies of thiamine [187], folic acid, and niacin are known to impair mood or cognitive and neurological function and frequently coexist with scurvy [52,188].

In conclusion, this review of case reports fails to confirm the common claim that fatigue or mood disturbance are necessary, consistent, or sensitive symptoms of scurvy. When fatigue does occur, it could be fostered by the primary physical or mental disease that led to scurvy, and be exacerbated by social isolation, poverty and drug abuse, anorexia, and the consumption of a diet deficient both in vitamin C and other nutrients. Fatigue and mood disturbance may accompany but not represent primary symptoms of scurvy.

Historical accounts and summaries of case reports repeatedly highlight the intensity of the fatigue and mood disturbance of scurvy. Perhaps it is not the presence of fatigue and mood disturbance, but rather its remarkable intensity, and because it improves so dramatically when scurvy is treated, that leads some authors to regard it as a primary symptom of the disease, and because these symptoms improve so dramatically when scurvy is treated. As noted by Walker [65], "a striking feature in all our patients was their severe depressive state at the time of admission. This cleared within a few days of starting vitamin C therapy. Initially we attributed this change in mood to the relief of pain, but in Case 1 the depression was cured long before the pain in her ulcerated legs settled." Several early authors stress that mental depression is part of the clinical picture of scurvy and is cured by treating it [57,59].

These observations suggest that psychological symptoms are inconstant in scurvy. When psychological symptoms develop, they may be caused by peripheral somatic lesions rather than primary brain dysfunction. Perhaps when mental symptoms do arise they are experienced more intensely by a vitamin C–deficient brain. It must be conceded that case reports and clinical impressions are unreliable vehicles for documenting the mental symptoms of scurvy, for they are confounded by the primary disease or disorder that led to the patient's scurvy and the many other nutritional and micronutrient deficiencies that accompany it.

Experimental Human Scurvy

The systematic review of case reports in the previous section indicates that fatigue and lassitude are common in scurvy but not an obligatory feature of it. When fatigue does occur, it could be a symptom of the primary disease that led to the patient's vitamin C deficiency or the consequence of other nutritional deficiencies that accompany it. More reliable information is provided by formal

clinical trials of vitamin C deficiency induced in healthy people.

In a classic self-experiment, Crandon, a young surgical resident in Boston, Massachusetts, continued full-time work while consuming a vitamin C–deficient diet that reduced his plasma vitamin C concentration to zero after 6 weeks. In the first of three publications, he described weight loss (with a reduction in resting metabolic rate) and mild anemia (corrected using an iron supplement) but "no increased fatigue on exertion as measured by tests of work output, while conceding that "subjectively there was a mild lassitude" [189]. In a second article, published the same year, he contradicted his earlier one by asserting that his experience confirmed other accounts of scurvy in that it was characterized by languor and incapacity for work. He first noticed easy fatigability and lassitude near the end of the third month of vitamin C deprivation; these symptoms became increasingly severe as time went on, and his exercise capacity became impaired [190]. He subsequently described lack of energy as one of his initial symptoms. He found the symptom vague and difficult to describe; it included lassitude, a desire for sleep, and a marked disinclination to exertion [191].

Farmer described a 7-month clinical trial of vitamin C and B depletion in healthy men, ages 20–30 years, carried out in the United States [192]. Two of the participants consumed a control diet, five consumed a diet deficient in vitamins C and B, and five consumed the same deficient diet supplemented with vitamin B. Plasma vitamin C concentrations fell to zero by 70 days. After 3–5 months of deficiency, error rates on a choice reaction time task increased; this observation was interpreted as indicating a decrease in interest or motivation. Emotions became more labile. Work output on a bicycle ergometer decreased. Severe fatigue developed after 5 months. Except for follicular hyperkeratosis, the typical skin and mouth lesions of scurvy were absent, even though wound healing was impaired. The observations in this trial are not well reported.

