Introduction
The literal meaning of the word 'Stress' is 'Constraining force', while the language of Life-science, defines 'stress' as an intense force, strain, agent or mental condition producing a defence reaction, which if continued or intensified, may lead to pathological lesion. According to Selye (1956), stress is the non-specific response of the organism to any demand made upon it. Rabkin and Struening (1976) said that stress like anxiety, was a broad and general concept describing organism's reactions to environmental demands. Chronic stress in human can cause psychological and physiological reactions (Cholst, 1996). Selye (1976) described the sequence of pathological changes occurring in the animals following exposure to stressful stimuli. He named it as "General Adaptation Syndrome" (G.A.S.) which develops in three stages comprising of : i) Alarm reaction or shock. ii) Stage of resistance and iii) Stage of exhaustion. Alarm reaction consisted of the triad of lymphothymic involution gastrointestinal ulceration, and loss of cortical lipid and medullary chromaffin substance from the adrenals. If the effect of stressful stimuli continues for a long period, the body develops the state of resistance. However, in case the stress is sufficiently severe and prolonged and the body fails to adapt, it may lead to the state of exhaustion in which the animal develops symptoms similar to those seen in the first stage.

Endocrinal, neurohumoral and antioxidant scavenging system's response to stress :

The relationship between stress, hormones and various metabolizing enzymes is now well established. During stress increase in the activity of
sympatho-hypothalamo-pituitary-adrenal system has been observed (Kvetnansky and Mikulaji, 1970 and D'Amato, 1992). In response to stress, the tropic hormones which in turn by acting on their target endocrine glands stimulate the synthesis and release of their respective hormones (Levi, 1967). Thus, due to stress the circulating levels of catecholamines, cortisol, ACTH, growth hormones, acetylcholine, histamine have been found considerably enhanced (Glick et al., 1965; Berson and yelow, 1968; Kvetnansky, 1972; Mikulaji et al., 1975; Pandey, 1976; Rai, 1976; Kopin et al., 1980 and Parrott, 1994).

An increased acetylcholine level is observed after stress (Aprison and Hington, 1969 and Parrott, 1994). The oscillation stress is found to deplete brain ACh levels and strain stress increases it in animals (Satio et al., 1976). The activity of the catabolizing enzyme of ACh i.e. AChE is found increased in the students with increased body temperature during examination (Yardanova and Gotsa, 1971), while a significant decrease in its activity is observed in experimental animals under stress (Litvak, 1969). Gupta et al., (1978) have reported an enhanced ACh level in psychic stress.

Increased levels of both ACh and AChE are reported after electric shock (Singh et al., 1980). The blood levels of ACh were found significantly enhanced in the patients of diabetes mellitus (Kamysheva and Gasperovich, 1978), and after exercise (Basu et al., 1975 and Weltman, 1994).

The metabolism of catecholamines have also been found altered in response to stressful stimuli (Subramanium, 1973; Scheider et al., 1974 and
Mason, et al., 1976). In various stressful conditions the activities of catecholamine synthesizing enzymes have been observed to be enhanced (Weinshilboum, et al., 1971; Kvetnansky, et al., 1976 and Rysanek, et al., 1978). Increased dopamine-β-hydroxylase activity with a decreased MAO activity has been recorded following stimulation of sympathetic nervous system or exposure to stress (Weinshilboum et al., 1971 and Sharma, 1978). However, hypophysectomized animals failed to exhibit such changes in DBH activity following exposure to stress (Molinoff, 1970). The activity of MAO is decreased in hypophysectomized animals or after hydrocorticosterone treatment (Parvez and Parvez, 1973), while an increase in brain MAO activity is found after adrenalectomy (Ceasar et al., 1970). MAO activity was found to be decreased significantly (Both A and B) in immobilization stress (Obata and Yamanaka, 1994). Guelman (1996) reported the change in the MAO (A & B) in adult rat cerebellum following neonatal X-irradiation.

Barchas and Freedman (1963) has reported that physiological stress modifies the serotonergic activity with an alteration in its metabolising enzymes. Several other workers have also reported the action of stress on central nervous system (Bliss et al., 1968; Bliss, 1973 and Modigh, 1974). 5-HT metabolism is found to be accelerated in the central nervous system by various stressors (Bliss et al., 1968; Bliss, 1973; Bourgoin et al., 1973 and Thierry, 1973). The plasma and urinary 5-HT levels have been found increased after exposure to a variety of stress such as cold stress, immobilization stress, electric shock etc. (Toh, 1960; Sarkar, 1978 and
Hirvonan et al., 1978), while some workers have reported a decrease in 5-HT level after stress (Corrodi et al., 1968). The involvement of stress associated with certain disease conditions is well known; such as in Schizophrenia (Smythies, 1976), Peptic Ulcer (Udupa, 1978), where central 5-HT metabolism is disturbed with the association of decreased platelet monoamine oxidase (Wyatt et al., 1973 and Domino et al., 1976).

The stress induced hyperactivity of adrenal cortex was originally described by Selye (1946). According to Henry (1977), the psychosocial stress activates either the pituitary-adreno-cortical system or the sympatho-adreno-medullary system. The adrenocortical system becomes activated when the organism fails to compete with the situation, a state leading to depression. In this type of stress the ACTH and corticosteroid levels are augmented with unaltered catecholamine levels. During the fight-flight reaction i.e. the organism fears a challenge to its integrity and maintenance of homeostasis, there occurs an increase in the sympatho-adrenomedullary system. This type of stress is characterized by an increased level of noradrenaline and adrenaline, while corticosterone remains unchanged. An increase in circulating and urinary levels of corticosteroids is found following various stressful stimuli, as surgical trauma, pain, anaesthesia and psychic stress (Thomasson, 1959 and Hume et al., 1962). Enhanced levels of cortico-steroids have also been reported in a variety of diseased conditions (Schimkin, 1943 and Lovegrovement et al., 1965) and experimental studies related to stressful conditions (Von Euler, 1969; Kvetnansky, 1972; Mikulaji et al., 1975 and
Principal pathways mediating the response to any stressor agents and conditioning factors which modify its effect (courtesy Sely, 1976).

(Butter worths Boston and London)
Szentendrci et al., 1980). In such situations the stress response is characterized predominantly by pituitary adreno-cortical system rather than the sympathetic adrenomedullary system, as described by Mason (1975). During depression, pituitary control of the adrenal cortex is affected with a consequent elevation of ACTH and plasma cortisol (Corroll, 1976 and Levine et al., 1978).

Glutathione as biological antioxidant, plays a role in the destruction of free radicals, (Sohal et al., 1984), and cellular protection during aging (Sohal et al., 1984 and Pruche et al., 1991). Enhanced level of lipid peroxides along with depletion of glutathione has been observed during stress (Younes and Siegers, 1980 and Katoh et al., 1989). Depletion of glutathione during immobilization stress is reported to stimulate oxidants and oxidative damage contributing to the degenerative diseases of ageing including brain dysfunction (Lin et al., 1996). Glutathione is essential for the repair process in brain exposed to oxidative damage by free radicals (Pellmur et al., 1992).

