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On the Genetic Etiology of Scurvy

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It is well known that humans deprived of ascorbic acid will develop scurvy and death will ensue in a few months. In the early nineteen-thirties, ascorbic acid was identified as the antiscorbutic principle in foodstuffs that provided the prophylaxis against this fatal disease. In the two decades prior to the discovery of ascorbic acid, the antiscorbutic factor was considered as some unknown trace substance in foods called « vitamin C ». For hundreds of years before this, it was known empirically that something in fresh vegetation, meat or fish would prevent or cure scurvy.

Scurvy is a very ancient disease; it was mentioned by Hippocrates (Hirsch, 1885) and the Egyptians had several hieroglyphs for writing about the disease (Ebbell, 1938; Bourne, 1944). In the long period of human prehistory and history, scurvy has caused more deaths, created more human misery and has altered the course of history more than any other single cause. As soon as Man or his primitive ancestors left their original tropical or semi-tropical environment and moved to the temperate climes where fresh vegetation was no longer available the year round, they were in trouble. When Man learned to cook his meat and fish, thus reducing its unstable ascorbic acid content, their scorbutic difficulties were further compounded. Each year in the late winter and spring, the whole population, weakened by the annually recurring ravages of scurvy, was decimated by the secondary invading virulent infections and other diseases. It is indeed fortunate for us, the present surviving human population, that the requirements for ascorbic acid for mere survival are low.

Basically, the cause of scurvy is the inability of the human liver to synthesize ascorbic acid. This synthesis is common to nearly all forms of life and is accomplished in the liver of most mammals (Chatterjee *et al.*, 1961). These mammals cannot normally contract scurvy no matter how little ascorbic acid or vitamin C is in their diet. They continually manufacture a steady supply of this important physiological substance in fairly large amounts. Up to 1907 scurvy was considered primarily a human disease because no other animal appeared susceptible to it. In that year it was found that guinea pigs could be made scorbutic (Holst and Frölich, 1907).

The mammalian liver produces ascorbic acid from glucose by a step-wise synthesis, each step being controlled by a separate specific enzyme (Grollman and Lehninger, 1957; Burns, 1959). This complete enzyme system is present in all mammals except

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Man, some monkeys, guinea pigs and an Indian fruit-eating bat, Pteropus medius (Chatterjee *et al.*, 1961). These few exceptions are the only mammals that will develop scurvy if deprived of ascorbic acid in their diet. The disease is rapidly fatal in guinea pigs; they succumb in about two or three weeks.

Man's liver lacks the last enzyme in the series needed to convert glucose to ascorbic acid. The lack of this one enzyme, L-gulonolactone oxidase, completely blocks the synthesis even though the human liver contains the other intermediate enzymes in the series (Chatterjee *et al.*, 1961). The absence of this enzyme is caused by the hereditary lack or defect in the gene required for its synthesis. Thus the syndrome of scurvy is a typical genetic disease similar in etiology to other recognized genetic diseases such as phenylketonuria (PKU), galactosemia, alkaptonuria and the many others in this continually growing list of genetic metabolic anomalies. These genetic diseases are all caused by an inherited defect in the gene which controls the synthesis of the particular enzyme whose absence or lack of activity causes the specific pathologic metabolic syndrome.

While the genetic defect involved in human ascorbic acid synthesis seems to be clearly defined in biochemical genetics, ascorbic acid is still regarded by Medicine as « vitamin C ». I have been unable to find any reference which attempts to change scurvy's present classification as a nutritional disorder or avitaminosis and assign it to its true position as a genetic disease. Because of this current lack of recognition of its genetic status I propose the name, *Hypoascorbemia*, for the genetic scorbutic syndrome, in deference to the generally abnormally low blood levels of ascorbic acid which can exist in the few mammals with this defective gene. Frank scurvy may then be considered as the extreme sequela of hypoascorbemia.

The genetic disease, hypoascorbemia, is of similar etiology to recognized genetic diseases like PKU and the many others with one notable difference in incidence. The other genetic anomalies are of comparatively low occurrence among the human population, while hypoascorbemia seems to afflict all of Mankind. Thus we have here a serious and, up to now, unrecognized genetic disease of apparent universal incidence among humans, which appears to have been only marginally or sub-marginally " corrected " throughout the whole history of Man. The lack of " full correction " of this genetic metabolic anomaly may be a very important factor in the incidence and morbidity of diseases, in the aging process and in the extent of the human life span. The term " correction " means supplying to the individual, ascorbic acid in amounts the liver would be synthesizing were this genetic defect not present. These " correcting " amounts calculated from the scant data available are indicated to be many times those suggested, as adequate, by the vitamin C theory.

The loss of the gene for the synthesis of the active enzyme, L-gulonolactone oxidase, probably took place in some remote Primate ancestor of Man by a conditional lethal mutation (Gluecksohn-Waelsch, 1963), possibly some fifty million years ago. It may be possible to better pinpoint where in Time this mutation occurred if the author's suggestion for examining various members of the Primate order for this enzyme system, is followed (Stone, 1965). The reason that this unfavorable mutation did not eradi-

cate the mutated animals was the presence of small amounts of ascorbic acid in their available foodstuffs, adequate to insure their survival.

