REVIEW OF LITERATURE

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The present study was undertaken to assess the role of antioxidants in health and disease during aging process. The related objectives were to study the information on local adults and elderly population with respect to socio-demography, nutritional status, dietary intake, and lifestyle related factors. The study also included collecting similar data on adults and elderly with cardiovascuiar diseases (CVD) and oral cancer. The other objectives also included assessment of antioxidants in diet as well as blood in the above mentioned subjects. Further, a small sample of caregivers were also studied for knowledge and practices (KAP) with respect to the health benefits of antioxidants rich foods for elderly.

The review of literature pertaining to the present study are categorised under the following heads:

- **AGING**
- **DEMOGRAPHIC TRANSITION**
- **NUTRITION AND HEALTH PROBLEMS OF THE ELDERLY**
- **FREE RADICAL THEORY OF AGING**
- **DEFENCES AGAINST FREE RADICALS**
- **ENZYMATIC DEFENCES**
- **NON-ENZYMATIC DEFENCES**
- **NUTRIENT ANTIOXIDANTS**
- **NON-NUTRIENT ANTIOXIDANTS**
- **ANTIOXIDANTS IN VARIOUS DISEASES OF AGING**
- **CARDIOVASCULAR DISEASES**
- **CANCER**
- **ORAL CANCER**
- **CAREGIVING OF THE ELDERLY**

AGING

Aging is the most universal of biological phenomenon known to human. It has been studied since the beginning of man. Biological aging can be described at a phenomenological level as a process that is observed in all living things. It consists of a systematic, continuous alteration of individuals, leading last to their death. According to Strehler (1995), the aging process can be characterised by the following four main features:

a. *It is destructive, i.e it decreases the functional ability*
b. *It is progressive, i.e irreversible*
c. *It is intrinsic, i.e it is determined by the internal characteristics of the living being or it does not depend exclusively on any external factors.*
d. *It is universal, i.e individuals of the same species display more or less uniform aging pattern, and on the other hand, all living beings show the aging phenomena.*

Exploring the mysteries of aging has been an obsession of the philosophers, spiritual and religious teachers and scientists of numerous disciplines for centuries. Aging even today remains full of riddles for which we have no answers. Even now aging is considered as a disease in most rural underprivileged communities.

DEMOGRAPHIC TRANSITION

Every nation is characterised by certain demographic changes in its population over the years. These changes are mainly influenced by rates of fertility and mortality which in turn are dependent on socio-economic progress and medical advances. Globally, increasing human longevity achieved during recent years is a story of man's triumph. Consequently, more and more people are surviving into old age; in other words, increasing number of nations are greying. There are significant implications of this demographic phenomenon.

Population aging - the process by which older individuals become a proportionally larger share of the total population - was one of the most distinctive demographic events of the 20th century. It will surely remain important throughout the 21st century. Initially experienced by more developed countries, the process has recently become apparent in much of the developing world as well. For the near future, virtually all countries will face population aging, although at varying levels of intensity and in different time frames.

GLOBAL SCENARIO

It is projected that the elderly population of the world will cross the one billion mark by the year 2020. As the older population has grown faster than the total population, the proportion of older persons relative to the rest of the population has increased considerably. At the global level, one in every 12 individuals was atleast 60 years of age in 1950 and 1 in every 20 was atleast 65. By the year 2050, more than 1 in every 5 persons throughout the world is projected to be aged 60 or over, while nearly 1 in every 6 is projected to be atleast 65 years old (United Nations 2002).

INDIAN SCENARIO

Demographic aging, a global phenomenon, has hit Indian shores as well. Improved life expectancy has contributed to an increase in the number of persons over 60 +. From only 12 million persons over 60 + in India in 1901, the number crossed 20 million in 1951 and 57 million in 1991. Population projections for 1996-2016 made by the Technical Group on population projections (1996) indicate that the 100 million mark is expected to be reached in 2013. Projections beyond 2016 made by the United Nations (1996) had indicated that India will have 198 million persons over 60 + in 2030 and 326 million in 2050. The percentage of persons over 60 + in the total population has seen a steady rise from 5.1 % in 1901 to 6.8 % in 1991. It is expected to reach 8.9 % in 2016. Projections beyond 2016 made by United Nations (1996) has indicated that 21 % of the Indian population will be 60 + by 2050.

NUTRITION AND HEALTH PROBLEMS OF THE ELDERLY

Health is a multi-faceted including positive and negative dimensions of physical, mental, and social well being. To the aging individual and society, health is of prime significance. Indices of health traditionally focussed on ill health as shown by morbidity, mortality and health service utilisation. In practice, health of the aged is defined in terms of how well a person is functioning, or in terms of absence or presence of disease. The spatial worlds of disease and health are defined by changing measures of well-being, morbidity or mortality. It is important to distinguish between aging process and disease.

Health of the elderly is determined by several factors. Normal aging and disease aging interact with each other. Factors such as gender, economic status, marital status, living standards, and availability of social supports influences health during old age.

Recent decades of research in elder populations in developed countries have documented the nutritional vulnerability of older individuals, even under relatively affluent circumstances. Elders may be more prone to nutritional deficiencies, which in turn causes significant adverse consequences in terms of functionality. The main reasons for their deficiencies are an increased prevalence of gastrointestinal diseases, changes in metabolic and synthetic function, changes in nutrient requirements, alterations in taste sensation, social isolation and poverty (Bunout et al 2001). Thus aging seems to be markedly affecting the food and dietary intakes.

Few Indian workers have carried out studies on elderly population with respect to their health and nutritional status. Series of studies carried out by Mehta (1999) on local elderly men and women reported deficit of energy and protein consumption by 70 % and 61 % respectively when compared with the recommended dietary allowances (RDA). Fat, vitamin C and calcium intakes were found to be exceeding the recommendations in these studies.

Assessment of nutrients intake and associated factors was also carried out on Indian elderly population by Natarajan et al (1993). A group of 420 elderly people (163 women and 257 men with a mean age of 65 years) from urban and rural populations in India were selected for the study. The caloric intake of 93.3 % was less than the recommended allowance, the mean daily calorie intake being 1191 kcal in men and 928 kcal in woman. Except for calcium, all nutrients were deficient in their diet. Illiteracy (53 %), lack of knowledge regarding daily allowances of nutrients (95 %), poor economic background (46.7 %), and breaking down of joint family system (63 %) were possible associated factors were reported.

Kapil et al (1998) studied the dietary intake of trace elements and minerals of 1277 adults of underprivileged communities of rural Rajasthan. The zinc intake was 69.7 % and 49.7 % of the recommended daily allowance in males and non-pregnant non-lactating females respectively. The intake of manganese and molybdenum were adequate when compared with the suggested daily intakes. The intake of iron was less than 20 mg/day for all female subjects studied.

Studies on the dietary intakes of elderly were also carried out by other workers from west. Wurtman et al in 1992, distinguished effects of aging from life style changes by examining intakes of young and elderly subjects living in a clinical research center where they offered identical foods. The elderly subjects consumed significantly fewer calories carbohydrates and fats than the younger subjects. Different patterns of eating were also seen in the two groups. Younger subjects ate more of their calories from snacks than the elderly.

Study undertaken by Groot et al (1999) evaluated the energy and micronutrient intake in elderly European participating in SENECA study. The data was collected on 486 men and 519 women (74 - 79 years) out of 13 centers selected from 12 European countries. The micro-nutrients that were studied were iron, thiamine, riboflavin and pyridoxin. The relationship of these micro-nutrients were studied with respect to the energy intake. Nineteen percent of men and 26 % of women had an inadequate micronutrient intake. The prevalence of inadequate intake of iron and riboflavin was very high in most of the people. Results revealed a decrease in the prevalence of an inadequate nutrient intake with higher energy intakes in elderly people.

The nutrient / energy intakes of elderly (60 - 103 years) were also assessed with respect to their income status and ethnic group (Protho and Rosenbloom 1999). Only 6 % of the sample had adequate energy intake. Fifty three percent had marginal deficiency whereas 41 % had submarginal deficiency of energy and nutrient intakes. Diets of men were better than those of women ($p<0.05$). Calcium ($p<0.05$) and potassium ($p<0.05$) were higher in diets of female elders above the poverty line than those below. A trend was observed for higher intakes of fatty components (total fat, cholesterol, % fat calories) for both men and women in the below poverty than in above poverty group.

In another cross - sectional study of 66 men and 279 women from North Carolina, nutrient intake in correlation in correlation to individual characteristics (age, race, education, income, marital status and living arrangements) and health related factors (physical, psychological, meal pattern and current nutritional health status) was evaluated (Sharkey et al 2002). The subjects did not meet the recommended dietary allowances - adequate intake (RDA-AI) for energy and 7 micro nutrients (Vitamin D, E, B_6, folate, calcium, magnesium and zinc). Diets of women (compared to men) met a significantly lower percent of RDA - AI for vitamin D, E and B_{12}, folate, calcium, iron, phosphorous, riboflavin and selenium. For both men and women, the nutrients for which the largest proportion of subjects had inadequate intakes were vitamin E (94 %), magnesium (81 %) and zinc (51 %). The results also suggested that the nutrient intakes

of a sizable proportion of subjects were inadequate for multiple nutrients ; 27 % for ≥ 6 nutrients, 40 % for 3 - 5 nutrients, 29 % for 1 or 2 nutrients. The study thus revealed that regardless of health related factors, women, blacks and those with low income and limited education were the most vulnerable for low nutrients intakes. Women had significantly lower intakes of total energy, protein and 15 of 16 vitamins and minerals as compared to men.

Differences in the nutrient intakes between men and women were observed by Marshall et al (2001). He assessed the dietary habits and nutrient intakes of an elderly population aged 65 years and above (n = 420) from Iowa. The energy intake of men was found to be higher than women (6775 kcal vs 6140 kcal). However, intake of protein (60 g vs 54 g), fat (57 g vs 51 g) and fiber (16 g vs 15 g) did not differ much between the genders.

A survey was carried out on 2213 Dutch elderly men and 3193 elderly women (55 years and above) from the district of Rottendam to assess the education and nutrient intake (Rossum et al 2000). Lower educated men and women had higher intake of almost all macronutrients compared with higher educated subjects. The total energy intake of men/women with lowest eduction vs highest education was 9.60/7.54 vs 8.94/7.17 MJ/day. Also intake of visible fat (46/37 vs 44/34 g/day) and meat consumption (130/100 vs 116/86 g/day) was higher in lower educated subjects as compared to the higher educated men and women. The higher educated used relatively more lean mean and low fat milk products. On the contrary, fibre intake was intake was lower in lower educated (1.88/2.17 vs 2.03/2.29 g/day). However, this study did not find difference in the intake antioxidants vitamins from food between educational groups.

Dietary patterns were also assessed by Dennis et al (1997) in a prospective study of cardiovascular disease (CVD) risk factors in four Chinese populations: Beijing urban (BJ-U) and rural (BJ-R), Guangzhou urban (GZ-U) and rural (GZ-R). A total of 10,076 men and women 35-54 years old were surveyed in 1983-84 and resurveyed in 1987-88. Comparison of mean intakes in the two periods showed increases in meat, poultry, fish (except GZ-R), eggs (rural only), milk (except BJ-R) and alcoholic beverages. The largest shifts were in meat intake (29%-39%), alcoholic beverages (71%-104%) and fats in the urban samples (33%-35%). These changes are reflected in increased mean intakes of animal protein, fat, saturated fatty acids (SFA). Mean total fat intake now exceeds the PRC recommended range of 20-25% of energy in three of the four samples.

The macro-nutrient intake of residents in Padang area, West Sumatra, Indonesia were studied by Masatoshi et al (1997). The daily energy intake (1130±420 kcal) of elderly people in a rural traditional group was significantly lower than that in an urbanised "modernised" group (1700±460 kcal) ($p<0.01$). Even in young urbanised people (younger than 60 years old), 44.2% were below 2000 kcal per day. In the case of elderly people, in rural and urbanised groups 90%, and 33% of the respondents were below 1500 kcal per day, respectively. As for individual nutrients, the daily protein intake of elderly people in both the urbanised and rural groups was rather low. However, daily fat intake and carbohydrate intake of the younger people in the urbanised group were adequate, but those in the elderly group were not. In the case of the rural elderly group, macronutrient and energy intake were extremely low.

Fu et al (1998) investigated the food consumption patterns of 430 Beijing Chinese adults and assessed the impact on these patterns of the following socio-demographic characteristics: gender, age, educational achievement, and gross household income. Men consumed more wheat products, red meat and tea, whereas women consumed more vegetables, fruit, nuts, fish, eggs and milk. Women also tended to consume a wider variety of food than did men. Furthermore, it was found that younger and more educated people tended to consume a wider variety of food. Age also had an important influence on the food intake. Younger and generally more educated adults tended to consume foods associated with affluence: meats, soft drinks and beer, while the older population tended to consume more vegetables (women only), milk and tea in their diets. The older members of this population, who probably have a decreased functional reserve of nutrients, and the less educated, appeared not to be taking advantage of the availability of a wide variety of food, further increasing the risk of nutrient deficiency. On the other hand, the younger and more educated, who tended to consume a wide variety of foods, were more likely to maintain adequate nutritional standards.

Antioxidants have been linked to protection against degenerative diseases associated with aging. Plasma concentrations were determined in a study by Hallfrisch et al (1994) on 200 women and 231 men aged 20- 95 years who took part in the Baltimore Longitudinal Study of Aging. Men consumed more vitamin A from animal and less from vegetable sources than did women. These sex differences are reflected in plasma concentrations of retinol and beta-carotene. About 20% of subjects had vitamin A intakes less than recommended dietary allowances; however, no men and only two women had marginal plasma retinol (< 0.35 mumol/L) concentrations. Older people had higher plasma alpha-tocopherol, which correlated with total intake. Forty - two men

and 35 women had plasma alpha-tocopherol concentrations that were considered marginal. Sex differences in sources of dietary and plasma vitamin A may have consequences in relation to aging and longevity. Apparent marginal intakes and plasma concentrations of vitamin E need to be further examined to determine effects on health status.

Data from a cross-sectional survey of 746 non-institutionalized, Boston- area elderly individuals (aged > or = 60 y) were analyzed by Jacques et al (1995) to assess the relation between antioxidant nutrient intake and plasma antioxidant status. Intakes of vitamin C and carotenoids and supplemental vitamin E were estimated by using 3-d diet records. Mean plasma concentrations of these nutrients were calculated within categories of intake, and polynomial contrasts were used to test for linear trends of the plasma nutrient concentrations across these categories. Adjustments for the corresponding intake of the plasma nutrient under consideration, as well as age, sex, and smoking status were made to minimize potential confounding. Plasma alpha-tocopherol concentrations were 18% greater in individuals consuming > or = 220 mg vitamin C/d compared with those with intakes < 120 mg/d (P for trend < 0.001). Plasma carotenoid concentrations were 13% higher across increasing categories of vitamin C intake (P for trend = 0.002). An increasing intake of carotenoids was moderately associated with higher plasma alpha-tocopherol (P for trend = 0.008) and unrelated to ascorbic acid status. An increasing intake of supplemental vitamin E was weakly correlated with plasma ascorbic acid (P for trend = 0.05) and unrelated to carotenoid status. These results provide epidemiologic evidence that increasing intake of either vitamin C, vitamin E, or carotenoids is associated with greater plasma concentrations of one or both of the other antioxidant vitamins and not associated with any impairment in antioxidant status.