Considerable interest has been directed towards concentrations of glutathione in brain and other tissues mainly because this tripeptide is considered to have important functions in protecting cells against oxidative damage (Orlowski and Karkowsky, 1976). In this capacity, reduced glutathione (GSH) can act as a free radical scavenger (Rink, 1974 and Jaroslava et al., 1979). It has been reported that mild hypoxia in rats reduces brain tissue concentrations of GSH (Wideman and Domanska, 1974 and Jaroslava et al., 1979). Effect of antioxidant and free radical scavenging systems exist in the
cell protection against the damage resulted by free radical produced as a part of normal cell respiration and other cellular processes such as inflammatory response (Flohe et al., 1973; Willson, 1980, 1983; Cohen, 1984; Tappel, 1984 and Kaplotiwitz et al., 1985). The involvement of free radical and free radical reactions have been observed in the etiology and development of a number of diseases, especially life limiting (Pryor, 1978). Role of reactive oxygen species have been reported in oxidative stress related diseases (Sies, 1991). Oxidative damage to lipids, protein and DNA in the brain has been observed during immobilization stress (Liu et al., 1996). Immobilization stress induces generation of reactive oxygen species and decreases the endogenous antioxidants defenses, which can be attenuated by extra cellular administration of antioxidant GSH. (Liu et al., 1994).

The enzyme superoxide dismutase has been demonstrated in a variety of tissues and cell types and appears to protect against the toxic effects of oxygen free radical and thus provides a mechanism whereby an organism can protect possible deleterious effects of this radical or other free radicals produced by its further reaction with cellular components (Fridovich, 1975 and McCord et al., 1971). SOD have been reported as the first enzyme of the scavenging enzyme series to controlled the damage caused in cells by free radical (Slater, 1984). Singlet oxygen and superoxide radical have been observed potentially toxic to living cells as they can participate in the oxidation of cell macromolecules like protein, lipids etc. in case of leakage from the original oxidation reactions (King et al., 1975).
Generation of superoxide anion during interaction of molecular oxygen with flavins, NADH, glutathione peroxidase and catecholamines has also been studied (Misra and Fridovich, 1972). It has been observed that immobilization stress induces antioxidant defense changes in the plasma of rats (Liu et al., 1994). Several workers have reported the role of oxygen free radical and the role of SOD in clinical study on stress gastritis prophylaxis (Kayabali et al., 1994 and Zhang, 1993). Decrease in the activity of SOD has been observed in peptic ulcer and in the patients with lesions of the hepatobiliary system along with depletion of glutathione (Kolomoets, 1992), whereas, no significant changes in the activity of glutathione-S-transferase was observed. It has been reported that GST has a major role in the detoxification of oxyradicals and their products (Mannervik and Danielson, 1988). Brain GST plays an important role in the detoxification of potential toxicants through their conjugation and biotransformation (Booth et al., 1961; Boyland and Chasseand., 1969; Dixit et al., 1980 and Kuboto et al., 1985). Greater accumulation of the toxic compound is reported to inhibit the GST activity (Boyland and Chasseaud, 1969).

**Cancer**

Uncontrolled proliferation of cells, their invasion into their surrounding normal tissue leading to its destruction, and metastasis establishing new foci of growth are the three basic and well-known characteristics of malignant tumor.
Cancer as a disease, has existed all along with man. Hippocrates, twenty five centuries ago, called it Karkinois because the swollen blood vessels going and coming from the tumor mass, gave the appearance of the claws of crab. Susruta described cancer as a tumor which would ulcerate and would not cure and "sow its seeds in other parts of the body" (Jaggi, 1990).

All of the various cell types of the body can give rise to cancer cells. Cancer cells are usually closer in their properties to immature normal cells than to more mature cell types. They respond abnormally to the control mechanisms that regulate the division of normal cells, and they continue to divide due to genetic alteration in a relatively uncontrolled fashion until they kill the host (Temin, 1970; Pierce et al. 1978 and Mderano and Pardee, 1980). Cancer can be thought of as a "wound that does not heal" (Beauchamp et al., 1989).

Susceptibility to cancer is a polygenic phenomena. In addition, the influence of non-genetic factors such as hormones, nutritional status or chronic inflammation may modulate the development of neoplasia in a manner parallel to the phase of initiation and promotion seen in chemical carcinogenesis (Miller, 1980).

It is now generally recognized that most exogenous carcinogens require metabolic transformation into an active form and that the ability to activate these substances varies widely from individual to individual (Miller, 1980). Similar genetic control may be operating with regards to endogenous carcinogens as well (Lewan and Reilly, 1974). A precise parallel exists
between the metabolism of exogenous carcinogens and the metabolism of pharmacologic agents. A limited immune deficiency may also play a role in the etiology of primary hepatocellular carcinoma (Larouze et al., 1977).

Furth (1975) hypothesized that hormones are not direct carcinogens but are indispensable components in carcinogenesis. The hormones enhance cell division and thus, favour the somatic mutation or unmasking mutations brought about earlier in response to carcinogens, in effect acting as promoters. The studies in mice showing the enhancing effect of hormones on breast cancer induction, supports this view (Bittner, 1957). Dyer et al., (1975) have shown that hypersensitive patients carry higher risk of cancer development under certain circumstances.

Cancer can arise as the result of exposure to a variety of agents, studies have revealed that pure chemicals themselves are able to produce cancer (Millor, 1978). It is generally accepted that a high proportion of human cancer is attributed to environmental agents, mainly chemicals. The distribution of carcinogens in the environment is essentially ubiquitous. The human diet contains a variety of naturally occurring mutagens and carcinogens (Ames, 1983). The N-nitroso compound form a large group of agents, occur widely in the environment (Bartsch and Montesano, 1984). Many of them are carcinogens in experimental animals (Bogovski and Bogovski, 1982 and Magee et al., 1982) and are causative agents in some human cancer (Bartsch and Mostesano, 1984). Major percentage of N-nitroso compounds are alkylating agents which react with nucleic acids and other cellular molecules.
and exert many of their biological effect as a result of the transfer of an alkyl group (Millor, 1978; Magee et al., 1982 and O'Connor et al., 1979). Majority of chemical carcinogens are known to form a covalent adducts with DNA, thus indicating DNA as a critical target in chemically induced cancer (Millor, 1978; O'Connor, 1981). Colon and digestive tracts are exposed to variety of carcinogens derived from the rancidity of fat (Simic and Karel, 1980; Bisckoff, 1969; Petrakis et al., 1981; Imai et al., 1980; Ferrali et al., 1980).

Hydrogen peroxide generated by the oxidation of dietary fatty acid by peroxisomes, is a known mutagen and carcinogen (Reddy et al., 1982 and Plain, 1955). Some hydrogen peroxide may escape in the peroxisomes and contribute to the supply of oxygen radicals (Speit et al., 1982 and Jones et al., 1981), which in turn can damage DNA and can start the rancidity chain reaction, leading to the production of the mutagens and carcinogens (Pryor, 1976-1982).

One of the theories of etiology of cancer which is being widely accepted, holds that the major cause of damage to DNA is by oxygen radical and lipid peroxidation (Ames, 1983 and Totter, 1980). Certain promoters of carcinogenesis act by generation of oxygen radicals. Fats and \( \text{H}_2\text{O}_2 \) are among the most potent promoters (Welsch and Aylsworth, 1983). Other well known cancer promoter are lead, calcium, phorbolesters, asbestors and various quinones. Many carcinogens which require the action of promoters and by themselves are able to induce carcinogenesis (Complete carcinogens), also
produce oxygen radicals (Demopoules et al., 1980). These include nitroso compounds, hydrazines, quinones and polycyclic hydrocarbons. Much of the toxic effect of ionizing radiation damage to DNA is also due to the formation of oxygen radical (Totter, 1980).

