INTRODUCTION
Scurvy has been known for centuries. It is a disease caused by the severe lack of vitamin C in the diet. Seamen on long voyages often became sick and died of scurvy but the cause of such deaths were unknown. While searching for possible cause of such unnatural deaths, James Lind in 1757 observed that want of fresh vegetables and greens led to the development of symptoms which were in entire accord with the human clinical scurvy and intake of fresh juices of citrus fruits could prevent and cure the disease. In 1912, Holst and Fröhlich produced scurvy in guinea pigs by feeding them restricted diet. But it was not until 1928, when "hexuronic acid" was isolated by Szent Györgi and was shown to be identical with vitamin C by Waugh and King (1932) who isolated it from lemons. The active agent is enolic form of 2-keto-L-gulofuranoc lactone named ascorbic acid or vitamin C.

Ascorbic acid is structurally related to the hexose. So it is likely that it is biosynthesized from a hexose sugar in biological system, the first evidence of which was given by Ray (1934). A definite advance in the problem of biosynthesis was made by Muslin et al. (1939) and Longenecker et al. (1939, 1940) who have shown that ascorbic acid excretion in rats can be greatly stimulated by compounds such as terpene like ketones and particularly by compounds which are used as nerve depressants namely chloretone. The accelerated ascorbic acid biosynthesis as mentioned above is also accompanied by increased excretion of D-glucuronic acid (Mosbach et al. 1950 and Burns et al. 1957).
The works of Jackel et al. (1950), Horowitz et al. (1952) and of Horowitz and King (1953) supported the contention that in animals D-glucose is directly converted into L-ascorbic acid without fragmentation but with the inversion of the carbon chain. Further studies pointed out that ascorbic acid is biosynthesized in animals from glucose via glucuronic acid pathway (King and Becker, 1959; Burns, 1960, 1961; Chatterjee, 1970; King, 1973). A schematic representation of ascorbic acid biosynthesis is shown in Figure 1 (Burns, 1960).

It has long been considered that all animals except the guinea pig, monkey and man can synthesize the vitamin. Recent additions to the list of animals incapable of synthesizing the vitamin are the flying mammals and highly evolved passeriformes birds (Roy and Guha, 1958a,b; Chatterjee et al. 1961a; Chaudhury and Chatterjee, 1969). The ability to synthesize ascorbic acid is also absent in the insects, invertebrates and fishes (Chatterjee, 1973a; Dutta Gupta et al. 1972).

Ascorbic acid biosynthesizing abilities of various species is correlated to their phylogeny (Chatterjee, 1973b). The biosynthetic capacity started in the kidney of the amphibians, remained in that of reptiles, became transferred to the liver of the mammals and finally disappeared from the flying mammals, the guinea pig, the monkey and man. The ascorbic acid-synthesizing abilities of various species of animals is schematically represented as shown in Figure 2 (Chatterjee, 1973b).
Fig. 1: Schematic representation of ascorbic acid biosynthesis in animals.
Fig. 2: Schematic representation of ascorbic acid synthesizing abilities of various species of animals in relation to their phylogeny.
The failure of the guinea pig, the flying mammals, the monkey and man to synthesize ascorbic acid is a common genetic defect and is attributed to the loss of the gene responsible for synthesis of the terminal enzyme L-gulono-oxidase (E.C. 1.1.3.8) which catalyzes the terminal step in the conversion of glucose to ascorbic acid (Burns, 1957; Chatterjee, 1973b; Chatterjee et al., 1975b).

The very fact that the biosynthetic capacity of vitamin C is absent in man leads us to the truth that it has to depend exclusively on an exogenous supply of the vitamin for growth and survival. Thus a severe depletion of the vitamin in the diet results in the manifestation or precipitation of the disease, named scurvy. Scurvy an illness now rare in its terrifying form is a syndrome of generalized tissue disintegration at all levels, involving the dissolution of intercellular ground substances, the disruption of collagen bundles and the lysis of interepithelial and interendothelial ground substances, leading to ulceration with secondary bacterial colonization and the vascular disorganization and interstitial hemorrhage.