Frequency of fruits and vegetables consumption and blood caerphilly cohort of men aged 55-69 years were assessed by (Strain et al 2000). Only 4.3% of the men met the recommended target of five portions, while 33.3% of the men consumed one or fewer portions of fruit and vegetables per day. Those men who consumed the poorest diets with respect to fruit and vegetable intakes were more likely to be from lower socio-economic classes, drink more alcohol and be current smokers. Fruit and vegetable intake reflected plasma concentrations of antioxidants, which showed a dose-response relationship to frequency of consumption.

FREE RADICAL THEORY OF AGING

Aging is a phenomenon which is genetically programmed, however, external factors such as environment, lifestyle factors modify the aging process significantly. Many theories have been put forward to explain aging as a consequence of some specific cumulative damage process. Among them, the well accepted theory refers to the increased levels of free radicals which was proposed by Harman (1956). The basic idea behind this theory was the assumption that aging results from the random deleterious effects of the tissues brought about by free radicals that are produced in the course of cellular metabolism.

Free radicals are molecules rarely occurring in nature, that contain one or more "unpaired" electrons. A free radical molecule containing a single unpaired electron is frequently denoted by R•, where the dot refers to the unpaired electron (Mehlhorn 1994).

Free radicals rarely arise naturally because of the familiar chemical principle that valence electrons in atoms form chemical bonds, each of which consists of an electron pair. Energy must be supplied to break chemical bonds and usually the resulting molecular fragments are free radicals. Once formed, these free radical fragments will combine rapidly with other free radical fragments, or with each other, to form non-radical products (Mehlhorn 1994).

Oxygen is a compound which is used for all the metabolic processes. During various metabolic processes, oxygen acts as a terminal electron acceptor and is eventually converted to a more stable state water. However, reduction of oxygen is frequently incomplete, even under normal conditions and a series of reactive chemical intermediates called "reactive oxygen species" (ROS) are produced (Sinclair et al 1991).

When an oxygen molecule collides with another free radical, the favorable energetics of electron pairing imply that a new addition product, called a ***peroxyl radical,*** will be formed. If oxygen reacts with some non radical molecule that has a sufficiently reducing chemical potential, a non-electron transfer to oxygen can occur, resulting in the ***superoxide radical.*** In such an electron transfer reaction, the energy that is required to break one bond is recovered in the formation of another bond. Fortunately, oxygen is inert towards most nonradical molecules so it cannot initiate free radical chain reaction. When oxygen reacts with an organic radical whose unpaired electron is associated with a carbon atom, the resulting peroxyl radical

molecules are, moderately reactive and will remove hydrogen atoms from a variety of other molecules, leading to chain reactions and an accumulation of hydroperoxides (Mehlhorn 1994).

The chemical products of most of the free radical reactions involving oxygen are so reactive themselves as to have gained many of they the designations of "active oxygen" molecules. Several active oxygen species are of interest in biological damage processes. These include the free radicals:

- *Hydroxyl radical, OH•*
- *Superoxide radical,* O_2^-
- *Singlet oxygen,* $^1O_2$
- *Nitric oxide NO•*
- *Hydrogen peroxide,* H_2O_2

The most reactive is the hydroxyl radical - virtually no biological molecule is immune to its attack. Hence, organisms have evolved elaborate defenses to ensure that the hydroxyl radical arises as infrequently as possible.

Singlet oxygen, which may arise during peroxyle radical reactions, is also reactive, although not as reactive as the hydroxyl radical

Hydrogen peroxide is of interest as a potential damaging species because, in the presence of freely dissolved or loosely bound iron or copper and mild reducing agents like ascorbic acid, it can decompose to produce hydroxyl radicals. Because of the destructiveness of hydroxyl radicals, hydrogen peroxide decomposition could be a major source of biological damage under conditions of iron or copper release from protein binding sites. Hydrogen peroxide can also interact with heme proteins to produce highly oxidising products (ferryl species) that can initiate free radical reactions.

The superoxide radical is not very reactive chemically, but its lack of reactivity may be offset by the abundance of the radical species in aerobic biological environments. It may exert its damaging effects by serving as a reductant for ferric iron, particularly when iron is sequestered within proteins, thus releasing the ferrous iron into aqueous solution. Superoxide radicals react with each other or with appropriate reducing agents to produce hydrogen peroxide (Mehlhorn 1994).

All transition metals, with the exception of copper contain one electron in their outermost shell and can be considered free radicals. Copper has a full outer shell, but loses and gains electrons very easily making itself a free radical (Halliwell and Gutteridge 1984). In addition iron has the ability to gain and lose electrons (i.e. (Fe2+«Fe3+) very easily. This property makes iron and copper two common catalysts of oxidation reactions. Iron is major component of red blood cells (RBC). A possible hypothesis is that the stress encountered during may break down RBC releasing free iron. The release of iron can be detrimental to cellular membranes because of the pro-oxidation effects it can have. Zinc only exists in one valence (Zn2+) and does not catalyze free radical formation. Zinc may actually act to stop radical formation by displacing those metals that do have more than one valence.

GENERATION OF FREE RADICALS

Free radical formation occurs continuously in the cells as a consequence of both enzymatic and non - enzymatic reactions. The sources for these enzymatic and non - enzymatic reactions can be internal as well as external. Some internally generated sources of free radicals include mitochondria, xanthine oxidase, reactives involving iron and other transition metals, arachidonate pathways, peroxisomes, exercise, inflammation, ischaemia / reperfusion (Langseth 1996). Externally generated sources of free radicals are cigarette smoke, environmental pollutants, radiation, ultraviolet light, certain drugs, pesticides, anaesthetics, industrial sovlents and ozone (Langseth 1996). Enzymatic reactions also include deliberate synthesis of reactive oxygen species as phagocytes to neutralise viruses and bacteria.

Mitochondria are the most investigated biological system in the field of free radical theory of aging. The reason being simple. Mitochondria are present in almost all cell types and in all tissues. Mitochondria are present in almost all cell types and in all tissues. Mitochondrial respiration is associated with energy conservation which supplies the cell with a continuous flow of ATP. The relatively high efficiency of the energy gain from citric acid cycle intermediates is because the O_2 forms the terminal e^- acceptor of mitochondrial respiration. Depending on cell type, between 85-99 % of the total cellular O_2 consumed is metabolised to water by respiring mitochondria. Thus, if mitochondria prove to be the ultimate target where oxidative stress is manifested severe consequences both on energy metabolism of the cell and on an increase in prooxidant formation above normal levels can be expected.

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All living tissues of the human body need oxygen to survive. If their supply of blood and oxygen is cut off (a situation called ischaemia) they begin to die. Irreversible damage can be prevented only by reperfusion - the restoration of blood flow and reintroduction of oxygen. Ironically, although reperfusion is necessary for recovery, it can damage tissues still further because harmful oxygen free radicals are formed during the reperfusion process (Langseth 1995).

Nitric oxide synthase (NOS) is an example of a family of heme-containing monooxygenases that, under the restricted control of a specific substrate, can generate free radicals. While the generation of nitric oxide (NO•) depends solely on the binding of L-arginine, NOS produces superoxide (O_2^-) and hydrogen peroxide (H_2O_2) when the concentration of the substrate is low. (Porasuphatana et al 2003).

Free radicals are known to be present in cigarette smoke and to react with a variety of biological molecules. Cigarette smoke has "tar phase" which can be extracted as a dark brown material on glass wool and extracted into ethanol. Another type of free radical found in filtered cigarette smoke, which is designated s "gas phase" contains 300 to 500 ppm of nitric oxide (NO•), a weakly reactive free radical and a potent vasodilator (Estefan et al 1970). NO• is converted to the nitrogen dioxide radical (NO_2•) in the presence of oxygen which is more reactive than NO•. Cigarette smoke is known to contain hydrogen peroxides, to generate hydrogen peroxides in aqueous solution and to stimulate peroxide production by leukocytes. (Cosgrove et al 1985)

Cigarette smoke is also known to contain powerful metal chelators, e.g., catechol, which would be expected to stabilise hemoglobin decomposition products and to bind iron that may be released during hemoglobin decomposition. Intercalculation of iron complexes into DNA can induce base modifications and strand breaks. This is particularly important damage mechanism because it may not be responsive to antioxidants. (Pryor et al 1983).

FREE RADICAL DAMAGE

If free radicals are not inactivated, their chemical activity can pose considerable hazard to biological systems (Mehlhorn 1994). The most of the damaging free radicals exhibit some or all of the following reaction pattern:

- *Attack other molecules indiscriminately.*
- *Produce oxygen-consuming chain reactions, such that a single free radical effectively damages a large number of other molecules.*
- *Cause fragmentation or cross-linking of molecules, including vital macromolecules like DNA and critically important enzymes.*

Because of the random reactions that can occur, some of the products of free radical chemistry are completely foreign to the repair or turnover enzymes of the cell thereby damaging all cellular macromolecules including protein, carbohydrates, lipids and nucleic acid. Biological organisms have the capacity to minimise such adverse chemical reactions or to repair the damage or to compensate for its effects (eg., by replacing an irreversible damaged cell with a new cell). However, no repair system or compensatory mechanism can be absolutely efficient if the damage to the macromolecules is so random that they are altered in virtually limitless variety.

The damage to cellular macromolecules due to free radicals reactions produce adverse changes. These changes are expected to get accumulated with age throughout the body. Such "normal" changes with age are relatively common to all. However, superimposed on this common patterns are patterns influenced by genetics and environmental differences that modulate the free radical damage. These are manifested as diseases at certain ages. Destructive effects of free radicals on proteins may play a role in the causation of cataracts; free radical damage to DNA is

implicated in the causation of cancer while its effects on LDL cholesterol is very likely responsible for heart disease. Oxidative processes have also been implicated in the causation of both cataract and age related disorder of retina - maculopathy along with certain neurological disorders like parkinson's disease. (Puri 1999) (Figure1)

FREE RADICAL DEFENSE MECHANISM

The aerobic organisms are protected by a defense system against oxidative damage induced by active oxygen and free radicals. The various defenses are complementary to one another because the antioxidants act on different oxidants as well as in different compartments. Antioxidant means "against oxidation." Antioxidants are effective because they are willing to give up their own electrons to free radicals. When a free radical gains the electron from an antioxidant it no longer needs to attack the cell and the chain reaction of oxidation is broken (Dekkers et al 1996.). After donating an electron an antioxidant becomes a free radical by definition. Antioxidants in this state are not harmful because they have the ability to accommodate the change in electrons without becoming reactive. The human body has an elaborate antioxidant defense system. Antioxidants are manufactured within the body and can also be extracted from the food humans eat such as fruits, vegetables, seeds, nuts, meats, and oil. There are two lines of antioxidant defense within the cell viz., the enzymatic defense that includes glutathione peroxidase, superoxide dismutase (SD), and catalase (Dekkers et al 1996). The second line of defense include a small molecular weight non-enzymatic defense which act as antioxidants; that is, they react with oxidising chemicals reducing their capacity for damaging effects. These antioxidants like vitamins such as vitamin E, vitamin C and β-carotene along with other micronutrients or even non-nontrient components like phytochemicals especially flavonoids and phenolic compounds. Some of the antioxidants are hydrophilic and others lipophilic. They function by suppressing the generation of free radicals and active oxygens, scavenging them and repairing the damage (Figure 2) (Kaczmarski et al 1999).

Figure 1 : Interaction between free radicals and antioxidants affecting aging

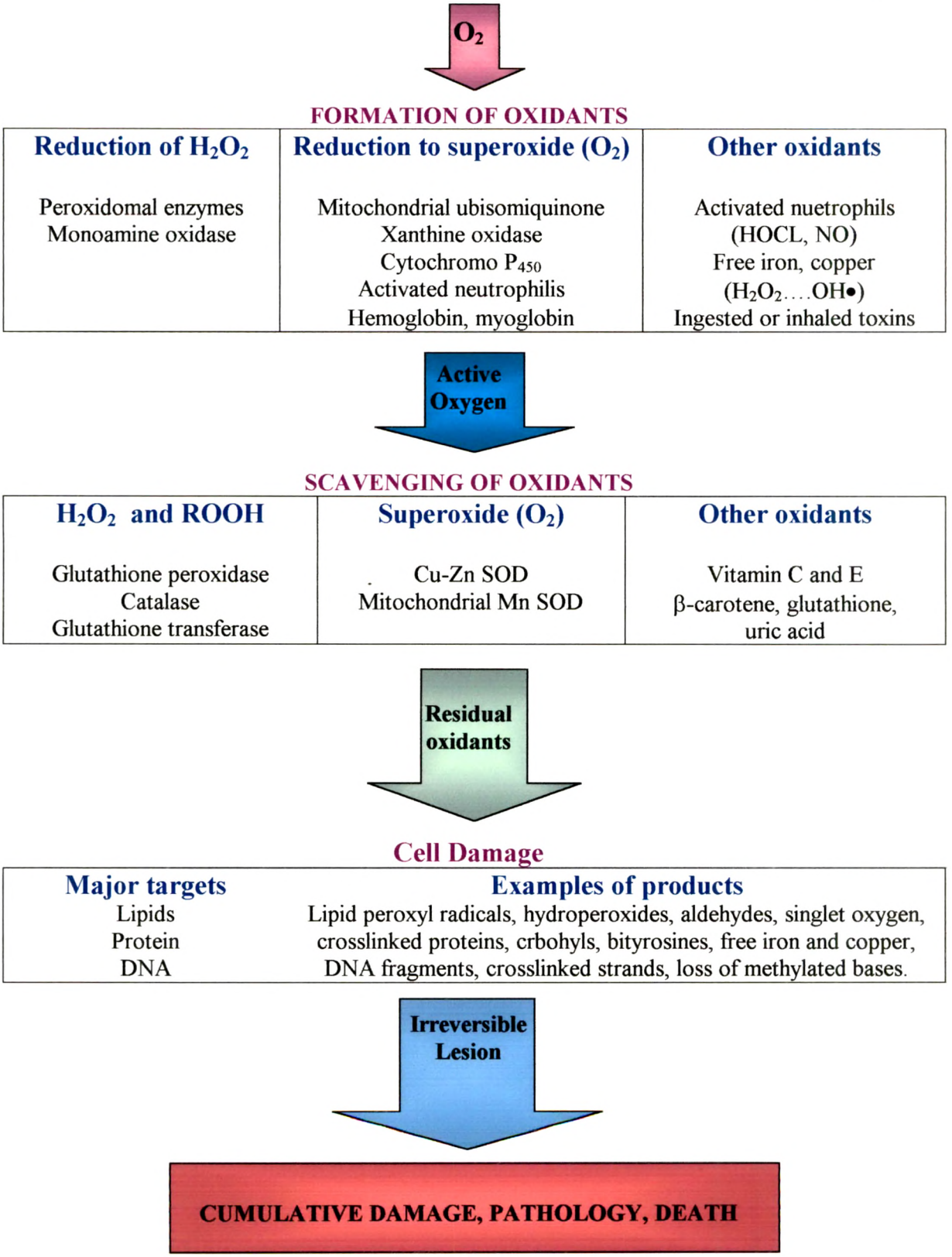
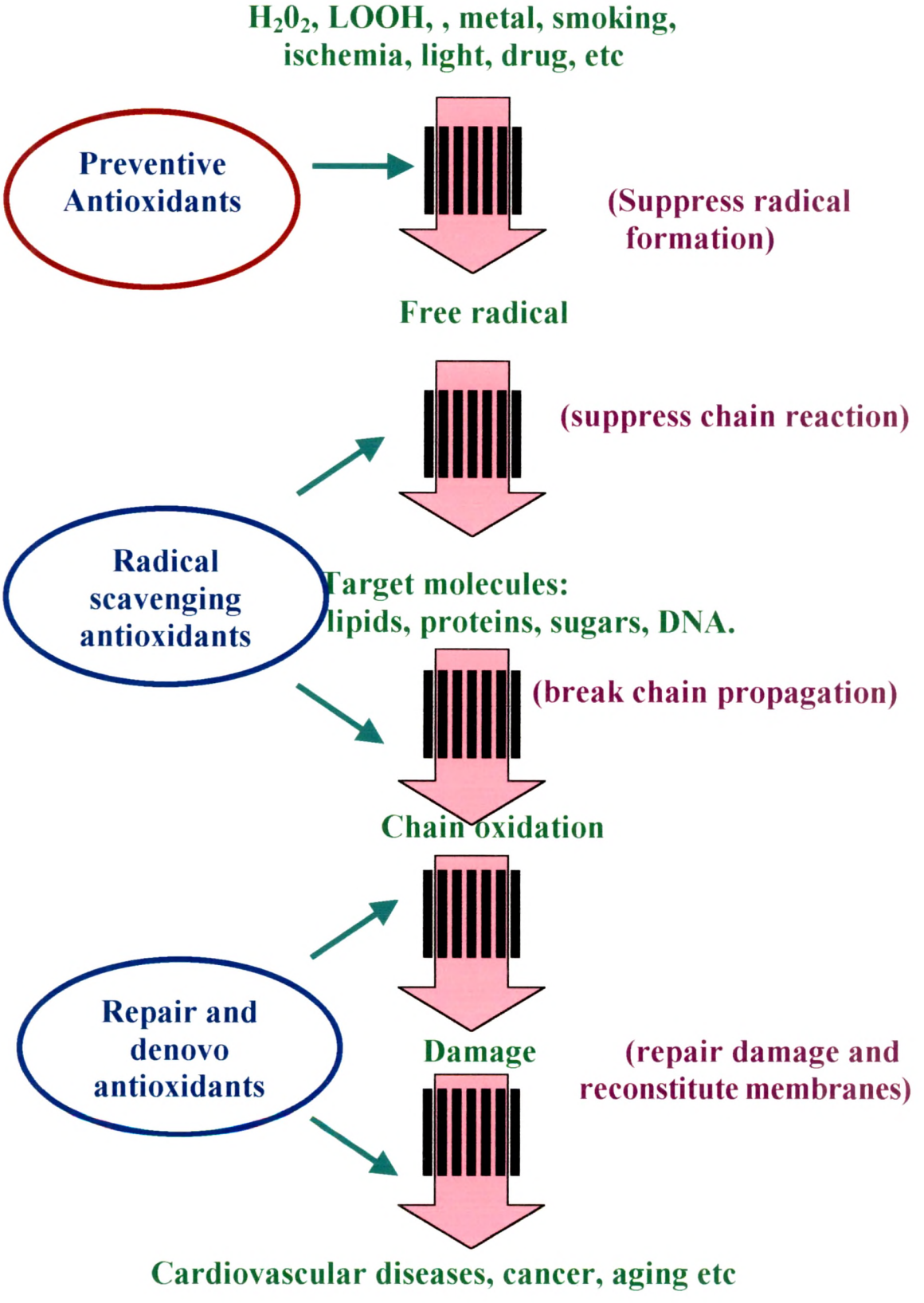


