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Vitamin C and Fatigue

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Fatigue: Its Meaning

Generally speaking, the dictionary defines fatigue with equally incomplete substitutes such as tiredness, lassitude, weakness, exhaustion, ennui, burnout and/or boredom. Some few larger lexicons go beyond this synonym chanting. When they do, fatigue and energy are somehow related. As energy goes down ... fatigue goes up!

Interestingly, one of the highly innovative health questionnaires developed by the Human Population Laboratory (HPL) in California utilizes energy reserve as the ultimate demarcating denominator.[1]

Apropos, according to the International Classification of Diseases,[2] fatigability is now recognized as a sovereign syndrome with its own distinctive designation (Chronic Fatigue Syndrome), its abbreviation (CFS) and its own number (780.7).

This new-found diagnosis must be viewed in the light of history. For a long time, every standard medical textbook[3-7] makes the point that one of the most consistent prodromal findings of practically all disease states is tiredness. It is recognized as one of the early findings in malignancies (e.g. leukemia), infectious conditions (i.e. mononucleosis), and even hormonal syndromes (diabetes mellitus, hypothyrodism). Hence, implied, if not stated, is that CFS is arrived at by exclusion.

The Measurement of Tiredness

Viewed in broad strokes, there are two approaches. The first is simple, inexpensive, but unfortunately highly qualitative. It consists of questionnaires. There are many, as one might expect, some more sophisticated than others.[8] The other option is more complex, costly, but surely more quantitative. Actually, it takes two forms. The direct includes gadgets such as hand ergometry, exercycles, treadmills, etc. The other, the indirect, centers about measures of oxygen consumption. This physiologic phenomenon will be addressed later in this report.

How Big a Problem is Fatigue?

According to a recent Department of Health and Human Services report entitled *Reasons for Visiting Physicians*, a staggering 14 million Americans go to the doctor complaining of exhaustion.[9] It is a report that presents a detailed tabular analysis of data collected in the National Ambulatory Medical Care Survey (NAMCS) of the National Center for Health Statistics. It is based on patients' reasons for visiting office-based physicians, determined from a classification system developed in 1977 for use in this survey.

Data collection and processing for the 1977 and 1978 NAMCS were the responsibility of the National Opinion Research Center at the University of Chicago. Sample selection was accomplished with the assistance of the American Medical (AMA) and the American Osteopathic (AOA) Associations.

Add to that uncounted millions who seek medical advice for other reasons but also mention significant exhaustion. And plus the fact there are millions more who never seek help but are nonetheless tired all the time. It becomes clear that fatigue is one of the major problems in America!

But, it may even be bigger. The HPL study (earlier mentioned) eventuated in several publications, one of which presented a unique approach to the measurement of health.[1] In a survey of a sample of the adult population of Alameda County in 1965, respondents were asked a number of questions regarding disability, chronic conditions, symptoms and energy status. From their answers, they have been categorized along a physical health spectrum ranging from a minimum condition defined by inability to work and/or care for personal needs (Level I), to an optimal state expressed by no complaints and high energy (Level VII).

Believe it or not, by this diagnostic system, only 6% qualify as energetic and healthy!

However viewed, it is safe to conclude that fatigue is one of the, or the most, common signal in the health/sickness spectrum.

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The Incidence and Prevalenc of Vitamin C

How many people suffer with hypoascorbemia?

C. J. Schorah of Leeds, England provides us with some exciting answers.[10] Table 1 summarizes the approximate frequency of classical scurvy in different samples as judged by the buffy coat layer. It is obvious that somewhere between zero percent of healthy young subjects (line 1) to one out of two institutionalized elderly (line 6) may possibly demonstrate biochemically full-blown classical scurvy. With regard to the shades of grey (Table 2), the evidence suggests that somewhere between three percent of young and healthy subjects (line 1) and 100 percent of institutionalized young (line 6) suffer from marginal hypovitaminosis C. Whatever the figures, what seems unquestioned is that a significant segment of the population shows biochemical evidence of ascorbate deficiency.