Recent advances in molecular biology have led to the concept that carcinomas arise from the accumulation of a series of genetic alterations involving activation of proto-oncogenes and inactivation of tumor suppressor genes. p53 is a tumor suppressor gene located on chromosome pl3 and mutation at this locus are the genetic abnormalities most frequently found in a variety of human malignancies, including gynaecologic cancer (Fearon et al., 1987; Okamato et al., 1991; Marks et al., 1992; Milner et al., 1993; Nigra et al., 1989, Takahashi et al., 1989).

Breast cancer is by far the most frequent cancer in women, and ranks third overall when both sexes are considered together. It is the most common cancer of women in all the "developed" areas (except for Japan, where it is second to stomach cancer) (Parkin et al., 1993). Several studies about breast cancer indicated that this disease is the result of a combination of factors, such as ionizing radiation, diet, socioeconomic status psychosocial stress and endocrinologic, familal or genetic (Mathew et al., 1990).

However, these pieces of information do not provide a complete picture of the pathogenesis of the disease, or of the mechanisms of interaction of the carcinogen with the target organ (Russo et al., 1986 & 1987). Therefore,
we still lack effective strategies for breast cancer prevention and cure.

Beside breast cancer, liver cancer is considered one of the major cancers of developed and developing countries (Parkin, et al., 1993). A number of reports have described the occurrence of liver cell adenomas in women using oral contraceptives (James et al., 1980). Circumstantial evidence derived from human and early experimental animal data, together with the reports of Tapper (1978) suggested that oral contraceptive steroids may be liver tumor promoters.

A number of studies have demonstrated many similarities between the pathogenesis and morphological changes of experimental and human liver cancer (Thomac, 1961 and Butler, 1971). Evidence that specific environmental chemicals from industrial, medical, and dietary sources are carcinogenic to the human has now become quite clear (Emmelot, 1977). Furthermore, there appears to be a role for at least one virus, the hepatic B virus, in the induction of human hepatic cancer (Tatematsu, et al., 1977). There is a functional evidence for the multiple stages in the natural history of human hepatocellular carcinoma, some data point to a marked degree of similarity in hepato carcinogenesis in the experimental animal and in the human beings (Henry, 1980).

Apart from uncontrolled proliferation of cells, their invasion into surrounding normal tissue, and metastasis establishing new foci of growth, the other adverse effects of the tumor on the structure and function of host cells that are not in direct contact with the tumor cells are reflected in altered
enzymes activities, metabolism, nutrition or hormonal imbalances and composition of blood. These changes are called paraneoplastic syndromes or tumor-host relations (Begg, 1958 and Hall, 1974). The well known examples of paraneoplastic syndromes are anorexia, cachexia, hypercalcemia of malignancy and anemia.

"It has been estimated that 20% of a group of patients at any time suffer from paraneoplastic syndrome at all stages of the disease and 75% of all patients will acquire one during the course of their disease". In some cases "disability or death will occur due to the syndrome than cancer per se" (Hall, 1974).

An interesting aspect of paraneoplastic syndrome is the mechanism by which they arise, i.e., the mechanism by which the tumor influences the host cells that are not in contact with it. Studies on paraneoplastic syndromes date back to earlier decades of this century. It has been shown that the liver catalase levels were greatly reduced in tumor-bearing animals and cancer patients (Begg, 1958; Hall, 1974; Bluementhal, 1910; Rosenthal, 1912 and Brahn, 1914).

The isolation stress is known to increase the activity of enzymes responsible for metabolic activation of carcinogens, without influencing their excretion, and may therefore adversely affect carcinogens (Capel and Williams, 1979). The stressful situations are known to increase plasma cortisol levels also (Capel and Williams, 1979). Plasma cortisol level is found significantly raised in cancer breast and liver and the increase is more
pronounced in the patients with distant metastasis than in the tumor patients without distant metastasis (Schaur et al., 1979; Khataibeh, et al., 1996). Urinary excretion of 17-ketosteroids, cortisol sulfate and cortisone sulfate is found enhanced in cancer breast patients (Stancakova and Klimesova, 1979). Zeidman (1962) and Fidler and Lieber (1972) have reported increase in the incidence of metastasis following intravenously injected tumor cells in animals treated with corticosteroids.

Two to three fold increase of LDH is associated with fall of plasma cholinesterase level. This relationship is most marked in lymphomas. Further fall in plasma cholinesterase level is found to indicate that the disease is fairly advanced and has probably spread to the liver (Ghooi et al., 1980). The elevation is highly marked in various cancers and more marked in primary and secondary liver cancer and certain other enzymes are elevated in the gastric juice of patients with gastric carcinoma (Smyrniotis et al., 1962).

Decreased activities of monoamine oxidase, cytochrome oxidase, succinic dehydrogenase are found in both benign and malignant neoplasma and also in hyperplastic lesions (Wattenberg, 1974; McGinty et al., 1973 and Banu et al., 1988). Generally, the activities of some enzymes which are not essential for the process of rapid growth of the tissues are decreased in such situations.

Lower concentrations of tissues c-AMP have also been reported in cancer breast (Patel et al., 1981), along with enhanced catecholamine levels
Serum lactate dehydrogenase level has been found enhanced in all the cases of cancers (Ts'ao, et al., 1996). Lactate dehydrogenase (LDH), serum glutamate pyruvate transaminase (SGPT) and serum glutamate oxaloacetate transaminase (SGOT) have been reported as tumor marker enzymes (Vinitha, et al., 1995). Cancer patients whose serum LDH was above the normal range or had not been normalized after 3 months of therapy were in the high risk group, and should be given more aggressive treatment (Masukagami, et al., 1996). Tumor cells appear quite resistant to oxidative stress. Cell damage precipitated by protease, elastase and Triton probably involves hydrolysis of protein and phospholipids in the cell membrane, leading to an increased leakage of intracellular protein such as LDH (Ts'ao et al., 1996).

Besides LDH, SGOT and SGPT, Glutathione-S-transferase (GSTs) have also been reported as tumor marker enzymes (Tatemasu et al., 1988; Vinita, 1995).

Glutathione-S-transferases (GSTs) as detoxificants and metabolizing enzymes have been linked with the susceptibility of tissues to environmental carcinogens (Stein, 1996). A hepatic GSTs are involved in hepatic detoxification and are considered to play important role(s) in chemical carcinogenesis (Arias et al., 1976; Chasseaud, 1979; Jakoby, 1980 and Mannervik and Jenson, 1982). Vahrmeijer (1996) observed a lack of glutathione conjugation in human during cancer. However, changes in GST forms during chemical hepatocarcinogenesis have not been fully investigated.
It is established beyond doubt that free radicals in tissues and cell can damage DNA proteins, carbohydrates and lipids. These potentially deleterious reactions are at least partly controlled by antioxidants capable of scavenging radicals. It is widely believed that a proper balance between free radicals and antioxidants is essential for the health of an organism (Rautalahti, et al., 1994). Reactive oxygen species and other free radicals are known to be the mediators of phenotypic and genotypic changes that lead from mutation to neoplasia. In erythrocytes reactive, oxygen species and other free radicals can result to hemolysis which is one of the pathogenetic mechanisms of anemia in cancer patients (Zima et al., 1996).