Figure 2 : Defense systems in vivo against oxidative damage



ENZYMATIC DEFENSE

The enzymatic defense against free radical damage is achieved by superoxide dismutase, catalase, and peroxidases.

SUPEROXIDE DISMUTASE (SOD)

SOD is an endogenously produced intracellular enzyme present in essentially every cell in the body. Cellular SOD is actually represented by a group of metalloenzymes with various prosthetic groups. The prevalent enzyme is cupro-zinc (CuZn) SOD, which is a stable dimeric protein (32,000 D).

SOD appears in three forms: (1) Cu-Zn SOD in the cytoplasm with two subunits, and (2) Mn-SOD in the mitochondrion (Mayes 1993; Warner 1994). A third extracellular SOD recently has been described contains Copper (CuSOD).

$2O_2 \cdot \square + 2H\square + SOD \rightarrow H_2O_2 + O_2$

SOD is considered fundamental in the process of eliminating ROI by reducing (adding an electron to) superoxide to form H_2O_2. Catalase and the selenium-dependent glutathione peroxidase are responsible for reducing H_2O_2 to H_2O.

The respective enzymes that interact with superoxide and H_2O_2 are tightly regulated through a feedback system. Excessive superoxide inhibits glutathione peroxidase and catalase to modulate the equation from H_2O_2 to H_2O. Likewise, increased H_2O_2 slowly inactivates CuZn-SOD. Meanwhile, catalases and glutathione peroxidase, by reducing H_2O_2, conserve SOD; and SOD, by reducing superoxide, conserves catalases and glutathione peroxidase. Through this feedback system, steady low levels of SOD, glutathione peroxidase, and catalase, as well as superoxide and H_2O_2 are maintained, which keeps the entire system in a fully functioning state (Fridovich 1993).

SOD also exhibits antioxidant activity by reducing $O_2^{\cdot}$ $^{\square}$ that would otherwise lead to the reduction of Fe^{3+} to Fe^{2+} and thereby promote · OH formation. When the catalase activity is insufficient to metabolize the H_2O_2 produced SOD will increase the tissue oxidant activity. Hence, it was found that the antioxidant enzymes function as a tightly balanced system, any disruption of this system would lead to promotion of oxidation.

GLUTATHIONE PEROXIDASE

The glutathione redox cycle is a central mechanism for reduction of intracellular hydroperoxides.

It is a tetrameric protein 85,000-D. it has 4 atoms of selenium (Se) bound as seleno-cysteine moieties that confers the catalytic activity. One of the essential requirements is glutathione as a cosubstrate.

Glutathione peroxidase reduces H_2O_2 to H_2O by oxidizing glutathione (GSH) (Equation A). Rereduction of the oxidized form of glutathione (GSSG) is then catalysed by glutathione reductase (Equation B). These enzymes also require trace metal cofactors for maximal efficiency, including selenium for glutathione peroxidase; copper, zinc, or manganese for SOD; and iron for catalase (Halliwell 1995).

$$H_2O_2 + 2\ GSH \rightarrow GSSG + 2\ H_2O \text{ (equation A)}$$

$$GSSG + NADPH + H^+ \rightarrow 2\ GSH + NADP^+ \text{ (equation B)}$$

CATALASE

This enzyme is a protein enzyme present in most aerobic cells in animal tissues. Catalase is present in all body organs being especially concentrated in the liver and erythrocytes. The brain, heart, skeletal muscle contains only low amounts.

Catalase and glutathione peroxidase seek out hydrogen peroxide and convert it to water and diatomic oxygen. An increase in the production of SOD without a subsequent elevation of catalase or glutathione peroxidase leads to the accumulation of hydrogen peroxide, which gets converted into the hydroxyl radical. Catalase is located exclusively in the peroxidomes of most cells. It is alsofound in red cells. Some humans lack this enzyme altogether, yet seem to suffer no adverse effects under normal circumstances, possibly because of the existence of another peroxide-decomposing enzyme like gluthatione peroxidase.

$2\ H_2O_2 \rightarrow 2\ H_2O + O_2$ (Krinsky 1992)

Nutrition plays a key role in maintaining the body's enzymatic defences against free radicals. Several essential minerals including selenium, copper, manganese and zinc are involved in the structure or catalytic activity of these enzymes. If the supply of these minerals is inadequate, enzymatic defences may be impaired (Langseth 1995).

NON-ENZYMATIC DEFENSE

A second line of defence is small molecular weight non-enzymatic which act as antioxidants; that is, they react with oxidising chemicals reducing their capacity for damaging effects. These antioxidants like vitamins and other micronutrients or even non-nontrient components like phytochemicals especially flavonoids and phenolic compounds (Puri 1999).

Although a wide variety of antioxidant in foods contribute to disease prevention, the bulk of research has focussed on three antioxidants which are essential nutrients or precurssor of nutrients - vitamin E, vitamin C, and β-carotene.

VITAMIN E

Vitamin E is the generic term used to describe a group of atleast eight compounds that exhibit the biological activity of α-tocopherol. The group comprises of α-, β-, γ-, and δ-tocopherol and α-, β-, γ-, and δ-tocotrienols. All of these compounds occur as a variety of isomers. α-tocopherol is the most active form of vitamin E (Rock et al 1996).

Vegetable oils are the primary source of vitamin E. Corn and soybean oil contain proportionately large amounts of γ-tocopherol accounting for 7 % and 15 % of the vitamin E present in these oils. In comparison, α-tocopherol predominates in olive, canola, safflower, and sunflower oils. Fruits and vegetables along with leafy vegetables are poor source of α-tocopherol (Rock et al 1996).

Absorption of tocopherols is rather inefficient. At physiologic doses, approximately 20 % to 40 % of α-tocopherol is absorbed and the percentage of absorption decreases as the dose increases (Traber et al 1993). Absorption is facilitated by the concurrent intake and digestion of dietary fat, because both bile salts and pancreatic secretions are necessary for absorption of vitamin E. The process consists of uptake by the enterocyte and secretion via the chylomicron, followed by liver uptake and release back into the circulation in association with very low density lipoprotein (Machlin 1991). The liver is the primary site of regulation, which exhibits a distinct preference for the α-form (Yoshida et al 1992; Traber et al 1989). Vitamin E appears to undergo little metabolism; fecal elimination is presumed to be the primary route of excretion (Machlin 1991).

In the plasma, vitamin E circulates in association with lipoproteins, with most found in the LDL fraction under steady-state conditions (Traber et al 1993). α-tocopherol is the predominant antioxidants found in association with LDL; it is reported to be present at the molar ratio of 6:1 (α-tocopherol to LDL) in well nourished humans (Esterbauer et al 1991).

In cells, most of the vitamin E is situated in the membranes, adjacent to unsaturated fatty acids that are vulnerable to free radical damage. Vitamin E is a potent chain-breaking antioxidant, scavenging oxygen radicals and terminating free radical chain reaction (Burton and Traber 1990).

VITAMIN C

Vitamin C is the generic descriptor for all compounds exhibiting the biological activity of ascorbic acid, which includes the oxidised form, dehydroascorbic acid (DHAA). Citrous fruits, and green leafy vegetables are the major sources of vitamin C in the diet.

Vitamin c is absorbed in the human intestine through an energy-dependent active process that is saturable and dose dependent. The intestinal absorption of ascorbic acid and its entry into cells may be facilitated by conversion into DHAA (Rock et al 1996).

The chemopreventive action of vitamin C is attributed to two of its functions. It is a water-soluble chain breaking antioxidant (Ishwarial et at 1991). As an antioxidant, it scavenges free radicals and reactive oxygen molecules. It also prevents formation of carcinogens from precursor compounds (Block and Menkes 1988).

Ascorbic acid is more effective in inhibiting lipid peroxidation. Than other plasma components (Frei 1989). This is due to its ability to trap peroxyl radicals in the aqueous phase before they can initiate lipid peroxd. Thus protecting the biomembrane against peroxidative damage (Sies and Stahl 1995).

CAROTENOIDS

Carotenoids are pigments that are found in plants and micro-organisms but are not synthesized in animals. Nearly 600 of these compounds have been identified and less than 10 % of these compounds can be metabolised to retinol and function as vitamin A. The predominant plasma carotenoids are lutein, β-cyptoxanthin, lycophene, α-carotene, and β-carotene, which accounts for 90 % of more of the circulating carotenoids in human beings (Rock et al 1996).

The antioxidant function of beta-carotene is due to its ability to quench singlet oxygen, scavenge free radicals and protect the cell membrane lipids from the harmful effects of oxidative degradation (Krinsky and Deneke 1982; Santamaria et al. 1991). The quenching involves a physical reaction in which the energy of the excited oxygen is transferred to the carotenoid, forming an excited state molecule (Krinsky 1993). It thus behaves like a chain breaker.

Ascorbic acid and α-tocopherol act as a potent, and probably the most important, hydrophilic and lipophilic antioxidants, respectively. They function at their own site individually and furthermore act synergistically. β-carotene has lower reactivity towards radicals than does α-tocopherol and acts as a weak antioxidant in solution. It is more lipophilic than α-tocopherol and is assumed to be present at the interior of membranes or lipoproteins, which enables it to scavenge radicals within the lipophilic compartment more efficiently than does α-tocopherol (Niki et al 1995).

NON-NUTRIENTS ANTIOXIDANTS

The non - nutrient antioxidants are consumed daily often at concentrations far exceeding nutritional antioxidants. These compounds are mainly polyphenolics especially flavanoids, phenolic acids, anthocyanidins etc (Deckar 1995). Flavonoids and other polyphenols belong to the group of phytochemicals. Research of flavonoids received added impulse with the discovery of the "French Paradox".

PHYTOESTROGEN

Flavonoids and other polyphenols belong to the recently popular phytochemicals i.e chemicals derived from plant material with potentially beneficial effects in human health (Bor et al 1996). The compounds are known as secondary plant metabolites, which indicates that most of these substances have been regarded as non essential and therefore secondary in function. Yet over the years they have been found to be an important part of the human diet and are considered an active principle in some medicinal plants. Many diverse functions have been attributed to them: aside from acting as antioxidants they are mutagenic and have biocidal effects, yet they are also anticarcinogens, have antifertility properties, and express beneficial effects in inflammatory and immunomodulatory systems and interact with signal transduction process.(Middleton 1984).

Epidemiologic studies suggest a protective role of dietary flavonoids against coronary heart disease (de Groot and Rauen 1998). An important effect of flavonoids is the scavenging of free radicals. In vitro experimental systems also showed that flavonoids possess anti-inflammatory, antiallergic, antiviral, and anticarcinogenic properties (Middleton 1998).

In 1986, in a prospective study of 34492 postmenopausal women in Iowa, Kushi et al (1999) examined the association of flavonoid intake with CHD and stroke mortality. Over 10 years of follow-up, 438 deaths from CHD and 131 deaths from stroke were documented. Total flavonoid intake was associated with a decreased risk of CHD dealth after adjusting for age and energy intake (p for trend=0.04). However, decreased risk was seen in each category of intake compared with the lowest. Relative risks and 95 % confidence intervals of CHD death from the lowest to highest intake category were 1.0, 0.67 (95 % CI:0.49-0.92), 0.56 (95 % CI:0.39-0.79), 0.86 (95 % CI:0.63-1.18), and 0.62 (95 % CI:0.44-0.87). There was no association between the total flavonoid intake and stroke mortality (p for trend = 0.83). Of the foods that contributed the most to flavonoid intake in this cohort, only broccoli was strongly associated with reduced risk of CHD death.

Dietary antioxidants flavonoids and risk of coronary heart disease was evaluated in the Zutphen Elderly Study by Hertog et al (1993). The flavonoid intake was assessed on 805 elderly men (65-84 years) in 1985 and were followed up for 5 years. The major sources of intake were tea (61 %), onions (13 %) and apples (10 %). Between 1985 and 1990, 43 men died of coronary

heart disease. Flavonoid intake (analysed in tertiles) was significantly inversely associated with mortality from coronary heart disease (p for trend=0.015) and showed an inverse relation with the incidence of myocaridial infarction which was of borderline significance (p for trend=0.08). The relative risk of coronary heart disease mortality in the highest versus the lowest tertile of flavonoid intake was 0.42 (95 % CI:0.20-0.88). After adjustment for age, BMI, smoking, serum total and high density lipoprotein cholesterol, blood pressure, physical activity, coffee consumption and intake of energy, vitamin C, vitamin E, β-carotene, and dietary fibre, the risk was still significant 0.32 (95 % CI:0.15- 0.71). Intakes of tea, onions, and apples were also inversely related to coronary heart disease mortality, but these associations were weaker.