The exact biochemical defect leading to scurvy is not known. The metabolic fate of ascorbic acid depends on a number of factors including the animal species, route of ingestion, nutritional status and the quantity of the material ingested. Ascorbic acid is oxidised to respiratory CO₂ in rats and
guinea pigs (Burns, 1960) whereas man cannot catabolize ascorbate to CO₂ (Baker et al., 1966). No specific ascorbic acid oxidase has been reported in animals. Ascorbic acid is first oxidized to dehydroascorbic acid by a variety of enzymic and non-enzymic processes. Enzymic delactonisation of dehydro-L-ascorbic acid then occurs (Kagawa and Takiguchi, 1962) thereby producing 2,3-diketogulonic acid which is in turn decarboxylated by a specific decarboxylase ultimately producing CO₂ and pentonic acids, namely L-xylonate and L-lyxonate (Ashwell et al., 1961; Shimazino and Mano; 1961; Kagawa and Takiguchi, 1962). In man there is no apparent formation of 2,3-diketogulonic acid and hence subsequent breakdown to a five carbon chain and CO₂ is not possible. Thus the catabolism to CO₂ does not appear to be a required function of the vitamin. A small amount of ascorbate is, of course converted to urinary oxalate in man (Baker et al., 1966). Oxalate and a number of other metabolites of which only ascorbate-2-sulfate has been identified (Baker et al., 1971a). Ascorbate-2-sulfate was initially discovered in brine shrimp cysts by Mead and Finamore (1969). Ascorbate sulfate was later shown to be a urinary metabolite in man, monkey, rat, guinea pig and fish (Baker et al., 1971a, 1975; Halver et al., 1975). The compound was found to be antiscorbutic in fish (Halver et al., 1972; Hatanaka, 1974). However, ascorbate sulfate is ineffective in preventing or curing scurvy in guinea pig whether given orally or by injection (Kuenzig et al., 1974).
It has been observed that in humans the highest concentration of ascorbic acid is in adrenal and pituitary glands (Hornig, 1975). Ascorbic acid concentration is also high in tissues having higher metabolic activity. The contents are high in brain, liver, spleen, pancreas, eye lens, kidney and heart muscle. The tissue contents usually decline with age.

Ascorbic acid and not dehydroascorbic acid is the preferred form of transport of the vitamin in pituitary and adrenal glands, lungs, liver, kidneys, bone, skin and nasal mucosa (Hornig, 1975). On the other hand, dehydroascorbic acid and not ascorbic acid is the preferred form of uptake by neutrophils, erythrocytes and lymphocytes (Bigley and Stankoiva, 1974). Analogues of ascorbic acid, namely D-ascorbic acid, D-isoascorbic acid and glucoascorbic acid are unable to cross cellular barriers and this may be an important factor in explaining their low antiscorbutic activity (Martin, 1961).

Ascorbic acid has a role in hematopoiesis (Bronte-Stewart, 1953) and is useful in prevention and treatment of certain types of anemia. May and his associates produced megaloblastic anemia in monkeys on diet deficient in ascorbic acid (May et al., 1955). Moore found that ascorbic acid in relatively large amounts increased assimilation of food iron (Moore, 1955). Greenberg et al. (1957) presented convincing evidence that a combination of ascorbic acid and vitamin E enhanced the synthesis and maintainence of hemoglobin more than did either vitamin alone.
The participation of vitamin C in the electron transport reactions was shown long ago (Szent-Györgyi, 1931). Knowledge about the possible role of vitamin C in the electron transport has been surveyed several times (Staudinger et al., 1961; Schneider and Staudinger, 1964; Mapson, 1967). Nevertheless investigations in this field is yet to lead to a complete knowledge. The redox reactions initiating from L-ascorbate as the electron donor gives rise at first to the non-isolatable oxidation product 3-monodehydroascorbic acid. In the second stage the 3-monodehydroascorbic acid disappears mainly by disproportionation producing L-ascorbate and dehydro-L-ascorbate (Weis, 1975). The reaction is very fast and could only be followed by EPR spectroscopy. There is no specific ascorbic acid oxidase in animal tissue. The stepwise conversion of ascorbic acid to dehydroascorbic acid through electron transfer involving ferricytochrome c (Cyt C<sup>+</sup>) may be illustrated as follows:

1. Cyt C<sup>+</sup> + AA ———> Cyt C<sup>+</sup> + AA

2. AA<sup>-</sup> + AA<sup>-</sup> ———> DHA + AA

Once monodehydroascorbic acid (AA<sup>-</sup>) is formed, the very fast disproportionation takes place.

