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## **CANCER RESEARCH AND RISK ASSESSMENT: IMPLICATIONS FOR ZIMBABWE\***

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I FEEL MOST honoured by the presence of this body of friends, relatives, academic colleagues and students. It is the aspiration of all academics at this university and the world over to be elevated to the status of Full Professor and to occupy the Chair of one of the departments of the University. For me this honour comes as one of the most fulfilling awards in my academic career. I want to acknowledge the part played by many of my students, both in the USA and here at the University of Zimbabwe, my several research collaborators over the years, and my wife in helping to make this dream come true. Although I had achieved the status of Full Professor at the University of Michigan in the USA, it means much more to me to have this recognition bestowed on me in my home country.

I have chosen the topic of cancer research and risk assessment as the theme of my inaugural address. One of the most distinguishing features of the human psyche is its curiosity revolving around the two questions: Where did I come from? and Where am I going? And perhaps to these two we can add a third question: How can I be doubly sure that I will get to my destination? The issues in the late twentieth century have coalesced around this third question. The issues of peace and war, food and shelter, and those of ensuring good health, all devolve upon one's need to ensure survival. As this is not the forum for me to address the issues of peace and war, I will focus on the issue of ensuring good health. Provision for the good health of any nation is an extremely elusive objective; even the so-called advanced countries are still struggling with this one.

In mankind's effort to maximize food production and the acquisition of apparel and shelter in order to promote socio-economic development, he has had to develop industries whose operation has brought with it multiple risk factors. The profit incentive is such that many industries, if unmonitored, have been known to discharge large quantities of hazardous materials into the environment. It is the effect of the mutagens and carcinogens present in some of these hazardous materials that I would like to now focus on.

### **CAUSES OF CANCER**

From both direct and indirect evidence, there is a clear consensus in support of the view that there are three types of agents that are implicated in the aetiology of

\* An inaugural lecture delivered before the University of Zimbabwe on 8 August 1985.

malignant cell transformation (cancer). These agents are chemicals, radiation, and viruses. It is understood that each of these three agents exerts its effect by altering the structure of genomic DNA in eukaryotic cells.

The chemicals enter our bodies with the food we eat or as a result of our being exposed to the various forms of industrial waste in our environment. It is both ionizing radiation (X-rays, gamma rays and cosmic rays) and non-ionizing radiation (ultraviolet light) that are implicated in the aetiology of cancer. One becomes exposed to these forms of radiation in the workplace, in diagnostic and therapeutic applications, as well as in the natural environment (cosmic rays). Likewise, humans pick up viruses in water, from the air, and when they establish physical contact with each other or with animals. Figure 1 presents a scheme illustrating how chemicals, radiation and viruses are thought to exert carcinogenic effects. Nutritional deficiencies or excesses can also be a cause of cancer.

The cancer cell is one whose normal functioning has been altered. As its rate of replication is no longer regulated, the cancer cell divides continuously.

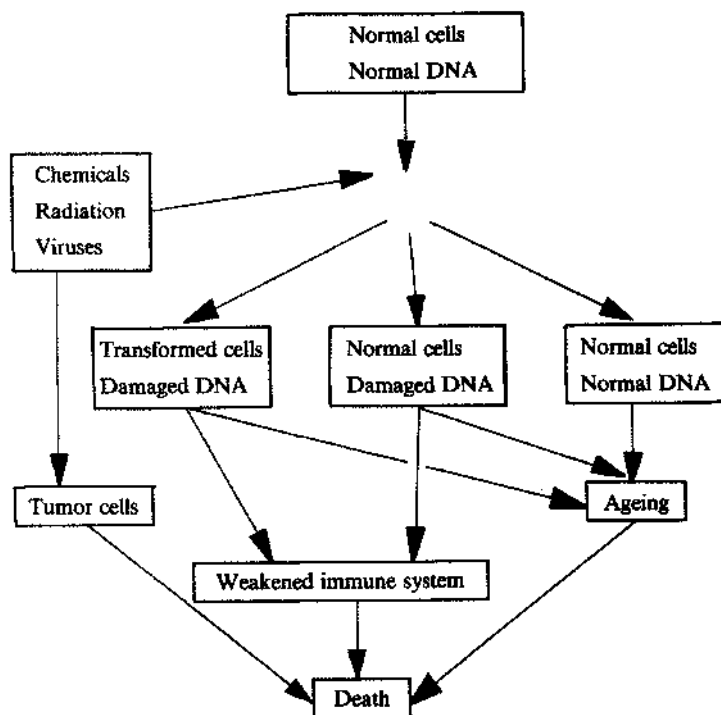


Figure 1: PROPOSED SCHEME FOR PROCESSES AND AGENTS ASSOCIATED WITH CARCINOGENESIS

Metastasis, or spreading of the malignancy, results from the loss of ability of cancer cells to obey zoning laws; they now spread to other tissues of the body. It is for these reasons that the cancer cell has been described as a delinquent cell. The topological consequence of the continuous division of transformed cells is the formation of lumps or tumours. Another phenotype of transformed cells is their ability to cause tumours when injected into an appropriate animal.