ANTIOXIDANTS IN VARIOUS DISEASES OF AGING

The various diseases which have been related to oxidant stress of aging are disorders of neurological system, degenerative disorders of eye, gastrointestinal damage, cardiovascular systems, cancer and inflammatory diseases (Aruoma 1994). However, the exact mechanism through which free radical damage leads to some of these disease are still unclear. Cardiovascular diseases and various forms of cancers are two of aging disorders that have been implicated in the free radical damage diseases and mechanism through which free radicals cause these disease are well understood.

CARDIOVASCULAR DISEASES

Increasing evidence implicates free radical-mediated cell damage in the development of a number of degenerative diseases and conditions. Cardiovascular diseases are implicated in the free radical damage diseases.

GLOBAL BURDEN

Cardiovascular diseases (CVD) is the leading cause of death in the world today (Padmavati 2000). According to the WHO (2002), it has been estimated that in 2001, 17 million people died of CVD of all types. The most important causes were ischemic heart disease (IHD), hypertension and rheumatic heart disease (RHD).

INDIAN SCENARIO

The projections made by Global Burden of Disease study indicates that developing countries would contribute 13 - 8 % of the CVD burden (Reddy 1999). Population based survey in India reported 10 % incidence of IHD (Reddy and Yusuf 1998).

RISK FACTORS FOR CVD

The traditional risk factors for CVD include (Miller 1996). These include gender, elevated serum lipids, hypercholesterolaemia, hypertension - diabetes Mellitus, cigarette smoking, physical inactivity, obesity.

Although cardiac risk factors in men and women are similar, differences do exist. Age is the strongest predictor of coronary artery disease in both sexes, but onset is usually 10 years later in women than in men. However, in women with diabetes mellitus or renal disease, CVD may begin at the same age as in men. First myocardial infarction occurs about 20 years later in women but is more likely to be fatal. This age gap is thought to be due primarily to beneficial effects of estrogen on lipid profiles, coagulation, and other factors yet to be elucidated (Jadin and Margolis 1998).

The fundamental importance of diet in the development of CVD is through its effects on the development of hypercholesterolaemia. Fats and oils, present in the diet, are important component of human diet with several nutritional and health functions.

The classic studies of Keys et al (1965) and Hegsted et al (1965) have shown that saturated fatty acids raise total and LDL cholesterol levels whereas C18:0 and monounsaturated fat (cis C18:1) are neutral when substituted for carbohydrates and n-6 polyunsaturated fatty acids (PUFAs) lower cholesterol. More recent studies have shown that long-chain n-3 fatty acids are hypotriglyceridemic and trans fatty acids are hypercholesterolemic. Epidemiologic studies have shown that saturated fat intake is associated with increased risk of coronary heart disease, the greatest risk reduction is associated with PUFA intake, and a lesser extent of risk reduction is associated with monounsaturated fat. Both n-6 (linoleic acid) and n-3 (linolenic acid) PUFAs are protective (Hu et al 1993).

In a 10 year follow up study of 667 men aged 64-84 years from Zutphen Elderly Study by Oomen et al (2001) revealed that the relative risk of CAD for the highest compared with the lowest tertiles of α-linolenic acid intake was 1.68 (95 % CI: 0.86,3.29) in 98 cases of CAD. α-linolenic acid intake from sources containing trans fatty acids was also non-significantly, yet positively, associated with CAD risk. Thus no beneficial effect of dietary α-linolenic acid intake was observed on the risk of 10 year CAD incidence in the follow up study.

Involuntary weight gains worsen all elements of the cardiovascular risk profile, including dyslipidemia, hypertension, insulin-resistant glucose intolerance, left-ventricular hypertrophy, hyperuricemia, and elevated fibrinogen. On the basis of data from the Framingham Heart Study and from other studies, it can be concluded that the degree of overweight is related to the rate of development of cardiovascular disease. After 26 y of follow-up in the Framingham study, each SD increment in relative weight was associated with 15% and 22% increases in cardiovascular events in men and women, respectively. Avoidance of weight gain after the age of 25 y is advisable to reduce cardiovascular mortality. There is a great potential benefit to weight loss, suggesting that weight control as a means for preventing and lessening cardiovascular disease become a national health priority. The optimal weight for avoidance of cardiovascular disease and prolonging life corresponds to a body mass index of 22.6 for men and 21.1 for women (Kannel et al 1996)

Overweight is associated with high rates of CVD deaths, especially sudden death among men and congestive heart failure among women The high death rate might occur largely as a consequence of the influence of overweight on blood pressure, blood lipid levels, and the onset of diabetes.

A review of 43 epidemiologic studies in 1987 indicated that physical activity reduces the risk of CHD. The relative risk for CHD associated with physical inactivity is approximately 1.9, slightly lower than the relative risks associated with increased systolic blood pressure (2.1), cigarette smoking (2.5), and elevated serum cholesterol levels (2.4). Several studies indicate that endurance exercise training among patients with documented CHD is associated with reduced morbidity and mortality and that physical activity might improve the likelihood of survival from a myocardial infarction (i.e., heart attack). In addition, evidence documents an association between regular, moderate - intensity physical activity and the lowering of several

other risk factors for CVD, including blood lipid levels, resting blood pressure among persons with borderline hypertension, body composition and overweight, and glucose tolerance and insulin sensitivity (Foster and Burton 1985).

SMOKING AND CVD

Whenever a person smokes a cigarette, the chemicals in cigarette smoke, particularly nicotine and carbon monoxide, damage the cardiovascular system.

- *Nicotine causes both immediate and longer term increases in blood pressure, heart rate, cardiac output and coronary blood flow*
- *Carbon monoxide binds to the haemoglobin, which is what normally carries oxygen from the lungs via the bloodstream, and therefore reduces the amount of oxygen reaching body tissues*
- *Smoking also makes blood vessels and blood cells sticky, allowing cholesterol and other dangerous fatty material to build up inside them. This is called atherosclerosis. This in turn can lead to raised blood pressure and clot formation.*

When a smoker inhales, the nicotine contained in the inhaled smoke reaches the brain via the bloodstream in a matter of seconds. It also quickly reaches muscle tissue. Nicotine receptors (clusters of cells that react specifically to nicotine) in the brain and muscles recognise its presence and a range of physical reactions take place, including the following:

- *an increase in heart rate (as measured by your pulse)*
- *increases blood pressure, causes small blood vessels to narrow, and slows down circulation. This is particularly noticeable in the hands and feet. Because of these, skin temperature is also lowered.*
- *increases tension in some muscles. This can be measured by testing hand tremors with a tremor testing machine before and after a cigarette. Strangely, nicotine can also relax some skeletal muscles at the same time.*
- *increases stomach secretions and changes brain activity. (US Department of Health and Human Services 1988).*

Evidence indicating cigarette smoking as a risk factor for CVD is substantial .Overall, smokers have a 70% greater level of CVD risk than nonsmokers; persons who smoke greater than or equal to 2 packs of cigarettes per day have a two- to threefold greater risk for CVD. The risk for CVD also increases with greater depth of inhalation and with increasing years of smoking, although persons who stop smoking eventually reduce their risk for CVD to a level approaching that of nonsmokers. Cigarette smoking has been reported to act synergistically with other known risk factors for CVD (White 1990).

High blood pressure is another major risk factor for CVD. Some evidence documents that blood pressure-related risk for CVD increases continuously from lowest to highest values for either systolic or diastolic blood pressure. Elevated blood pressure is often associated with other well-known risk factors, including dietary intake, elevated blood lipid levels, obesity, smoking, diabetes mellitus, and physical inactivity (American Heart Association 1998)

The glucose intolerance that accompanies diabetes mellitus is a direct effect of overweight and is often associated with hypertriglyceridemia, hypertension, elevated LDL cholesterol, and depressed HDL. Some evidence documents that diabetes mellitus has a vasculotoxic effect, which is greatest for occlusive peripheral vascular disease; however, CHD and stroke are its most common manifestations. The risk for CVD is three times as high among diabetic women as it is among women without diabetes mellitus. Similarly, the risk for CVD is twice as high among diabetic men as it is among men without diabetes mellitus (American Heart Association 1998).

Many CVD risk factors interact physiologically in the etiology of CVD. Persons with risk factor combinations are at an increased risk for CVD. Obesity is an example of a risk factor for CHD that influences other risk factors, including hyperlipidemia, hypertension, and diabetes mellitus. Physical inactivity has been related to obesity, lipid abnormalities, hypertension, and diabetes mellitus.

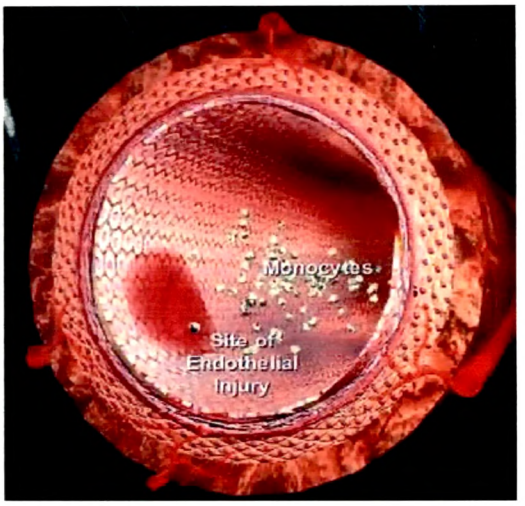
ROLE OF FREE RADICALS IN CVD

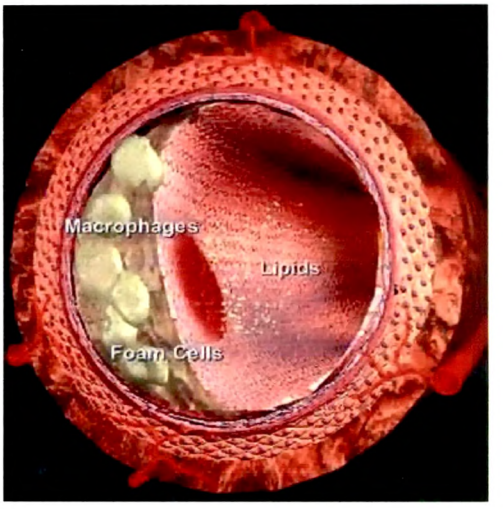
Atherosclerosis, a chronic inflammatory disease of the arterial wall, is the major cause of morbidity and mortality from cardiovascular disease (CVD) in much of the world's population. It is a complex process involving the deposition of plasma lipoproteins and the proliferation of cellular elements in the artery wall. This chronic condition advances through a series of stages

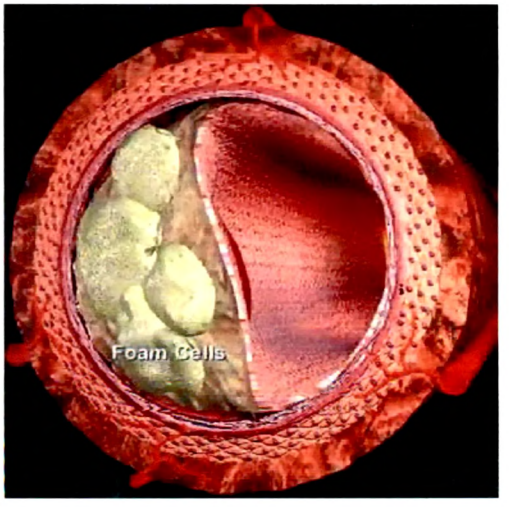
beginning with fatty streak lesions composed largely of lipid-engorged macrophage foam cells and ultimately progressing to complex plaques consisting of a core of lipid and necrotic cell debris covered by a fibrous cap (Ross 1993) (Figure 3).

LDL is an important target of free radicals, and oxidation of LDL is believed to be an important event in development of atherosclerosis (Sato et al 1990). Oxidation of LDL, also termed as lipid peroxidation, is well explained by the "Oxidative - modification hypothesis" (Diaz et al, 1997). LDL initially accumulates in the extracellular subendothelial space of arteries and through the action of resident vascular cells, is mildly oxidised to a form known as minimally modified LDL (Figure 4). This minimally modified LDL induces local vascular cells to produce monocyte chemotactic protein 1 and granulocyte and macrophage colony-stimulating factors, which stimulate monocyte recruitment and differentiation to macrophages in arterial walls. The accumulating monocytes and macrophages stimulate further peroxidation of LDL. The products of this reaction make the protein component of LDL more negatively charged. By virtue of its increased negative charge, this completely oxidised LDL is recognised by scavenger receptors on macrophages and internalised to form so-called foam cells. In contrast to the uptake of oxidised LDL by the scavenger-receptor pathway is not subject to negative-feedback regulation and thus results in massive uptake of cholesterol (from oxidised LDL) by the macrophages.

Figure 3b : Progression of lipid-engorged macrophage foam cells in the arterial wall

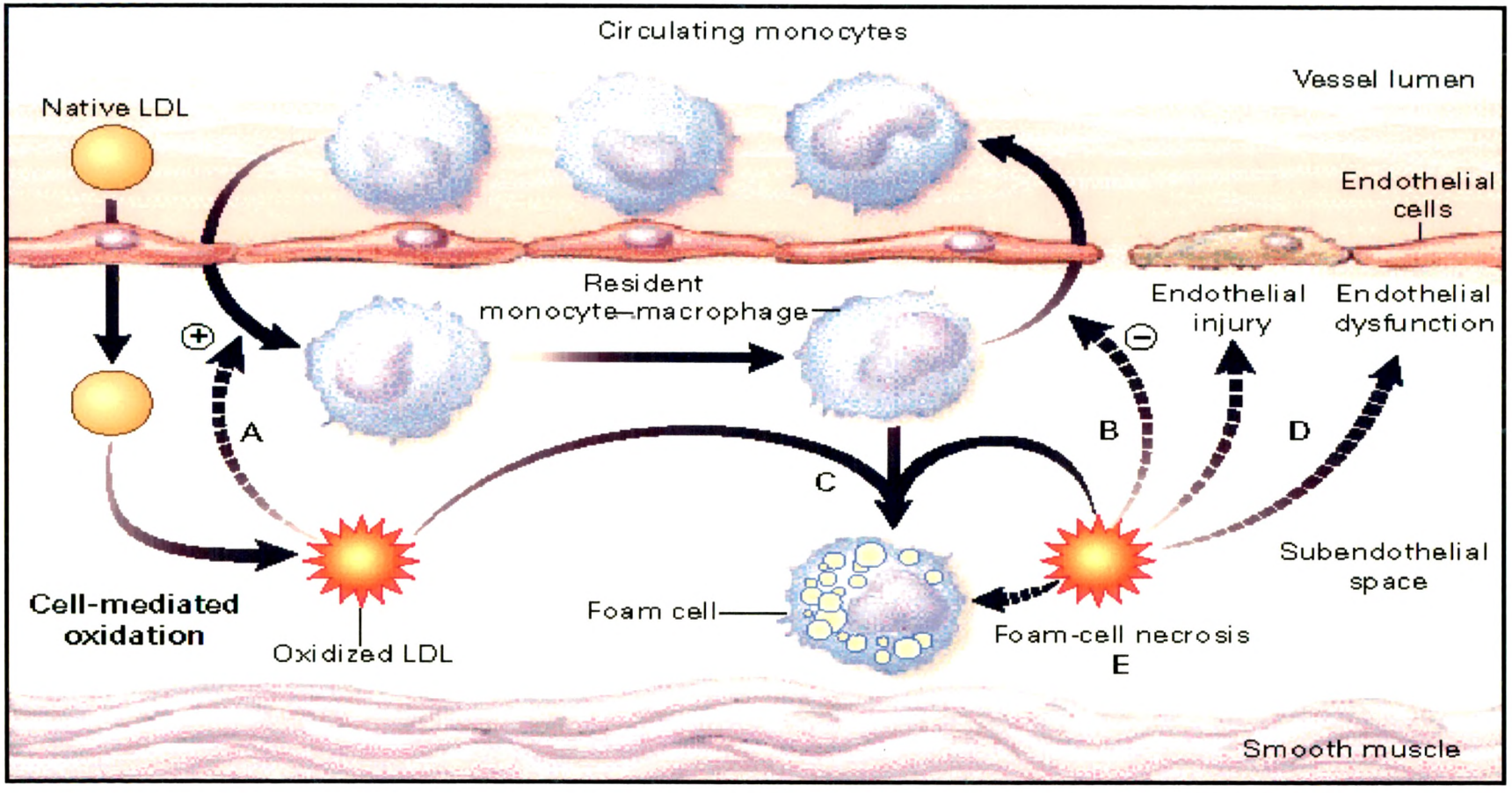






Source : www.strokecentre.org

Figure 4 : Oxidation of LDL via oxidative-modification hypothesis



Source : Diaz et al (1997)

Most of the scientific literature published in the past 15-20 years on nutrition and CVD primarily focused on macro-nutrient intake, mainly fat and cholesterol intake. Although this research is valuable, in that it has helped to educate the public and create a greater awareness of the connection between diet and health/disease, it may have created a greater-than-necessary emphasis on dietary cholesterol and saturated fat, and has given birth to an entire industry of low-fat or no-fat foods and fads designed to help people "eat right". Also over the last few years, a number of researchers have studied the relationships of various micro-nutrients and heart disease. The oxidation of LDL cholesterol and micro-nutrients which act to inhibit this oxidation has been a much-researched topic.