Free radicals and reactive oxygen metabolites due to increased production or reduced inactivations, following a decrease in the antioxidant burden in the mucosa, might cause damage to DNA, thereby resulting in genetic alterations. This might represent the cause of the transformation process (Pappalardo et al., 1996). Apart from oxidants (free radicals), cigarette smoke contains such a multitude of (pre) carcinogens that it is astonishing that not every heavy smoker becomes a victim of malignancy. This points to the interindividual variability in susceptibility to carcinogens; several lines of evidence suggest that metabolic and personality factors are involved in such variability (Russo et al., 1987). Metabolism of carcinogenes as well as the subsequent (multi) steps of carcinogenesis are affected by host factors and governed by the balance between opposing forces, such as metabolic activation and detoxification, formation and scavenging of radicals and DNA
activation and detoxification, formation and scavenging of radicals and DNA damage and repair, which seem to imply that carcinogenic compounds can initiate tumor growth only in amount saturating detoxification mechanisms. In this context it is well known that reduced glutathione (GSH) plays a critical role in the detoxification process, which is reported to be a safe agent without major side effects and has been emerged as a most promising cancer chemopreventive agents (Van Zandwijk, 1995). Some workers have implicated the loss of antioxidant glutathione in the pathogenesis of parkinson's disease (Drukarch et al., 1996).

Antioxidant, vitamins which include beta carotene, vitamin E, vitamin C and related micronutrients are hypothesised to decrease cancer risk by preventing tissue damage by trapping organic free radical and/or deactivating excited oxygen molecules, a by-product of many metabolic functions (Hennekens 1994) where the lowest fruits and vegetable intake has been consistently associated with increased risk of cancer (Van Zandwijk, 1995; Romeny 1995; Bowen and Mobarhan, 1995; Schwartz 1996). But much less evidences show that such low intake can encourage the development of cancer which are under hormonal control (Schorah 1995).

Erythrocytes have a life span of about 120 days, Smith (1995) reported that exercise, cycling, running and swimming have been shown to cause RBC membrane damage. The neutral amino acids are found to reduce the hypotonic hemolysis at pH 5.0 but enhance it at pH 8.0 (Morimoto et al., 1995). Thus, these amino acids controlled the osmotic fragility of cell membrane showing a protective effect.
The osmotic fragility test is used to determine the extent of red blood cell hemolysis produced by osmotic stress. Erythrocyte hemolysis is dependent upon cell volume, surface area, and functional integrity of cell membranes. The dependence of RBC hemolysis on concentration of sodium chloride has been determined spectrophotometrically by measuring the absorbance of released hemoglobin (Orcutt et al., 1995). Incubation of RBC with lactic acid for one hour at 37 °C increased the osmotic fragility of erythrocytes. Even in the absence of lactic acid, RBC subjected to heat shock at 42 °C showed increased osmotic fragility as compared to 37 °C (Kogawa et al., 1995).

Reactive oxygen species and other free radicals can cause erythrocytes hemolysis, which is one of the pathogenic mechanisms of anemia in cancer patients. In multiple myeloma patients, the activities of superoxide dismutase and glutathione peroxidase were significantly lowered. These results proposed a possible role of free radicals with reduced antioxidant activities of SOD and glutathione peroxidase (GPs) in multiple myeloma (Zima et al., 1996).

**Stress and Cancer**

Interest in the involvement of personality factors or stress in the evolution of human cancer dates back to 175 A.D. when Galen stated that 'Melancholy' women were more prone to cancer than their 'Sanguine' counterparts. Other workers also reported that grief and mental depression is associated with breast cancer (Cutter, 1954). Later Snow in 1893 found
that the occurrence of malignant disease of the breast and uterus is preceded by a previous history of emotions of a depressive character. Further, Leshan and Worthington (1956) and Schmale and Iker (1971) have demonstrated a relationship between the malignant disease and preceding stress, several eminent clinicians have reported that temperament, depression and life stresses appear to be related to the life development and course of cancer (Kowal, 1955; Leshan and Worthington, 1956; Guy, 1967 and Snow, 1967). Moore (1969) suggested that stress and strain of modern life may also be one of the causes for oncogenesis. Moore (1969) proposed that sociological stress in women may be one of the factors in the etiology of breast cancer. Several other convincing evidences are there to incorporate the involvement of stress in the development of tumors (Seifter, 1976; Udupa et al., 1980 and Banu et al., 1988). Many workers have correlated the psychological factors with human cancer (Cobb, 1952; Cutter, 1954; Corson, 1966). Cholst, (1996) proposed that chronic stress in human can cause psychological and physiological reactions.

Riley (1975) observed that the incidence of mammary tumors in experimental mice could be increased to 90% by exposing them to a variety of stressors whereas the incidence in control mice was only 7%. Thus, he concluded that moderate, chronic or intermittent stress may predispose such mice to increased risk of mammary cancer and adequate protection from physiological stress may reduce mammary tumor occurrence in mice. Chronic stress can be lessened in the treatment of cancer (Cholst, 1996).
Malignant neoplasma undoubtedly elicit the typical manifestations of the G.A.S. both in animals and in man (McEuen and Selye, 1935; Moore et al., 1969 and Ertl, 1973). Many types of cancer develop at sites of chronic local stress (Selye, 1979). According to Cole (1973), stress enhances metastasis in experimental tumor bearing animals. In susceptible persons, a severe emotional distress can trigger carcinogenesis, whereas various educational measures can inhibit the growth of cancer (Reichel, 1977). Various other workers have suggested that suppressed anger and difficult early relationship with parents could be one of the predisposing factors in the oncogenesis (LeShan, 1966; Thomas and Duszynski, 1974).

To establish a relationship between stress and cancer an experimental system is needed that mimics the human disease and therefore rats were considered as one of the most widely studied and useful models of mammary carcinogenesis (Dao 1962; Huggins 1959 and Young and Hallowes 1973). The commonly used strains, Spraque-Dawley and wistar-Furth are most susceptible to DMBA carcinogenesis. (Isaacs, 1986). Thus, Spraque-Dawley strain of rats were employed in the present study of cancer by infusion with 7,12-Dimethylbenz(a)anthracene (DMBA) (Rogers et al., 1990).

DMBA is one of the most potent carcinogenic polycyclic hydrocarbons (Brookes and Lawley, 1964 and Slaga et al.,1974). Roger and Lee (1986) reported that the two most widely used experimental systems for the study of mammary tumorigenesis are the models in which tumors are induced in the Spraque-Dawely (S-D) rat by 7,12-Dimethylbenz(a)anthracene (DMBA), or in
the S-D or Fischer 344 rats by N-methylnitroso urea (NMU). DMBA, given by gavage in a single dose of 3.5-30 mg induces tumors with latencies that generally range between 8-12 weeks with and final tumor incidences close to 100% if sufficient time elapses before recropsy.

