The Genetic Disease, Hypoascorbemia

A Fresh Approach to an Ancient Disease and Some of its Medical Implications

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At the present time, the liver enzyme, L-gulonolactone oxidase, is not too widely known and yet this enzyme was involved in what may be eventually regarded as the greatest single physiological and biochemical catastrophe to have happened to Man in the course of Evolution. This enzyme is the final one of a series of enzymes utilized by the mammalian liver to synthesize ascorbic acid from glucose. This biosynthesis of ascorbic acid is a basic and vital process occurring in nearly all living organisms both plant and animal.

In the course of Evolution a Primate ancestor of Man suffered a conditional lethal mutation (Gluecksohn-Waelsch, 1963) on the site of the gene controlling the production of the enzyme protein, L-gulonolactone oxidase, destroying its ability to produce an active enzyme. This mutated animal, and all its progeny carrying this defective gene, were no longer able to synthesize ascorbic acid and made them wholly dependent upon exogenous sources of ascorbic acid for their survival.

After many millions of years Man eventually evolved from this biochemically handicapped animal and present day Man is still afflicted with this genetic defect (Stone, 1965). As far as is known, the whole human race carries this defective gene and it is this inherited defect that sets Man apart, biochemically and physiologically, from nearly all the other mammals.

For the past fifty years, the human need for ascorbic acid has been regarded as a nutritional or dietary requirement for "vitamin C". The fatal disease, scurvy, resulting from complete deprivation of exogenous ascorbic acid, has been considered as a Dietary Deficiency Disease or an Avitaminosis. It has recently been pointed out that this human need for ascorbic acid is the result of a typical genetic disease syndrome due to the inherited lack of the active enzyme, L-gulonolactone oxidase in the human liver (Stone, 1966). Scurvy, then is the extreme sequela resulting from this hereditary metabolic anomaly. The genetic disease has been named, Hypoascorbemia. The concept of the genetic etiology of scurvy provides an important new
outlook and broader perspectives regarding ascorbic acid in quantitative human biochemistry and in human physiology which were completely lacking in the old “vitamin C” hypothesis. Some of the medical implications of this new approach is the subject of this paper.

Man, some monkeys, guinea pigs and an Indian fruit eating bat (*Pteropus medius*) are the only mammals known to be unable to produce ascorbic acid in their livers. These few species are the only mammals that can contract and die of scurvy if deprived of exogenous ascorbic acid. The other mammals all synthesize ascorbic acid in fairly substantial amounts. The inability of the human liver to supply this important, biochemically active secretion places Man’s physiological chemistry on a distinctly inferior level to that of the other mammals. The response of these other mammals to biochemical stress is to increase their production of ascorbic acid to take care of the increased needs, while the response in Man is to further deplete his already low stores of this metabolite. An important factor in maintaining biochemical homeostasis in these mammals is their inborn ability to increasingly produce ascorbic acid under stress.

Over the countless centuries Man’s physiology has become adapted to very low intakes of ascorbic acid because his foodstuffs, even in the best of times, could never supply the amounts of ascorbic acid that his liver should be synthesizing and pouring into his bloodstream. Man was fortunate to be able to obtain milligram amounts of ascorbic acid per day while the synthesis in an equivalent sized mammal would be measured in many grams a day (Stone, 1966). An adult gorilla in the wild state (who had no occasion to adapt to the peculiar human diet) consuming enormous volumes of fresh vegetation has been estimated to get about 4.5 gm of ascorbic acid per day (Bourne, 1949). The gorilla presumably suffers from the same genetic defect as Man.

With the discovery of fire and the development of cooking, the fresh raw meat and fish of Man’s early dietary which were fairly rich sources of exogenous ascorbic acid lost much of this vital substance because of its sensitivity to heat-enhanced oxidation. Dietary inhibitions against eating raw insects and other invertebrates deprived Man of another rich source. Primitive agriculture with its emphasis on the easily storable cereal crops provided foodstuffs essentially devoid of any ascorbic acid. It is mute testimony to the ruggedness and adaptibility of the human organism that Man was able to survive on such low levels of ascorbic acid compared with the amounts produced by other mammals. Survive he did but the toll in disease, misery and death must have been great.