VITAMIN E AND CVD

The oxidation of lipids proceeds by a free radical - mediated chain mechanism in which the lipid peroxyl radical acts as a chain carrier, the important chain propagation step being a hydrogen atom abstraction from lipid by peroxyl radical (reaction 1).

$$LO_2\bullet + LH \xrightarrow{K_r} LOOH + L\bullet \qquad (1)$$

Where LH, L•, LO_2•, and LOOH are lipid, lipid radical (carbon centered), lipid peroxy radical, and lipid hydroperoxide, respectively, α-tocopherol scavenges lipid peroxyl radical before it attacks substrate.

$$LO_2\bullet + TOH \xrightarrow{K_P} LOOH + TO\bullet \qquad (2)$$

Where TOH and TO• are α-tocopherol and A-tocopheroxyl radical, respectively. The competition between reaction 1 and 2, or the relative importance of these two reactions, determines the antioxidant potency of α-tocopherol (Niki 1996).

A number of epidemiologic studies have been performed which point towards a connection between dietary vitamin E intake and heart disease.

Stampher et al (1993) reported data from 87245 Nurses' Health Study participants who were followed up for periods of ≤ 8 years. Risk of major coronary disease was lowest in women within the highest compared with those within the lowest quintile of reported vitamin E intake after adjustment for age and smoking status (relative risk - 0.66; 95 % CI: 0.5-0.87). Lower risk was associated with levels of vitamin E intake that were achievable only by supplementation. Subsequent analysis revealed a 43 % lower risk for vitamin E supplement users versus nonusers and an inverse relationship between risk and duration of supplement use.

Rimm et al (1993) described similar benefit for vitamin E on 39910 male participants of the Health Professionals Follow-up Study (aged 40-75 years). He found that men consuming more than 60 IU per day of vitamin E had a relative risk of 0.64 as compared with those consuming less than 7.5 IU per day (a 36 % decreased risk).

In a prospective cohort study in Finland (Knekt et al 1994), 2748 men and 2385 women were followed for a mean of 14 years. During follow-up, 186 men and 58 women died of coronary heart disease. Only 3 % of the study sample took vitamin supplements. Compared with men in the lowest tertile of intake (intake of vitamins through diet and supplements, < 4.5 IU/d), men with the highest intake of vitamin E (mean > 6.0 IU/d) had a non significant relative risk reduction (RRR) of 34 % (CI:11% to 58 %) after adjustment for age, smoking, serum cholesterol levels, hypertension, body mass index and energy intake. Compared with women in the lowest tertile of vitamin E intake (mean < 3.5 IU/d), women in the highest tertile (mean > 4.7 IU/d) had a RRR of 65 % (CI:12 % to 86%).

Rimm et al (1993) also observed a lower risk of major coronary events in men reporting high versus those reporting low intakes of β-carotene, but in the subgroups analysis, this relationship was only significant in current and former smokers. These findings are consistent with several other studies that indicated an inverse association between dietary intake of β-carotene or provitamin A carotenoids and risk of cardiovascular disease, particularly among smokers (Gaziano et al 1995 ; Kritchevsky et al 1998). Our results are in line with these observations as the intake of β-carotene was significantly higher in men and women without CVD as compared to their respective cases, selected for the present phase of the study.

VITAMIN C AND CVD

A study carried out by Enstrom et al (1992) on > 11000 US adults examined in the first National Health and Nutrition Examination Survey (NHANES I). Individuals reporting high intakes of vitamin C exhibited significantly lower risk of death from all causes, particularly from coronary heart disease, over a 10 year follow up period. Among men, multivariate - adjusted relative risk was 0.75 (95% CI:0.53-0.97) in individuals within the highest versus those within the lowest vitamin C intake group (50 mg/d dietary vitamin C plus regular supplements containing vitamin C versus < 50 mg/d dietary vitamin C). Results were not adjusted for the intake of other antioxidants, however.

In the Western Electric Study, dietary vitamin E and vitamin C intake was assessed over a 20 + year span in 1556 men. For the means of the highest vs the lowest quartile of vitamin C intake, patients with the higher intake had a 30 % decreased risk of death from CAD (Pandey et al 1995).

Similar findings were obtained in the Health Professionals Study (Rimm et al 1993), which included more than 39000 men, participants in the highest quintile of carotene intake (mean 19034 IU/d) had a RRR of 29 % (CI 14 % to 47 %) for coronary reveascularization, myocardial infarction, and death from coronary heart disease compared with those in the lowest quintile (mean 3969 IU/d) after adjustment for cardiovascular risk factors and intake of vitamins E and C. Significantly, reduced risk was seen only in the highest quintile compared with the lowest quintile, corresponding to 4.8 fold difference. The benefit was largely confined to current smokers (RRR 70 %), with no benefit seen in nonsmokers (RRR, -9%).

In the Finnish study of 2748 and 2385 women (Knekt et al 1994), risk for death from coronary heart disease was not significantly reduced in men in the highest tertile of carotene intake (mean > 258 mg) compared with those in the lowest tertile (mean < 147 mg) (RRR, - 2 %; CI: -48 % to 30 %) after adjustment for cardiovascular risk factors . A non-significant reduction was seen for women (RRR 38 %; CI - 29 % to 70 %) in the highest tertile (mean 383 mg) compared with those in the lowest tertile (mean < 182 mg). No adjustment was made for vitamin E or C.

In another study of male pharmaucetical employees (Kok et al 1987), mortality from coronary heart disease was non significantly higher in men with low baseline carotene levels (relative risk 1.53; CI: - 29% to 70 %).

Similar study was carried by Trout (1991) in a small cohort of 730 elderly persons in the United Kingdom followed for 20 years, stroke among persons in the highest tertile of vitamin C intake (mean > 45 mg/d) was significantly reduced (RRR 50 %; CI: 20-70 %) compared with the lowest tertile (mean < 28 mg/d). However, in the Nurses' study and Male Health Professional study, persons using vitamin C did not have a significantly lower risk for myocardial infarction or death from coronary heart disease after adjusting for vitamin E intake.

β-CAROTENE AND CVD

Like vitamin E, the lipid soluble antioxidants β-carotene also associates itself with lipoproteins. Even though the β-carotene content of LDL cholesterol is less than 1/20th the amount of vitamin E (Easterbauer et al 1991), it is an equally potent antioxidants .

In a small prospective study of 1299 elderly nursing home residents (Gaziano et al 1992), risk for death from cardiovascular disease was reduced among residents with a high dietary intake of β-carotene (RRR 46 %; CI 13 % to 66%).

Rimm et al (1993) observed a significal lower association between β-carotene intake and incident of coronary heart disease in a population of 39990 men aged 45 - 75 years participating in Male Health Professional Study.

In a cross-sectional relation between antioxidants vitamin status and carotid atherosclerosis in a 468 men and women aged 66-75 years living in Sheffield, United Kingdom was investigated by Gale et al (2001). The results revealed that in the men, after adjustment for age and cardiovascular disease risk factors, a 20 % higher plasma vitamin C concentration was associated with a 0.004 mm smaller intima media thickness; a 20 % higher β-carotene concentration was associated with 0.005 mm smaller intima-media thickness. Compared with men with high blood concentrations of β-carotene or cholesterol adjusted vitamin E, those with low blood concentrations of these vitamins were 2.5 times as likely to have carotid stenosis of $\geq$ 30 %. Thus it was concluded that a high antioxidants vitamin status may help to prevent initiation and progression of early atherosclerotic lesions in men.

Influence of combined antioxidants nutrient intakes on their plasma concentrations in an elderly population (n=746) aged $\geq$ 60 years from Boston was analysed by Jacques et al (1995). Intakes of vitamin C and carotenoids and supplemental vitamin E were estimated by using a 3 day diet records. Plasma α-tocopherol concentrations were 18 % greater in individuals consuming $\geq$ 220 mg vitamin E/d compared with those with intakes < 120 mg/d (p for trend , 0.001). Plasma carotenoid concentrations were 13 % higher across increasing categories of vitamin C intake (p for trend=0.002). An increasing intake of carotenoids was moderately associated with higher plasma α-tocopherol (p for trend=0.008) and unrelated to ascorbic acid status. An increasing intake of supplemental vitamin E was weakly correlated with plasma ascorbic acid

(p for trend=0.05) and unrelated to carotenoid status. These results provide epidemiologic evidence that increasing intake of either vitamin C, vitamin E or carotenoids is associated with greater plasma concentrations of one or both of the other antioxidants vitamins and not associated with any impairment in antioxidants status.

For the prolongation of life expectancy and reduction of ischemic heart disease (IHD) dietary guidelines generally recommend lowering saturated mammalian fat with partial replacement by vegetable oils and increasing generously vegetables, legumes, and fruits, which provide more essential antioxidants. Plasma antioxidants as assayed in epidemiological studies of complementary type (ie the cross-cultural MONICA Vitamin Substudy reevaluation considering the "Finland-Factor", the Edinburgh Angina-Control Study, and the Basel Prospective Study) consistently revealed an increased risk of IHD (and stroke) at low plasma concentrations of antioxidants, with the rank order as follows: lipid-standardized vitamin E >> carotene = vitamin C > vitamin A, independently of classical IHD risk factors. These studies suggested a decreasing IHD risk through nutrition may be possible when plasma concentrations have the following values: > 27.5-30.0 mumol vitamin E/L, 0.4-0.5 mumol carotene/L, 40-50 mumol vitamin C/L and 2.2-2.8 mumol vitamin A/L (Gey et al 1993).

Osganian et al (2003) carried out a study on women to examine the relation between intakes of carotenoids and risk of coronary artery disease (CAD) in women. In 1984, 73 286 female nurses completed a semiquantitative food-frequency questionnaire that assessed their consumption of carotenoids and various other nutrients. The women were followed for 12 y for the development of incident CAD (nonfatal myocardial infarction and fatal CAD), and dietary information was updated in 1986, 1990, and 1994. During 12 y of follow-up (803 590 person-years), 998 incident cases of CAD were identified. After adjustment for age, smoking, and other CAD risk factors, modest but significant inverse associations was observed between the highest quintiles of intake of ß-carotene and -carotene and risk of CAD but no significant relation with intakes of lutein/zeaxanthin, lycopene, or ß-cryptoxanthin. For women in the highest compared with the respective lowest quintile of intake, the relative risks for ß-carotene and -carotene were 0.74 (95% CI: 0.59, 0.93) and 0.80 (95% CI: 0.65, 0.99), respectively. The association between the specific carotenoids and CAD risk did not vary significantly by current smoking status. Higher intakes of foods rich in -carotene or ß-carotene were thus found to be associated with a reduction in risk of CAD in this study.

FRUITS AND VEGETABLES AND CVD

Understanding the association between fruits and vegetables intake and other health behaviors is important for properly interpreting the rapidly growing number of studies that link low intakes of fruits and vegetables to the risk of cancer and cardiovascular disease.

Johnsen et al (2003) studied the association between intakes of fruits and vegetables and the risk of ischemic stroke in a cohort of 54506 Danish men and women in the Danish Diet, Cancer and Health Study from 1993 to 1997 using a semi quantitative food frequency questionnaire. During 168388 person years of follow up, 266 cases of ischemic stroke involving hospitalisation were identified. After adjustment for potential confounders, persons in the top quintile of fruit and vegetable intake (median 673 g/d) had a risk ratio of ischemic stroke of 0.72 (95 % CI: 0.47, 1.12) relative to persons in the bottom quintile of intake (median 147 g/d) (p for trend = 0.04). When comparing the top quintile with the bottom quintile, an inverse association was most evident for fruit intake (risk ratio: 0.60; 95 % CI: 0.38, 0.95; p for trend = 0.02). Similar risk estimates were seen for most types of fruits and vegetables, although the risks were significant only for citrous fruits. He thus concluded that an increased intake of fruit may reduce the risk of ischemic stroke.

Similar study was carried out by Hung et al (2003) to evaluate the association between fruit and vegetable consumption and peripheral arterial disease. In a cohort of 44059 men initially free of cardiovascular disease and diabetes, 295 cases of peripheral arterial disease were documented during a 12 year follow up. Fruits and vegetable consumption was assessed by food frequency questionnaire. The results revealed that in the age-adjusted model, men in the highest quintile had a relative risk of 0.55 (95 % CI: 0.38-0.80) for overall fruit and vegetable intake, 0.52 (0.36-0.77) for fruit intake and 0.54 (0.36-0.81) for vegetable intake, compared with those in the lowest quintile of intake. However, the associations were greatly weakened after adjustment for smoking and other traditional cardiovascular disease risk factors. Comparing men in the highest quintile versus the lowest quintile, relative risk and 95 % CI were 0.95 (0.62-1.44) for overall fruit and vegetable intake, 0.97 (0.64-1.48) for fruit intake and 0.76 (0.50-1.17) for vegetable intake. Thus this study did not find evidence that fruit and vegetable consumption protects against peripheral arterial disease, although a modest benefit cannot be excluded.

In the first NHANES epidemiologic follow up study by Bazzano et al (2002), fruit and vegetable intake was examined in relation to the risk of cardiovascular disease in 9608 US adults aged 25-74 years, using a food frequency questionnaire. Consuming fruit and vegetables ≥ 3 times / d compared with < 1 time/ d was associated with a 27 % lower stroke incidence (RR:0.73; 95 % CI: 0.57, 0.95; *p* for trend=0.01), a 42 % lower stroke mortality (RR:0.58; 95 % CI: 0.33, 1.22; *p* for trend=0.05), a 24 % lower ischemic heart disease mortality (RR:0.76; 95 % CI: 0.56, 1.03; *p* for trend=0.07), a 27 % lower cardiovascular disease mortality (RR:0.73; 95 % CI: 0.58, 0.92; *p* for trend=0.008), and a 15 % lower all cause mortality (RR:0.85; 95 % CI: 0.72, 1.00; *p* for trend=0.02) after adjustment for established cardiovascular disease risk factor. Thus an inverse association of fruit and vegetable intake with the risk of cardiovascular disease and all cause mortality in the general US population was observed.