Ascorbate is also oxidized to monodehydroascorbate by ferricytochrome b<sub>5</sub> in presence of the enzyme ascorbate : ferricytochrome b<sub>5</sub> oxidoreductase (EC 1.10.2.1). Monodehydroascorbate is in turn reduced back to ascorbate by the NADH-dependent enzyme,
NADH-monodehydro-L-ascorbate oxidoreductase (EC 1.6.5.4) present in animal tissues (Staudinger et al., 1961). The physiological role of this enzyme may be supposed to economize ascorbate.

The fact that ascorbic acid is a very good protective agent against free radical damage may be due to a combined effect of ascorbate and its free radical which is a relatively non-reactive species and decays mainly by disproportionation thereby terminating the propagation of free radical reaction (Bielski et al., 1975).

Among the important biological functions of ascorbic acid the most discussed function is in some key biochemical hydroxylation reactions. The need for vitamin C to maintain normal tyrosine oxidation has been referred to many times as one of the examples of requirement for this vitamin. The locus of action of the vitamin appeared to be on the enzyme p-hydroxyphenylpyruvic acid oxidase which converts p-hydroxyphenylpyruvic acid to homogentisic acid. The enzyme was protected by ascorbic acid from inhibition by its substrate. However, the role of ascorbic acid was non-specific because the vitamin could be completely replaced by 2,6-dichlorophenolindophenol (La Du and Zannoni, 1961). Ascorbic acid has been discussed as a cofactor of dopamine-β-hydroxylase (Kaufman, 1966) but it was also observed that graded oral doses of the vitamin did not affect nor-epinephrine or dopamine concentrations of guinea pigs (Dashman et al., 1973).
Staudinger et al., (1961) indicated that ascorbic acid was involved in the biogenesis of corticosteroids in adrenal homogenates but according to Kitabachi and West (1975) steroidogenesis was fully preserved in the absence of ascorbic acid in scorbutic guinea pigs. Cooper (1961) has also described the hydroxylation of tryptophan to 5-hydroxytryptophan in presence of Cu\(^{2+}\) ion to be dependent on ascorbic acid, it could be replaced by D-ascorbic acid, D-isoascorbic acid or dehydroascorbic acid. Nakashima et al., (1970, 1972) showed that the activity of tyrosine hydroxylase decreases in the adrenal gland of scorbutic guinea pigs but increases upon realimentation with ascorbic acid. Therefore a role of ascorbic acid at the level of tyrosine hydroxylase biosynthesis has been established. The vitamin has also been reported to play an important role in the regulation of lipolysis through its participation in the process in which the enzyme lipase become converted to its inactive form when energy demands are satisfied (Tsai et al., 1973). The rate of inactivation of lipase is proportional to the ascorbic acid concentration in the range 0.3 to 3\(\mu\)M and the presence of ATP and MgCl\(_2\) is essential for the process. Attempts to replace ascorbic acid in the process of inactivation by other reducing agents were unsuccessful.

Direct involvement of ascorbic acid in collagen synthesis is well known and perhaps the most clearly defined biochemical
role of the vitamin. The absence of wound healing and occurrence of fractures that fail to repair, are classically recognized features of scurvy. These can be attributed to impaired collagen formation arising from lack of vitamin C. Claims were made that for the synthesis of collagen molecule the presence of ascorbic acid was needed (Stone and Meister, 1962; Gottlieb et al., 1966; Manning and Meister, 1966).

