INTRODUCTION

My interest in cancer research needs no justification other than the gnawing fear that haunts the middle-aged psyche.
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Cancer exacts an incredible destructive toll on the human population. The overall death rate from cancer at various sites computed at the global scales is about one out of every six deaths. In United States alone, cancer kills at the rate of 1068 per day - roughly one death every eighty seconds (Rapaport, 1978). This staggering statistics and the absence of universal method for its cure, 50 years of active cancer research notwithstanding, have made cancer the most dreaded, enigmatic, and inexorable disease of this century. The modern man is further threatened by the contention of the epidemiologists (Doll, 1977 & 1980; Higginson & Muir, 1979; Hutter, 1983) that 70 to 90% of human cancer are causatively related to environmental factors. These carcinogenic environmental factors fall under three categories namely certain radiations, viruses and chemicals. Solar ultraviolet radiation in large dosage is the major cause of skin cancer in light skinned persons (Upton, 1977). The role of viruses in the etiologies of human cancer is debatable. Therefore, chemicals have been recognised as the main culprits in the etiology of various kinds of human cancer. The production of synthetic chemical compounds (inorganic & organic) is progressively increasing and the number as estimated in 1979 (See Miller & Miller) was four million. Most of these substances remain in the laboratories and never
reach the human environment. However, about 63,000 of these chemical compounds have been estimated to be in common use in the human environment. Experimental and clinical data reveal that a large array of chemicals like Polycyclic Aromatic Hydrocarbons (PAH), Aminoazodyes, Ethyl carbamate (Urethane, Aceytylamino fluorene) Vinyl carbamate, Vinyl chloride, Arsenic, Nickel, Baryllium, and Cadmium etc. are carcinogenic. Indeed, the roster of chemical carcinogens is alarmingly inexhaustible. These carcinogens are structurally diverse and exhibit various species and tissue selectivities. A few of these display profound specificity for certain tissues and others are more dangerous being multipotential carcinogens. Now-a-days PAH's are the most ubiquitous carcinogens in the human environment. The major source of PAH in the environment arises from various forms of inefficient combustion of carbonaceous materials. Cigarette-smoking, coke production, fossil fuel combustion, internal combustion engines, like, cars, aeroplanes, motor vehicles etc. generate complex polycyclic structures which contaminate drinking water, green vegetables and aquatic life including plankton, molluscs and fish - fish with higher fat contents have greater capacity to accumulate benzopyrene (See Dipple, 1983). Shabad (1980) reported that approximately 5,000 tons of Benzopyrene (BP) are emitted into the human environment worldwide and a resident of a large modern city
unintentionally inhales daily about 0.6 μg BP from car exhausts; approximately the same quantity is contained in the smoke of 50 cigarettes. Benzopyrene and other polynuclear hydrocarbons are also formed on the surface of meat subjected to open-flame charcoal broiling (Lijinsky & Shubik, 1964).

In addition to this heavy load of manufactured carcinogens in the human environment, a good number of naturally occurring products have been identified in foods, mainly as metabolites of fungi and green plants (Miller and Miller, 1976; Tazima, 1974). Some of which are as follows:

(a) Cycasin (Methylazoxymethanol-β-glucoside)
(b) Aflatoxin B (A product of the mold Aspergillus flavus)
(c) Safrole (1-allyl-3, 4-methylene dioxy benzene)
(d) Braken fern
(e) Naturally fermented foods and beverages such as beers and wines, containing detectable but very low levels (less than 5 μg/kg) of Ethyl carbamate (Ough, 1976).

Some drugs, such as immunosuppressive agents (Hoover, 1977), oral contraceptives (Pike et al., 1977), antischistosomal drugs (Bueding & Batzinger, 1977) have also been associated with human cancer. Moderate but statistically significant association between coffee use and fatal colo-rectal cancer has been reported by Phillips & Snowdon (1983).
Thus the physical environment of man including sunlight, his diet, drinks, and drugs are not free from carcinogenic potential. The omnipresence of carcinogens gives rise to the misgiving that the human race is immersed in an uncontrolable sea of carcinogens. This led Burck (1979) to state that "cancer from manmade chemicals - the environmental cancer has come in recent years to rival, if not replace nuclear holocaust as the major specter of technology gone amock".

It is now agreed that carcinogenesis is a two-stage phenomenon in its evolution and multifactorial in its etiology. The ultimate realization of the carcinogenic process appears to rest more with the influence of various factors, (determinants), both endogenous and exogenous, than with the carcinogens themselves (Kouri, 1980; Lesca, 1981; Farber, 1984). The endogenous factors include age, sex, hormonal status and the genetic susceptibility. The exogenous factors include all environmental and factors but mainly food, life style, drug multiple exposure to a wide variety of agents. The multifactorial nature of cancer occurrence in human population becomes increasingly more evident with each epidemiological analysis (Wynder et al, 1978; Hecker, 1979). These factors, may influence the carcinogenic process in two ways. These may either augment/precipitate or may inhibit/arrest the process.

Accurate knowledge of causation of disease is considered indispensable for prevention while a proper understanding of
the disturbances in the diseased tissue must serve as a basis for diagnosis and treatment. Since we are better equipped with information about the causation of cancer than about the specific disturbances in the cancer cell, one might hazard the guess that we are probably closer to cancer prevention than to a satisfactory cure. That is why Bailar (1979) and Berenblum (1981) posited that it was time to give serious attention to research on cancer prevention. In 1983, Hutter, President of the American Cancer Society, in his welcome address at the Workshop Conference on Nutrition in Cancer causation and prevention stated that "prevention is really our great hope for the future".