The largest and only double-blind clinical trial of experimental vitamin C deficiency was the British Medical Research Council study carried out in Sheffield in 1944 [193–195]. The trial enrolled 19 healthy men and one healthy woman, 10 of whom were made vitamin C deficient. The first sign of ill health was follicular hyperkeratosis, which developed after 21 weeks of vitamin C deprivation. Muscle coordination was unimpaired, but the volunteers required slightly more time to complete their task, an observation interpreted as evidence of increased fatigue. There were no indications of serious psychiatric disturbances. An attention test, carried out as an indicator of apathy, was unaffected by vitamin C deficiency. All symptoms of vitamin C deficiency were prevented or cured by 10 mg vitamin C per day [193]. In a summary of this trial, one of its authors, the noted biochemist H.A. Krebs, remarked on the absence of complaints of general pains or weakness among the vitamin C–deficient volunteers [196].

In the famous Iowa Study, prisoner volunteers from the Iowa State Penitentiary participated in two clinical trials of vitamin C deficiency lasting several months [184]. Among many other measurements, observations were recorded about their behavior, cognition, and mood. In a report of the first of two studies, the authors pointed out that, as in any prolonged metabolic study, it was difficult to differentiate between subjective complaints and actual symptoms of deficiency, and particularly problematic for the prisoner volunteers, whose special social and emotional problems inclined them to complain of trivial conditions and exaggerate any discomfort. The investigators nonetheless judged, on intuitive grounds, that muscular fatigability, aching, and mild general malaise developed insidiously around the same time that objective manifestations of scurvy became evident. No emotional changes attributable to vitamin C deficiency were observed [197].

In a second trial in which five prisoner volunteers participated, it was necessary to deliver the vitamin C–deficient diet three times daily by gastric tube because of its extreme unpalatability. Fatigue, muscular fatigue and pain, and emotional disturbance became apparent after approximately 90 days of vitamin C deprivation; these symptoms coincided with the appearance of the physical signs of scurvy [198]. Detailed formal psychological tests were administered after days 23, 72, and 107 of vitamin C deprivation. Individual items of the Minnesota Multiphasic Personality Inventory indicated increased fatigue, lassitude, and depression after approximately 72 days of deficiency, coincident with the appearance of follicular hyperkeratosis, gingival edema, and hemorrhage. By day 72, test scores

for hypochondriasis increased moderately, whereas depression and hysteria scores increased slightly. At some time between days 72 and 107, all three test scores (and the social inversion score) increased yet further. These personality changes preceded decrements in psychomotor performance, arousal, and motivation [199]. When the psychological test scores were analyzed in relation to plasma vitamin C concentrations, there were no differences in cognition or coordination test scores for plasma vitamin C concentrations of 11.3 versus 119 μmol/L.

When considered from a modern ethical and psychological perspective, the ethical integrity and scientific reliability of the psychological test scores reported in this clinical experiment are defective. The prisoners were treated in a coercive, inhumane way, and the investigators demonstrated cultural and emotional bias against them. The trial was unblinded. Nevertheless, objective evidence of fatigue and mood disturbance emerged only when physical signs of scurvy developed. Despite claims sometimes made about it to the contrary, this study does not support the assertion that emotional fatigue or mood disturbance are prodromal or sentinel symptoms of impending scurvy.

Twenty-three healthy men participated in a 10-week double-blind study of combined restriction of vitamin C and three of the B vitamins. By week 6 of vitamin C deprivation, plasma vitamin C concentration had fallen to 9 μmol/L. The 12 vitamin-deficient men experienced no adverse effects on health, ordinary physical activity, or mental performance, although there was a significant decrease in aerobic power and the time of onset of blood lactate accumulation during exercise [44]. (Either thiamine or vitamin C deficiency could account for this decrement in physical performance [43,45,46].)

In a pharmacokinetic study of vitamin C depletion and repletion, normal male volunteers consumed a vitamin C–deficient but otherwise adequate diet for several weeks.

Consistent with other reports, plasma vitamin C levels fell below 20 μmol/L after 3 weeks of vitamin C deficiency [200–202], at which point mild but consistent feelings of fatigue and irritability were reported by six of the seven volunteers; physical signs of scurvy were absent. The mental symptoms of three volunteers disappeared within 1 week after vitamin C therapy began. There were no differences in psychometric test scores at the lowest and highest vitamin C doses [26].

In conclusion, and contrary to common opinion, there is little or no good evidence that fatigue and mood disturbance herald or precede the physical manifestations of scurvy in experimental volunteers, who either fail to experience fatigue or develop it at the same time the classic skin lesions and other hemorrhagic manifestations of scurvy appear. This analysis leaves open the possibility that vitamin C deficiency may not induce abnormal fatigue or mood change in nonstressed individuals, but these symptoms may be experienced more intensely when triggered by physiologic or even emotional stresses.

