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Vitamin C and wound healing

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VITAMIN C AND WOUND HEALING

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INTRODUCTION

The concept of the relationship between vitamin C and wound healing has been known since the time of Hippocrates, yet only in relatively recent years has the theory been brought into practice. Previously, the relationship between vitamin C and wound healing was known through clinical observation but the method of action was unknown. The cases observed were true clinical scurvy and not the latent type of scurvy which appears to be more prevalent today.

The object of this thesis is to evaluate the clinical and experimental material on vitamin C as concerned with wound healing with the hope that the data and information thus brought into strong focus will be useful.

The subject matter of this thesis has arbitrarily been divided into two sections. The first section deals with a general resume of the history, chemistry, physiology, and pathology of vitamin C as related to wound healing. The second section contains experimental and clinical evidence of the action of vitamin C on wounds.

PART I

HISTORY

The earliest account of vitamin C deficiency appeared at the time of Hippocrates and Pliny at which time scurvy was discussed as a clinical entity of unknown etiology. At this time scurvy was widespread and appeared as outbreaks following wars and in congested areas. Richard Walters described scurvy in his narration of Lord Andson's, "Voyage Around the World," in 1740. "Scars of Wounds that had been for many years healed were forced open..... one of the invalids....who had been wounded fifty years before... and had continued well for a great number of years past, yet on his being attacked by scurvey, his wounds in the progress of the disease broke out afresh and appeared as though they had never been healed." (Vedder 1921)

In the Medical and Surgical History of the War of the Rebellion mention was made of the relationship between wound healing and scurvy in a description of the clinical picture of scurvy. "This was further manifested by the indisposition of wounds to heal, slight scratches becoming converted into indolent

ulcers or affected with erysipelas of gangrenous inflammation....Doctor Jones refers to the ulcerations induced among the prisoners at Andersonville by slight injuries as the prick of a splinter or the scratching of a mosquito bite." (Wolfer and Hoebel 1939)

The relationship between scurvy and wound healing was also noted at the time of the Civil War between the states. In 1866 Eve stated in the Nashville Journal of Medicine and Surgery, "It certainly did complicate wounds and seriously interfered with surgical operations and was itself aggravated by erysipelas, syphilis, spurious vaccination. Secondary hemorrhage became more frequent from wounds and operations after the battles of Chickamauga and Missionary Ridge, September and December 1863; attributable justly to the increased scorbutic tendency in the soldiers as the war progressed." (Wolfer and Hoebel 1939)

Probably the earliest record of the application of vitamin C for treatment of scurvy was back in the fourteenth century when Jacques Cartier in 1535 described a disease similar to scurvy which was cured by a decoction made of the bark and needles of the spruce tree. In 1734 Bachstram advised fresh green vegetables as a protection against scurvy. (Dubnove 1938) In 1757

James Lind prepared the first detailed account of the disease and presented the paper as a "Treatise on Scurvy." He also advocated the use of lemon juice as a preventive measure for scurvy. (Eddy and Dalldorf 1941) In 1907 Holst and Frohlich noted the development of scurvy in guinea pigs when placed on certain diets. The possibility that scurvy was a result of an avitaminosis was then recognized. (King 1939)

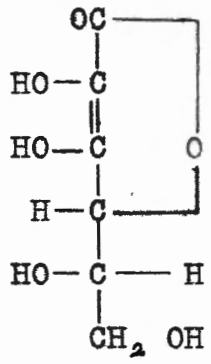
In 1928 Szent-Gyorgyi isolated a substance from the adrenal cortex which was found to be a highly reducing hexose derivative. To this substance he gave the name hexuronic acid. By 1931 King and Waugh had succeeded in isolating vitamin C by fractionation of lemon juice. Following their report that vitamin C had antiscorbutic properties Svirbely and Szent-Gyorgyi reported that the material that he had isolated from the adrenals also had antiscorbutic properties. Following these observations it was established that the products obtained from the adrenal in one case and from the lemon juice in the other were identical. (King 1939)

One of the first experiments to show the relation of vitamin C to wound healing was accomplished in 1923 by Ishida who observed a delayed healing of wounds in

scorbutic guinea pigs. This was confirmed by Saitta in 1929 who likewise observed retarded healing of wounds in guina pigs which were fed on a vitamin C deficient diet. He also noted that if extracts of vitamin C were placed on the wound the rate of healing increased irrespective of whether the test animal was in a state of scurvy or not. (Bourne 1942)

CHEMISTRY

Vitamin C has been shown to be closely related to hexuronic acid and according to Hirst it has the following structural formula



The physical form of vitamin C consists of dense radiating clusters of colorless crystals having a melting point of 192 degrees centigrade; a specific rotation of + 24, and an acidic dissociation pK of 4.17. In the dry state the crystals are quite stable.