7,12-Dimethylbenz(a)anthracene, present in cigarette smoke and charcoal broiled foods is carcinogenic. Some carcinogens act directly, while other, such as benz(a) anthracene must undergo prior hydroxylation by arylhydroxylases, present mainly in the liver, before their carcinogenic potential can be expressed.

\[
\begin{align*}
\text{Benz(a)anthracene} & \rightarrow \text{5,6-Epoxide} \\
\text{} & \text{(Carcinogenic)}
\end{align*}
\]

The susceptibility of the mammary gland to DMBA-induced carcinogenesis is strongly age-dependent and is maximal when the carcinogens are administered to animals between the ages of approximately 45-60 days, that is the age of sexual maturity (Grubbs. et al., 1986 and Rose, 1980). Active organogenesis and high rate of proliferation of the glandular epithelium are characteristics of that period (Rose et al., 1980). In virgin rats treated with DMBA, tumors that develop are largely carcinomas although the proportion can be altered by carcinogen dose and dietary fat (Chan et al., 1983).
The administration of DMBA to rats of different ages induces tumors with an incidence which is directly proportional to the density of highly proliferating terminal end buds (TEB) (Russo et al., 1978). A 100% incidence of carcinomas is obtained when DMBA is administered to rats aged 30-55 days, but with the highest number of tumors/animal is observed when the carcinogen is given to animals when they are 40 to 46 days of age (Russo et al., 1990). Pregnancy occurring early after carcinogen exposure increases tumorigenesis (Grubbs, 1983). Caffeine increased mammary gland development in mice, apparently by increasing the response to trophic hormones (Welsch et al., 1988).

Epidemiologic studies strongly indicate that alcohol intake is a risk factor for breast cancer (Rogers et al., 1988). The increased risk is 1.3 to 3 folds depending upon the population studied and the amount of alcohol consumed (Barsky et al., 1984 and Geschicker, 1945). Vitamin A and related retinoids reduced mammary tumorigenesis (Aylsworth et al., 1986 and McCormick, 1981).

**Acetylcholine strase (AChE) : (EC.3.1.1.7)**

It is the enzyme which catalyses the hydrolysis of acetylcholine into choline and acetate and thereby inactivates the esters. The name acetylcholinesterase was proposed by Augustinsson and Nachmansohn (1949). One molecule of enzyme may split one molecule of ACh in about 3-4 microseconds. Extensive studies on the concentration and distribution of AChE in
conductive tissues have shown that significant amount of ACh may be split per gm of tissue within milliseconds, ie within a period of time which the impulse passes (Nachman Sohn, 1939). The concentration of enzyme is high in all nerve tissues. Nerve fibres are capable of hydrolyzing amount of ACh ranging usually from 5 to 50 mg per gm fresh tissue per hour. Alles and Hawes (1940) showed that erythrocyte esterase differ markedly from serum esterases. Richter and Croft (1942) confirmed that red cell esterase is highly specific for ACh. Zeller and Bissegger (1963) found that brain esterase is fundamentally similar to red cell esterase. The rate of hydrolysis of ACh was found to be optimal at about 6 to 8 x 10⁻³ M substrate concentration. Higher concentrations increasingly inhibit the rate of hydrolysis. The function of acetylcholine in RBC is unknown but Brauer and Root (1945) found the enzyme is localized in the surface of the red cells. The membrane environment of red cell is also important for the enzyme reactivity (Flis, 1979). Characterization and investigation of AChE with respect to its kinetics has been reported in W. aegyptia venom (Al Jafari et al., 1995). AChE has also been isolated from rat liver (Mansee et al., 1995). Several workers have reported the inhibition of anesthetics like halothane, methoxy flurane, di-ethyl ether, chloroform on erythrocyte bound AChE activity (Yoshimura et al., 1995). N-Benzylpiperidine derivatives have been found to inhibit the metabolic breakdown of ACh via AChE, hence alleviating memory defects in patients with Alzheimer's disease by potentiating cholinergic transmission (Tong et al., 1996).
Fig. 2: Metabolism of acetylcholin.

Fig. 3: Metabolism of histamine.
Acetylcholine

\[ \text{HS-CoA} + \text{ATP} + \text{acetate} \xrightarrow{\text{acyethylthiokinase}} \text{Acetyl CoA} + \text{H}_2\text{O} + \text{ADP} \]

\[ \text{Acetyl CoA} + \text{choline} \xrightarrow{\text{choline acetylase}} \text{Acetylcholine} + \text{HS-CoA} \]

\[ \text{Acetylcholine} + \text{H}_2\text{O} \xrightarrow{\text{cholinesterase}} \text{Choline} + \text{acetate} \]

Fig. 2

Histidine

\[ \text{HC}=\text{C}-\text{CH}_2\text{CH}^{-}\text{COOH} \]

\[ \xrightarrow{\text{aromatic L-amino acid decarboxylase}} \]

Histamine

\[ \text{HC}=\text{C}-\text{CH}_2\text{CH}_2\text{NH}_2 \]

\[ \xrightarrow{\text{imidazole-}N\text{-methyltransferase}} \text{CH}_2\text{N}^+\text{C}^-\text{CH}_2\text{NH}_2 \]

Methylhistamine

\[ \xrightarrow{\text{diamine oxidase (histaminase)}} \text{HC}=\text{C}-\text{CH}_2\text{COOH} \]

Imidazoleacetic acid

\[ \xrightarrow{\text{monoamine oxidase}} \text{HC}=\text{C}-\text{CH}_2\text{COOH} \]

Methylimidazoleacetic acid

Fig. 3
Fig. 4

Catabolism of catecholamine.
**Monoamine Oxidase (MAO)**: (EC.1.4.3.4)

Monoamine oxidase is a flavin-containing enzyme located on the outer membrane of the mitochondria (Cost and Sandler, 1972). It was first reported in liver by Hare (1928). Oxidative deamination of primary monoamines by the mitochondrial enzyme monoamine oxidase produces $\text{NH}_3$, aldehyde and $\text{H}_2\text{O}_2$, agents with established or potential toxicity (Cooper et al., 1978; Benedetti and Dosteret, 1989).

MAO is one of the major mammalian neuronal enzymes. It is active in both neuron and glial cells in the brain. MAO plays a strategic role in inactivating catecholamines that are free within the nerve terminals and not protected by the storage vesicles (Coyle and Synder, 1981). When monoamines leak from the synaptic vesicles, MAO acts within the nerve fibre itself. The concept of two distinct form of MAO has gained wide acceptance (Johnston, 1968; Houslay et al., 1976 and Leung et al., 1981). Type A deaminates neurotransmitter amines such as 5-hydroxytryptamine (5-HT) and noradrenaline (NA) and is inhibited specifically by glergyline, whereas type B oxidizes benzylamine and $\beta$-phenylethylamine and is preferentially inhibited by deprenyl phenyl isopropyl methyl propinyl amine (Tipton and Della Corte, 1979). Both form deaminate substrate such as dopamine, tyramine and tryptamine (Houslay et al., 1976).

However, both forms of the enzymes are not found in all the tissues (Fuller and Roush, 1972). The deamination mechanism for both types are the same.

\[
\text{MAO} \\
\text{RCH}_2\text{NH}_2 + \text{O}_2 + \text{H}_2\text{O} \xrightarrow{\text{MAO}} \text{RCHO} + \text{NH}_3 + \text{H}_2\text{O}_2
\]
One mole of O\textsubscript{2} is required for the oxidation of one mole of substrate. MAO acts only on those which have an amino group attached to the terminal carbon atom (Blaschko, 1952). When the amino group is directly attached to the benzene ring, deamination does not occur, but terminal carbon atom of the amines as in amphetamine and epinephrine, they are not metabolized by MAO, MAO is known as the principal enzyme taking part in the deamination reactions (Yasunobu et al., 1968). Generally all the vertebrates contain MAO. The usual sources of MAO are the mitochondria of liver, brain (Weiner, 1960), adrenal gland, kidney and peripheral and central nervous system (Blaschke et al., 1955). It is also found in heart, salivary gland, spleen, and noradrenergic granules (Tripton et al., 1976).