Free hydroxyproline and hydroxylysine are not incorporated in collagen. Probably hydroxylation of particular prolyl and lysyl residues, previously incorporated in the peptide linkage, occurs concurrent with translation when the growing polypeptide chain is still attached to the ribosome (Grant and Prockop, 1972; Bornstein, 1974; Cardinale and Undenfriend, 1974). Hydroxylation is followed by association of three chains to form a triple helical unit known as 'protocollagen' which leads to the formation of tropocollagen fibrils. The fibrils are finally converted to mature, insoluble highly cross-linked extracellular collagen fibers. The first step, synthesis of polypeptide chain, is unaffected by ascorbate status, but all the subsequent steps are potentially dependent on the second step, hydroxylation, which is inhibited by ascorbic acid deficiency.

The participation of ascorbic acid in the hydroxylation of peptide-bound collagen proline was perhaps first clearly indicated by Meister and Undenfriend and their associates (Stone and Meister, 1962; Gottlieb et al., 1966; Manning and Meister, 1966).
These workers demonstrated that when minces of granuloma tissue, formed in scorbutic guinea pigs, were incubated in presence of labeled proline, there was little incorporation of radioactivity in collagen hydroxyproline. Addition of ascorbic acid to the medium prior to incubation caused a stimulation of incorporation of radioactivity into collagen hydroxyproline.

Ascorbate seems to have two separate roles in controlling hydroxylation of peptide bound proline: (1) activation of an inactive enzyme to active prolyl hydroxylase (2) hydroxylation of peptide-bound proline by active prolyl hydroxylase. The enzyme prolyl hydroxylase has been isolated in highly purified form and extensively characterised (Cardinals and Undenfriend, 1974; Berg and Prockop, 1973; Stassen et al., 1974). Molecular oxygen is needed for these enzymes. With the requirement of molecular oxygen, prolyl and lysyl hydroxylases could be regarded as mixed-function oxidases operating according to the following reaction

\[ R + XH_2 + O_2 \rightarrow ROH + X + H_2O \]

where \( R \) is the substrate undergoing hydroxylation (peptidyl proline or lysine), \( XH_2 \) is the cosubstrate and \( ROH \) is the hydroxylated product (peptidyl hydroxyproline or hydroxylysine). Besides molecular oxygen, the enzyme requires as cofactor \( Fe^{+2} \) ion, \( \alpha \)-ketoglutarate and a reducing agent such as...
ascorbic acid (Hutton et al., 1967; Kivirikko and Frockop, 1967). With the establishment of ascorbic acid as a cofactor, it was assumed that the vitamin was required as a cosubstrate in the mixed function oxidation, as occurs for example in the hydroxylation of dopamine by the copper dependant enzyme dopamine-ß-hydroxylase (Friedman and Kaufman, 1966). It was thought that α-ketoglutarate might act as an allosteric activator (Hutton et al., 1967). But it became apparent subsequently the role of cosubstrate was undertaken by α-ketoglutarate itself which underwent a stoichiometric decarboxylation to succinate, during the course of hydroxylation (Rhoads and Undenfriend, 1968; Kivirikko et al., 1972). It was shown that one half of the oxygen molecule was incorporated into the substrate undergoing hydroxylation while the other half in contrast to the reaction depicted above appeared in succinate rather than in water (Cardinale et al., 1971). These enzymes have therefore been classified as dioxygenases (Hayaishi, 1974).

After isolation of prolyl hydroxylase in a homogeneous form it became apparent that this enzyme could be grouped together as belonging to a newly recognised class of hydroxylase (mixed function oxidase), requiring as cofactors molecular oxygen, Fe²⁺ ion, α-ketoglutarate and a reducing agent such as ascorbic acid. The requirement for α-ketoglutarate is absolute and specific (Cardinale et al., 1971; Levene et al., 1974). However, the requirement of ascorbic acid is not highly specific and ascorbate may be replaced by various reduced pteridines,
and by a number of thiol compounds including dithiothreitol and cysteine. Thus the impairment of collagen synthesis in scurvy reflects a role of ascorbic acid which might be indirect.