In solution, however, oxidation readily takes place. Two steps are involved in the oxidation of vitamin C by air; the first of these consists of l-ascorbic acid being oxidized to dehydro-ascorbic acid and is reversible. The second step consists of a breakdown of dehydro-ascorbic acid to oxalic and threonic acids. The oxidation reaction may be speeded up by adding traces of copper. (King 1939) Vitamin C also has the property of becoming hygroscopic when combined with any of many poorly soluable substances. (Ruskin 1944)

Vitamin C concentration may be determined by titrating against an indicator, 2,6, dichloro-phenol-indophenol which is quantitatively reduced by vitamin C in acid solution to form a colorless compound. (King 1939)

The exact relationship of vitamin C to the formation of normal connective tissue is unknown but it is suspected to play some part in the change of pre-collagen to mature collagen. Schmidt in 1939 observed that collagen fibers are made up of longitudinally orientated polypeptide chains. It is also believed that the chains are bound together by side chain linkages. Possibly, vitamin C has some effect on the attachment of these side chains, the length of which

determines the strength of the fiber.

The theory is held that vitamin C serves primarily as a respiratory catalyst, or hydrogen-transport agent, but evidence is lacking in support of the theory. The fact that scorbutic tissues does not show a reduction in respiratory activity is a strong point against the theory. (King 1939)

Further suggestion for the relationship of vitamin C to the production of mature collagen may be brought out by the fact that the molecular structure of vitamin C closely resembles that of a hexose sugar. Hexose sugars have been found in the collagen fiber. (Bourne 1942)

PHYSIOLOGY

Vitamin C is essential for proper maintainence of body function and since man is unable to synthesize the vitamin, he must acquire it by way of outside sources. Vitamin C appears to be selectively absorbed by the small intestine and in turn is carried to the various tissues by the blood. It is found throughout the body but in general it is present in higher concentrations in the tissues having a high metabolic rate.

The following tissues are in the order of decreasing concentration of vitamin C: pituitary body, corpus luteum, adrenal cortex, young thymus, liver, brain, testes, ovaries, spleen, thyroid, pancreas, salivary glands, lung, kidney, intestinal wall, heart, muscle, spinal fluid and blood. (King 1939)

There appears to be a direct relationship between the intake of vitamin C and the urinary output. It has been shown that there is a diminished urinary excretion of vitamin C when the dietary intake is deficient. It has also been noted that when vitamin C is initially administered to a patient with a vitamin C deficiency, the tissues are first restored to their normal content before urinary excretion begins. This is a useful test to determine the degree of vitamin C deficiency or to determine the amount of vitamin C used in the body daily. This value apparently varies considerable with different persons but may be estimated to fall in the range of from 25 to 50 milligram daily. (Harris and Ray 1935)

The average content of the blood plasma is approximately 1.2 milligrams of vitamin C per one hundred cubic centimeters. Depletion reduces this to approximately 0.8 milligrams per cent as the prescorbutic

state is reached and to approximately 0.5 milligrams per cent with the appearance of clinical scurvy (King 1939) These findings have been confirmed by other investigators who consider the tissues to be saturated if the blood values range from 0.6 milligrams per cent or higher; that a prescurvy condition exists, in which failure of wound healing may occur, when the blood values range from 0.1 milligrams per cent to 0.6 milligrams per cent; and that scurvy is present and failure of wound healing is likely when the blood values range from 0.0 milligrams per cent to 0.2 milligrams per cent. (Wolfer and Hoebel 1939)

Experiments demonstrating a relationship between vitamin C and wound healing began in 1919 when Aschoff and Koch reported changes in animals with scurvy which they described as resulting from a lack of intracellular cement substance. (Hartzell 1942) It was then observed that in the absence of vitamin C, the skeletal structures formed a fluid phase and with the addition of vitamin C there was a prompt return of the fluid phase to the normal phase. (Wolbach and Howe 1926) Previous to this Hojer in 1924 noted a decreased amount of collagen in guinea pigs having scurvy. (Bourne 1942) In 1936 Jeney and Toro found that if

they added vitamin C to a culture of fibroblasts there was an increase in the production of fibrills. (Lanman and Ingalls 1937) It was then demostrated that in an absence of vitamin C the development of mature collagen fibers was delayed although the reticular or precollagen fibers continued to develop. Furthermore, the mature collagen fibers appeared to regress to the immature form. (Hunt 1941)

Two theories have been proposed to explain the action of vitamin C in connective tissue formation. The first of these is the theory previoulsly mentioned and brought out by Wolbach and Howe in 1926. They believed vitamin C was necessary to bring about the change of connective tissue from the fluid to the normal phase. (Bourne 1942) The second theory, elaborated by Fish and Harris in 1934 and Ham and Elliot in 1938, proposes that a deficiency of vitamin C results in a change in the metabolism of the fibroblast which is responsible for the production of the collagen fiber. Neither of the theories have been definitely proven but most workers are of the opinion that the second theory is more plausible.(Bourne 1942)