Inhibitors of MAO play a significant role in the metabolism of catecholamine, serotonin and other amines (Zellet et al., 1952). The first monoamine oxidase inhibitor i.e. hydrazine was found in 1952. The use of such inhibitors increases the concentration of neurohumors and decreases the excretory metabolities like VMA and HVA. However, the concentration of normetanephrine, metanephrine and octopamine are increased following administration of MAO inhibitors (Sjoerdona, 1970). The evidence that the two forms of MAO result from differences in membrane lipid binding suggests that the activity of the enzyme in vivo might be affected by drugs and diseases that affect lipid metabolism.
Fig. 5: Metabolism of 5-hydroxy tryptamine.
Cortisol

Cortisol is a corticosteroid hormone, which is secreted from the adrenal cortex. The hormones of the pituitary-adrenocortical axis are involved in the regulation of functions of the central nervous system (Holsboerm, 1989). They not only coordinate the neuroendocrine processes to stress itself, but also affect psycho-physiological processes. In 1936 Selye observed that diverse noxious agents cause an enlargement of the adernal cortex as a consequence of the "stress syndrome". Yates and Maran (1974) reported that a variety of stressful events cause a release of ACTH from the anterior pituitary. The secreted ACTH stimulates the synthesis of corticosteroids in the adrenal cortex. The elevated corticosteroid levels in plasma then inhibit the further release of ACTH from the pituitary. In a series of elegant experiments, Harris (1948) demonstrated that the release of ACTH from the pituitary is regulated by a corticotropin-releasing factor (CRF) from the hypothalamus. The CRF is synthesized in the hypothalamus. The CRF synthesized in the hypothalamus reaches the pituitary by a private portal blood supply. It then stimulates the secretion of ACTH from the pituitary. After a long period of intensive investigations, CRF was isolated and purified, and its structure was characterized as a 41 amino acid peptide by Vale and co-workers (1981). CRF was thought to be the major, if not the sole means, of releasing ACTH from the pituitary. ACTH can also be released and regulated by catecholamines and other hormones (axelrod and Reisine, 1984).
There have been a number of investigations using cortisol to assess the reaction of the pituitary-adrenocortical axis under various conditions. Lundberg and Frankenhaeusr (1980) found increased cortisol levels in situations which were accompanied by boredom, impatience and tiredness (vigilance task). In situations characterized by a high controllability and predictability (self-placed RT-task), Lehmann et al., (1992) reported an adrencortical suppression. Furthermore, there is increasing evidence that cortisol modulates brain function in humans. This principal endogeneous glucocorticoid in humans increases slow-wave sleep and decreases rapid-eye-movement sleep (Born et al., 1991). There is some evidence that heart rate changes are accompanied by cortisol changes dependent on personality. Furthermore, an increasing heart rate is related to increasing difficulty of a task (Eason and Dudley, 1971; Carrol et al., 1986).

**Glutathione**

Sulfhydryl (-SH) group is also known a thiol group. It plays a key role in active enzymatic sites of many important enzymes (Hoch and Vallee, 1959). In principle, any enzyme bearing an accessible thiol, essential for activity is capable of forming protein mixed disulfides or intramolecular disulfides by reacting with small disulfides. Formation of mixed disulfides or intramolecular disulfides can increase or decrease catalytic activity and examples of both are known. Furthermore, the extent of enzymes-S-thiolation would depend on the thiol-disulfide redox potential as well as the nature of the small disulfide and the micro-environment
around the accessible protein thiol. These parameters are at least potentially capable of conforming the specificity required for a biological control mechanism through signal transmitted by changes in the thiol-disulfied redox potential as function of different metabolic states.

Glutathione (GSH) protects hemoglobin and other critical erythrocyte proteins from preoxidative injury. Sulfhydryl groups derived from the side chain of cysteine residues, occur in a number of enzymes. Sulfhydryl (-SH) group and disulfide (-SS) bond of cysteine are highly reactive and are apparently involved in the maintenance of the conformation and biological activity of certain proteins. As the receptors are protein in nature, the reagents, which modify -SH groups may influence the interaction of neurotransmitters with their recognition sites (Sobrino and Del Castillo, 1972).

Sulfhydryl groups play an important role in GST induced detoxification against electrophilic xenobiotics and toxicants by conjugating with such compounds and thus neutralizing their electrophilic sites (Habig et al., 1974).

Glutathione has been considered to function as biological antioxidant. It plays a pivotal role in the destruction of free radical as well as inorganic and organic peroxides (Sohal et al., 1984). GSH is a naturally occurring and widely distributed tripeptide. It consists of glycine, cysteine and glutamic acid moieties (Allen and Balin, 1989). \(\gamma\)-glutamyl cysteinyl glycine molecule is the major nonprotein thiol compound present in cells in concentration which range between 0.1 and 10 mM (Kosower, 1976a). It is synthesized intracellularly by the consecutive action of glytamyI cysteine synthase and GSH synthase. Its concentration is dependent
on metabolic rate and the level of oxidative stress (Allen and Sohal, 1986). It has been implicated in a wide variety of biological functions, such as the maintenance of all membranes, destruction of metabolic peroxides and free radicals, detoxification of foreign compounds, removal of H₂O₂ maintenance of thiol group of enzymes and proteins, control of redox status, disulfide exchange reaction, transport of amino acids and peptides across membranes (Hazelton and Lang, 1980; Meister and Aderson, 1983 and Ziegler, 1985) besides the presence of low pH, lactate is the main factor causing depletion of intracellular glutathione (Breborwicze et al., 1996)

**Glutathione-S-Transferase (GST) : (EC. 2.5.1.18)**

Glutathione-S-transferase is a non-selenium dependent glutathione peroxidase (Sies et al., 1979). GST was first identified in 1961 (Booth et al., 1961 and Coombs and Stakelum, 1961). The enzyme was subsequently named glutathione-S-aryl transferase. Later on, several other GSTs were demonstrated depending upon the substrate specificity.

Among many enzymes discovered to be important for toxicity of chemicals in humans, glutathione-S-transferases are of most interest in occupational toxicology (Goergens, 1996). The enzymes are almost ubiquitous in nature, and their activities have been identified in man, non-human primates, rats, mouse, hamster, guinea pig, chicken, cow, sheep, troup and shark (Mannervik, 1985). The concentration of GST is in general, high in mammals (upto10% of cytosolic proteins in some organs), in other species
The level of activity is quite low (Sugiyama et al., 1981). In addition, it is generally present in most mammalian organs.