There are different types of cancer, most being specific to a tissue. The cancers of different organs can be so different that they can be viewed as different diseases. The prevalence of the different types of malignancies varies with the region of the world. For example, the three most prevalent types of cancer in North America are cancer of the lungs, the intestines (colo-rectal) and female breast. About 24 per cent of all deaths from cancer in North America are due to lung cancer, 13 per cent to colo-rectal cancer and 9 per cent to breast cancer.

### HOW CHEMICALS CAUSE CANCER

The mechanism of carcinogenesis is still a phenomenon without a confirmed candidate. The most widely accepted model is that cancer results from a modification of DNA structure. The first step appears to be the formation of covalent adducts between DNA and a chemical carcinogen. Such adducts become harmful lesions which represent damage in DNA structure. If the damage represents a short-lived and transient aberrancy, the affected cell retains normalcy. It is my view that the majority of interactions between carcinogens and cells do not lead to cell transformation but result in abortive effects. The reason for this is that, in addition to the anti-cancer effect of the cell's DNA repair mechanisms, the carcinogenic effects of some chemical carcinogens represent an initiation event that must next be promoted by the correct agent for malignancy to occur. Furthermore, if the carcinogenic lesion in DNA is to be 'fixed' into the permanent register of the genome, the event must be retained during successive cycles of DNA replication.

The multifactorial aetiology of carcinogens is now better appreciated. Some chemical carcinogens may have a role in simply predisposing an organism to tumour formation, with the actual triggering of the tumour awaiting the action of the promotor which serves as a co-factor. The predisposing (initiation) may be effected by a virus or a chemical carcinogen. Chemicals initiate carcinogenesis by inducing damage in DNA. The response of the host may be to marshal its defences against the lesion. This involves setting in motion any of the various modes of DNA repair.

The repair may begin by the excision of the lesion followed by unscheduled DNA synthesis (repair synthesis) and ligation by DNA ligase. Elaborate mechanisms are involved in these repair pathways that restore the structural integrity of DNA. There is evidence that errors can be made resulting in

misreplication of DNA. Mutagenic lesions can be a result of misrepair of damaged DNA. It is these mutagenic lesions that are implicated in triggering malignant cell transformation.

Chemicals that alkylate DNA appear to be major offenders in inducing cancer. The carcinogenicity of a number of alkylating agents has been demonstrated in experimental animal models. The acetylaminofluorene and aflatoxin B<sub>1</sub> have been shown to cause hepatocellular carcinoma in rats (Kriek, 1980); burnt food products and nitroso compounds to cause oesophageal cancer (Laker et al., 1980); smoking to cause lung cancer (Hammond, 1980); and viruses and some types of irradiation to cause leukemias.

My laboratory has been studying the mechanisms by which alkylating chemicals cause cancer. We have focused our activities on the alkylation of guanines in DNA that leads to a fission of the imidazole ring of guanine (Kohn and Spears, 1967; Chetsanga and Lindahl, 1979). We have also studied the radiogenic cleavage of imidazole rings of non-alkylated adenine and guanine in aqueous solution of DNA treated with ionizing radiation ( $\gamma$ -irradiation) (Chetsanga and Grigorian, 1983). Garret and Mehta (1972) have shown that the imidazole ring of non-alkylated adenine can also be opened by treatment of DNA with 0.8 M potassium hydroxide at 80°C. We have proposed a model of how alkali induce imidazole ring cleavage in alkylated guanine (Chetsanga and Makaroff, 1982).

#### *Repair of DNA containing alkylated ring-opened guanine*

In 1978, while in Sweden on sabbatical leave from the University of Michigan, I undertook a search for an enzyme that could recognize and excise from DNA the imidazole ring-opened 7-methylguanine, also known as methylated formamidopyrimidine (meFAPy). I was fortunate to isolate an enzyme from *E.coli* that removes meFAPy from DNA (Chetsanga and Lindahl, 1979). We gave this enzyme the name formamidopyrimidine-DNA glycosylase (FAPy-DNA glycosylase). In 1981, Margison and Pegg were able to identify this enzyme activity in rat-liver DNA.