It appears that vitamin C is also related to calcium metabolism. Experiments have indicated that

vitamin C promotes phosphatase activity and may aid in precipitation of the bone salts. (Bourne 1942) Other workers have noted that decalcification is often associated with a vitamin C deficiency. Since the decalcification involves predominately the neck of the femur, this observation may aid in explaining some of the decalcifications of obscure origin in that region. (Mouriquand and Dauvergne 1940) It is also believed that a synergistic action exists between ascorbic acid and the parathyroid hormone and that vitamin C is especially related to the organic calcium metabolism. (Giangraso 1939) Vitamin C also promotes activity of the fibroblast cell and makes possible its differentiation into the osteoblast. (Bourne 1942)

With altered metabolic activity of the body there is also some alterations in the metabolism of vitamin C. In 1937 Lauber, Bersin and Naffiger found a decrease in the urinary output following the use of an anesthetic. This finding was quite constant irrespective of whether a local or general anesthetic was used. In 1938 Griebel found negative balances of vitamin C after surgical operations and also in febrile diseases. (Lund 1939) It had also been observed in test animals that following a wound a decreased con-

centration of vitamin C in the blood occurs but that the concentration of vitamin C surrounding the wound is increased. (Lauber and Rosenfeld 1938)

In 1939 Dellie and Zilva pointed out that to completely saturate the tissues in a human, 30 to 40 milligrams of vitamin C daily were required. It has also been demonstrated that tissue saturation is not necessary for complete physiological activity of the tissues, but there is a probability that smaller wounds require less vitamin C then larger wounds for proper healing. (Bourne 1944) Other investigators have shown that 80 to 100 milligram of vitamin C daily is necessary for saturation of the tissues and 18 to 25 milligrams daily of vitamin C is adequate for maintaining proper tissue metabolism as far as vitamin C is concerned. (Pizoon and Lozner 1944)

PATHOLOGY

The primary effects of vitamin C deficiency occur in those supporting structures which are of mesenchymal origin. Histologically, the change seen is a lack of mature collagen fibers in the ground substance.(Wolbach

and Howe 1926) Histological studies of bone in animals on a completely deficient vitamin C diet demonstrated a failure of the cells in the cambial layer of the periosteum to multiply and a failure of the fibroblasts to migrate to a site of injury. There was also a decrease in the inflammatory response of the tissue. (Bourne 1942) In partial deficiency there is a tendency for collagenous material to form instead of osteoid. (Dalldorf 1938) McLean in 1939 noted a delay in the transformation of osteoblasts from fibroblasts. (Bourne 1942) Furthermore rarefaction in the cortex of the bone and replacement by collagen connective tissue has been found. This suggests that in the absence of vitamin C the osteoblasts are unable to form bone or they fail to develop and the fibroblasts attempt to carry on the construction of bone by forming a fibrous union. (King 1939) Subsequently it was observed that not only was there an inhibition of the growth and activity of the fibroblast but also a decrease in the phagocytic activity. (Hunt 1941)

PART II

EXPERIMENTAL EVIDENCE OF THE EFFECT OF VITAMIN C DEFICIENCY ON WOUNDS

In 1937 Lanman and Inglas demonstrated a direct relationship between vitamin C concentration and wound healing. They selected 24 guinea pigs and divided them into two groups, one of which received a diet deficient in vitamin C and the other, a diet adequate in all respects. Incisions were made upon the abdominal wall which were carried on through the wall of the stomach. The animals were sacrificed on the tenth, twentieth, and thirtieth days. Air was injected into the peritoneal cavity and the pressure necessary to rupture the wounds in the stomach and abdominal wall was noted. Pressure measurements were made with the aid of a mercure sphygmomanometer. They observed the wounds in the guinea pigs on a scorbutogenic diet ruptured at about one third the pressure required to rupture the wounds in the control animals. Normally, a wound is expected to attain the greater part of its strength in ten days, however, in scorbutic animals a longer period was necessary. Histological studies of the wounds in the scorbutic animals revealed defective

repair of the corium and poor collagen production. (Lanman and Ingalls 1937)