The GSTs are a family of multifunctional protein that function both as important enzymes of detoxification and intracellular binding proteins (Boyer, 1989). At least six forms of rat liver GST have been characterized by physiochemical properties (Arias et al., 1976; Chasseaud, 1979; Jakoby, 1980; Mannervik and Jensson, 1982 and Pabst et al., 1974). As enzymes, they catalyze the reaction between nucleophil reduced GSH and large number of electrophilic compounds such as polycyclic aromatic hydrocarbons, aromatic amines, azo dyes, alkylating agents, carcinogens and neurotoxins (Boyland and Chasseaud, 1969; Habig et al., 1974; Jakoby, 1978 and Chasseaud, 1979). They also bind a number of amphipathic compounds that they do not metabolize (non-substrate ligands) and have been suggested to act as intracellular transport proteins for compounds that have limited solubility in water (Levi et al., 1969).

**Superoxide Dismutase (SOD) : (EC 1.15.1.1)**

All aerobic organisms utilized O₂ and must have some mechanism by which they can minimize O₂ toxicity. One mechanism is the production of suerioxide radical and its dismutation reaction, catalyzed by the enzyme superoxide dismutase (Harman, 1956 and 1971). The superoxide anion is a free radical formed by one electron transfer to oxygen.

\[
\text{O}^\cdot + e^- \rightarrow \text{O}_2^{2-}
\]

Superoxide dismutase (SOD) catalyzes the dismutation between two moles of
superoxide anion to yield one mole of oxidized product (oxygen) and one mole of reduced product (hydrogen peroxide) (Klug et al., 1972).

\[ \text{O}_2^- + \text{O}_2^- + 2\text{H}^+ \rightarrow \text{O}_2 + \text{H}_2\text{O}_2 \]

This is analogous to the dismutation of hydrogen peroxide to oxygen and water catalyzed by catalase ordinarily, electrostatic repulsion between two molecules of superoxide anion limits their approach to one another; SOD overcomes the barrier and greatly increases the dismutation rate (Fridovich, 1976 and 1978).

Several forms of SOD have been identified since the enzyme was first discovered in 1969 by McCord and Fridovich. They identified the enzymatic activity associated with erythrocuperein, a copper-zinc protein of erythrocytes. The copper is associated with enzymatic activity, whereas the zinc is structural. Similarly, SOD activity is associated with a family of Cu-Zn proteins, cerebrocuprein in brain (Fried, 1979) and hepatocuprein of liver. In mammalian tissues, a second form exists in which manganese is the prosthetic group (Fridovich, 1976). In rats and mice the Mn-SOD is localized to mitochondria, whereas Cu-Zn SOD is cytoplasmic. However, this distribution does not hold in other species.

Fried and Mandel (1975) indicated that very high levels of activity are present in liver, while the adrenals, kidney and red blood cells have intermediate activity and lower activities were found in most other tissues including brain. Regional distribution studies in the rat by Thomas and his co-workers (1976) showed a relatively homogenous distribution in brain, about a two-fold range from the highest area (medulla oblongata) to the lowest area (cortex). Subcellular distribution studies in the rat (Thomas et al., 1976) showed the highest level in the cytoplasm while myelin has very low levels.
Fig. 6

Action mechanism of free radicals on membrane permeability.
**Transaminases (Aminotransferases)**

The transaminases constitute a group of enzymes that catalyze the interconversion of amino acid and α-ketoacid by transfer of amino group. The α-ketoacid glutarate/L-glutamate couple serves as one amino group acceptor and donor pair in all amino transfer reaction; the specificity of the individual enzymes derives from the particular amino acid that serves as the other donor of an amino group. Thus, aspartate amino transferase (GOT): (EC. 2.6.1.1) and alanine aminotransferase (GPT): (EC. 2.6.1.2) catalyze the reactions as follows:

\[
\begin{align*}
\text{COO}^- & \quad \text{COO}^- \\
H - C - NH_2 & \quad C = O \\
\text{CH}_2 & \quad \text{CH}_2 \\
\text{COO}^- & \quad \text{CH}_2 \\
\text{L- Aspartate} & \quad \text{COO}^- \\
\alpha\text{-Ketoglutarate} & \quad \text{Oxaloacetate} \\
& \quad \text{L- Glutamate}
\end{align*}
\]

\[
\begin{align*}
\text{COO}^- & \quad \text{COO}^- \\
H - C - NH_2 & \quad C = O \\
\text{CH}_3 & \quad \text{CH}_2 \\
\text{L- Alanine} & \quad \text{CH}_2 \\
\text{COO}^- & \quad \text{CH}_2 \\
\alpha\text{-Ketoglutarate} & \quad \text{Pyruvate} \\
& \quad \text{L- Glutamate}
\end{align*}
\]

The reactions are reversible, but the equilibria of the GOT and GPT reactions favor formation of the Aspartate and alanine respectively.
Transaminases are widely distributed in animal tissues.

Asparate transaminase (GOT) have been isolated from the thermophilic microorganism Bacillus isothermophilus (Bartsch Klaus et al., 1996). In viral hepatitis and other forms of liver diseases associated with hepatic necrosis, serum GOT and GPT are found elevated even before the clinical signs and symptoms of disease appear (e.g. jaundice). Five to ten fold elevations of the two enzymes occurs in patients with primary or metastatic carcironmas of the liver, with GOT usually being higher than GPT. (Vinitha et al., 1995). Rapid increase in the activities of the two enzymes in serum have been reported during restraint stress (Sun et al., 1995) and a slight or moderate elevations of both SGOT and SGPT activities may be observed after intake of alcohol and after administration of a variety of drugs (e.g. ampicillin) (Norbert, 1996).

**Lactate dehydrogenase (EC.1.1.1.27)**

Lactate dehydrogenase is a hydrogen transfer enzyme that catalyzes the oxidation of L - Lactate to pyruvate with the mediation of NAD+ as hydrogen acceptor. The reaction is reversible and the reaction equilibrium strongly favours the reverse reaction, i.e. reduction of pyruvate to lactate.

\[
\begin{align*}
CH_3 & \quad H-C-OH + NAD^+ \underset{LDH}{\xrightarrow{\text{CCH}_3}} C=O + NADH + H^+
\end{align*}
\]

Lactate       Pyruvate
Two isozymes (LDH -5 & LDH - 4) of lactate dehydrogenase have been purified 21 fold from the liver of the reptile Varanus bengalensis (Masood et al., 1997). Lactate dehydrogenases are inhibited by reagents with reactivity against thiol groups such as mercuric ions and p-chloromercuribenzoate. Inhibition can be reversed by the addition of cysteine or glutathione. LDH activity is present in almost all cells of the body. Enzyme levels in various tissues are very high compared to serum. Serum levels of LDH were found elevated at 2 hours and increased continuously up to 8 hours of restraint stress (Sun et al., 1995). LDH have been proved as tumor marker for their changes in concentration in serum, liver and kidney (Vinitha et al., 1995). Exposure of rats to hypoxia produced a proportional loss of body and heart weight with an equal decrease in both LDH subunits H (heart) and M (Muscles) (Kaaja and Ari, 1996). Pleural fluid LDH isoenzyme pattern may be helpful for the differential diagnosis of the most common causes of pleural effusions; congestive heart failure, infections and malignancy (Lassos, Izidores et al., 1997). Elevation of LDH activity was observed in liver disease, but these elevations are not as great as the increases seen in transaminase activity.