Table 1. Percentage of Population Groups With Unequivocally Low Leukocyte Vitamin C Reserves

Lines	Groups	Percentage of Subjects with Classical Scurvy
1	young, healthy	0
2	elderly, healthy	3
3	elderly, outpatients	20
4	institutionalized young	30
5	patients with cancer	46
6	institutionalized elderly	50

Table 2. Percentage of Population Groups With Marginal Leukocyte Vitamin C Reserves

Lines	Groups	Percentage with Marginal Vitamin C Deficiency States
1	young, healthy	3
2	elderly, healthy	20
3	elderly, outpatients	68
4	patients with cancer	76
5	institutionalized elderly	95
6	institutionalized young	100

We too have been studying this problem in our clinic at the University of Alabama Medical Center for a number of years in five unique populations with over 4,000 subjects including: (1) a dental school patient population,[11] (2) participants in a dental prepayment program,[12] (3) orthodontic candidates,[13] (4) selected groups of Floridian dentists and their staffs,[14] and (5) dental students.[15] Depending upon the tests and the criteria for optimality, we have concluded that somewhere between 17 and 72 percent of the subjects studied by us demonstrated suboptimal to clearcut ascorbic acid deficiency levels.

If indeed the figures summarized by Schorah and those cited by us reflect the true epidemiologic status of ascorbic acid deficiency, then hypovitaminosis C is a very real and common, probably epidemic, problem which clearly has not been properly viewed and surely not adequately reported.

So, What is the Connection Between C and Fatigue?

The correlations are abundant beginning with the earliest medical writings and still appear in the most recent professional literature.

A Look Back Into the Future

There is the old adage, variously described that, those who have not read history are destined to repeat it. At the end of the Middle Ages, sailors began to make ever more daring voyages out from western Europe. This could be explained, in part, by technical developments in the design of the ships that allowed sailing at a greater angle from the direction of the wind, and in methods of navigation with a more reliable compass. There were also strong commercial inducements to find a more profitable sea route in lieu of the overland trade of silk and spices between Europe and the Far East.

We know that Portuguese sailors began to explore Africa in the 1400s finally rounding the Cape in 1487. It soon became obvious, though, that on such voyages the men at sea became quite ill. Their hands and feet swelled and their gums grew over their teeth, which made eating difficult if not impossible. One of the earliest, most impressive and relevant findings was inordinate tiredness. As a matter of fact, many a sailor was asked to walk the gangplank because the captain accused him of malingering. The truth of the matter was the poor soul was too tired to perform his duties.

For our purposes, we can skip the subsequent experiences with the French, English and the Dutch. There is ample documentation that their navies suffered the same fate.

Back to the Portuguese who quite by accident encountered Moors who were carrying oranges which seemed to provide a magical cure.

One naval surgeon who became particularly interested in the devastation of scurvy at sea was James Lind, now the most celebrated name in the history of this subject. It was during one such outbreak of scurvy that this British physician carried out his now famous experiment, probably the first controlled trial in clinical nutrition, or even in any branch of clinical science. He studied a group of sailors all with scurvy under what today would be viewed as an acceptable double-blind experience. Without delving into all the particulars, it became evident that this terrible syndrome responded almost magically to the consumption of oranges and lemons.

The Now and New Scurvy

As we have just learned, the vitamin C connection was established with the recognition that an absence of what later became known as vitamin C led to a fatal disease identified as scurvy. When the correlation was finally and firmly established, the scientific community rested with the happy thought that here was a specific substance associated with a specific syndrome. From this time on until the middle of the 1900s, not much occurred clinically. True, there were some isolated brilliant discoveries like the identification of vitamin C by Albert Szent-Gyorgyi. However, from a practical clinical standpoint, the two centuries from 1750 to the early 1900s could be viewed as the dark ages.

In October 1939, John Crandon,[16] a resident surgeon attached to Harvard Medical School placed himself on a diet of bread, crackers, eggs, cheese, beer, pure chocolate, and sugar with supplements of yeast and all the then known vitamins other than C. At the beginning of the trial, chemical analysis of his blood plasma for ascorbic acid gave a value of 1.0 mg%. (Incidentally, in our judgement, this is probably the "ideal" plasma concentration.) After 21 days, the value had fallen to 0.1 mg%, and from six weeks on, none could be detected. The buffy coat concentration was 28 mg% (which is viewed as marginal) when early measured and crashed to a non-detectable value only after eight weeks without vitamin C.

Crandon had continued his surgical work all this time. And most important to point out, before he demonstrated any physical signs, there was an obvious feeling of tiredness. After 26 weeks, Crandon was given a fatigue test. He could run at seven miles per hour for only 16 seconds and showed rapid exhaustion in other measurements. One gram of C was given intravenously each day for a week. A subjective improvement was noticed in the first 24 hours.

There are a number of other reasonably well-designed observations on the possible connection between tiredness and the ascorbates.

To set the scene, one must recall for most of us, health/sickness is a black and white, either/or concept. By this definition, making healthy kids healthier is a contradiction in terms. Even our health experts, by act if not by word, assume that the majority of children are healthy. Unless the youngster has brittle diabetes, the swollen joints of classical rheumatic fever, or a glaring congenital defect, we take it for granted that there is health.