A study of the relationship between vitamin C deficiency and the healing of bones was reported by Lexer in 1939. Experimental fractures in guinea pigs were studied, one group of which received a diet deficient in vitamin C and the other group, a normal diet. In the normal course of healing hyperemia was present from the sixth day on. Callus formation also began on the sixth day and proceeded to the twelfth day, at which point it reached its strongest formation. This callus formation persisted until the sixteenth day at which time it began to decrease and the process of ossification began. The process of ossification was complete on the twenty-sixth to the twenty-ninth day. In the animals receiving the vitamin C deficient diet, however, it was observed that even after twelve days following the fracture, the bones were unstable and the callus formation small. Between the twenty-first and the twenty-third day the callus began to soften and appeared to be jelly like in consistency. In another group of test animals he was able to return the callus formation to its normal course by adding vitamin C to the diet. This was true in all cases in which the fracture

had not been inflicted past the twenty-second day on the deficient diet. After the twenty-second day, addition of vitamin C failed to restore the healing process to normal. (Lexer 1939)

Experiments pertaining to the relationship between vitamin C, parathyroid glands and the healing of experimentally produced fractures in guinea pigs were presented by Giangrasso in 1939. The experiments were carried out on thirty-six adult rats which were kept in the same envirement prior to the time of the experiment. The animals were divided into six groups of six each. Both bones were broken in the right fore leg of each animal at the time the experiment began. The first group served as controls. The second group was given 5 milligrams of vitamin C every three days. The animals in the third group were subjected to an operation in which the thyroid and parathyroid glands were removed. This group,likewise, received 5 milligrams of vitamin C every three days. The animals in the fourth group were subjected to the fracture, thyroidectomy and parathyroidectomy, but received 10 milligrams of vitamin C instead of 5 milligrams every three days. The animals in the fifth group were subjected to the same treatment as the fourth group, but they received 15 milligrams of

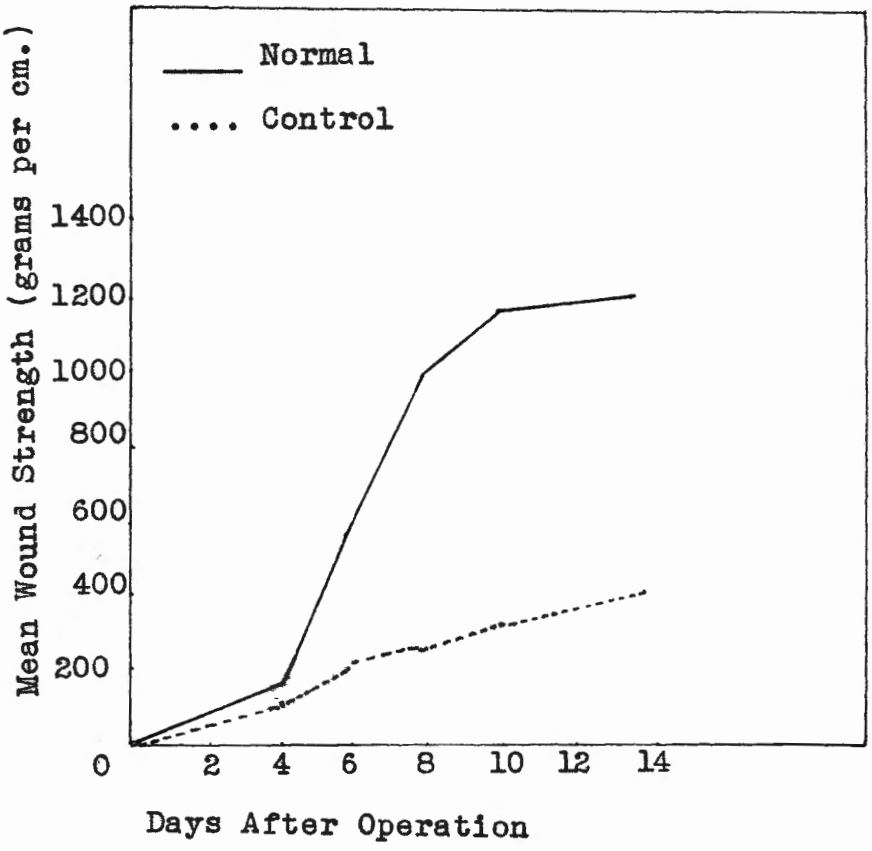
of vitamin C every three days. The animals in the sixth group were subjected to the fracture, thyroidectomy and parathyroidectomy but were denied vitamin C. The sixth group served as controls. One animal from each group was sacrificed after 10, 15, 20, 25, and 30 days, respectively. The last group of animals were sacrificed on the fortieth day. Examination revealed healing of the fractures in all groups with the exception of the sixth which had received no vitamin C. This group showed a lack of consolidation even though the position was good. It was concluded that healing of fractures was possible even though the thyroid and parathyroid glands had been removed provided vitamin C was administered. The rate of healing was some what delayed in those rats having the thyroidectomy and parathyroidectomy; however, with the administration of vitamin C there was a prompt increase in the rate of healing. (Giangrasso 1939)