**Indigenous drugs:**

**Sage (Salvia officinalis Labiatae)**

Medicinally, Sage is used as a mild tonic, a stringent and carminative. An infusion of the leaves is used as a gargle in the
Fig. 9: Sage (Salvia *Officinalis*).
treatment of sore-throats; hot infusion is said to be diaphoretic. Extracts of sage leaves are also reported to be antipyretic (Sharma, 1965). In Chinese medicine it is a yin tonic with a well deserved reputation as a nerve tonic helping both to calm and stimulate the nervous system (Andrew, 1996). Sage is a valuable remedy for female disorders since ancient times. Though its hormonal action is not completely understood, there is no doubt it reduces sweating, which is coupled with its tonic and estrogenic effects, making it an excellent remedy for the meno-pause, not only reducing hot flushes, but helping the body to adapt to the hormonal changes involved (Andrew, 1996). The estrogenic substances have been extracted from the dried leafy tops (Hanson and Hocking, 1950 and Sastri, 1956).

Sage has a slight warm, noticeable bitter and astringent taste. It is rich in flavonoids and phenolic acids (Andrew, 1996). The leaves of sage contain an essential oil. Small amounts of triterpenoids and steroids are also reported to be present in its oil (Sharma, 1965).

Sage and sage oil exhibit antioxidant properties, five antioxidant fractions with antioxidant indices between 8.8 and 10.0 have been isolated from leaves of *S. officinalis*, one of which appears to be a polyhydric phenol (The Sastre, 1956). Edible plants containing variety of substances such as phenols and flavonoids (Nagao *et al.*, 1977), have a wide spectrum of pharmacological properties (Bertz *et al.*, 1977), have been reported to inhibit
carcinogenesis and mutagenesis in experimental animals (Ames, 1983 and VanHoff et al., 1984), and implicated as novel antiviral (Dawson, 1934). Flavonoids have been reported to have antioxidant properties and act as scavengers of free radicals (Puppo, 1992). The inhibitory action of such compounds may be due to the induction of cytochrome P-450 and other metabolic enzymes (Boyd et al., 1982)

Garlic (*Allium sativum* Liliaceae):

Known for its pungent odour and taste, garlic is an ideal herbal medicine, being completely safe for home use and a powerful treatment for a host of health problems.

Selenium, Vits A, B, C and E, organosulfur compounds i.e. diallyl disulfide (DADS) S-allyl cysteine (SAC) and related compounds, like diallyl trisulfide (DATS) are some of the important components of garlic (Lea, 1996; Singh, et al., 1996; Sundaram, et al., 1996). Various dietary constituents may influence the incidence and severity of human cancer (Milner, 1989). However, the impact of these dietary contents is dependent on the composition of the entire diet. Although interactions between essential and nonessential ingredients of the diet are recognized, their significance in the cancer process remains largely unexplored. There is also evidence that several antioxidant nutrients in human diet such as selenium, vits A, B, C and E and flavonoids in dietary plants have a protective effect against coronary heart disease and cancer.
Garlic (Allium Sativum), proclaimed for its medicinal properties for centuries appears to possess anticarcinogenic properties. Gastric and colon cancer risks are reported to be lowered in individuals consuming increasing quantities of garlic (Mei et al., 1982 and Steinmetz et al., 1994). Unfortunately, the impact of dietary garlic on other types of human cancer remains largely unexplored. Nevertheless, laboratory investigations with animals suggest that garlic may inhibit chemically induced cancers including breast, skin, forestomach, lung and colon (Liu et al., 1992; Perchellet et al., 1990; Sparnins et al., 1988 and Sumiyshi and Wargovich, 1990).

Studies by Liu et al., (1992) suggest that garlic inhibits both the initiation and promotion phases of 7,12-dimethylbenz(a) anthracene (DMBA) carcinogenesis. The organosulfur compounds including allyltrimethylsulfide, diallyl trisulfide, allylmethyldisulfide, diallyl disulfide (Sparnin et al., 1988; Singh et al., 1996) and selenium enriched garlic (Thompson, 1996) inhibited chemically induced tumors. Ip (1996) reported that selenium enriched garlic inhibits the early stage but not the late stage of mammary carcinogenesis.

Selenium is also recognized as an anticarcinogenic agent present in many plants. The protective functions are not only due to its action through glutathione peroxidase but it appears to operate by several
mechanisms depending on dosage and chemical form of selenium and the nature of the carcinogenic stress. Selenium is proposed to prevent the malignant transformation of cells by acting as a "redox switch" in the activation-inactivation of cellular growth factors and other functional proteins through the catalysis of oxidation-reduction reactions of critical SH group of S-S bonds. Selenium may also alter carcinogen metabolism and protect DNA against carcinogen-induced damage (Schrauzer, 1992).

Recent studies have shown that dietary garlic supplements provided to rats consuming a semipurified diet markedly suppressed the occurrence of DMBA induced adducts bound to mammary cell DNA and inhibited the incidence of DMBA induced mammary tumors (Amagase and Milner, 1993 & Liu et al., 1992). Amages et al., (1993) have noticed that addition of garlic powder to rat's diet reduced the binding of DMBA metabolites to mammary cell DNA and reduced the incidence of DMBA-induced mammary tumors.

Amagase and Milner (1993) found that the different allyl sulfur compounds, S-allyl cysteine, accounted for much of the ability to inhibit DMBA induced DNA adducts. Because the quantity of DMBA metabolites bound to mammary cell DNA 24 hours after carcinogen treatment correlates with final tumor incidence, changes in adducts do serve as an early indicator of alterations in initiation phase of DMBA carcinogenesis (Liu et al., 1991 and 1992 and Amagase et al., 1996).
Except the effect of garlic on DNA, the detailed mechanism by which it inhibits the DMBA carcinogenesis remains unknown. However, changes in both phase I and II enzymes involved in carcinogen bioactivation and detoxification are recognized to occur in animals treated with various garlic preparations (Dalvi, 1992). In rats, tissue glutathione content and activities of glutathione-S-transferase have been shown to increase following consumption of garlic or related sulfur compounds (Sparnins et al., 1988 and Sumiyoshi and Wargovich, 1990).

In the present study, the work has been divided into two parts: i) Clinical and ii) Experimental. An attempt has been made to gather information on alteration of various biochemical parameters mentioned earlier.

In clinical part, the changes in the activities of AChE, MAO and the levels of cortisol, SGOT, SGPT and LDH were estimated in anxiety neurotic, cancer breast and cancer liver patients before and after treatment. The alterations observed were compared with their respective normals.

In the experimental part, the alterations in the circulating activities of AChE, MAO, the levels of cortisol, SGOT, SGPT and RBC membrane osmotic fragility were assayed in experimental rats to evaluate the effect of restraint stress on DMBA induced cancer. Cancer was induced by single oral dose of DMBA (Roger et al.,
The tissues (liver, kidney, heart, brain and spleen), the activities at AChE, GST, SOD and levels of reduced glutathione (total, free and protein bound) were also estimated in these rats.

The surgical treatments and modern therapies available for cancer have their own limitations and side effects. In Ayurvedic literature indigenous drugs, Garlic (*Allium sativum* Liliaceae) and Sage (*Salvia officinalis* Labiatae) are said to have some preventive and curative properties in cancer and other diseases. The preventive effects of these drugs on both initiation and promotion of DMBA induced carcinogenesis were studied. These drugs were selected because of their antioxidant properties and phenol/flavonoid contents, as flavonoid and phenols are reported to show anti-cancer properties. The possible mode of action of these drugs on DMBA carcinogenesis is evaluated in terms of biochemical parameters.