Man’s present physiology thus has accomplished a pretty good job of adapting to conditions of very low intake levels of ascorbic acid without showing symptoms of frank scurvy. This does not mean, however, that all of the many ascorbic acid-dependent biochemical processes are operating at peak, optimal or even marginal levels of efficiency. The human organism can be suffering from biochemical scurvy without showing the signs of clinical scurvy. There is evidence that minimal levels of intake “are not satisfactory for the preservation of optimum health through long
periods of time or when the body is subjected to common forms of stress” (National Research Council, 1964a). And when aren’t humans subjected to stress?

It is interesting, therefore, to speculate (speculate is all we can do because there is no direct information available in the medical literature) as to how the various aspects of Man’s physiology would respond to full “correction” of this long-standing genetic defect. The word “correction” is used loosely and by “correction” we mean supplying ascorbic acid to humans for long periods of time in the amounts that the human liver normally would be producing had this mutation not occurred (cf. Note in bibliography).

The full “correction” of this genetic defect has only been possible in the last thirty years since the availability of pure ascorbic acid in large quantities. It is impossible to establish full “correction” by dependence on foodstuffs as the source of the exogenous ascorbic acid because of the meager amounts present and the physical limitations upon the volumes of food that can be consumed. No one in these thirty years has undertaken a comprehensive program to determine the effects on humans of the long time administration of ascorbic acid in amounts approaching those synthesized by the mammals under normal and stressed conditions. In the thousands of papers that have appeared in the three decades since the discovery of ascorbic acid, there is only scant information on the amount produced in mammalian metabolism. Opinions still differ widely as to the approximately optimal levels of intake for Man (National Research Council, 1964a). On the other hand, a vast literature has developed on finding the minimal intakes of ascorbic acid to prevent the appearance of frank scorbutic symptoms. A substance with such wide and vital functions, in so many biochemical processes of life as ascorbic acid, would appear to be much more useful to Man than just preventing scurvy. About all that this tremendous expenditure of research time in finding minimal levels has accomplished, has been to determine how well human physiology has adapted to its enforced low levels of intake for so long a time.

The false notions and narrow concepts of the “vitamin C” hypothesis, as the dietary cause of the scorbutic syndrome, has dominated medical thinking for so long that it has been a big factor in restricting the pursuit of clinical research with the vigor and depth required. By definition a vitamin is a trace substance in foodstuffs. Most workers in the past thirty years, investigating the therapeutic applications of ascorbic acid to diseases other than scurvy, have regarded it as a trace “vitamin” substance and used it at the trace levels found curative for scurvy. They never attempted administration at the large dosage levels approaching that which the mammals would be synthesizing under comparable conditions of the stresses of pathology. After an extensive review of this medical literature in connection with the preparation of a book on the subject, it is the author’s belief that we have hardly scratched the surface of the potential uses of ascorbic acid in therapy. The lack of consistent and clear cut clinical results in this prior work being due to the investigators concentrating on relieving a trace “vitamin deficiency” and neglecting to give the high dosages of ascorbic acid necessary to maintain continuous supra renal-threshold blood levels

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that might be therapeutically effective. They, of course, did not have the advantage of the logic and rationale for these large doses which are inherent in this new genetic disease concept. Clearly much new clinical work is required in this area but it should now be planned on the broader base that Man is just another mammal and his original optimal biochemical and physiological requirements for ascorbic acid were similar to other mammals.

All our present statistics relating to Man, such as Life Expectancy, the Incidence and Morbidity of Disease is based on data obtained from studies on the so-called “normal” population. However, this “normal” population, in its entirety, has been suffering from this uncorrected genetic disease throughout their lives, the lives of their parents and grandparents and so on. The intake of ascorbic acid by this “normal” population would be grossly submarginal from the standpoint of the genetic disease concept and for a large proportion of the population at some time or other during their lives it would have been considered low even by “vitamin” standards. It has long been known that there is less resistance to infection in the scorbutic state. What, therefore, would happen to the statistics on Disease Incidence and Morbidity and to Life Expectancy in a population where this genetic defect was fully “corrected” continuously from infancy on? Our so-called “normals” may eventually be found to be quite abnormal when compared to a population of fully “corrected” individuals.