For example, in a combined historical review and analysis of experimental vitamin C deficiency trials, Norris concluded that physical exertion and physical stress increase vitamin C requirements and promote the development of scurvy [195]; other reviewers conclude the opposite [203,204]. Current evidence suggests that even mild vitamin C deficiency can reduce peak physical performance [43,45,46]. Perhaps some people, but not others, perceive this adverse somatic effect and are emotionally disturbed by it.

Movement Disorder

The dopamine-containing neurons of the basal motor nuclei are particularly susceptible to oxidative destruction in a process that is accelerated by vitamin C deficiency [2,11,17,51,205]. Destruction of these neurons causes a movement disorder typical of Parkinson disease. The hypothesis that clinically encountered hypovitaminosis C directly impairs brain function is supported by case reports of patients with scurvy or near scurvy who developed parkinsonian movement disorders that disappeared when their vitamin C deficiency was corrected [51,152,206,207]. Patients admitted to a residential treatment center and found to have the symptoms of early Parkinson disease were also highly likely to have hypovitaminosis C and corkscrew hairs [208].

A pilot clinical trial suggested that the combination of high-dose vitamin E and C delayed the progression of Parkinson disease [209,210]. Subsequent large clinical trials of antioxidants to delay the progression of Parkinson disease tested only high-dose vitamin E and were negative. Scholarly reviews of this topic ignore the plausible

hypothesis that the combination vitamin E and C, as used in the early pilot trial, would be more effective than high-dose vitamin E alone [17].

Mental Effects of Treating Hypovitaminosis C

The fatigue associated with scurvy is frequently reported as dramatically remitting when vitamin C is provided. Does providing vitamin C to people with marginal vitamin C status reduce fatigue or improve mood?

Schorah et al. carried out two double-blind randomized controlled trials (RCTs) in which 1000 mg/d vitamin C or placebo were provided to long-term inpatients with a high prevalence of hypovitaminosis C. In the first trial, 118 patients with an average plasma vitamin C concentration of 11 μmol/L received 1000 mg vitamin C or placebo daily for 1 month. Vitamin C status improved in the active treatment group and was accompanied by borderline statistically significant reductions of apathy and improved well-being [211]. In the second trial, 94 elderly long-term care patients with average plasma vitamin C concentration 10 μmol/L received 1000 mg vitamin C or placebo for 2 months. The treated patients experienced slight improvements in body weight and reductions in purpura and petechial hemorrhages but no improvement in mood or mobility [212].

Gosney et al. [213] carried out an 8-week placebo-controlled RCT of micronutrient supplementation in 73 elderly nursing home residents among whom depression and anxiety were highly prevalent; two-thirds of the participants had hypovitaminosis C (average concentration 20 μmol/L). After 8 weeks of micronutrient therapy that included 240 mg vitamin C per day, the average plasma vitamin C concentration had increased to 64 μmol/L. There was no overall improvement in psychological symptoms. A post hoc analysis indicated that patients with an initially high depression score experienced an important reduction in the score if in the active but not if in the placebo group.

Clausen et al. [214] carried out a year-long double-blind placebo-controlled trial that examined mental performance and psychological scores of 94 elderly nursing home residents before and after consuming an antioxidant vitamin cocktail that included 270 mg vitamin C per day. Antioxidant supplementation had little effect on mental performance, and there were few associations between plasma vitamin concentrations and mental functioning (plasma vitamin C was not measured). There were slight but statistically significant improvements in psychological scores in the vitamin-treated patients.

We carried out one small open clinical trial [215] and two small double-blind RCTs that measured the effect of vitamin C therapy (500 mg twice daily for approximately 1 week) on mood in acutely ill surgical and medical inpatients with a high prevalence of hypovitaminosis C. These clinical trials compared the effects of vitamin C with those of a safe and clinically plausible (but subsequently determined to be inadequate) dose of vitamin D [216,217]. All three trials indicated a prompt 50%–70% reduction in mood disturbance or psychological distress in patients treated with vitamin C but little or no change in patients treated with vitamin D.