Man has suffered from this genetic defect throughout his entire existence and has been absolutely dependent upon his food supply to provide him with marginal amounts of this important physiological substance that his liver fails to synthesize. He was never able to obtain in his foods amounts of ascorbic acid that his liver should have been producing, if we judge this by the amounts synthesized by another mammal, the rat, endowed with the complete enzyme system. The unstressed normal rat synthesizes ascorbic acid at the rate of 70 mg per Kg. of body weight per day (Salomon and Stubbs, 1961) and the stressed rat increases this to 215 mg. per Kg. per day (Conney *et al.*, 1961). This is equivalent to the production of 4.9 to 15.0 gm. of ascorbic acid per day calculated to the 70 Kg. weight of an adult human. Because of the meager amounts of the unstable ascorbic acid in foods, it is just physically impossible to ingest enough weight of food material to supply these gram quantities of ascorbic acid.

This is not the first time that the possible inadequacy of foods for supplying optimal levels of ascorbic acid has been questioned. Bourne, in 1949, noted that for our closest mammalian relatives, the great apes, their chief foodstuff is vegetation. He estimated that a gorilla in its natural habitat consumes about 4.5 gm. of ascorbic acid per day. The gorilla presumably also suffers from the same genetic defect as Man. Bourne also suggested that the currently recommended mg. per day intakes may be wide of the optimal amount and perhaps should be measured in gm. per day instead. He stated " Perhaps it is normal for our blood and tissues always to be saturated with the vitamin and for large quantities to be flushing constantly through our urinary system and excreted in our sweat. We may find that continuous doses of vitamin C at this (high) level over a considerable period of time may have pronounced and unequivocal anti-infective action ".

In the above estimate of ascorbic acid production based on rat data, it is realized that there is a large disparity in body size of rats and humans which may affect the extrapolation. However, this is the only data presently available and sharply points up the need for much more work in the long-neglected area of the quantitative synthesis of ascorbic acid by the larger mammals. If these high figures are valid, then Man throughout his entire existence has been getting along on extremely low quantities of ascorbic acid in contrast to the other mammals. It certainly raises questions as to what has happened to Man's physiology during this long period of time and if he would benefit by being supplied with ascorbic acid in amounts comparable to that produced by other mammals. It also bespeaks well of the ruggedness of human physiology to have been able to adapt to ascorbic acid levels so much below that of the other mammals.

Scurvy has been with us since prehistory but the concept of genetic diseases or the inborn errors of metabolism dates only from 1908 (Garrod, 1908). Over the centuries, there has been a close association of scurvy with the lack of fresh foods, thus the medical profession has long regarded the scorbutic syndrome merely as a

nutritional disturbance. The development of the nutritional sciences in the latter part of the nineteenth century and of the vitamin theory in the early decades of the twentieth century further strengthened the hold of these erroneous nutritional concepts. When they were postulated, these hypotheses seemed to be a clear and logical explanation of the facts available. In the light of our present knowledge, however, there is no reason for continuing the untenable vitamin C theory of the etiology of scurvy whose only justification now is a historical one. If scurvy were a disease only discovered in the last decade there is no doubt that it would have been assigned its rightful place as a genetic disease.

The implications of the fact that the scorbutic syndrome is a genetic metabolic anomaly rather than a nutritional disturbance is much more than a fascinating hypothesis or a mere matter of semantics. The recognition of the genetic etiology of scurvy and the need for supplying ascorbic acid at levels the human liver should be synthesizing would have extremely important consequences in medicine and therapy. At present, Medicine generally regards ascorbic acid not as an important missing endogenous biochemical product that is involved in practically every physiological process of the living organism but instead as vitamin C – merely a specific exogenous nutrient which in trace amounts will prevent or cure scurvy.

The whole field of the therapeutic use of ascorbic acid in many diseases other than scurvy is now dismissed because of the confusing and conflicting clinical results in the thousands of papers published in the last thirty years. The application of these genetic concepts to this vast medical literature brings a measure of order out of the chaos. Most of the clinical investigators reporting in these papers were trained to think of ascorbic acid as " vitamin C " and hence they treated these other clinical entities as if they were scurvy, giving only vitamin-like dosages of mg. per day and they reported poor or indifferent clinical results. A few other workers fortuitously using ascorbic acid in doses of many gm. per day were the ones who were able to report clinical success and even dramatic cures. Unknowingly, these investigators had used ascorbic acid closer to the range occurring in mammalian synthesis and thereby had overcome the hypoascorbemia in their patients. In this manner they maintained physiological responses at optimal levels and were able to take advantage of many of ascorbic acid's unique therapeutic properties. We have been engaged in the preparation of a comprehensive and critical review of the clinical work on the therapeutic use of ascorbic acid in diseases other than scurvy during the past three decades (Stone, in preparation). The results of this survey, to date, support the above thesis.