Similar study was also carried out by Rissanen et al (2003) to assess the association of dietary intake of fruits, berries, vegetables with all cause CVD related and non-CVD-related mortality in Finnish men aged 42-60 years examined in 1984-1989 in the prospective Kuopio Ischemic Heart Disease Risk Factor (KIHD) Study. The risk of all cause mortality and non-CVD-related deaths was studied in 2641 men and the risk of CVD related death in 1980 men who had no history of CVD at baseline. During a mean follow-up time of 12.8 years, cardiovascular as well as non-CVD and all cause mortality were lower among men with highest consumption of fruits, berries and vegetables. After adjustment for the major CVD risk factors, the relative risk for men in the highest fifth of fruit, berry and vegetable intake for all cause death, CVD-related and non-CVD-related death was 0.66 (95 % CI: 0.50, 0.88), 0.59 (95 % CI:0.33-1.06) and 0.68 (95 % CI:0.46-1.00), respectively, compared with men in the lowest fifth. These data showed that a high fruit, berry and vegetable intake is associated with reduced risk of mortality in middle aged Finnish men.

A prospective study of consumption of carotenoids in fruits and vegetables and decreased cardiovascular mortality in the 1299 elderly Massachusetts was carried out by (Gaziano et al, 1995). For total CVD death and fatal myocardial infarction, risks were lower among those residents in the highest quartile for consumption of carotene-containing fruits and vegetables as compared with those in the lowest. For death due to CVD, the relative risk (RR) was 0.54 (95 % CI:0.34-0.86; *p* for trend=0.004). For myocardial infarction, the RR was 0.25 (95 % CI:0.09-0.67; *p* for trend=0.002).

Flavonoids, a group of phenolic compounds found in fruits and vegetables, are known to have antioxidants properties. They prevent low density lipoprotein oxidation in vitro and thus may play a role in the prevention of coronary heart disease. In 1986, in a prospective study of 34492 postmenopausal women in Iowa, Kushi et al (1999) examined the association of flavonoid intake with CHD and stroke mortality. Over 10 years of follow-up, 438 deaths from CHD and 131 deaths from stroke were documented. Total flavonoid intake was associated with a decreased risk of CHD dealth after adjusting for age and energy intake (p for trend=0.04). However, decreased risk was seen in each category of intake compared with the lowest. Relative risks and 95 % confidence intervals of CHD death from the lowest to highest intake category were 1.0, 0.67 (95 % CI:0.49-0.92), 0.56 (95 % CI:0.39-0.79), 0.86 (95 % CI:0.63-1.18), and 0.62 (95 % CI:0.44-0.87). There was no association between the total flavonoid intake and stroke mortality (p for trend = 0.83). Of the foods that contributed the most to flavonoid intake in this cohort, only broccoli was strongly associated with reduced risk of CHD death.

Dietary antioxidants flavonoids and risk of coronary heart disease was evaluated in the Zutphen Elderly Study by Hertog et al (1993). The flavonoid intake was assessed on 805 elderly men (65-84 years) in 1985 and were followed up for 5 years. The major sources of intake were tea (61 %), onions (13 %) and apples (10 %). Between 1985 and 1990, 43 men died of coronary heart disease. Flavonoid intake (analysed in tertiles) was significantly inversely associated with mortality from coronary heart disease (p for trend=0.015) and showed an inverse relation with the incidence of myocaridial infarction which was of borderline significance (p for trend=0.08). The relative risk of coronary heart disease mortality in the highest versus the lowest tertile of flavonoid intake was 0.42 (95 % CI:0.20-0.88). After adjustment for age, BMI, smoking, serum total and high density lipoprotein cholesterol, blood pressure, physical activity, coffee consumption and intake of energy, vitamin C, vitamin E, β-carotene, and dietary fibre, the risk was still significant 0.32 (95 % CI:0.15- 0.71). Intakes of tea, onions, and apples were also inversely related to coronary heart disease mortality, but these associations were weaker.

CANCER

The other chronic disease that occurs with advancing age is Cancer. Cancer is the end point of multi-step process involving a sequence of events that occur over a period of years or even decades. In this process, a single cell can develop from an otherwise normal tissue into malignancy that can eventually destroy the organism (Guyton and Kensler 1993).

AN OVERVIEW

Cancer is a disease of aging and a major cause of morbidity and death. By the year 2020, the population will have increased by 12 % over that of 1990, but the total cancer incidence will have increased by 60 %, providing that no changes occur in the environment or health care (Kennedy et al 1994). In the United States, 60 % of new cancer cases occur among those age 65 years or older, with more than 50 % of cancer deaths occurring among persons older than 70 years (Kennedy 1997).

Men and women aged ≥ 65 years are at high risk for the major cancers. Data show that persons in this age group have a risk 11 times greater than persons aged < 65 years. The overall age-adjusted mortality rate for the age group ≥ years is 15 times greater than the rate for persons aged < 65 years. Older persons bear the brunt of the cancer burden. (Yancik 1997).

Cancer in humans and animals is a multistep disease process. In this process, a single cell can develop from an otherwise normal tissue into a malignancy that can eventually destroy the organism. Active oxygen species and other free radicals have long been known to be mutagenic.

Experimental carcinogenesis proceeds through at least 3 distinct stages. In **initiation**, a single, somatic cell undergoes non-lethal, heritable mutation. This initiating mutation may provide a growth advantage during the second stage, **promotion.** Tumour promotion produces relatively benign growths that can be converted into cancer in third stage, **malignant conversion.** Like initiation, conversion requires genetic alteration in which cellular growth is further deregulated and thus proceeds uncontrolled (Guyton and Kensler 1993).

Cancer is a very serious health problem at any age, but the diagnosis of a tumor concomitant with the normal and pathologic changes associated with advancing age create a special situation for those providing care and treatment to the elderly. The increase in cancer incidence with age may be attributed to several factors (Mehlhorn 1994):

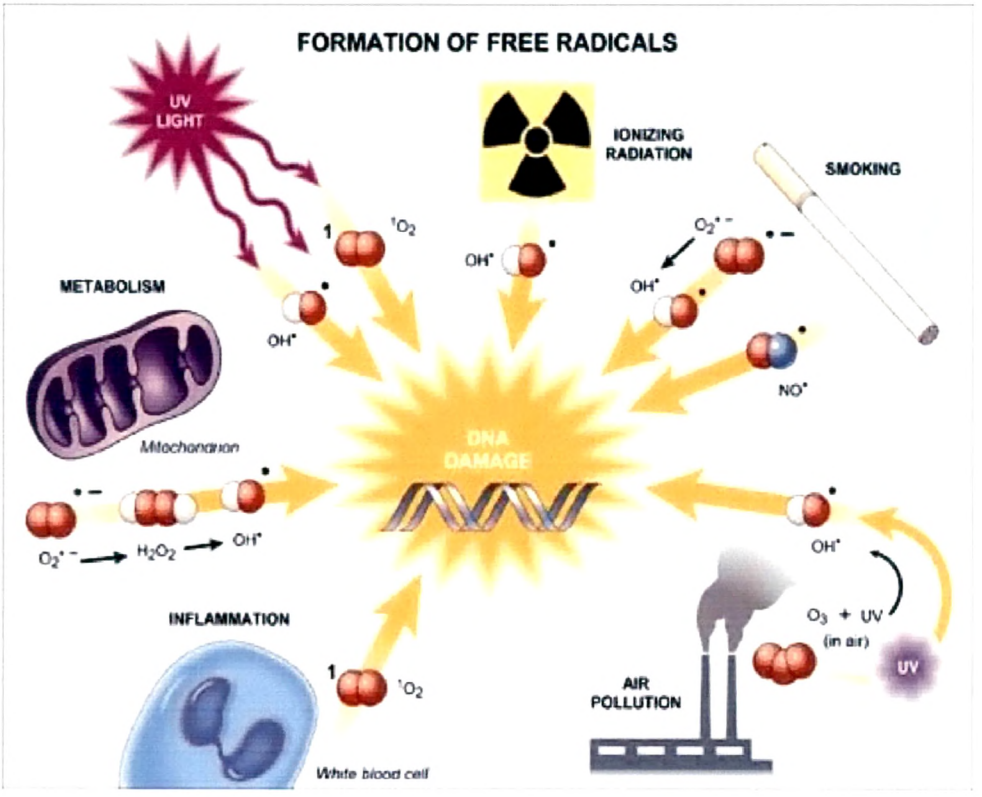
- *Long term carcinogen exposure increases the risk of initiation*
- *The prolong period required for one malignant cell to multiply and develop into a detectable tumor.*
- *Aging itself increases the risk because of*
  - *a possible reduction in natural killer or other immune surveillance function*
  - *an increase in the activation of procarcinogens*
  - *other factors including demethylation-induced epigenetic instability and free radical-induced DNA damage.*

ROLE OF FREE RADICALS IN CANCER

Oxidative stress can cause mutagenicity, cytotoxicity and stimulate changes in gene expression (Figure 6). Furthermore, these effects are likely to interplay in the development of carcinogenesis by oxidants. Mutations induced by oxidants may initiate carcinogenesis; oxidative modification of the genetic material may also participate in the progression of benign to malignant neoplasms. Alteration of the pattern of gene expression by oxidants may function in the stimulation of the initiated cell during tumour promotion (Harris 1989).

Much evidence indicates that DNA-damaging hydroxyl radicals are produced through the interaction of hydrogen peroxide and superoxide with transition metals. For example, hydrogen peroxide and superoxide do not directly interact with DNA to produce oxidative lesions in vitro. An unstable radical like the hydroxyl radical will interact indiscriminantly with all components of the DNA damage produced lesions in vitro. An unstable radical like the hydroxyl radical will interact indiscriminately with all components of the DNA molecule, producing a broad spectrum of DNA damage. Indeed, the forms of DNA damage produced by active oxygen species in experimental systems include modification of all bases as well as the production of base-free sites, deletions, frameshifts, strand breaks, DNA-protein crosslinks, and chromosomal rearrangements (Halliwell and Aruoma 1991).

Figure 5 : Formation of free radicals from various sources and its damage to the DNA



source : www.medscape.com

Active oxygen species and other free radicals have long been known to be mutagenic. Mutagenic capacity of oxygen is due to the direct interaction of hydroxyl radicals with DNA (Parshad and Sanford 1971). An unstable radical like the hydroxyl radical will interact indiscriminately with all components of the DNA molecule, producing a broad spectrum of DNA damage.

ORAL CANCER

Cancer of oral cavity is the fifth most commonly occurring cancer in the world. The term oral cancer refers to cancer found in the oral cavity and the orophayrnx. The oral cavity includes the lips, the lining inside the lips and the cheeks, the tongue, the teeth, the floor of mouth under the tongue, the hard palate, and the gums. The oropharynx includes the soft palate, the tonsils, the back of the throat. *The tongue is the most common site of oral cancer.*

GLOBAL BURDEN

In 1996, an estimated 57500 new cancer cases were diagnosed worldwide accounting for 5.6 % of all new cancers (American Cancer Society 1997). The American Cancer Society estimates about 28,260 new cases (18,550 in men and 9,710 in women) of oral cavity and pharyngeal cancer will be diagnosed in the United States during 2004. An estimated 7,230 people (4,830 men and 2,400 women) will die of oral cavity and oropharynx cancer in 2004.

INDIAN SCENARIO

In parts of India and Asia where chewing tobacco or betel-nut is very common, the incidence of oral cancer is very high. As much as 7 % of all cancer deaths in males and 4 % in females have been reported to be due to oral cancer. It constitutes nearly half (48.51 %) of all cancers in men and 16.01 % of all cancers in women in Gujarat (Gujarat Cancer Registry 1998).

RISK FACTORS FOR ORAL CANCER

Various risk factors have been implicated in the causation of oral cancer. These include age, gender, smoking, alcohol consumption, tobacco use, stress factors, lack of fruits and vegetables in the diet, chronic irritation, dental and oral hygience (American Cancer Society 2004).

The likelihood of developing oral and oropharyngeal cancer increases with age, especially after age 35.

Oral and oropharyngeal cancer is twice as common in men as in women. This may be because men are more likely to use tobacco and alcohol.

About 90% of people with oral cavity and oropharyngeal cancer use tobacco, and the risk of developing these cancers increases with the amount smoked or chewed and duration of the habit.

Smokers are 6 times more likely than nonsmokers to develop these cancers. About 37% of patients who persist in smoking after apparent cure of their cancer will develop second cancers of oral cavity, oropharynx, or larynx, compared with only 6% of those who stop smoking. Tobacco smoke from cigarettes, cigars, or pipes can cause cancers anywhere in the oral cavity or oropharynx, as well as causing cancers of the larynx, lungs, esophagus, kidneys, bladder, and several other organs. In addition, pipe smoking has a particularly significant risk for cancers in the area of the lips that contact the pipestem.

Smokeless tobacco ("snuff" or chewing tobacco) is associated with cancers of the cheek, gums, and inner surface of the lips. Smokeless tobacco increases the risk of these cancers by about 50 times. Often cancer associated with smokeless tobacco will begin as leukoplakia or erythroplakia. Working in a smoking environment or living with a smoker (called passive smoking) is also a risk factor.

Drinking alcohol strongly increases a smoker's risk of developing oral cavity and oropharyngeal cancer. About 75% to 80% of all patients with oral cancer drink a lot of alcohol. These cancers are about 6 times more common in drinkers than in nondrinkers. People who drink alcohol but don't smoke have a higher risk of cancer if they are particularly heavy drinkers. It is the combination of the two habits that is the most deadly.

More than 30% of patients with cancers of the lip have outdoor occupations associated with prolonged exposure to sunlight.

Long-term irritation to the lining of the mouth caused by poorly fitting dentures has been suggested as a risk factor for oral cancer. But many research studies have shown no difference between denture wearers and non-denture wearers in the occurrence of oral cancer. As poorly fitting dentures can tend to trap proven causative agents of oral cancer beneath them, such as alcohol and tobacco particulates, denture wearers should have their dentures evaluated by a dentist at least every 5 years for good fit. Hence removing of the dentures at night and thorough cleaning and rinsing thoroughly every day is recommended by the American Cancer Society (2004).

Some studies have suggested that mouthwash with a high alcohol content is associated with an increased risk of oral and oropharyngeal cancer. However, recent research has found these studies to be flawed, pointing out that smokers and frequent drinkers (who are therefore already at increased risk) are likely to use more mouthwash than people who neither smoke nor drink.

Human papillomavirus (HPV) infection also have been shown to cause oral cancer. Papillomaviruses are a group of about 80 related viruses. Most HPV types cause warts on various parts of the body. A few HPV types are at least partly responsible for more than 90% of cancers of the cervix. These HPV types are also associated with some cancers of the vagina, vulva, and penis. The situation for oral cancers is less clear, however. The types of HPV found in cervical cancer are found in about 20% to 30% of oral cancers, but are also found in over 10% of samples of normal oral tissue. The current view is that HPV may be a factor that contributes to the development of oral cavity and oropharyngeal cancers in around 20% of people. People with oral cancer associated with HPV infection have a better outlook than those without HPV. They are also less likely to be smokers and drinkers.