The other role of ascorbic acid, activation of prolyl hydroxylase, has been observed in 3T6 mouse fibroblast culture by Levene et al., (1974) and in L-929 culture by Stassen et al., (1973) and Cardinale et al., (1975). However, in this case also ascorbate may be replaced by high concentration of lactate (Levene et al., 1974; Comstock and Undenfriend, 1970). Recent investigations favour the idea that activation is produced by the association of inactive sub-units of the enzyme. Prolyl hydroxylase from chick embryo is composed of four sub-units (Berg and Prockop, 1973). However, Stassen et al., (1973) from study of cultures of mouse fibroblasts (L-929 cells) suggest the presence of three enzymatically inactive sub-units which aggregate to form active prolyl hydroxylase.

It is interesting to note that while certain other naturally occurring substance can mimic ascorbic acid in either hydroxylation of peptide bound proline or activation of prolyl hydroxylase, none has yet been found that can replace both roles entirely.

Another most important biological function concerns the role played by it in the metabolism of drugs. Vitamin C deficiency in guinea pig results in decreased metabolism of a variety of
pharmacological agents. Richards et al., (1941) found a prolonged sleeping time in scorbutic guinea pigs given phenobarbital compared with that of normal animals and the administration of ascorbic acid reversed the effect. Axelrod et al., (1954) reported up to a threefold increase in plasma half-life of such agents as acetanilid, aniline or antipyrine in scorbutic guinea pigs and that was attributed to decreased rate of metabolism. There are reports of decreased oxidation of such agents as zoxazolamine, acetanilid, coumarin, diphenylhydramine, and mepiridine in microsomes prepared from guinea pigs depleted of vitamin C. Studies have demonstrated that O-methylation, N-demethylation and hydroxylation reactions as well as individual microsomal electron transport components such as cytochrome P 450 and NADPH cytochrome P 450 reductase are decreased in guinea pigs depleted of ascorbic acid. However, the decreased drug enzyme activities can be restored to normal levels provided the deficient animals are given the vitamin for a period of 6 to 10 days (Zannoni and Sato, 1975).

Detoxification of histamine takes place in presence of ascorbic acid. Autooxidation of ascorbic acid in presence of histamine, resulted in the histamine breakdown, leading to biological inactivation of histamine. The process of histamine breakdown is non-enzymatic and histamine is converted to aspartic acid via hydantoin acetic acid (Chatterjee et al., 1975a).

The basic function of vitamin C is the prevention of scurvy (Lack of collagen synthesis). The question of whether
or not a larger intake could lead to a better health and
greater control of diseases was raised. It was also estab­li­shed that vitamin C was non-toxic virtually at any dosage.
Since the exact biochemical function of vitamin C is not clear,
fully satisfactory and reliable biochemical procedures reflec­ting the vitamin C status is yet to be developed. As a result
indirect informations such as serum, leukocyte and blood levels
are utilized. The determination of vitamin C in white blood
cells requires large amount of blood samples and is technically
difficult so the procedure is not practical for routine use in
nutrition surveys. Du Plessis (1967) in nutrition surveys con­duct­ed in South Africa, measured the serum, blood and urinary
vitamin C in each subject investigated and concluded that blood
and serum vitamin C levels are considered to give satisfactory
indication of vitamin C status in population groups while the
determination of urinary vitamin C in such surveys may in fact
be superfluous.

The Interdepartmental Committee on Nutrition for National
Defense (Mannual for Nutrition Surveys, 1963) has given guidelines
for interpreting the serum ascorbic acid data which has come
out from the aforesaid survey work.

Similar guidelines have been given by The Ten State
Nutrition Survey (1972) and the Nutrition Survey of Canada
(1973). A revision of the guidelines based on the observations
of Hodges et al., (1971) has been suggested as: serum ascorbate levels less than 0.2 mg/100 ml as "deficient", levels from 0.20 to 0.29 mg/100 ml as "low" and levels from 0.30 mg/100 ml and above as "acceptable". Persistent low serum ascorbic acid level, less than 0.20 mg/100 ml might eventually lead to clinical symptoms of scurvy. Although cases of frank clinical scurvy is rare in modern times, cases of subclinical scurvy are there and if overlooked may cause physiological disorders.