This genetic concept provides a new rationale for the therapeutic use of high levels of ascorbic acid either alone or in combination with other medicaments, and opens vistas of clinical testing in many areas that have lain fallow in the three decades since the discovery of ascorbic acid. These include areas of such fundamental importance to Man as the infectious diseases, the collagen diseases, cardiovascular conditions, cancer and the aging process. It is hoped that the publication of this paper will stimulate further thinking on this subject and give impetus toward initiating the required clinical research.

Summary

Scurvy, now regarded as a nutritional disorder due to the lack of the trace food constituent, vitamin C, is shown to be the end result of a typical genetic disease. This genetic disease syndrome has been named *Hypoascorbemia.* Its primary cause is the hereditary lack of — or defect in — the gene controlling the synthesis of the enzyme, L-gulonolactone oxidase. This is a mammalian liver enzyme, the last one in the series for converting glucose into ascorbic acid. Man is one of the few mammals that lacks this enzyme and hence is unable to sythesize his own ascorbic acid. The gene defect occurred during the course of evolution by a conditional lethal mutation. The replacement of the present vitamin C theory regarding the etiology of scurvy by this genetic concept gives important new viewpoints to the quantitative aspects of ascorbic acid in human physiology and also provides new rationales for the use of high levels of ascorbic acid in normal physiology and in the therapy of clinical entities other than scurvy.

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— In Preparation. The Application of Modern Concepts of Ascorbic Acid to Health and Therapy.

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RIASSUNTO

Lo scorbuto, attualmente considerato come una malattia alimentare dovuta alla mancanza di vitamina C, viene presentato come risultato ultimo di una malattia tipicamente genetica. Questa sindrome genetica è stata chiamata ipoascorbemia. La sua causa prima è l'assenza ereditaria del gene deputato alla sintesi dell'enzima L-gulonolattossidasi.

Si tratta di un enzima del fegato dei mammiferi, l'ultimo della serie addetta alla conversione del glucosio in acido ascorbico. L'uomo è uno dei pochi mammiferi cui manchi tale enzima, ed è quindi incapace di sintetizzare il proprio acido ascorbico. Il difetto genico è intervenuto nel corso dell'evoluzione a seguito di mutazione.

La sostituzione dell'attuale teoria della vitamina C sull'eziologia dello scorbuto con questa concezione genetica fornisce nuove importanti interpretazioni agli aspetti quantitativi dell'acido ascorbico nella fisiologia umana, ed anche nuove basi per l'uso di alti tassi di acido ascorbico nella normale fisiologia e nella terapia di forme cliniche diverse dallo scorbuto.

RÉSUMÉ

Le scorbut, regardé jusqu'ici comme une maladie alimentaire, due au manque d'un constituant nutritif, la vitamine C, est décrit comme étant la conséquence d'une maladie génétique typique. Le syndrome de cette maladie génétique est connu sous le nom de hypoascorbémie. Il est causé, en premier lieu, par l'absence héréditaire ou le défaut d'un déterminant qui contrôle la synthèse de l'enzyme L-gulonolactone oxydase. Celui-ci est un enzyme du foie des mammifères, le dernier dans une série d'enzymes qui transforment le glucose en acide ascorbique. L'homme est un des quelques mammifères qui manquent de cet enzyme et qui, par conséquent, n'est pas capable de synthétiser lui-même l'acide ascorbique. Ce défaut génétique c'est produit au cours de l'évolution à cause d'une mutation. La substitution de cette conception génétique à la théorie actuelle concernant le rôle de la vitamine C dans l'écologie du scorbut, donne de nouveaux points de vue aux aspects quantitatifs de l'acide ascorbique dans la physiologie humaine, et fournit des raisons nouvelles pour l'utilisation de dosages élevés d'acide ascorbique dans la physiologie normale et dans la thérapeutique des maladies autres que le scorbut.

ZUSAMMENFASSUNG

Der Skorbut, den man zur Zeit als eine durch Mangel an Vitamin-C bedingte Krankheit ansieht, wird hier als Endergebnis einer typischen Erbkrankheit vorgestellt. Dieses Erbsyndrom wird Hypoaskorbinämie genannt. Die Hauptursache dieser Erkrankung ist das erbbedingte Fehlen des Gens, dessen Aufgabe die Synthese des Enzyms L-Gulonolaktoxidase ist.

Dies ist ein Enzym, das sich in der Leber der Säugetiere findet. Es ist das letzte, dem die Verwandlung der Glukose in Askorbinsäure obliegt. Der Mensch ist eins der wenigen Säugetiere, dem dieses Enzym fehlt, und deshalb ist er nicht fähig, seine Askorbinsäure aufzubauen. Dieser Erbfehler hat sich im Laufe der Evolution durch Mutation herausgebildet.

Wenn man die derzeitige Theorie, welche den Mangel an Vitamin-C als Ursache des Skorbut betrachtet, durch dieses neue Erbkonzept ersetzt, so ergeben sich neue wichtige Ausdeutungen in Bezug auf die quantitativen Aspekte der Askorbinsäure und auch neue Basen für die Anwendung hoher Dosen Askorbinsäure in der normalen Physiologie und bei Behandlung der vom Skorbut verschiedenen Krankheitsformen.