We have just mentioned “correcting” the genetic defect from infancy on, but how about “correcting” the defect prenatally? It is now recognized that pregnancy is a biochemical stress requiring more ascorbic acid and under the quantitation of current “vitamin” theory an increase in intake is conservatively recommended of from 70 mg to 100 mg per day (National Research Council, 1964b). Would full “correction” of this genetic disease by administering ascorbic acid to potential human mothers, in the large amounts the mammals synthesize under similar stresses of pregnancy, produce better and healthier babies with less trouble in labor and less chance of miscarriage? It has long been known that scurvy in pregnant guinea pigs produces pronounced deleterious changes in the maternal tissues and in the embryo and causes a high rate of abortions (Harman and Gillum, 1937; Harmon and Warren, 1951; Ingier, 1915; Kramer et al., 1933). Here too, there is much room for more thought and many more tests.

The synthesis of the important tissue protein, collagen, is an ascorbic acid-dependent process. Collagen is a main supportive and structural tissue component and comprises about one-third of the body protein. The derangement of this vital biochemical synthesis by deprivation of ascorbic acid causes some of the most distressing symptoms of scurvy. Submarginal levels of ascorbic acid intake, too high to produce the noxious acute reactions of scurvy but too low for too long to maintain collagen synthesis at optimal levels, may be the trigger that sets off the organism down the path of the collagen diseases - the arthropathies, the rheumatoid diseases and even the aging process; all conditions of biochemical stress in which the bodily requirements for ascorbic acid are increased and the levels usually present are very low.
It has recently been shown (Steven, 1965) that the structure of collagen derived from rheumatoid tissue is different from normal collagen. Full "correction" of this genetic defect, by keeping collagen synthesis and repair at optimal levels throughout lifetime, may produce an organism highly resistant to the rheumatoid disease process. This new concept also provides a basis for a rationale for the therapeutic use of ascorbic acid in these diseases at possibly 25 to 50 gm per day or even higher. While much work has been reported in the last three decades on the therapeutic use of ascorbic acid in rheumatoid conditions at "vitamin" levels without conspicuous success, there has been no clinical work reported where ascorbic acid was consistently used at dosages approaching the levels of full "correction". Only in the area of the viral diseases have doses of ascorbic acid of this magnitude been employed in therapy. While ascorbic acid has long been known as a potent, non-toxic virucidal agent (Amato, 1937; Holden and Molloy, 1937; Holden and Resnick, 1936; Jungeblut, 1935; Kligler and Bernkopf, 1937; Langenbeck and Dnderling, 1937; Lojkin, 1936; Lominski, 1936; Martin, 1940), it was only when tested at doses approaching or exceeding these "corrective" levels, has clinical success been consistently reported (Greer, 1955; Klenner, 1949, 1951, 1952, 1953).

In the aging process, collagen is of prime importance. Being the main supporting tissue protein of the skin, vascular and musculo-skeletal systems, any molecular changes induced in this protein with age would have widespread bodily effects. In work on the physical biochemistry of aging, collagen has responded with a regularity and magnitude not found in other human tissues. On aging, collagen will lose osmotic swelling ability and there will be a resulting alteration of elasticity. The acid solubility of collagen decreases and it becomes more resistant to digestion with collagenase with age (Kohn, 1963). The highest rate of loss of swelling ability of human tendon collagen appears to be at the ages of thirty to fifty years, after maturity is attained. The changes occurring in collagen due to aging have been ascribed to intermolecular cross linking resulting in increased rigidity of the tissues due to the firm association of the constituent molecules. The nature of the cross links in collagen and the agents accelerating the cross linking process are not known. Coenzyme Q or ubiquinone is suspected as being involved in this process (Bjorksten, 1962). This is a naturally occurring long chain, substituted derivative of o-catechol which on oxidation could form cross linking agents. Another cross linking reaction in the proteins is the formation of stable disulfide cross links on the peptide chains due to oxidative combinations of the sulfhydryl groups contained in these chains. Both these oxidative reactions should be inhibited by the continued presence in the tissues of high levels of the strongly reducing ascorbic acid in a fully "corrected" individual, and possibly the concomitant aging effects. In a paper, discussing clinical tests on the inhibition by ascorbic acid of the abdominal striae of pregnancy, because of improved collagen production and maintenance, McCormick (1948) makes the following prophetic statement regarding ascorbic acid, "the young women of today, will be able to have recourse to a veritable internal cosmetic, a dietetic measure, at the same time practical and pleasant, to avoid premature loss of elasticity of their still youthful tissue." A fresh
outlook on aging phenomena is now provided by this genetic concept and the possibility of doing something about it is feasible. For the first time in millions of years, it is possible to fully “correct” this genetic defect.