Average healthy adult man has a body pool of 1.5 g of ascorbic acid, which is used at an average rate of 3% of this amount i.e., 45 mg per day. The Recommended Dietary Allowance (1974) for vitamin C was set at 45 mg per day for an adult and with this intake serum ascorbate level of approximately 0.6 mg/100 ml and a leukocyte level of 20 mg/100 ml of cells could be expected and the body pool could be expected to remain close to a maximum 1.5 gm (Harper, 1975).

Though ascorbic acid requirement is controversial, yet it is generally accepted that ascorbic acid utilization is greatly increased in stress conditions. Physical stress such as occurs following severe burns, shock of any type or during surgical operations induces a precipitous fall in plasma ascorbic acid level and the amount excreted in the urine with or without loading test (Lund et al., 1947; Lund and Crandon, 1941). According to Levenson stress accentuates the need for
the vitamin and the seriously injured human behaves essentially in a manner similar to that is observed in ease of scorbutics (Levenson et al., 1957).

Numerous investigations in experimental animals have indicated a relationship between ascorbic acid, stress situations and the function of the adrenal glands. Kark summarized some of the pertinent finding in this area (Kark, 1953). He quoted Lund and Levenson and their colleagues as finding that both the plasma level and the urinary output of ascorbic acid dropped to low values in the post-operative period despite the treatment with very high dose of the vitamin. Studies in rats showed that the ascorbic acid and cholesterol contents of the adrenal gland decreased when the animals were stressed or their adrenal cortices were stimulated with corticotropin thereby indicating increased utilization of the vitamin by the adrenal gland. Kark also pointed out that interrelationships between ascorbic acid metabolism and adrenocortical activity need reorientation, at least with regard to the guinea pig, monkey and man who are unable to synthesize ascorbic acid. Observations of the adrenal activity in patients with scurvy indicate that the adrenal cortex functions normally, excretion of 17-ketosteroids is also normal and adrenal glands respond normally to stimulation by corticotropin. It seems obvious therefore that the adrenal glands can not consume much ascorbic acid in the synthesis of cortical hormones. In Cushings
syndrome, in man, in which there is hyperactivity of the adrenal glands, ascorbic acid levels of the blood is normal.

The surgical requirements for vitamin C have called for even further revaluation. The immediate effect of surgery on plasma and buffy coat ascorbic acid has been studied (Crandon et al., 1961). The overall average drop in plasma ascorbic acid was 17% and the same in buffy coat ascorbic acid was 20%. The patient with higher preoperative level of the vitamin showed the sharpest drop (Crandon et al., 1961).

The requirement of the vitamin under stress conditions such as exposure to cold is increased and larger doses of the vitamin has been found to be beneficial in rats, guinea pigs and monkeys (Dugal and Therien, 1947; Dugal and Fortier, 1952). Eisentein and Boniface (1952) showed the prevention of adrenal hypertrophy in ascorbic acid pretreated rats exposed to cold. The beneficial effects of ascorbic acid in cold exposed animals have also been confirmed by other workers (Mayer, 1949; Desaulniers, 1950; Gaarenstrom et al., 1953; Booker et al., 1955).

Exposure to high altitude is a severe form of stress because the rarefied atmosphere induces oxygen deprivation, known as hypoxia. Peterson in 1941 showed that mice injected with ascorbic acid were able to withstand repeated exposure to air pressure that were 1/6 normal (Peterson, 1941). Wesely and coworkers reported that in guinea pigs exposed to low air pressures, there was a drop in plasma ascorbic acid levels and
corresponding increase in the more toxic dehydroascorbic acid levels. The tests were made on human subjects who responded similarly to hypoxia (Stone, 1974). However, it has been established later on that ingestion of large amounts vitamin C diminish the high-altitude resistance (Schrauzer et al., 1975).

Exposure to radiation is an extremely stressful situation for the living organisms. There are many reports showing that exposure to X-rays reduces ascorbic acid level of the body and that ascorbic acid gives effective protection against radiation damage (Monier and Weiss, 1952; Dolgova, 1962; Shapiro and Kollman, 1967).