We observed that FAPy-DNA glycosylase is able to remove from DNA those FAPy residues that were alkylated with either phosphoramidate mustard (Chetsanga et al., 1982) and aflatoxin B<sub>1</sub> (Chetsanga and Frenette, 1983). The reaction in which AFB<sub>1</sub>FAPy is removed from DNA by FAPy-DNA glycosylase has a higher K<sub>m</sub> than the reaction in which the enzyme removes meFAPy from DNA.

#### *Repair of non-alkylated imidazole ring-opened purines in DNA*

We have observed that FAPy-DNA glycosylase is unable to remove non-alkylated FAPy from DNA. This was in contrast to the work of Breimer and Lindahl (1984) who observed a low-level excision of non-alkylated FAPy by

FAPy-DNA glycosylase. We have, on the other hand, identified a novel pathway for the repair of non-alkylated FAPy in DNA. The repair involves a reclosure of the imidazole ring of FAPy catalysed by the enzyme purine imidazole ring (PIR) cyclase (Chetsanga and Grigorian, 1985). The enzyme recloses the opened imidazole rings of both adenine and guanine. This ring reclosure appears to be the major pathway for the repair of non-alkylated FAPy.

The conversion of alkylated guanine to the imidazole ring-opened derivative occurs *in vivo* in rats treated with carcinogens such as dimethylnitrosamine or dimethylhydrazine (Beranek *et al.*, 1982) as well as in rats treated with aflatoxin B<sub>1</sub> (Chetsanga and Frenette, 1983). The existence of a mechanism for the repair of these ring-opened purines suggests that, intracellularly, they are deemed undesirable and deleterious. It has now been demonstrated that the presence of ring-opened alkylated guanine in DNA leads to replication errors at the chain-elongation step (Boiteux and Laval, 1983). It has similarly been shown that the presence of ring-opened aflatoxin-guanine adducts in the primer-template polynucleotide leads to replication errors (Chu and Saffhill, 1983).

These observations provide evidence for a physiological significance of purine imidazole ring-fission. This ring-cleavage perturbs the integrity of DNA, and leads to discordant consequences to normal cellular metabolism. It is a system that deserves more research attention than it has received so far. There remains the need to test the hypothesis that it is the ring-cleavage caused by carcinogenic alkylating agents that forms the basis for carcinogenesis.

## CANCER PREVALENCE DURING THE LAST TWENTY YEARS

The best data available on cancer prevalence come from developed countries. I would like to examine some of the leading forms of cancer and attempt to assess the putative basis for their aetiology.

### *Lung cancer*

This is the most prevalent type of malignancy in the Western world. Since 1960 the number of fatalities due to lung cancer has increased by 116 per cent in men and by 200 per cent in women. The evidence shows that lung cancer is caused by smoking cigarettes. The precipitous rise in its prevalence among women is attributed to the great increase in the number of smokers since 1920. Among the sixteen leading cancers, lung cancer is responsible for the greatest number of cancer deaths. It appears to be epoxides, acroleins, formaldehyde and acetaldehyde in smoked cigarettes that are responsible for inducing lung cancer.

### *Stomach cancer*

Stomach cancer is the most frequent type of malignancy world-wide. Fortunately, its incidence is decreasing. Since 1960, there has been a 12 per cent decline in the number of mortalities caused by stomach cancer. It remains the leading type of

cancer in Japan. The observed decline in its prevalence seems to be due to changes in lifestyle, particularly changes in diet as certain foodstuffs contain carcinogens (Sugimura, 1984).

### *Hepatocellular carcinoma*

This malignancy is the main cause of cancer-related mortalities in Africa, in some Asiatic countries and in most Third World countries situated in the tropics. My laboratory has been investigating the aetiology of hepatocellular carcinoma (HCC) during the last six years.

There are two schools of thought with regard to the aetiology of HCC: one school holds that HCC is caused by aflatoxins, while the other holds the view that it is induced by hepatitis B virus (HBV). Our working hypothesis is that HCC aetiology entails the combined action of HBV and aflatoxins. In this synergism, HBV probably acts as an initiator while aflatoxins act as co-factor (promotor). It has also been proposed that alcohol or cigarette-smoking may also act as promoters of HCC once it has been induced by HBV (Rigby and Wilkie, 1985). From a number of studies, it has now been concluded that HBV infection and ingestion of aflatoxins in contaminated foodstuffs are important risk factors for HCC.

From a mechanistic consideration, it appears that the entrance of HBV DNA into hepatocytes somehow provides an element of susceptibility (Fig. 2). It is reasonable to surmise that the subsequent exposure of these cells to aflatoxins provides for a chemical interaction between the mycotoxins and the HBV DNA now lodged in the host cell genome.