Hemorrhage has long been considered a pathognomonic sign of scurvy. This is another result of disturbance in the ascorbic acid-dependent collagen synthetic system producing defective structural tissue protein in the vascular system. Full “correction” should produce a human whose arterial, venous and capillary systems are second to none in mechanical strength and resistance to the physical stresses of blood flow and thus be less prone to mechanical and chemical damage and hemorrhaging. Long term “correction” of this genetic disease by administration of necessary large levels of ascorbic acid throughout life, may have some startling effects on the incidence of heart disease, cardiovascular conditions and strokes.

In cancer, the maintenance of collagen synthesis at optimal levels, may provide such tough and strong tissue ground substance around any growing cancer cells so that they would be firmly anchored and could not break away and metastasize (McCormick, 1954, 1959). In addition, ascorbic acid has potent detoxicating effects and at the high levels of intakes for “correcting” the genetic defect there could be definite inhibition of the action of carcinogens on tissues (Warren, 1943). The mammalian reaction to exposure to carcinogens is to increase the synthesis of ascorbic acid (Boyland and Grover, 1961), while in Man the stresses of cancer induces large deficits in ascorbic acid levels (Antes and Molo, 1939; Gaehgens, 1938; Griebel, 1939; Kudlac and Storck, 1938; Schneider, 1938; Spellberg and Keeton, 1939; Vogt, 1939). Provocative results have been reported in clinical tests on the use of ascorbic acid in cancer but the investigators never administered more than a gram or two a day. While this amount would relieve a “vitamin” deficit, it would be much below the level required to “correct” the genetic defect. These workers did not give ascorbic acid in amounts approaching that which the mammals would be synthesizing under equivalent stresses and thus never reproduced the typical mammalian biochemical response in their patients. Cancer therapy is still another area where the application of these new genetic concepts of ascorbic acid provides clearer insights and new rationales for programs of clinical testing, using massive daily doses.

These are but a few of the many possibilities derived from the logic of the concept of the genetic etiology of scurvy and the human need for ascorbic acid for the maintenance of biochemical homeostasis. The discussion has been limited mainly to only one of the biochemical systems in which ascorbic acid is intimately involved. The treatment has been necessarily brief because of the survey nature of this article which has been written mainly to stimulate thinking along these lines. The author will treat these and other diseases in greater depth in a book now in preparation.

In any proposed clinical testing of these “corrective” doses, there is an additional “dividend” that should be mentioned and that is, that these doses can be administered without danger to the participants. Ascorbic acid is probably the least toxic of any known substance of comparable physiologic activity (Abt and Farmer, 1938;
Cass et al., 1954; Demole, 1934; Kieckebusch, 1963; Lamden and Schweiker, 1955; Lowry et al., 1952). The administration should be in spaced doses throughout the day to duplicate as far as possible its continuing synthesis in the mammalian liver. It can be given both orally and intravenously (neutralized to the proper pH). There is a good evolutionary reason for this complete lack of toxicity. Living organisms have been exposed to fairly high levels of ascorbic acid throughout eons of Time, if this can be judged from its widespread occurrence in all forms of present day life from the simplest to the most complex. If ascorbic acid had any toxicity that would have been detrimental to survival, it would have been eliminated long ago by the evolutionary process.