In 1941 Bourne revealed the fact that if guinea pigs with fractured femurs were placed on a vitamin C deficiency diet, healing was retarded. If vitamin C was then given the degree of healing was proportional to the amount of vitamin C given. (Bourne 1942)

A study by Hartzell in 1942 demonstrated that

vitamin C is a definite factor in determining the tensile strength of wounds. Two groups of guinea pigs were chosen for the experiment. One group was fed a scorbutogenic diet and the other group, a normal diet. Incisions were made in the abdominal wall and the animals were sacrificed four, six, eight, ten, and fourteen days later. Blood was obtained at the time the animals were sacrificed and vitamin C and blood proteins were determined. The plasma protein levels were 4.63 grams per one hundred milliliters in the control animal and 4.55 grams per one hundred milliliters in the deficient animal, a difference small enough to be insignificant as far as wound healing and tensile strength are concerned. Strips were cut from the belly wall of the animals at the site where the incisions were previously made. Weights were applied to the strips and the tension necessary to pull the edges of the wound apart was noted. Observation of those animals kept on a subscurvy diet revealed a decrease in the tensile strength of their wounds of approximately one-half normal on the sixth postoperative day and approximately one-quarter normal from the eighth through the fourteenth day. The following graph illustrates the relative relationship of tensile strength of wounds of test animals of a

vitamin C deficient diet as compared with the normal wound strength.



Furthermore, it was noted that if high dosages of vitamin C was given to guinea pigs operated in the subscurvy state the wounds reached the same tensile strength by the eight postoperative day as the normals. The healing

of the abdominal incisions in the normal guinea pigs was quite rapid and appeared well healed by the sixth day. From the tenth to the fourteenth day the incision was completely healed and appeared white and smooth. Those on a vitamin C diet revealed a hard raised scar which showed edema and redness on the fourteenth day. Histological sections of the wounds in the deficient animals showed an absence of mature collagen fibers with collections of serum, red and white blood cells. Hemorrhagic effusions were a constant finding in all of the deficient animals. It was concluded that the low tensile strength of the wounds of partially vitamin C deficient animals was due to a failure of collagen production. (Hartzell 1942)

In 1942 Bartlett studied the effect of vitamin C content in tissues and its relationship to the tensile strength of wounds. Four groups of guinea pigs were studied which are as follows: Group one consisted of those animals on a preoperative and a postoperative scorbutic diet. Group two consisted of those animals on a preoperative and postoperative high vitamin C diet. Group three consisted of those animals on a preoperative scorbutic diet and a postoperative high vitamin C diet. Group four consisted of those animals on a preoperative high vitamin C diet and a postoperative

scorbutic diet. In each of these groups the vitamin C content in the various tissues were studied. The scars of animals receiving 33 mg. of vitamin C twice daily had an average of 7.64 mg. of vitamin C per one hundred grams of tissue and burst at a pressure of 258 mm. of mercury. In guinea pigs on a scorbutic diet the vitamin C content of the scars averaged 0.31 mg. per one hundred grams of tissue and burst at a pressure of 127 mm. of mercury. He concluded that vitamin C has a direct relationship to the tensile strength of the wounds. (Bartlett 1942)

The results obtained from the experiment of Bartlett were confirmed by Zerbini in 1943. The strength of experimentally produced scars of guinea pigs with scurvy were measured and compared with guinea pigs on a normal diet. Elevation of intra-abdominal pressure was the method used to determine the strength of the scar. It was noted that five times more pressure was required to rupture the scar in control animals than in animals with experimental scurvy. (Zerbini 1943)

The evidence presented is quite conclusive that a deficiency of vitamin C is related to delayed wound healing and to decreased tensile strength of the wound during the process of healing. In all of the experiments the test animals were either in a state of frank

scurvy or they were recovering from the condition. It would be interesting to see the results of such experiments when the test animals were kept on a partially deficient vitamin C diet for a long period of time as is seen with asymptomatic scurvy in humans. The next problem arising is whether the human and the guinea pig react the same, as far as wound healing and tensile strength is concerned, in a vitamin C deficient diet.

CLINICAL EVIDENCE OF THE RELATIONSHIP BETWEEN VITAMIN C AND WOUND HEALING

Only in relative recent years has the term asymptomatic scurvy been brought into practice. It has been defined as follows: "Scurvy existing in a patient without characteristic symptoms, physical signs or roentgenologic evidence during life, but in whom the histological changes of early scurvy are demonstrable at autopsy. (Lanman and Ingalls 1938)

In 1928 Hans Aron noted that in children with scurvy there was a tendency for their wounds to heal slowly. It was likewise observed that following therapy for their scorbutic condition their wounds promptly healed. (King 1939)