Depletion of ascorbic acid and cholesterol have been reported in various other stress conditions such as burns, ether anesthesia, effect of toxins, effect of histamine, non-fatal hemorrhage (Dugal and DesMarias, 1949; Kuchel and Mitchell, 1956; Ghose, 1959; Sayers and Sayers, 1947, 1949; Pasqualini, 1946; Santome and Gomez, 1963). Ungar (1942) was able to prevent traumatic shock and death in injured guinea pig by an injection of ascorbic acid 100 mg or more per kg of body weight. Chakrabarty and Banerjee (1955) found that blood ascorbic acid level went down and the blood dehydroascorbic acid level went up in human subjects, as the patients became sick and finally died from meningitis, tetanus, pneumonia and typhoid fever.
In human requirement for vitamin C is increased during pregnancy. The rationale for the increased requirement is primarily based on the findings of a downward trend in plasma ascorbic acid in the successive trimesters of pregnancy (Macy et al., 1954; Martin et al., 1957; Mason and Rivers, 1971; Vobecky et al., 1974; Rivers and Devine, 1975).

Development of cancer and proliferation of tumor cells is at any rate an intense form of biochemical stress. Of interest is the theory postulated by McCormick, the factor which preconditioned the body to the development of cancer is the degenerative changes caused by continued low levels of ascorbic acid (McCormick, 1954, 1959 and 1963). Schlegel and coworkers showed that the bladder cancer due to smoking or other causes could be prevented by ascorbic acid (Schlegel et al., 1969). In 1969, Dean Burk and his group showed that ascorbate is highly toxic to the cancer cells using Ehrlich ascites carcinoma cells and caused profound structural changes in the cancer cells in the laboratory cultures (L.Benade, T.Howard and D.Burk, 1969).

There is evidence from both human and animal experiments that the development and progress of cancer evokes an increased requirement for ascorbic acid. Collective evidence suggests that the vitamin is involved in the inhibition of the invasive tumor enzymes and the vitamin may allow the resistant patient to enmesh his tumor cells in a barrier of new fibrous tissue (Caméra, et al., 1979).
According to Stone (1974), in leukemia the biochemical stresses of the disease process has reduced the body stores of ascorbic acid to very low levels, the plasma ascorbic acid level is zero or close thereto. Consequently the tissues are in a condition of biochemical scurvy explaining thereby the reason for which these depleted tissues are so susceptible to the characteristic hemorrhaging of leukemia and the infections that kill so many leukemics.

Investigators from various parts of the world have shown that mental disease patients have high demands for ascorbic acid and have subnormal body levels of the vitamin (Punekar, 1961; Hoffer and Osmond, 1963; Milner, 1963; Slowik, 1965). Vanderkamp found that schizophrenics metabolised ascorbic acid at a very high rate than that of control group (Vanderkamp, 1966). He gave to a group of ten schizophrenics 36 to 48 g of ascorbic acid per day, all the patients showed signs of definite clinical improvement. In 1967; Linus Pauling introduced the concept of orthomolecular psychiatry (Pauling, 1968) which means treatment of the mental disease by the provision of the optimal molecular environment for the mind especially the optimum concentrations of substances normally present in the human body. Ascorbic acid is a substance that has been used in the treatment of mental diseases and according to Pauling an optimal intake of this vitamin which is supposed
to be much higher, perhaps 3 to 15 g per day will lead to better management of cases of mental disorder.

With the above informations at hand, the object of the present investigation is to explore in detail

(1) The ascorbic acid nutritional status of human subjects under various stressful situations, namely, head injury, lacerated injury, crush injury, fracture, burns, pregnancy, cancer and mental derangement.

(2) To elucidate the mechanism of reduction of dehydroascorbic acid to ascorbic acid in erythrocytes and tissues.

(3) To investigate the cause of accumulation of dehydroascorbic acid in blood and plasma of traumatic subjects.

(4) To examine the ascorbic acid nutritional status of diabetic subjects, considering that diabetes mellitus is a stress condition.