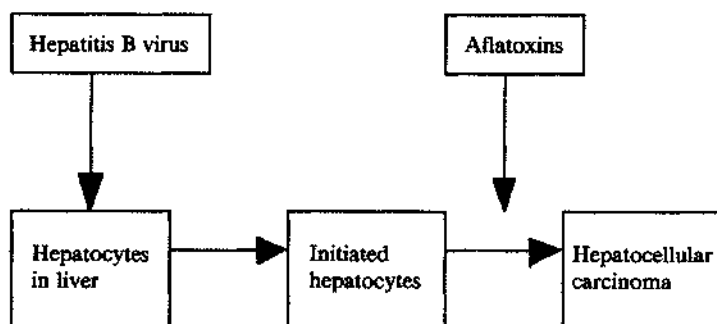


Figure 2: SCHEME OF INITIATION AND PROMOTION OF HEPATOCELLULAR CARCINOMA

In 1985, I received a Z\$12,000 grant from the Cancer Association of Zimbabwe to investigate the putative involvement of HBV in the aetiology of HCC. A current experimental limitation of HBV studies is the lack of a suitable mammalian cell-culture system in which the virus can be propagated. To get round this problem, we have cloned HBV DNA in *E.coli* and are studying the expression of viral functions in this bacterial host. We now propose to use this system as a source of HBV DNA with which we can proceed to identify HBV variants in the Zimbabwe population with a view to determining the variant that is prevalently associated with HCC.

#### *Skin cancer*

This malignancy, in the form of cancer of the scrotum, was first observed in chimney-sweeps. In Zimbabwe, this cancer is largely found in exposed parts of the skin. The ease of its early detection is the reason for its successful clinical management.

#### *Cancer of the cervix*

This malignancy is the most prevalent cancer among young women in Zimbabwe. The clinical management of cervical cancer is relatively well worked out and relief can be provided as long as early diagnosis has been made. The aetiology appears to include papilloma virus and a mix of limited opportunities for adequate genital hygiene among the victims, as well as female cultural practices in vaginal care. Unfortunately, there is no systematic research on cervical cancer in Zimbabwe today. If such research were to lead to a fundamental understanding of this malignancy, it may subsequently become feasible to design appropriate strategies for its management, and perhaps prevention as well.

### FUTURE PROGNOSTICATION FOR ZIMBABWE

All indicators suggest that the cancer trends in the developed world will be duplicated sooner or later in Third World countries, including Zimbabwe. The data from the Zimbabwe Cancer Registry for 1986 show that cancer of the cervix (*cervix uteri*) in women is the most predominant of all malignancies in this country (see Table). The other leading forms of cancer in Zimbabwe are those of the oesophagus, liver, bladder, breast, stomach, skin, prostate and lung in descending order. The mortalities column shows that HCC is the leading cause of death, followed by oesophageal cancer. Although lung cancer shows an incidence of 4.8 per cent, it is the fourth leading cause of death in Zimbabwe. Compared with the incidence data from the Bulawayo Cancer Registry (Parkin, 1986), there is clear evidence that many types of cancer are on the increase. These developments lend credence to the prediction now being made that there will be a cancer epidemic in a majority of the developing countries by the year 2000.



## CANCER INCIDENCE DATA IN HARARE IN 1986\*

<i>Site</i>	<i>Percentage of cases</i>	<i>Percentage of mortalities</i>
Cervix	24.0	8.3
Oesophagus	10.8	20.0
Liver	8.2	22.0
Bladder	7.9	9.6
Breast	7.7	1.4
Stomach	6.6	12.0
Skin	6.5	1.4
Prostate	5.6	4.8
Lung	4.8	10.0
Others	17.9	10.5

\*Data are based on sample pool of a total of 1,984 patients.

Cancer is now characterized as a disease predominant in old age. The continued increase in life expectancy in developing countries will be accompanied by increased incidences of cancer. A successful execution of the current campaign against infectious diseases will increase life expectancy and, consequently, the likelihood of an increase in the frequencies of malignancies.

### CONCLUSION

Since 80-90 per cent of cancers are believed to be preventable upon early diagnosis, we can cure significant proportions of existing cancers. We need public awareness campaigns that can sensitize the general public to the importance of early diagnosis. This, in conjunction with the provision of medical specialists trained in the treatment of the various forms of the predominant cancers, will ensure our ability to provide both cure and relief to victims of this dreadful disease.

With a greater research base, it may be possible for us to understand the aetiology of the most predominant malignancies in the country. This knowledge will in turn sharpen our capabilities of carcinogen risk assessment and enhance the success with which we can launch effective preventive measures.

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