These preliminary indications of rapid and dramatic improvements in mood and psychological distress in vitamin C–treated acutely ill hospitalized patients with hypovitaminosis C stand in contrast to the negative or mostly negative findings reported in other, larger, and longer-term clinical trials of vitamin C therapy in clinically stable, long-term care patients with hypovitaminosis C.

Conclusions

Fatigue, mood disturbance, and related symptoms are striking features of scurvy, but only some patients experience or report them. As many as 60% of case reports of scurvy fail to mention or report fatigue. It is possible that patients in these case reports did experience fatigue, but they or the authors of the case reports did not consider it disproportionate enough to their general clinical condition to merit comment. When fatigue and mood disturbance occur in people with scurvy, they may be at least partly caused by coexistent anemia, systemic inflammation, disability, drug intoxication, protein-energy malnutrition, and other micronutrient deficiencies. Some but not all studies of experimental vitamin C deficiency describe fatigue as a symptom. Fatigue or mood disturbance were specifically absent in the largest and most rigorous, double-blind trial of experimental human scurvy. Except for one small study, in which fatigue was reported very early in vitamin C deficiency, the clinical evidence indicates that when fatigue develops, it does so at the same time as the physical manifestations of scurvy and

hence could reflect the response of a normally functioning brain to peripheral tissue damage.

This analysis raises the possibility that when tissue damage, systemic inflammation, or even emotional distress cause fatigue, concurrent vitamin C deficiency increases its intensity. Thus, in roughly the same way that starving, severely thiamine-deficient people may develop Wernicke encephalopathy when glucose is infused, or people with adrenal insufficiency experience a clinical crisis when exposed to trauma or surgery, or people with pellagra develop a phototoxic skin rash when exposed to sunlight, or people with scurvy develop hemorrhagic gingivitis only when they have teeth to chew with, the exaggerated fatigue and mood disturbance of scurvy occur when people are physically or emotionally stressed in ways that trigger "normal" fatigue.

Very few clinical trials have tested the mental effects of correcting hypovitaminosis C. None of them are conclusive, and their results are discordant. Our own three small clinical trials yielded consistent and reproducible evidence that correcting hypovitaminosis C in acutely ill, hospitalized patients rapidly reduces emotional distress, whereas three larger and longer-term trials indicated little or no benefit from vitamin C provision to clinically stable long-term nursing home patients with a high prevalence of hypovitaminosis C.

It is impossible to draw conclusions from such scanty evidence. Active-care, acutely ill patients are different from chronic nursing home patients. Does correcting systemic inflammation-associated hypovitaminosis C in acutely ill patients improve their mood by ameliorating distress signals sent from the peripheral tissues to the brain? Must one be experiencing at least moderately severe mental distress for it to improve when hypovitaminosis C is corrected? Are the forces driving the low mood of chronic nursing home patients so overwhelmingly strong that normalizing their somatic or brain vitamin C stores is futile?

These same questions arise when one considers the mental effects of vitamin C deficiency and its treatment in diseases of the brain, including mental illness.

BRAIN DISEASES

This section provides information about the mental effects of vitamin C deficiency and therapy in acute brain injury, ischemic brain infarction, delirium, dementia, and mental illness.

Acute Brain Injury

Plasma vitamin C concentrations are reduced in patients with brain trauma, and reflect the severity of the injury [218]. More importantly, the vitamin C content of CSF is severely depleted in head-injured adults (77 versus 203 μmol/L in control samples) [219] and infants (54 versus 164 μmol/L) [220]. There is promising, but extremely limited, clinical evidence that antioxidant therapy reduces neurological symptoms and improves recovery in patients with traumatic brain injury [221]. Razmkon et al. compared the effects of low-dose intravenous ascorbic acid (500 daily for 7 days), high-dose ascorbic acid (10 g on days 1 and 4 followed by 4 g on days 5, 6, and 7), vitamin E (400 IU daily), or placebo on clinical outcomes and brain edema in young men with severe brain trauma; the results were inconclusive [222]. This topic was recently reviewed [223]. The most biologically plausible therapy would employ a combination of micronutrients, including vitamin C [224,225].