People taking immunosuppressive drugs to treat certain immune system diseases, or to prevent rejection of transplanted organs, may be at increased risk for cancers of the oral cavity and oropharynx. (American Cancer Society, 2004)

Epidemiological studies worldwide have implicated dietary and nutritional factors in the development of oral and pharyngeal cancer. Dietary information in these case-control studies

generally was collected through food-frequency questionnaires. Consistently, these studies observed a protective effect of a diet high in fruit intake, reflected in a 20-80% reduction in oral cancer risk. A high intake of foods considered to be dietary staples in particular cultural groups, possibly indicating a generally impoverished diet, has been linked to excess risk. Indigenous dietary practices that in single studies were found to increase risk include a high intake of chili powder and wood stove cooking. Supplementation with various vitamins has been protective in a few studies. Chemoprevention trials generally have found that chemopreventive agents reduce the size of oral leukoplakia lesions or the frequency of second primary oral cancers. The most consistent dietary findings across multiple cultural settings are a protective effect of high fruit consumption and the carcinogenic effect of high alcohol intake (Winn 1995).

Low intakes of fruits and vegetables have been implicated in the occurrence of oral cancer. Both prospective and retrospective studies suggest that vegetable and fruit intake may reduce the risk of cancers of mouth, phaynx, larynx, and esophagus (Ziegler 1991). Epidemiologic evidence of a protective effect of vitamin C for non-hormone dependent cancers is strong. Of the 46 such studies in which a dietary vitamin C index was calculated, 33 found statistically significant protection with higher vitamin C intakes (Block 1991).

β-CAROTENE AND ORAL CANCER

Recent data suggests that retinoids and carotenoids may be effective in reversing a putative "field cancerization" defect in the epithelium at risk for oral cancer. Animal experiments have shown that these compounds can inhibit cancer formation. Several clinical trials have demonstrated the ability of retinoids to reverse oral leukoplakia. However, toxicities associated with retinoids at the doses used in these studies limits their potential for chemoprevention. Because of its lack of toxicity, beta-carotene is a very attractive agent for chemoprevention. It suppresses micronuclei in exfoliated oral mucosal cells from subjects at risk for oral cancer and recently has been shown to be active in reversing leukoplakia. Another area under investigation is the possibility of preventing second primary tumors in patients cured of their initial cancer who have an increased risk of developing new cancers of the upper acrodigestive tract. (Garewal 1991)

Tuyns et al (1987) reported significant lower risk (RR=0.47) with dietary intake of β-carotene in 743 men and women from Calvodos, France.

Significant lower mean carotene levels for all cancers were reported in 2421 men survivors of the Basel study which was started in 1959 (Stahelin et al 1991).

A lower risk of oral and pharygeal cancer was associated with increased intake of fiber, carotene and vitamin C and vitamin E in men and vitamin C and fiber in women in a study carried out by Gridley et al (1990) on 190 subjects from United States.

VITAMIN C AND ORAL CANCER

Epidemiologic evidence of a protective effect of vitamin C for non- hormone-dependent cancers is strong. Of the 46 such studies in which a dietary vitamin C index was calculated, 33 found statistically significant protection, with high intake conferring approximately a twofold protective effect compared with low intake. Of 29 additional studies that assessed fruit intake, 21 found significant protection. For cancers of the esophagus, larynx, oral cavity, and pancreas, evidence for a protective effect of vitamin C or some component in fruit is strong and consistent. For cancers of the stomach, rectum, breast, and cervix there is also strong evidence. Several recent lung cancer studies found significant protective effects of vitamin C or of foods that are better sources of vitamin C than of beta-carotene. It is likely that ascorbic acid, carotenoids, and other factors in fruits and vegetables act jointly (Block 1991).

Marshall *et al* (1982) assessed the effect of L-AA on 425 oral cancer patients and 588 controls. Odd's Ratio (OR) for those in the lowest quartile *vs* the highest quartile of L-AA intake was 1.7 after adjustment for smoking and alcohol consumption ($P < 0.05$).

Similar study was carried out by McLaughlin et al (1988) on 871 oral cancer patients and 979 age- and sex-matched controls; OR for males and females in the lowest quartile for L-AA intake was 1.0 compared with the OR for the highest quartile at 0.6 ($P < 0.001$) and 0.5 ($P < 0.04$) respectively after adjustment for smoking and alcohol consumption.

Oropharyngeal cancer patients (N=166) and 547 age- and sex-matched controls were examined by Rossing et al (1989). OR for those in the lowest quartile *vs* the highest quartile for L-AA intake was 2.5 after adjustment for smoking and alcohol consumption ($P = 0.017$).

The OR for L-AA intake was found to 0.3 and 0.6 in males and females respectively in the highest quartile after adjustment for smoking and alcohol ($P = 0.05$) in a study carried out by Gridley et al (1990) on 190 oropharyngeal cancer patients and 201 population controls

Antioxidant nutrients have been hypothesized to be protective against cancer. Vitamin C is a major circulating water-soluble antioxidant, and vitamin E is a major lipid-soluble antioxidant. Many case-control and cohort studies have related cancer risk to estimates of nutrient intake derived from food intake reports. Diets high in fruit and vegetables, and hence high in vitamin C, have been found to be associated with lower risk for cancers of the oral cavity, esophagus, stomach, colon, and lung. Diets high in added vegetable oils, and hence high in vitamin E, have been less consistently shown to be associated with cancer protection. This may be because vitamin E offers less protection against cancer or because the estimation of vitamin E intake is less accurate than is the estimation of vitamin C intake. In contrast with the findings from epidemiologic studies based on foods, observational studies of nutrients consumed in supplements and recent experimental trials provide little support for a strong protective role for vitamins C or E against cancer. If vitamins C or E are indeed protective against cancer, that protection may derive from their consumption in complex mixtures with other nutrients and with other bioactive compounds as found in the matrix provided by whole foods.

FRUITS AND VEGETABLES AND ORAL CANCER

Ecological, case-control, and cohort studies present convincing evidence that diets rich in fresh fruit and vegetables protect against several common epithelial neoplasms. Studies of the Mediterranean diet are of particular interest to better understand and quantify this effect in view of the frequency and range of fruit and vegetable consumption by these populations. Tavani and Vecchia (1995) reviewed the results of a large- scale, Italian, case-control study of dietary intake of fruit and vegetables and risk of cancer at several sites. The relative risks (RRs) for most common neoplasms ranged from 0.2 to 0.5 for the highest compared with the lowest tertile of vegetable intake. Protective effects of vegetables were also observed against hormone-related neoplasms. Higher intakes of fruit were related to a reduced RR for cancers of the oral cavity and pharynx, esophagus, stomach, or larynx, as well as of the urinary tract, although protection was less evident for other digestive tract sites, as well as for other epithelial cancers. No association was observed between fruit and vegetable consumption and nonepithelial

neoplasms. For upper respiratory and digestive tract cancers, population attributable risks for fresh vegetable and fruit intake ranged from 18% to 40% in men and from 15% to 30% in women; attributable risks for fresh vegetable and fruit intake, combined with tobacco and alcohol, exceeded 85% for men and 55% for women.

Similarly, in 1998 - 1999, a case-control study was conducted in Uruguay to assess vegetables, fruits, related dietary antioxidants and risk of squamous cell carcinoma of esophagus by Stefani et al (2000). For this purpose, 111 cases with squamous cell carcinoma of the esophagus and 444 controls with conditions unrelated to tobacco smoking, alcohol drinking, or recent changes in the diet were frequency matched on age, gender, residence, and urban/rural status. Vegetables and more markedly, fruits were associated with strong reductions in risk. On the other hand, 12 of 15 dietary antioxidants displayed significant inverse associations with esophageal cancer risk. The strongest effect was observed for high intake of beta-cryptoxanthin (OR=0.16, 95 % CI=0.08-0.36). Also, α-carotene, lycopene, and β-sitosterol were associated with significant reductions in risk. Most antioxidants lost their effect when they were further adjusted for a term for all vegetables and fruits. β-carotene showed an increased risk with high intakes. On the other hand, vegetables and fruits remained as significant variables after adjustment for each antioxidant, suggesting that other substances or other mechanisms could explain this effect.

To investigate the clinical outcome of unbalanced diet in patients with oral precancerosis and to assess a possible relationship between dietary factors and the development of oral leukoplakia, a case-control study was carried out by Cianfriglia et al (1998) within a cohort of 53 subjects treated at Regina Elena Institute for Cancer Research Centre in Rome from October-November 1997. Enrolled subjects and suitable controls underwent a careful interview on their own alimentary habits with a particular interest in retinol and carotenoids major sources. An individual qualitative and quantitative assessment of retinol-equivalents dietary intake, yielding average values for each group, allowed to compare the cohorts and to relate data also to tobacco use and to the severity of histopathological findings. Case levels were always significantly lower than controls ($P<0.001$), disregarding smoking, whilst no difference resulted between smokers and non smokers within the same groups. No statistical influence seemed to link alimentary vitamin A to the development of oral dysplasia but this work strengthen the

epidemiological opinion that specific dietary factors are of great importance in oral oncology.

Possible relationship between dietary factors and the development of multiple primary cancer was investigated in a nested case-control study was carried out within a cohort of 1,090 oral and pharyngeal cancer patients by Day et al (1994). This patient group, enrolled in 1984-1985 in a population-based case-control study conducted in four areas of the United States, was followed up through June 1989 for the occurrence of second primary cancer. Information on a number of risk factors, including diet, ascertained from interviews conducted at baseline (1984-1985) and at follow-up were compared between 80 patients with histologically confirmed second primary cancers (39% in the upper aerodigestive tract, 32% in the lung, 29% elsewhere) and 189 sex- and survival-matched control patients free of second cancers. Although few significant trends emerged, the results were suggestive of a protective effect provided by higher intake of vegetables. Risk of second primary cancers was 40-60% lower among those with the highest levels of intake for total vegetables and most vegetable subgroups, including dark yellow, cruciferous, and green leafy vegetables and legumes. Risks were also nonsignificantly lower among those with high consumption of vitamin C and carotenoids, with the adverse effects of alcohol being most evident among heavy drinkers with low vitamin C or carotenoid intake. There was also some evidence of an interaction between smoking and vitamin C consumption, but numbers of nonsmokers were small. Among other dietary factors considered, positive associations were found with increasing consumption of meats, liver, and retinol. The findings suggest that dietary factors contribute along with alcohol and smoking to the excess risks of second primary cancers among patients with oral and pharyngeal cancers.

A population-based case-control study of oral and pharyngeal cancer conducted in four areas of the United States was carried out by McLaughlin et al (1988) to provided information on a number of risk factors, including diet. Interviews were obtained from 871 oral cancer patients and 979 controls among whites, frequency matched for age and sex. Consumption frequency of 61 food items was assessed in the questionnaire; attention was given to foods that are sources of vitamins A and C and carotene. The major finding was an inverse relationship between fruit intake and risk of oral and pharyngeal cancer; individuals in the highest quartile of intake had about half the risk of those in the lowest quartile. Vitamin C, carotene, or fiber in fruit did not appear to account completely for this relationship, since these nutrients in vegetables did not provide similar protection. This finding suggests the influence of other constituents in fruits, although it is possible that cooking vegetables may have a nutrient-diminishing effect. Dietary

intake of other nutrients, such as the B vitamins, vitamin E, folate, and iron, showed no consistent relationship to risk of oral and pharyngeal cancer. Coffee or other hot beverage consumption did not increase risk; intake of nitrite-containing meats or cooking practices, such as smoking, pickling, or charcoal grilling, also did not increase risk. All analyses were adjusted for the effects of tobacco and alcohol, strong risk factors for oral and pharyngeal cancer.

SMOKING AND ORAL CANCER

Cigarette smoke contains about 4000 chemical agents, including over 60 substances that are known to cause cancer in humans(carcinogens). In addition, many of these substances, such as carbon monoxide, tar, arsenic, and lead, are poisonous and toxic to the human body. Nicotine is a drug that is naturally present in the tobacco plant and is primarily responsible for a person's addiction to tobacco products, including cigarettes. During smoking, nicotine is absorbed quickly into the bloodstream and travels to the brain in a matter of seconds. Nicotine causes addiction to cigarettes and other tobacco products that is similar to the addiction produced by using heroin and cocaine.

CO is formed when a cigarette is lit. It has a number of toxic effects on the body, the most important of which is that it reduces the amount of oxygen that is carried in hte bloodstream of smokers. CO binds with the haemoglobin in the blood instead of oxygen, meaning that less oxygen is available to body organs and tissue. The heart has to pump harder to make sure that enough oxygen can get to all parts of the body. In pregnant women, the unborn baby also has less oxygen available to it through the umbilical cord. Lack of oxygen also affects muscle performance.

Every time cigarette smoke is inhaled, tar goes into the lungs. Some is breathed out, but much of it condenses deep inside the airways of the lungs. Coughing is the body's way of trying to get rid of this tar, but the cilia (tiny hairs that have the job of sweeping foreign material out of the airways) are paralysed by chemicals in tobacco smoke. Tar is a sticky brown substance, the same one that causes smokers' fingers to go brown, and teeth to stain yellow. It also causes throat and lung cancer. (US Department of Health and Human Services 1988).

Understanding differences in dietary patterns by smoking status is important for nutritionists and health educators involved in helping individuals to make healthy dietary and lifestyle

choices. A study was conducted by Palaniappan et al (2001) to compare dietary habits of smokers with non smokers in terms of nutrient intake, food groups contributing to nutrient

intake, nutritional adequacy and day to day variation in nutrient intake. Non institutionalised adults aged 18-65 years (n=1543) who participated in the Food Habits of Canadians Survey (1997-1998) were studied. Subjects, selected from across Canada using a multistage, random sampling strategy completed an in home 24 hour dietary recall. Repeat interviews were conducted in a subsample to estimate variability in nutrient intake. Smokers had higher intakes of total and saturated fat, and lower intakes of folate, vitamin C and fiber than non smokers. There were no significant differences in calcium, zinc and vitamin A intakes or day to day variation in nutrient intake by smoking status. Smokers consumed significantly fewer fruits and vegetables than non smokers, leading to lower intakes of folate and vitamin C. Thus it was concluded that smokers have a less healthy diet than non smokers, placing them at higher risk for chronic diseases as a result of both dietary habits and smoking. Diet may act as a confounder in smoking-disease relationship.

A recent case-control study conducted in a rural area of India was designed to test the relationship between precancerous changes in the mouth and dietary intake of fruits, vegetables, and specific dietary nutrients. Researchers decided to use oral precancerous lesions as a marker for oral carcinoma to avoid the potential for measurement bias. This potential for bias is due to the fact that oral carcinoma affects the physical sensation of food, as well as the amount of food consumed, while precancerous lesions have little or no effect on dietary intake.

A survey of 5056 tobacco users in Kerala, India, was conducted by Gupta el al (1999), which identified 226 individuals with precancerous lesions. A control group of equal size was gathered and matched to the cases for age, gender, residence, and use of tobacco. A food frequency questionnaire (FFQ) was specifically developed for the population, which was used to estimate intake of the various nutrients being studied.

Total fruit intake and beta-carotene consumption showed a significant inverse relationship with precancerous lesions even after controlling for tobacco use. Total vegetable intake exhibited a strong but not significant correlation. Associations with certain vitamins and minerals appeared to differ according to gender. A 20% reduction in risk per milligram of zinc consumed per day

among men was found, while there was an increased risk of oral precancerous lesions among those women in the lowest quartile of iron and ascorbic acid intake.