But, for the purists, health/sickness represents a spectrum ranging from the untimate in health (white) to disease and death (black) with an infinite number of intermediate gradations. There is, in fact, average health versus optimal, ideal, and possibly the perfect state. With this in mind, it now becomes conceivable for healthy kids to be made healthier.

Five investigators from Zagreb, in the former Republic of Yugoslavia,[17] looked beyond this traditional concept. They sought the acme (the ultimate in well-being) through a continuing series of vitamin studies extending over a number of years. One phase emphasized the effect of ascorbic acid supplementation on physical working capacity in adolescent boys. After daily administration for two months of 70 mg ascorbic acid, the mean plasma vitamin C in the 49 subjects in the experimental group rose four and one-half fold. There was a bonus of improved oxygen utilization. Conversely, no convincing changes in biochemical state or in oxygen consumption could be shown in the 42 placebo-supple-

mented children. Hence, according to Suboticanec-Buzina and his Yugoslavian colleagues from the Department of Nutrition at the Institute of Public Health, it is clear that overall performance can be heightened even in seemingly healthy kids.

There is much more to the story. One vitamin C expert (Doctor C.A.B. Clemetson, author of a monumental three-volume review of the subject)[18] best described the picture:

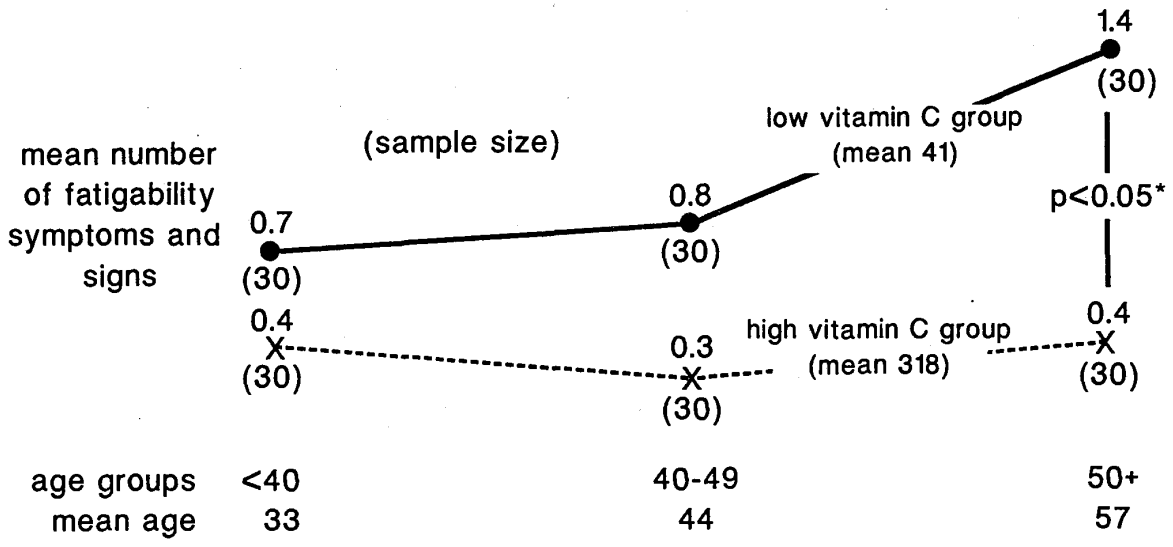
> Clearly about half the boys in the supplemented group showed a very marked increase in working capacity, such as would likely make the difference between losing and winning their next soccer game. Moreover, their improved ascorbate status could lift their spirits and would most probably improve their resistance to infection.

We here at the University of Alabama Medical Center have also looked at this connection.[19] The vitamin C intake of 411 dentists and their spouses was determined from data on daily vitamin C consumption in a food-frequency questionnaire. The mean number of fatigue symptoms listed in answers to the seven questions comprising Section I of the Cornell Medical Index Health Questionnaire (CMI) was designated the fatigability score. The relationship between the two variables was determined by calculating the tiredness grade for different levels of vitamin C intake.

The 81 subjects who consumed less than 100 mg of ascorbic acid per day reported a fatigability mark averaging 0.81. Conversely, the 330 participants ingesting more than 400 mg of the ascorbates per day reported an exhaustion index of 0.41. The mean difference was statistically significant. Phrased another way, these limited data suggest that individuals consuming the generally accepted RDA for vitamin C report approximately twice the fatigue symptomatology as those taking about sevenfold the RDA.