It is hoped that the publication of this paper will trigger much wider and deeper thought in the above and other areas of Medicine. Especially, the recognition of the fact that the general mammalian reaction for maintaining homeostasis under biochemical stress, by increasing available ascorbic acid, is also applicable to Man. Exogenous ascorbic acid should not be merely presumed a limited trace-level nutritional specific for scurvy. The maintenance at optimal efficiency of many long-term biochemical reactions in human physiology may require ascorbic acid in the large amounts produced in the other mammals.

Note

The author has been consistently ingesting, at least, 3 to 5 gm of ascorbic acid daily for the past 10 years (his estimate of the amount the adult human liver should be synthesizing under unstressed conditions). Under conditions of stress (severe injuries from a near fatal auto accident) this was increased to 20 to 40 gm a day for several months. During this decade he has suffered no other illness (not even a common cold) and has otherwise enjoyed vibrant health.

Summary

It has been recently shown that the human requirement for exogenous ascorbic acid and the disease, scurvy, are the result of a typical genetic disease syndrome caused by a defect on the gene controlling the synthesis of the enzyme protein, L-gulonolactone oxidase. The lack of this active enzyme in the human liver prevents Man from producing his own ascorbic acid; a synthesis which is regularly carried out by nearly all other mammals. This genetic disease has been named, Hypoascorbemia. This new concept of the genetic etiology of scurvy gives a much broader outlook and opens perspectives which were lacking in the previous fifty year old nutritional or trace "vitamin C" hypothesis. "Correction" of this genetic defect in Man is now possible since the availability of ascorbic acid in large quantities. By "correction" is meant the long-term administration of ascorbic acid in the large amounts the human liver would be synthesizing had this genetic defect not occurred. The mammals have long used the increased liver biosynthesis of ascorbic acid, under stress, to maintain homeostasis. The genetic defect prevents Humans from utilizing this important mammalian biochemical protective mechanism. Supplying exogenous ascorbic acid

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at the proper high dosage for full "correction" is merely duplicating a normal mammalian reaction. The medical implications of the full "correction" of this genetic disease are discussed and speculations on the effects of "correction" in the rheumatoid diseases, cardiovascular conditions, strokes, cancer and the aging process are extrapolated from the meager data already in the medical literature. This paper is mainly a plea for more thought along the medical possibilities opened by this new concept and for more clinical tests based on the rationales derived from the genetic disease viewpoint.

**Literature**


**HOLDEN M., MOLLOY E.** (1937). Further experiments on inactivation of herpes virus by vitamin C. *J. Imm.,* **33**: 251.


È stato recentemente dimostrato che il fabbisogno umano di acido ascorbico esogeno e lo scorbuto sono il risultato di una sindrome tipicamente genetica, causata da una mutazione a livello del gene deputato alla sintesi dell’enzima L-gulonolactossidasi. La mancanza di questo enzima attivo nel fegato umano impedisce all’uomo di produrre il proprio acido ascorbico — una sintesi che viene regolarmente effettuata da quasi tutti gli altri mammiferi. La malattia genetica è stata chiamata ipoascorbemia. Questo nuovo concetto dell’eziologia genetica dello scorbuto è molto più vasto ed apre prospettive assolutamente nuove rispetto alle vecchie teorie nutrizionistiche e della vitamina C. Oggi è possibile « correggere » questo difetto genetico nell’uomo, data la notevole disponibilità di acido ascorbico. Per « correzione » si intende la prolungata somministrazione di acido ascorbico in quelle larghe quantità che il fegato umano avrebbe sintetizzato se tale difetto non avesse avuto luogo. Sotto sforzo, i mammiferi usano l’accresciuta biosintesi di acido ascorbico per mantenere l’omeostasi. Il difetto genetico impedisce all’uomo di utilizzare questo importante meccanismo protettivo biochimico dei mammiferi. Somministrando acido ascorbico esogeno nel dosaggio elevato necessario per una completa « correzione » si riproduce una reazione normale dei mammiferi. Vengono discussi gli aspetti medici della completa « correzione » di questa malattia genetica, estrapolando dai pochi dati disponibili della correzione in malattie reumatoidi, condizioni cardiovascolari, infarto, cancro e processi di invecchiamento. Questo lavoro vuole fondamentalmente richiamare l’attenzione sulle possibilità mediche che questo nuovo concetto fa intravedere e sulla necessità di più test clinici basati su analisi ragionate dal punto di vista della genetica medica.
On a montré récemment que les demandes humaines en acide ascorbique exogène et le scorbut sont le résultat d'un syndrome typique de maladie génétique causé par un défaut du gène contrôlant la synthèse de la protéine enzymatique, l'oxydase L-gulonolactone. L'absence de cet enzyme dans le foie humain empêche l'homme de produire son propre acide ascorbique; cette synthèse est produite normalement par presque tous les autres mammifères. Cette maladie génétique a été nommée hypoascorbémie.