The strategies for prevention of cancer involve:

(a) Elimination of the causative agents (carcinogens);
(b) Elimination of the precipitating factors; and
(c) Introduction of anticarcinogenic agents into human environment.

Since carcinogens have become an inseparable component of our environment, complete elimination of all human carcinogenic factors from our environment is a remote possibility. It may necessitate a complete rearrangement of our environment that the society may not approve of. Thus in this front the only sensible course is to restrict or regulate our exposure to such agents - a threshold for which is nonexistent (Boutwell, 1964).
The strategy of cancer prevention by manipulation of modifiers appears to be more practicable. The growing recognition of the importance of modulators in cancer prevention has brought about the current surge of interest in this area of cancer research. Manipulation with modifiers has two aspects: (a) Identification and elimination of precipitating factors, (b) identification and introduction of anti-carcinogenic agents into the human environment. A good number of precipitating factors (risk factors) have been identified. Hirayama (1979) reported that beer promoted cancer only when drunk heavily. The higher incidence of breast cancer in Japanese women of high socio-economic group has been traced to their daily meat taking habit (Hirayama, 1979). Hecker (1979) identified some plants of Euphorbiaceae and Thymelaeaceae as active amplifiers of carcinogens. Much more remains to be done in this area of identification of the precipitating factors. Whereas the anticarcinogenic studies have engaged the attention of a large number of investigators (See Wattenberg, 1983). In recent years a considerable number of dietary constituents such as phenols, indoles, coumarins, plant sterol etc. have been found to protect against the occurrence of neoplasia. The chemical diversity of naturally occurring inhibitors, that have already been identified, makes it likely that others exist.

The present investigations aim at assessing the potential of some environmental factors as modifiers. The four
factors taken up for investigation include two dietary factors, one drug factor and one physical stress factor. These are:

(a) Garlic (*Allium sativum*)
(b) Mustard (*Brassica nigra*)
(c) Mercaptopropionyl glycine (MPG)
(d) Thermal stress (Hyperthermia and hypothermia).

Garlic (*Allium sativum*):

The rationale for choosing garlic as a modulator stems from its wide-spectrum prophylactic and curative uses in India, for ailments like lumbago, piles, asthma, epilepsy, ear-ache etc. It is also considered to be an aphrodisiac (Nadkarni, 1954; Kirtikar & Basu, 1975). The strong-scented, pungent bulb is very commonly used as a condiment.

In China, garlic is used against cryptococcal meningitis, senility, impotence, menstrual disorder and heart diseases. In Soviet Union a garlic extract allicin is used as antibiotic, sometimes called Russian penicillin.

Stoll & Seebeck (1951) detected the presence of Vitamins A, B, and C in garlic. Garlic had been used as a prophylactic and curative agent on a purely empirical basis. In fact, the scientific basis is yet to be created. The medicinal value of garlic is not confined to India alone. The low incidence of cancer in France and Bulgaria has been traced
to high consumption of garlic (Hartwell, 1968).

Mustard (*Brassica nigra*):

Mustard belongs to the family Cruciferae - which includes vegetables like cabbage, cauliflower, radish and turnips. Cabbage and cauliflower have been reported to possess anticarcinogenic properties (Wattenberg & Loub, 1978). The epidemiological investigation by Graham *et al* (1978) indicated that consumption of cabbage and other cruciferae vegetables could be correlated with the decreased incidence of bowel cancer.

Mustard oil is a popular edible oil particularly in the eastern India. Mustard seed is much used for food seasoning or as a condiment in every household of India. The green leaves are used as food by man. The oil-cake obtained after extraction of the oil from seed is used as nutritious cattle feed and also as manure. It is believed that mustard oil has healing power against some afflictions - such as ear-ache. It is also used in the manufacture of soap.

Therefore it was considered worthwhile to evaluate the modulating role of mustard on DMBA-induced skin tumorigenesis in mice.

Mercaptopropionyl glycine (MPG):

MPG is used clinically as a detoxicating agent in various countries. It protects against radiation at a very low
dose (20 mg/kg) in mice. This dose is far below its toxic dose of 2100 mg/kg. MPG as a chemical protector has the advantage over other Sulfhydryl compounds in being quite effective in very small doses and its toxicity is also very low.

The role of MPG as a protector against radiation is well established. Its protective role against carcinogenesis has not been studied so far. Being a powerful detoxicant, it could affect directly or indirectly the biotransformation of DMBA and the interaction of DMBA/its metabolites with macromolecules.

Thermal stress (Hyperthermia and hypothermia):

The epidemiological studies on incidence of cancer do not reveal any correlation between the incidence of human cancer and the thermal belts of the world. Data on the modulating influence of thermal stress on carcinogenesis are scantily available.

An evaluation of the role of a modifier on carcinogenesis requires a biological system in which the influence of the modifier can be studied in the target tissue which is free from systemic metabolic influences. The two-stage system of skin tumorigenesis meets these requirements. The superficial layers of the skin being almost avascular and alymphatic, the interaction between the carcinogen and the modifiers, through systemic metabolism, is least affected. Therefore a large number of investigators (Kinoshita & Gelboin, 1972; Slaga & Bracken, 1977; DiGiovanni
et al., 1980; Lesca, 1981; Boutwell, 1983; Dipple et al., 1984), had preferred skin model to other model systems. In the present experimental designs skin of the Swiss albino mice has been used as the target site.

As carcinogenesis is a two-stage phenomenon, the importance of investigating the effect of modifiers (variables/modulators) on each of the steps has been recognised since 1944 by Tannenbaum. In the present study, attempts have been made to assess the modulating potential of some environmental factors (stated above) at the initiation component of DMBA-induced skin tumorigenesis in Swiss albino mice.