PRIMARY OESOPHAGEAL TUMOURS

ESSAY

SUBMITTED IN PARTIAL FULFILLMENT FOR THE
REQUIREMENTS OF THE MASTER DEGREE IN
GENERAL SURGERY

BY

RAMEZ MOUSSA GHOBRIAL SAROUFEEM
M. B., B. Ch.

SUPERVISED BY

PROF. DR. SHAMEL ABDALLA ALI
PROFESSOR OF SURGERY
AIN SHAMS UNIVERSITY

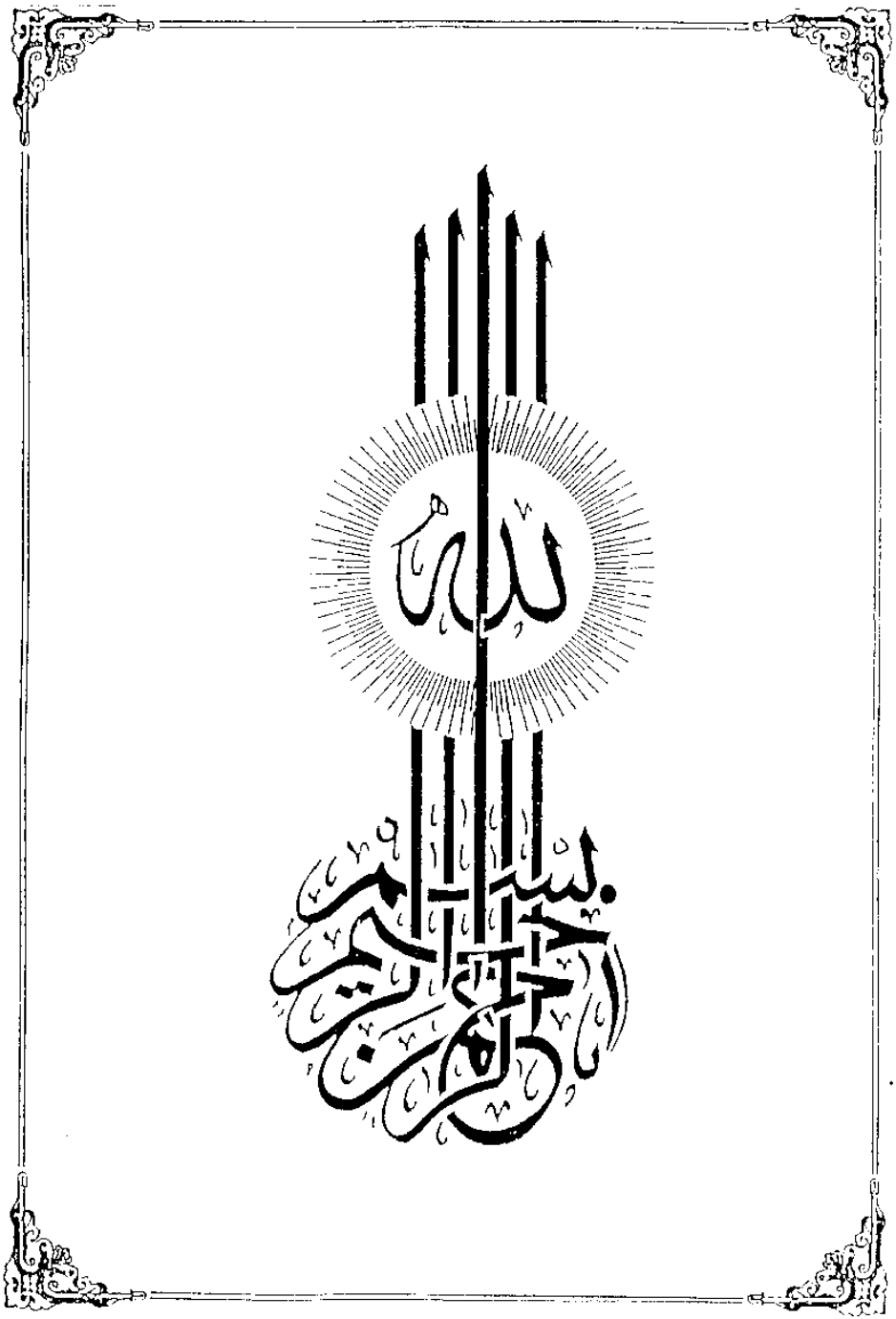
1987

ACKNOWLEDGEMENT

It gives me great honour and pleasure to express my deepest gratitude and thanks to prof. Dr. SHAMEL ALI for his kind care, masterful guidance and invaluable advices which were of great help to me in all the steps of this work.

My sincere thanks are also due to Dr. ALLAA OTHMAN for sacrifycing a great deal of his time to guide and help me through this work.

Ramez Saroufeem



CONTENTS

AETIOLOGICAL FACTORS

As in other tumours, the aetiology of cancer of the oesophagus remains obscure. Many causes have been incriminated, but none proven. The tumour shows a peculiar and outstanding geographical distribution seldomly met with in any other tumour.

In the west the incidence is low. In fact it is less than 5/100.000 population (Rensburg, 1981). Other areas have a quite higher incidence. This high-incidence cancer belt extends from the Tukoman region on the Caspian Littoral in northern Iran, it passes through the central asiatic republic of Khazakhstan in the Soviet Union, and it ends in north china where the Linxian county in the Henan province (sometimes called Lin-Shien) has the highest incidence in the world. It has been estimated that about 50 percent of the males above the age of 50 die of cancer of oesophagus, (Parker et all, 1982). In China the disease has been known for generations, and such was the concern and fear of this disease that a `Throat God Temple´ was built, (Yang, 1980).

In the Transkei territory in South Africa the situation is different because the disease emerged from a virtually unknown condition 50 years ago to attain full epidemic incidence in recent years, (Cook, 1971). The disease is diagnosed by the illiterate laymen, and they call it chronic ulceration of the gullet.