The plasma vitamin C concentrations of 15 patients with acute bacterial meningitis were extremely low and similar to those in 14 comparison patients with other neurological diseases (headache, seizure, transient ischemic attack, or facial palsy without meningitis; 10.3 versus 9.3 μmol/L); but remarkably, their CSF vitamin C concentrations were fantastically reduced (11.9 versus 144 μmol/L) [226]. Vitamin C concentrations in plasma (16 versus 76 μmol/L) and CSF (66 versus 218 μmol/L) were dramatically reduced in 11 adults with septic encephalopathy as compared with 14 healthy individuals [227]. Serum and CSF vitamin C concentrations of patients with tick-borne encephalitis were normal and similar to those in normal individuals [228].

Ischemic Brain Infarction

Plasma vitamin C concentrations decrease immediately after an acute ischemic stroke [229] and reflect the severity of the injury [218]. In view of basic evidence that vitamin C adequacy or administration could prevent or mitigate the effects of acute ischemic brain injury [20,230], Rabadi and Kristal [231] evaluated the effects of

vitamin C supplementation on functional recovery after an ischemic stroke in a retrospective, case-control study of 23 patients with ischemic stroke treated with vitamin C matched with 23 other patients with ischemic stroke who were not vitamin C supplemented. No significant differences in outcome were observed. Lagowska-Lenard et al. administered 500 mg vitamin C or placebo intravenously for 10 days to patients immediately after an ischemic stroke; no acute or long-term clinical benefit was observed [232].

Delirium

Unlike with certain B vitamin deficiencies [233,234], the possibility that hypovitaminosis C could contribute to delirium appears never to have been investigated. A MEDLINE search from 1948 to 2019 revealed no publications dealing with the potential role of hypovitaminosis C in precipitating or worsening delirium (or alcohol-withdrawal delirium), despite the biological plausibility it could do so and the high prevalence of hypovitaminosis C in delirium-prone people [235].

Dementia

Despite continuing interest in antioxidant therapy to delay or slow the progression of dementia [11,18–20,236–238], there is neither strong nor consistent observational and clinical evidence that supplements of vitamin C or other antioxidants prevent cognitive decline or slow the progression of dementia [239]. Nor is it obvious that vitamin C deficiency accelerates neuronal death. A vitamin C–deficient diet reduced plasma ascorbate and dramatically reduced CSF and brain ascorbate in aging guinea pigs but did not accelerate the progression of old age–related brain pathology [240]. Associations between hypovitaminosis C and cognitive dysfunction [241] and lowered plasma vitamin C concentrations in dementia [10] could be explained by inadequate vitamin C consumption or concurrent deficiencies of other micronutrients. However, a recent cross-sectional observational trial indicated that plasma concentrations of vitamin C (and other antioxidants) were substantially lower than normal in both people with Alzheimer disease and those with mild cognitive impairment, a condition that precedes dementia and would not be predicted to be associated with poor nutritional status. This interesting observation argues against dietary deficiency as the sole explanation for hypovitaminosis C in dementia [242]. A large, recent prospective observational trial indicated that vitamin C and E supplements were associated with a slower rate of cognitive decline in people with dementia [243].

This field of nutritional investigation is confounded by heterogeneity in study design, short observation periods, and varying definitions and evaluation methods [18,244]. It is important, but not always appreciated or acted on, to document the vitamin C status of the patients enrolled in observational and clinical trials. For example, in one study, plasma and CSF vitamin C concentrations of patients with Alzheimer disease were similar to those of control patients [36], whereas in another, long-term observational study of elderly people, poor vitamin C status was strongly associated with cognitive dysfunction, stroke, and death. Only one-third of the patients in the latter study had a normal vitamin C concentration [241].

Having earlier found that one month of supplementation with vitamin C and E increased vitamin C and E concentrations in the CSF and reduced CSF lipid peroxidation [245], Arlt et al. carried out an RCT of vitamin C (1000 mg/d) and E (400 IU/d) administered to 12 patients with Alzheimer disease (11 patients served in the control group). Vitamin supplementation increased CSF antioxidant vitamin concentrations after 1 month and 1 year of therapy but nevertheless failed to slow the progression of Alzheimer disease [246].

Mental Illness

There is increasing recognition of the role of appropriate nutrition in the prevention and amelioration of mental illnesses [247–251]. Does hypovitaminosis C worsen mental illness? Does mental illness increase vitamin C metabolism and its nutritional requirement? Does vitamin C therapy reduce the symptoms of mental illness?