Quite apart, it is well-known that, with advancing age, there is increasing weariness. Old people get more tired than young folks. With that in mind, these same data were reexamined in terms of the aging process.[20] Figure 1 shows that, with time, there is a rise in fatigability in those individuals consuming approximately 41 mg of C. In contrast, it is equally evident from this figure that persons ingesting an average of 318 mg of the ascorbates do not display this increment. What is particularly noteworthy is that the average 57 year old utilizing about seven times the RDA showed a mean score (0.4) which is less than the average 33 year old (0.7) demonstrating the RDA for vitamin C.

Figure 1. Relationship of reported relatively low daily (mean 41 mg/day) and high (mean 318 mg/day) vitamin C consumption versus fatigability symptoms and signs

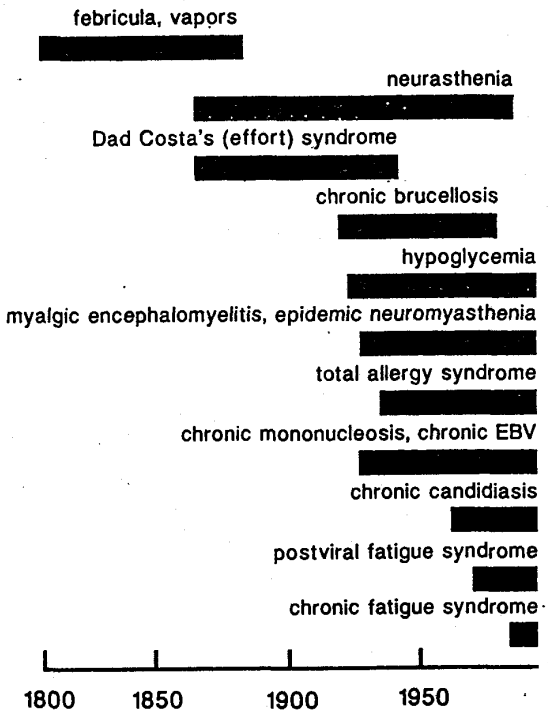


*statistically significant difference of the means

Fashions in Fatigue in the 90s

In the last few years, there has appeared what now seems to be the gospel,[21] official pamphlets for the layman[22] and the physician,[23] several international symposia, a plethora of books,[24-32] and even a video proporting a "new" disorder, Chronic Fatigue Syndrome (CFS).

Figure 2. Timeline graph from 1800 to the present of other diseases with symptoms very similar to CFS



Two points are worthy of special mention. Figure 2 shows the timeline graph from 1800 to the present of diseases with symptomatology very similar to CFS.[23] From this figure, it is clear that CFS is likely not new. Secondly, the information cited here suggests that Chronic Fatigue Syndrome is viewed by many as an infectious disorder, by others as a psychiatric/psychologic problem and finally classified neither of the above. For purposes of this report, it is safe to conclude that not one of the above cited references recognizes the potential role of vitamin C in fatigue. As a matter of fact, we have communicated with experts in CFS.[33,34] From their correspondence, it appears that in their studies vitamin C was not even considered as a possible factor in the syndrome.

Summary and Conclusions

There is the proverbial good/bad news. On the positive side, it is comforting that the ubiquity and devastation associated with fatigue is now being recognized. This is borne out by the fact that the problem has been ordained as Chronic Fatigue Syndrome with its own abbreviation (CFS) and even a special number (780.7) in the International Classification of Diseases. Unfortunately, having pigeonholed the problem has not added to our general body of fact.

The ecology of disease in general (and this clearly applies here) has been ignored. Some of the evidence for multifactoriality are cited in the three forthcoming experiments.

In a study in Glasgow[35] muscular strength was measured by grip pressure and was found to decrease with lower potassium consumption. Approximately half of the participants showed low blood potassium. Twenty-eight subjects[36] complaining of tiredness completed a double-blind cross-over trial of injections of B_{12} (5 mg twice weekly for two weeks) followed by a fortnightly rest period and then a similar course of matching placebo injections. Appetite, mood, energy, sleep and general feeling of well-being were assessed. Conclusion ... significant reduction in tiredness with vitamin B_{12} administration. Approximately 45% of adult male workers[37] on a rubber plantation in West Java (Indonesia) were anemic. Hemoglobin values and performance as measured by the Harvard Step Test (HST) were significantly correlated. Treatment with 100 mg of elemental iron for 60 days resulted in a significant improvement in their performance, work output and morbidity.

Because of its history and subsequent course, we have been particularly concerned with the role of the ascorbates in fatigue. Strangely, in a very recent book on CFS,[38] absolutely no mention is made of vitamin C. The evidence presented here suggests that increased efforts in this area might help clarify this seemingly sovereign syndrome.

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