In 1941 Lund and Crandon studied the effect of prolonged vitamin C deficiency in the human. The experiment consisted of placing a subject upon a complete scorbutogenic diet and noting the effect the diet had upon the healing of wounds experimentally inflicted. They found that scurvy could be produced in approximately five to six months if the patient was kept on a completely deficient vitamin C diet. At the third month an incision was made going down to the deep fascia of the back and at six months an identical incision was made through the skin and down to the deep fascia of the back. The wound healed well after the subject had been on a scorbutic diet for three months, but after six months on this diet the wound failed to heal. The vitamin C content of the plasma was found to fall to zero in forty-two days, likewise the white cells fell to zero in one hundred and twenty-two days. They concluded that a moderate deficiency in vitamin C reserves did not effect the healing of an experimentally wound inflicted in a human. This observation was based on the fact that wound healing was normal even though the blood plasma vitamin C had been zero since the forty-second day. They did note a high percentage of postoperative hernias in patients having

had biliary surgery in the presence of low vitamin C levels. (Lund and Crandon 1941)

Bartlett in 1941 studied the effect of low vitamin C concentration in blood plasma and its relation to the tensile strength of fascia in patients with hernias. Fascia, skin and blood were taken at the time of operation and vitamin C determinations were made. Ten days later fascia and skin were taken from the same area of operation and the tensile strength was determined. They noted that the fasting plasma level must remain below 0.20 milligrams per one hundred cubic centimeters of plasma before significant changes occured. Low vitamin C levels definitely led to decreased tensile strength in both skin and fascia. When vitamin C was administered postoperatively the fascia responded to normal vitamin C levels much more rapidly then did skin. Vitamin C was found to be quite important postoperatively and wound healing progressed satisfactorily in spite of low vitamin C levels at the time of operation, provided vitamin C was given postoperatively. (Bartlett 1941)

A case reported by Housel in 1942 revealed a failure of healing following a laryngectomy for carcinoma. During this period in which the wound failed to heal the patient developed symptoms of scurvy but upon the

addition of orange juice to the diet the wound properly healed. (Housel 1941)

In 1944 Pijoon and Lozner observed a patient placed on a vitamin C deficient diet until there was a linear decline in the vitamin C concentration of the white blood cells. There was no scorbutic manifestations or failure of experimental wounds to heal after twenty-one months on this diet. (Pijoon and Lozner 1944) This observation was confirmed by Williams and Bissell in 1944 in which they found vitamin C concentration to have no effect on the strength of the wound nor upon the histological structure of the wound. (Williams and Bissell 1944)

Zerbini stresses the fact that good scar formation is necessary for proper results in chest surgery. It is his opinion that a normal concentration of vitamin C in the blood and tissues is vitally important for good scar formation. He states that the chest condition is often responsible for the low vitamin level and the operation per se is partially a cause of the low vitamin concentration. He maintains normal levels in his patients by giving 1000 milligrams of vitaminC every twenty-four hours pre and postoperative.

In 1946 Carney studied vitamin C levels in 100 soldiers in Italy with vitamin C plasma levels below

0.7 to 1.0 milligrams per one hundred cubic centimeters of plasma. None of the soldiers with low levels of vitamin C showed any clinical evidence of scurvy. Sixty-eight per cent of the soldiers had wounds, however, only eight per cent of the soldiers had wounds which failed to heal and of the eight per cent a few had normal plasma levels. It was the authors opinion that there was no relationship between vitamin C deficiency and wound healing. (Carney 1946)

Two series of patients undergoing tonsillectomies were studied. One series of patients with normal blood levels of vitamin C were compared with those having subnormal values. Most of the hemorrhages occured in those patients with a vitamin C deficiency. (Neivert, Pirk and Engeberg 1946)

According to Wolfer and Hoebel vitamin C deficiency should be thought of in cases in which the patient has been on a deficient diet, those taking large doses of alkalies by mouth, those with obstructive gastro-intestinal lesions, those with a history of vomiting over long periods, those with hypermotility of the small intestine, syphilitics and alcoholics. (Wolfer and Hoebel 1940)

The realization of the importance of vitamin C to wound healing is being accepted by various hospitals.

A report by Nixon reveals the fact that vitamin C is given routinely to surgical patients at the King County Hospital in Seattle, Washington. (Nixon 1942)

From the evidence presented it is quite probable that vitamin C is more directly concerned with the tensile strength of the wound rather than the rate of healing per se. In the cases presented the only ones where there was a complete absence of wound healing were in those having symptoms and signs of scurvy. Therefore, it seems logical that a partial depletion of vitamin C is more related to wound disruption and should be considered in those cases where strength of the scar tissue is important, as in chest surgery, or in abdominal surgery where postoperative evisceration is a probability.

SUMMARY

Vitamin C deficiency has been known since the time of Hippocrates. Likewise, the application of vitamin C for its treatment has been used since the fourteenth century. The relationship between scurvy and wound healing has also been observed since that time, yet only since 1937 has there been extensive studies

carried on concerning the subject.