Stich et al (1991) carried out a study on fishermen from Kerala, India, who chewed tobacco-containing betel quids daily before and throughout the study period. Frequency of oral leukoplakia, micronuclei in oral mucosal cells, and alterations in nuclear textures were used as endpoints. Administration of vitamin A (60 mg/wk) for 6-mo resulted in complete remission of leukoplakias in 57% and a reduction of micronucleated cells in 96% of tobacco-chewers. beta-carotene (2.2 mmol/wk) induced remission of leukoplakia in 14.8% and reduction of micronucleated cells in 98%. Vitamin A completely suppressed and beta- carotene suppressed by 50% formation of new leukoplakia within the 6-mo trial period. After withdrawal of vitamin A or beta-carotene treatment, oral leukoplakias reappeared, frequency of micronuclei in oral mucosa increased, and nuclear textures reverted to those present before the administration of chemo-preventive agents. The protective effect of the original treatment could be maintained for at least 8 additional months by administration of lower doses of vitamin A or beta-carotene.

A population-based case-control study was designed by Nagao et al (2000) for the investigation of any association between serum micronutrient levels and oral leukoplakia. Out of a total of 9536 subjects over the age of 40 years who participated in the oral mucosal screening programme in Tokoname city, 48 cases detected with oral leukoplakia (38 male:10 female) were recruited. For each case, four controls matched by age and sex were selected from the same cohort. We examined the fasting serum levels of retinol, alpha-tocopherol, zeaxanthin and lutein, cryptoxanthin, lycopene and carotenoids (alpha-carotene and beta-carotene) by high-performance liquid chromatography. Among males with leukoplakia mean serum lycopene and beta-carotene levels (0.175+/-0.202, 0.357+/-0.295 micromol/l) were significantly lower than those of controls (0.257+/-0.252, 0.555+/-0.408 micromol/l) ($P<0.05$, $P<0.005$). Logistic regression analysis with leukoplakia as the dependent variable showed that high serum levels of beta-carotene were related to low risk of oral leukoplakia (odds ratio 0.160, 95% C.I.: 0.029-0.866, $P<0.05$). There were no significant differences in any of the serum nutrients estimated in female subjects. The results thus suggested that high serum levels of beta-carotene may provide protection against oral precancer for the Japanese male.

To investigate the relationship between serum micronutrients and the subsequent risk of oral and pharyngeal cancer, a nested case-control study was conducted within a cohort of 25,802 adults in Washington County, MD by Zheng et al (1993) The serum levels of nutrients in 28 individuals who developed oral and pharyngeal cancer during 1975 to 1990 were compared with levels in 112 matched controls. Serum levels of all individual carotenoids, particularly beta-carotene, were lower among subjects who developed oral and pharyngeal cancer. The risks of this malignancy decreased substantially with increasing serum level of each individual carotenoid. Persons in the highest tertile of total carotenoids had about one-third the cancer risk as those in the lowest tertile. High serum levels of alpha-tocopherol also were related to a low oral cancer risk in later years, but the risks were elevated significantly with increasing serum levels of gamma-tocopherol and selenium. The findings from this study are consistent with many previous epidemiological investigations of dietary factors for oral and pharyngeal cancer and provide further evidence for the potential role of carotenoids and alpha-tocopherol in the chemoprevention of these malignancies.

Free radicals in cigarette smoke may cause oxidative damage to macromolecules, contributing to cardiovascular diseases and cancer. Decreased plasma antioxidant concentrations may indicate cigarette smoke–related oxidative stress. The effects on plasma antioxidant concentrations in cotinine-confirmed active and passive smokers with those in nonsmokers, independent of differences in dietary intakes and other covariates were compared by Dietrich et al (2003). Plasma samples from 83 smokers, 40 passive smokers, and 36 nonsmokers were analyzed for total ascorbic acid, - and -tocopherols, 5 carotenoids, retinol, and cotinine. After adjustment for dietary antioxidant intakes and other covariates, smokers and passive smokers had significantly lower plasma ß-carotene concentrations than did nonsmokers (0.15, 0.17, and 0.24 μmol/L, respectively) and significantly higher -tocopherol concentrations (7.8, 7.8, and 6.5 μmol/L, respectively). Smokers had significantly lower plasma ascorbic acid and ß-cryptoxanthin concentrations than did nonsmokers and passive smokers (ascorbic acid: 43.6, 54.5, and 54.6 μmol/L, respectively; ß-cryptoxanthin: 0.12, 0.16, and 0.16 μmol/L, respectively) and significantly lower concentrations of lutein and zeaxanthin than did nonsmokers (0.33 compared with 0.41 μmol/L). The *P* values for all the differences described above were < 0.05. No significant differences in plasma concentrations of -tocopherol, -carotene, total carotenoids, lycopene, or retinol were observed. The results thus indicated that cigarette smokers and nonsmokers exposed to cigarette smoke have a significantly lower plasma antioxidant status

than do unexposed nonsmokers, independent of differences in dietary antioxidant intakes.

Pan masala is a dry complex mixture of areca nut, catechu, lime, cardamon, unspecified flavouring agents etc., with (PMT) or without tobacco (pm). An antigenotoxic effect of alpha-tocopherol (AT) and ascorbic acid (AA) against the PM/PMT induced genotoxic on Chinese hamster ovary (CHO) cells have been studied using chromosone aberration (CA) assay. AT and AA, per se, had no effect on CA frequency at the concentrations used in the present study. The short-term treatment of AT with aqueous extracts of PM/PMT yielded lower frequencies of CA as compared to the cultures treated with aqueous extracts of PM/PMT alone. However, a statistically significant reduction in CA frequency was observed with continuous treatment only. AA had no statistically significant protective effect except for continuous treatment with 10 ug/ml AA against the aqueous extract of PMT. The results indicate the possible use of AT to reduce the risk of oral cancer among PM/PMT chewers. (Patel et al 1998).

Dietary factors in oral leukoplakia and submucous fibrosis was studied in a population-based case control study in Palitana taluk of Bhavnagar district of Gujarat, India by Gupta et al (1998) He investigated the relationship of specific nutrients and food items with oral precancerous lesions among 5018 tobacco users out of which 318 were diagnosed as cases. A protective effect of fibre was observed for both oral submucous fibrosis (OSF) and leukoplakia, with 10% reduction in risk per g day-1 ($P < 0.05$). Ascorbic acid appeared to be protective against leukoplakia with the halving of risk in the two highest quartiles of intake (versus the lowest quartile: OR = 0.46 and 0.44, respectively; $P < 0.10$). A protective effect of tomato consumption was observed in leukoplakia and a suggestion of a protective effect of wheat in OSFIn addition to tobacco use, intake of specific nutrients may have a role in the development of oral precancerous lesions.

A preliminary study on serum vitamins' status in oral leucoplakias was undertaken by Ramaswamy et al (1996). The objective of this study was to establish the baseline circulating levels of these vitamins in our normal population with and without tobacco use and to compare these levels with the values obtained in cases of oral leucoplakias. Fifty normal controls with 25 each in chewers and non-chewers, matched for age and sex, were selected. 50 cases of oral leucoplakias (clinically detectable white patches) from the field constituted the study group.

Simultaneous measurement of serum vitamin B12 and folate were carried out by radioassay. The other serum vitamins were estimated spectrophotometrically. Except for serum vitamin E, all the other serum vitamin levels were significantly decreased in oral leucoplakias compared to the controls. Cancer chemopreventive agents acting as inhibitors of both initiation and promotion, as analysed in our population, is promising for further intervention trials.

Dietary intake in male and female smokers, ex-smokers, and never smokers was assessed by Dyer et al (2003) in the INTERMAP Study. The 4680 participants aged 40-59 years-from 17 population samples in four countries (China, Japan, UK, USA)-provided four 24-h recalls to assess nutrient intakes and two 24-h urine collections to assess excretion of urea, sodium (Na), potassium (K). Compared to never smokers, current smokers generally consumed more energy from alcohol and saturated fats (SFA), less energy from vegetable protein and carbohydrates, less dietary fibre, vitamin E, beta carotene, vitamin C, thiamine, riboflavin, folate, vitamin B6, calcium, iron, phosphorus, magnesium (Mg), and K per 1000 kcal, excreted less K and urea (marker of dietary protein), had a lower ratio of polyunsaturated fat (PFA) to SFA intake, higher Keys dietary lipid score, and higher dietary and urinary Na/K. There were few differences between smokers and never smokers for total energy intake, energy from total and animal protein, monounsaturated fats, PFA, omega 3 and omega 6 PFA, dietary cholesterol, total vitamin A, retinol, vitamin D, vitamin B12, and urinary and dietary Na. Compared to ex-smokers, smokers generally consumed less energy from vegetable protein, omega 3 PFA, carbohydrates, less dietary fibre, beta carotene, vitamin E, vitamin C, thiamine, riboflavin, folate, vitamin B6, iron, phosphorus, Mg, had lower PFA/SFA, and excreted less urea and K. In conclusion, INTERMAP results are consistent with other reports indicating that smokers have less healthful diets than nonsmokers. Public health interventions in smokers should focus not only on helping them to quit smoking but also on improving their diets to further reduce cancer and cardiovascular disease risks.

Macfarlane et al (1995) pooled analysis of three case-control studies to assess the risk of oral cancer with alcohol, tobacco, diet This combined analysis of data from three large case-control studies of oral cancer confirms the important effect of tobacco in the aetiology of the disease. The studies have been conducted in the United States, Italy and China and results for risks associated with tobacco smoking were generally consistent across centres, while those for alcohol were not; increased risks amongst alcohol drinkers were evident in two centres but not

in the study conducted in Turin, Italy. In addition, the combined analysis had large enough numbers to analyse the risk of tobacco consumption in non-drinkers. In females these showed increased risks while in males the effect of tobacco alone was weaker. Given the popularity of tobacco smoking, and its consequent high attributable risk in terms of oral cancer it is reassuring, in terms of public health, that cessation will result in a substantial reduction in risk; a 30% reduction in risk for those stopping smoking between 1 and 9 years, and a 50% reduction for those stopping more than 9 years. Although encouraging smokers to stop should be the principal aim, decreases in risk for everyone could be achieved by encouraging high fruit and vegetable consumption.

CAREGIVING OF THE ELDERLY

According to the most National Long-term Care Survey (1994), more than seven million persons are informal caregivers providing unpaid help to older persons who live in the community and have at least one limitation in their activities of daily living. In the family, there is usually one primary caregiver -a role traditionally held by a woman. Seventy to eighty percent of all primary caregivers are women - wives, daughters, daughters-in-law and granddaughters. The typical profile of today's female caregiver is that of a middle-aged individual between the ages of 40 and 60 with "2.3" children who may still be living at home and who also may demand her attention and care.

Lack of a caregiver is a serious problem for those older persons who have chronic conditions and limitations on their ability to care for themselves and their homes. Their problems are often compounded by increased medical costs due to poor health and the need for more supportive services.

Much has been written about how the help and support of families, friends, neighbors and formal care providers have helped elderly individuals to: cope more effectively with the stresses of illness or disability; enhance their feelings of self-worth and value; comply with prescribed medical regimen, and where applicable, make a speedy recovery from illness or disease. Although these findings are generally true, they do, however, mask a much more complicated pattern of interaction between caregiver and care-receiver, which can contain instances of negative elements.

The physical and mental changes taking place in the elderly need to be identified to help restore the elderly person to as functional, satisfying and healthy a life as possible. If more people were able to recognize and distinguish between diseases that may accompany old age and those changes that are related to the normal aging process, then perhaps they would be less negative about the aging process themselves.

Advancing age brings about various problems which interferes in the day to day routine activities of the elderly. These problems can be with respect to reduced mobility, diminished vision along with other physical and functional impairments. These, in turn, affect the nutritional status of the family. However, even in joint families, the health and nutritional status of the elderly depends on the caregiver, to a large extent. The existing knowledge of the caregiver with respect to the dietary care and health needs of the elderly determines the awareness regarding various aspects of aging. However, actual practices of the knowledge would be effective in improving the nutritional status of the elderly.

Existing knowledge about nutrition and aging suggests that nutrition has the power to make a substantial impact on the health and functional status of older individuals. The size and rapidity of the ongoing demographic and nutrition transition demand that nutrition for aging adults receive equal priority in a family. Social changes are also placing the elderly at even greater risk of food insecurity and malnutrition. This burden of undernutrition and chronic diseases poses a tremendous challenges for the care givers of the elderly. Various types of nutritional deficiences and co-morbidities occur in elderly even if they are staying in a joint families. This is basically because there is no change in the dietary habits of the elderly with advancing age. They continue to take the same diet as they were used to during their adulthood years. Moreover, in a joint family system, the proirity about the food preferences is given to the other members of family especially children since it is believed that they requirement of food is more in this age group. Elderly tend to eat what is cooked for the whole family. It thus becomes important to educate the care giver with respect to the physiological changes taking place in old age and importance of micronutrients especially dietary antioxidants in preventing deficiences and chronic diseases. However, before targetting the care givers for any intervention programs, it is necessary to assess their existing knowledge about importance of diet in old age and to know if

they are able to put that knowledge into practice. This will help to plan the intervention program in more detail as the investigator can concentrate to emphasis only on those areas.

A study was carried out by Ryan (1997) to determine the nutritional knowledge of the caregivers of the clients. Seventy-eight caregivers completed the questionnaire. Scores indicated that the caregivers' knowledge of nutrition was minimal, despite the fact that many of the caregivers were educated beyond high school. However, the majority of caregivers did believe their elder received proper nutrition on a daily basis. Data suggest that caregivers' perceptions of proper nutrition may not be based on accurate nutrition knowledge. The study concluded that focus on the education of caregivers regarding nutritional needs of older adults and recognition of signs and symptoms of malnutrition may better maintain nutritional status and quality of life of the elderly adult. This study thus emphasised the importance of nutrition education programs that should be made available to caregivers to increase their knowledge of nutrition.

According to Gettings and Kiernan (2001), a need exists to determine the necessity and focus for education given senior citizens' vulnerability for food-borne illness,. Seniors rely of the distant past for knowledge and identify barriers to altering practices but state that information from educators about the health effects of inappropriate practices will convince them to change. For future food safety education, seniors recommend programs, videotapes, television, newspapers, radio, church bulletins, and written educational pieces. This will be helpful in the present setup as it will ultimately make the elderly themselves more aware of the various physiological changes taking place with increase in age and thus make them more adaptive with the much required dietary changes.

Scientific evidence increasingly supports that good nutrition is essential to the health, self-sufficiency, and quality of life of older adults. With the elderly population living longer than ever before, the older adult population will be more diverse and heterogeneous in the 21st century. The oldest-old and minority populations will grow more quickly than the young-old and non-Hispanic white populations, respectively. According to the American Dietetic Association (2000), for the current 34 million adults 65 years of age and older living in the United States, there are about 12 million caregivers who provide formal or informal care. A broad array of culturally appropriate food and nutrition services, physical activities, and health and supportive care customized to accommodate the variations within this expanding

population of older adults is needed. With changes and lack of coordination in health care and social-support systems, dietetics professionals need to be proactive and collaborate with aging-services and other health c are professionals to improve policies, interventions, and programs that service older adults throughout the continuum of care to ensure nutritional well-being and quality of life. The American Dietetic Association supports both the provision of comprehensive food and nutrition services and the continuation and expansion of research to identify the most effective food and nutrition interventions for older adults over the continuum of care.

A major goal of our public health system should be to maintain health among successful agers and prevent or delay chronic disease morbidity. Major strides should be made in making the caregivers identify the dietary needs of elderly people that are different from those of younger adults. However, nutrition education programs to promote those dietary needs have lagged behind. Thus, there is a need to keep pace with recent findings and develop national and state-sponsored programs that will provide nutrition education and information transference to older people in the communities as well as their caregivers.

In light of the findings from the studies reviewed above, the present study was planned to assess the role of antioxidants in health and disease during aging process. Further, an attempt was also made to evaluate the knowledge and practices of the caregivers of the elderly regarding the role of antioxidants in the diets of the elderly.

Methodology which has been used to carry out this study are discussed in the next chapter