Although unrecognized by most psychiatrists and other physicians, hypovitaminosis C and even scurvy are common in severe mental illness [13,94,108,130,137,155,252–263]. Obvious causes are inadequate diet [264,265], cigarette smoking, and possibly the effects of pharmacotherapy [130,266–268]. It has been suggested that schizophrenia increases vitamin C catabolism, predisposing schizophrenic people to hypovitaminosis C.

This hypothesis is based on the observation that patients with schizophrenia excrete subnormal amounts of vitamin C in their urine following the administration of a test dose [255,269], but the biological and clinical evidence supporting it are weak and inconsistent [270,271]. Mentally ill patients could excrete subnormal amounts of vitamin C for many reasons [258,271,272].

The oxidative stress theory of schizophrenia, initially proposed more than 50 years ago [13], continues to attract interest [2,11,12,273–275]. A holistic nutritional and lifestyle therapy, orthomolecular psychiatry, is motivated by the concept that abnormal brain metabolism in severe mental illness can be improved administering large doses of certain micronutrients, including vitamin C [276–279].

Case reports and small clinical trials indicate, unsurprisingly, that when psychotic people who are deficient in vitamin C [254] (are likely to be [280,281]) receive vitamin C, they improve greatly. The adverse effects of hypovitaminosis C in these patients are likely exacerbated by other micronutrient deficiencies [81,261,282,283].

A small, open clinical trial indicated that high-dose vitamin C therapy potentiated the clinical benefit of the antipsychotic drug, haloperidol [284], but was followed shortly after by a negative report [285]. Vitamin C dramatically improved the symptoms of mental illness of a vitamin C–deficient child suffering from depression and liver disease [286]. One small clinical trial indicated that vitamin C increases the effectiveness of fluoxetine therapy in major depression [287]. A second one indicated no benefit from adding vitamin C ("up to 1000 mg" per day) to citalopram [288]. Neither study determined baseline vitamin C status of the participating patients. Elderly patients suffering from major depression were reported to have higher than normal concentrations of vitamin C in their CSF (304 versus 240 μmol/L). The interpretation of this counterintuitive observation is hampered by the failure to measure plasma vitamin C concentrations [289].

As reviewed (but not always completely) by other authors [11,12,247–249,290], a small number of clinical trials have been published describing the use of vitamin C alone [254,280] or in combination with other micronutrients [291–294] as adjunctive therapy for chronic schizophrenia; the results are inconsistent. As is common in pharmacologic trials involving vitamin C, the interpretation of most of these trials is hindered by the failure to determine the baseline vitamin C status of the participants [24]. In a small, placebo-controlled RCT hindered by a high dropout rate, depressed patients with subnormal plasma vitamin C concentrations benefited from the addition of a daily dose of 500 mg vitamin C to their treatment regimen [295]. There is evidence that the provision of multiple micronutrients (not specifically vitamin C) improves mental function in people with attention deficit disorders [247,290].

PHARMACOLOGIC VITAMIN C AND MENTAL FUNCTION

The mental effects of pharmacologic doses of vitamin C, provided alone or together with other nutrients, have been tested in RCTs involving people with normal vitamin C status.

In a double-blind crossover RCT, the consumption of 160 mg/d of vitamin C or placebo for 4-week periods had no effect on psychomotor or other cognitive function in healthy young men with normal vitamin C status [296]. In two different articles that described the same clinical trial [297,298], healthy ambulatory elderly men and women participated in an approximately year-long clinical trial that tested the effects of daily consumption of an antioxidant vitamin supplement containing 500 mg vitamin C on mood, cognition, and intelligence. One of the articles asserted that despite very few significant differences between the placebo and vitamin groups, increases in plasma vitamin C concentration at 12 months were associated with more positive mood, greater improvements in intellectual functioning, and a reduction in everyday errors of memory, attention, and action. These effects were greatest for those people with more severely depressed mood and lower levels of cognitive function at baseline [297]. The other article concluded that provision of the antioxidant supplement had little or no effect on mental performance [298].

In a 6-month clinical trial, daily consumption of a multiple vitamin supplement containing 600 mg vitamin C had no effect on mood or cognition in elderly people with normal baseline vitamin C status [299]. By contrast, and in disagreement with this trial, three other clinical trials indicated that daily consumption of 500 mg vitamin C as part of a multiple vitamin–mineral supplement

reduced fatigue and improved cognitive function in normal adults [300–302].