Vitamin C is essential for maintainence of body function and appears to be related to the normal functioning of the tissues of mesenchymal origin. It is probable that vitamin C is a factor in the formation of mature collagen. The mechanism of the relationship between vitamin C and collagen formation is not known but the most popular theory is that vitamin C is essential for proper metabolism of the fibroblast which is responsible for the production of collagen.

A deficiency of vitamin C results in constant changes in the tissues consisting of a lack of mature collagen fibers in the ground substance. There also appears to be an inhibition of the growth and activity of the fibroblast.

Evidence has been brought out experimentally on test animals showing a direct relationship between vitamin C concentration and the tensile strength of wounds and also on the rate of healing, but to a lesser degree. It has been demonstrated that there is a direct proportion between the concentration and the tensile strength of wounds.

Although there is varied opinion among writers there appears to be the general consensus of opinion that vitamin C is a requirement for proper wound

healing. A few of the authors believe that vitamin C determinations should be done routinely before surgery is attempted and if low levels are found, therapy with vitamin C should be promptly instituted.

CONCLUSIONS

1. Vitamin C is necessary for proper functioning of the supporting tissues of the body, and a deficiency primarily effects these tissues.
2. Patients with a history of poor nutrition, metabolic disorders and chronic infections should be seriously considered as possible candidates for asymptomatic scurvy and should have vitamin C levels run before surgery is attempted.
3. Vitamin C deficiency results primarily in decreased tensile strength of the wound, rather than a diminished rate in the healing process.
4. Patients having blood levels below 0.6 mg. per cent may have difficulty in wound healing. Failure of wounds to heal is likely if the blood level is below 0.2 mg. per cent.
5. Patients with low plasma levels of vitamin C should receive the vitamin both preoperatively and postoperatively. Normal levels may be main-

tained by giving 1000 mg. of ascorbic acid every 24 hours both preoperative and postoperative.

BIBLIOGRAPHY

Aron, Hans: Die Nahroschaden des Kindes, Berlin and Vienna, Urban und Schwarzenberg, 1928, p. 103.

Aschoff, L., and Koch, W.: Skorbut: Eine pathologische-anatomische Studie, Jena, Gustav Fisher 1919.

Bartlett, M.K., Jones, C.M., and Ryan, A. E.: Vitamin C and Wound Healing. I. Experimental Wounds in Guinea Pigs. II. Ascorbic-acid content and Tensile Strength of Healing Wounds in Human Beings. New England J. Med. 1942, 226: 469, 474.

Bourne; C. H.: Vitamin C and Repair of Injured Tissues Lancet, London, 1942, 243:661

Bourne, C. H.,: Effect of Vitamin C Deficiency on Experimental Wounds.: Lancet, 1: 688-691, May 27, 1944.

Carney, H. M. Wound Healing with Low Vitamin C Levels. Ann. Surg., 1946, 123: 1111.

Dubnove, A.: Vitamins A,B,C,D, and their influence upon the Healing of Fractures: Hebrew M. J., 2: 226, 1938.

Eddy, W.H., and Dalldorf, G.: The Avitaminoses,. The Williams & Wilkins Company, Baltimore, 1941.

Fish, E. W. and Harris, L.J. (1934) Philos. Trans. B. 223, 489.

Giangrasso, G.: Parathyroid Glands, Vitamin C and Experimental Fractures; italiana di biologia sperimentale, 14:525 (October) 1939.

Griebel, C. R., : Vitamin C Belanz im operierten und fleberhoften Organismers. Deutche Med. Wchuschr. 64-147-49, 1938.

Ham, A. W., and Elliot, H. C., Bone and Cartilage lesions of protracted moderate scurvy, Am. J. Path. 14: 323-336, May, 1938.

Harris, L.J., and Ray, R. N.: Diagnosis of Vitamin C Subnutrition by Urine Analysis, with a note on the Antiscorbutic value of Human Milk, Lancet 1:71 (Jan 12) 1935.

Hartzell, J. B.,: Relation of concentration of ascorbic acid of blood to Tensile Strength of Wounds.: Surg. Gyn. & Obstet. 75: 1-5, July 1942.

Hirst, E. L. : Constitution of Ascorbic Acid, J. Soc. Chem. Ind. 52: 221, 481 (Nos. 1,2) 1933.

Hojer, J. A.: Studies in Scurvy, Acta paediat. (supp.) 3:8-278, 1924.

Holst, A., and Frolich, T. : Experimental studies Relating to Ship Beriberi and Scurvy, J. Hyg. 7:634, 1907.

Housel, E. L.,: Delayed Healing associated with Scurvy.: Penn. M. J. 46-21-23, Oct. 1942.