Ce nouveau concept de l'étiologie génétique du scorbut donne une vue d'ensemble plus pénétrante et ouvre des perspectives plus vastes qui manquaient à l'hypothèse « Vitamine C » pendant les dernières 50 années.

Il est possible, maintenant, de « corriger » ce défaut génétique de l'homme, grâce aux grandes quantités d'acide ascorbique disponible. « Corriger », veut dire prescrire, pendant des périodes prolonguées, les quantités considérables d'acide ascorbique que le foie humain aurait synthétisé si ce défaut n'aurait pas survenu.

Les mammifères ont utilisé depuis longtemps l'augmentation de la biosynthèse de l'acide ascorbique par le foie, pour maintenir, sous tension, l'équilibre homéostatique. Le défaut génétique empêche les êtres humains d'utiliser cet important mécanisme biochimique de protection. Fournir l'acide ascorbique exogène dans les quantités élevées nécessaires pour la « correction » complète, n'est que reproduire les réactions normales des mammifères. Les implications médicales de la « correction » de cette maladie génétique ont été discutées et les effets des « corrections » dans les maladies rhumatoïdes, cardio-vasculaires, apoplexie, cancer et le processus de vieillissement ont été extrapolés des quelques données existant déjà dans la littérature médicale. Cet article est principalement un appel pour attirer l'attention aux possibilités médicales mises à découvert par ce nouveau concept et aussi pour induire une augmentation du nombre d'expérimentations cliniques basées sur une analyse raisonnée du point de vue des maladies génétiques.

ZUSAMMENFASSUNG

Es wurde kürzlich bewiesen, dass der menschliche Bedarf an exogener Askorbinsäure sowie der Skorbut die Folgeerscheinungen eines typischen Erbsyndroms sind, welches durch eine Mutation bei dem Gen bedingt wird, dem die Synthese des Enyzms L-Gulonolaktosidase obliegt.

Das Fehlen diesen aktiven Enzymes in der menschlichen Leber hindert den Menschen daran, selbst Askorbinsäure zu produzieren—eine Synthese, welche fast alle anderen Säugetiere regelmäßig vollziehen. Die Erkranckheit wurde Hypoaskorbämie benannt. Dieses neue Konzept in Bezug auf die Erbtiologie des Skorbutes ist viel grosszögerig und öffnet ganz andere, völlig neue Perspektiven als die alten ernährungswissenschaftlichen und Vitamin-C-Theorien.

verabfolgen, bedeutet also, eine normale Reaktion der Säugetiere nachzuahmen.

Es werden dann die medizinischen Aspekte der vollständigen "Korrektion" dieser Erkrankheit erörtert. Dabei werden auf Grund der wenigen Angaben aus der medizinischen Literatur Vermutungen über die Wirkung der Korrektion bei den rheumatoiden Erkrankungen, bei den verschiedenen Herz-Kreislaußbedingungen, bei Infarkt, Krebs und den Altersprozessen angestellt.

Der Hauptzweck dieser Arbeit ist es, die Aufmerksamkeit auf die Möglichkeiten zu lenken, welche dieses neue Konzept der Medizin eröffnet und auf die Notwendigkeit, mehr klinische Tests auszuführen, die sich auf vom medizingenetischen Standpunkt überdacht Analysen stützen.