Participants in the large Age-Related Eye Disease Study (AREDS) received a daily vitamin and mineral supplement containing 500 mg vitamin C, or placebo. After a median of 6.9 years of treatment, there were no differences in any of six cognitive test scores [303].

Healthy young adults recorded their sexual activity and completed the Beck Depression Inventory before and after consuming 3000 mg/d of sustained-release vitamin C or placebo for 14 days [304]. Sexual activity increased in the active treatment group, and their Beck Depression score improved. The latter observation is of doubtful importance, however, since none of the participants were depressed, and the change in the test score was clinically trivial. In a second, similarly designed trial, volunteers randomized to 3000 mg/d vitamin C exhibited less subjective distress and less intense blood pressure changes in response to psychological stress [305]. The authors suggested that vitamin C acts directly on the brain by activating or disinhibiting neurotransmission.

Healthy office workers received a single injection of 10 g vitamin C with normal saline or normal saline alone. A fatigue score was tabulated 2 hours and 1 day after the injection. Fatigue scores decreased in the vitamin C group after 2 hours and remained lower for 1 day, especially in people with a lower baseline plasma vitamin C concentration [306].

Healthy high school students participated in a 14-day clinical trial that tested the effects of 500 mg vitamin C per day or placebo on blood pressure and anxiety. The Beck Anxiety Inventory score decreased significantly from 22 (mild anxiety) to 17 in the vitamin C group but was unchanged in the placebo group [307].

Despite the frequent assertion that pharmacologic doses of vitamin C modify brain function in a way that reduces anxiety and improves mood when administered to people with normal vitamin C status, there is very little convincing evidence supporting it. The scanty clinical trial evidence summarized here is unconvincing that pharmacologic doses of vitamin C have important brain effects in people who are not vitamin C deficient, and the phenomenon of brain homeostasis makes the hypothesis biologically implausible.

It is challenging to design and interpret clinical trials that depend on subjective (or psychologically modifiable) endpoints like fatigue and mood [308]. Placebo effects are complicated, powerful, and subtle. Imperfect blinding of study participants and investigators as to treatment assignment, and imperfectly crafted placebos can confound the results of clinical trials with soft subjective endpoints that are prone to expectation effects. Placebos are frequently imperfect [309]. Study participants could consciously or subconsciously identify physical characteristics of vitamin C (e.g., increased plasma osmolarity) and register effects that are mediated more by expectation than any fundamental physiologic action of the vitamin in the body or brain.

CONCLUSIONS

How Does Vitamin C Deficiency Affect the Brain?

Because the central nervous system has an absolute requirement for vitamin C, it maintains CSF vitamin C concentrations approximately three times higher than in the peripheral circulation and in much higher concentrations yet in neurons and glial cells. Because the brain conserves vitamin C more effectively than other tissues, it may be less adversely affected by dietary vitamin C deficiency than other tissues. Case reports and observations in experimentally induced scurvy do not provide good evidence of primary brain dysfunction. The clinical evidence is most consistent with the hypothesis that the dominant cause of the fatigue, lassitude, and mood disturbance that develop in some, but not all, people with scurvy is somatic tissue damage and the physiologic and emotional response to it. The possibility that scurvy directly causes mental symptoms is, nevertheless, suggested by the common observation that when fatigue does occur it is unusually severe, and it remits almost immediately after vitamin C is provided, a response that seems too rapid to be solely attributable to peripheral tissue repair. Another indication of primary brain dysfunction in vitamin C deficiency emerges from rare case reports of parkinsonian movements in some people with severe hypovitaminosis C and their disappearance after vitamin C provision.

Perhaps vitamin C deficiency does not primarily cause fatigue and mood disturbance but rather intensifies them when they are triggered by the physical effects of scurvy, other nutritional disorders, or the diseases that led the patient to

become vitamin C deficient. This notion could explain why clinical trials of vitamin C provision indicated no effect on fatigue and mood disturbance in debilitated, vitamin C–deficient chronic nursing care patients but a major improvement in acute-care, medical and surgical patients who entertain hope of clinical improvement and discharge from hospital. The paucity of clinical trial evidence makes any conclusion unreliable.