Hunt, A. H.: Role of Vitamin C., Brit. J. Surg., 1941, 28:436.

Ishido, B., Compensatory action of ultraviolet rays on avitimotic disturbances of bone marrow, Klin. Wchnschr. 2: 353, Feb. 19, 1923.

Jeney, A., and Toro, E.: Die Wirkung der Ascorbinsaure auf die Faserbildung in Fibroblastkulturen, Virchows Arch. f. path. Anat. 298:87-97,1936.

Kellie, A. E., and Zilva, S.S., Vitamin C requirements of man, Biochem. J. 33:153-164. Feb., 1939.

King, C. G., and Waugh, W. A.: The Chemical Nature of Vitamin C, Science 75: 357 (April 1) 1932.

King, C. G.,: Vitamin C. In The Vitamins. Chicago: American Medical Association, 1939.

Lanman, T. H., and Ingalls, T. H.: Vitamin C defiency and wound healing: Experimental and Clinical Study, Ann. Surg. 105: 616 (Aoril) 1937.

Lauber, H. J., Bersin, T., and Nafziger, H.: Der Einfluss der Narkose und Operation auf den Vitamin C Haushalt, Klin. Wachnschr. 16:1272, (Sept. 11) 1937.

Lauber, H. J., and Rosenfeld, W.: Histologic Examimation Regarding the Behavior of Vitamin C in Various Organs During the Healing of Wounds, Klinische Wochenschrift, 17:1587 (November 5) 1938.

Lexer, E. W.: The Importance of Vitamin C for Callus Formation and Reactive Hyperemia, Archiv fur klinische Chirurgie, 195:611 (May 20) 1939.

Lind, J.: A treatise of the Scurvy. ed. 3, London, S. Crowder, 1772.

Lund, C. C.: The Effect of Surgical Operations on the Level of Cevitamic Acid in the Blood Plasma, New England J. Med. 221: 123-127 (July 27) 1939.

Lund, C. C.: Human Experimental Scurvy and the Relation to Vitamin C: J. A. M. A. 116:663-668 Feb 22, 1941.

McLean, D. D., Sheppard, M. and McHenry, E.W.: Tissue Changes in Ascorbic Acid Deficient Guinea Pigs, (1939) British. J. exp. Pathol. 20, 451.

Mouriquand, G., Dauvergne, M., and Edel, V.: Osteopathy from Deficiency; "Irreversible" Decalcification of the Neck of the Femur in Chronic Vitamin C Deficiency, Presse medicale, 48:268 (March 12) 1940.

Neivert, H., Pirk, L.A., and Engleberg, R.: Late Secondary Tonsillar Hemorrhage; Studies of Ascorbic Acid. Arch. Otolarl, Chic., 1946, 43:568.

Nixon, E. A.: Three C's, Northwest Med. 41: 129-131 Apr. 1942.

Pijoon, M., and Lozner, E. L.: Vitamin C Economy in the human subject: Bull. Johns Hopkins Hosp., 1944, 75:303.

Ruskin, S. L.: Vitamin C-Sulfonamide Compounds in the Healing of Wounds. The Use of Sulfanilamide Ascorbate in the Treatment of Chronic Suppuration of the Wound After Radical Mastoidectomy, Archives of Otolaryngology, 40:115 (Aug) 1944.

Saitto, S., Sul' importanza del rilevamento dela grande aperature delle braccia, Monetare zool. ital. 40: 27-30, Jan. 31, 1929.

Schmidt, F. O.: The Ultrastructure of Protoplasmic Constituents. Physiol. Rev. 19, 270, 1939.

Sjent-Gyorgyi, Albert: Observations on the Functions of

the Peroxidase Systems and the Chemistry of the Adrenal Cortex, Biochem. J. 22:1387 (Dec.) 1928.

Vedder, E. B.: Scurvy, in Tice, Frederich: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1921, vol.9, chap. 9, p. 162.

Williams, R. H., and Bissell, G. W.,: Effect of Topical Applications of Vitamins. : Arch. Surg. 49: 225-227, Oct. 1944.

Wolbach, S. B., and Howe, P. R.: Intercellular Substances in Experimental Scorbutus, Arch. Path. 1:1 (Jan.) 1926.

Wolfer, J. A., and Hoebel, F. C.: The Significance of Cevitamin Acid Deficiency in Surgical Patients, Surg., Gynec. & Obst. 69:745-755 (Dec.) 1939.

Zerbini, E. D.: The influence of ascorbic acid deficiency on the processes of surgical cicatrization, Rev. de cir. de Sao Paulo 9:639-669, December, 1943.

Zerbini, E. D.: The Importance of Ascorbic Acid in Chest Surgery. J. Thorac. Surg., 1945, 14:309.