Brain Diseases

Severe brain injury drastically depletes the CSF of vitamin C, possibly severely enough to reduce brain vitamin C concentrations. Brain injury from trauma, infection, and inflammation is dangerous and commonly leads to serious permanent disability. There is a strong argument for carrying out clinical trials of high-dose intravenous vitamin C in severe brain injury with the goal of fostering clinical improvement and reducing its complications. Nevertheless, despite the biological and clinical plausibility of this hypothesis, almost no clinical research has been carried out in this area.

Observational and physiologic evidence suggests that normal vitamin C status (possibly in combination with overall good nutritional status) protects the brain against ischemic injury and could limit the extent of an ischemic infarction, but the extremely limited clinical trial evidence currently available does not demonstrate that vitamin C supplementation improves clinical outcomes when commenced immediately after an acute ischemic stroke. These are, in fact, two different hypotheses. Does chronic, lifelong hypovitaminosis C increase the risk of dementia? Does lifelong supplementation with vitamin C (and other antioxidants) in the absence of deficiency reduce the risk of dementia? Despite their biological plausibility, these hypotheses are difficult, if not impossible, to test definitively. The existing observational and clinical trial evidence is inconsistent and unconvincing in any direction.

Hypovitaminosis C is common among people suffering from severe mental illness. Mentally ill people will be affected at least as badly by vitamin C deficiency as mentally normal people, perhaps even more so. Clinical trials are notoriously difficult and unreliable in patients with psychotic mental illness. A few clinical trials have been carried out using low-pharmacologic doses of vitamin C (either alone or with other nutrients) as adjunctive therapy in patients with chronic stable psychotic mental illness or depression but without determining their baseline vitamin C status; the results are inconsistent. They do not support any general conclusion other than the commonplace one that nutritional deficiencies of every kind should be strictly avoided and promptly corrected in everyone, and especially in people already burdened with severe mental illness.

Pharmacologic Vitamin C and Mental Function

The body tightly regulates its plasma, CSF, and brain vitamin C concentrations—at least in health—and this physiologic fact challenges the plausibility of claims that large oral (even intravenous) doses of vitamin C relieve anxiety and improve mental function in people whose baseline vitamin C status was already normal. There is more plausible (but still inconsistent and inclusive) evidence that continuous supplementation with a combination of several micronutrients, including vitamin C, may have cognitive benefits in some people despite their lack of diagnosed deficiencies. The power, complexity, and subtlety of the placebo effect are increasingly apparent. Imperfect blinding of study participants and investigators as to treatment assignment, and imperfectly crafted placebos can confound the results of clinical trials with soft subjective endpoints, like anxiety, well-being, and cognitive symptoms, all of which are highly prone to expectation.

Mind–Body Problem

Patients and their caregivers are more interested in mental and physical well-being than whether the mechanism for it originates in their brain or their body. I have tackled this question in this review because it is pertinent to the plausibility, design, and interpretation of clinical trials investigating the mental effects of vitamin C. The available evidence indicates that, except in certain brain diseases, an intake of vitamin C that is adequate for the body is also adequate for the brain. Vitamin C deficiency should be avoided because it adversely affects the body and, possibly secondarily, the brain. Pharmacologic doses of vitamin C may (or may not) improve a specific somatic disease and secondarily relieve distress, anxiety, and fatigue.

What Is the Best Dose of Vitamin C for the Brain?

What is best for the body is best for the brain. Public health authorities in different countries recommend very different levels of vitamin C consumption by healthy people, from as low as 40 mg to as high as 110 mg/d [27]. Cigarette smokers (and presumably people experiencing equivalent or more severe oxidative stress from disease and systemic inflammation) require more vitamin C. The higher dose recommended in Canada and the United States is based on determinations of the vitamin C intake required to nearly maximize tissue saturation for most people [27]. Several authorities offer plausible physiologic arguments that daily intakes of 200–1000 mg will better guarantee tissue saturation for some individuals [310–313].

Hypovitaminosis C increases the vitamin C requirement until tissue stores are replenished [314,315]. Moreover, people with hypovitaminosis C are at risk of other nutritional deficiencies that must be diagnosed and treated.

Severe tissue injury and systemic inflammation greatly increase the vitamin C dose necessary to normalize plasma and CSF vitamin C concentrations. Normalizing vitamin C concentrations under these conditions may improve clinical outcomes and mental function. People with brain injury or delirium could especially benefit from correction of vitamin C deficiency in their plasma, CSF, and brain.

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