France has the highest mortality rate from oesophageal cancer in Europe (13.6/100.000), Basse-Normandie and Brittany have high mortality rates of 40/100.000. Alcoholism seems to play an important role as an aetiological factor particularly cider-based liquors (Mandard et al, 1981).

Areas of moderate incidence 5-10/100.000 include USA blacks, in Detroit and Washington DC, and Puerto Rico, where the incidence is 12.9/100.000 (Ransburg, 1981).

The disease also shows variable incidence rates in different parts within the same country. In Britain, Ashley, (1969) reports that the welsh are more commonly affected. In the USA, where the higher incidence are among emigrants than among US borne individuals, even higher than in their country of origin. In Linxian-China, the mortality rate is 115/100.000 for females, and 151/100.000 for males; but in Lanxian which is 150 kilometer away the incidence rate is only 16/100.000 for females and 35/100.000 for males (Lu et al, 1986). In northern Iran, the incidence drops 34 fold for males and 47 for females upon entering the neighboring province, (Ghadirian, 1985).

The aetiological factors for cancer oesophagus are different in low risk areas from those of high risk areas. It has been found that intake of alcohol and tobacco which risk factors in low incidence areas, appears to play a minor role in high incidence areas where other environmental factors may

be more important, (Lu et al, 1986). These environmental factors are mostly dietary and take the form of presence of some carcinogen in the diet and the added deficiency of protective agents from such diet.

Possible aetiological factors for cancer of the oesophagus include: Age, Sex, Alcohol, Tobacco,...etc.

AGE

The disease is more common after the age of 50 years. In Linxian, the highest incidence is in the 60-69 year group, accounting for 38 percent of cases. Next comes the above 70 group with value of 28 percent, and the 50-59 group which accounted for 23 percent of cases (Yang, 1980). Reviewing 300 cases, in USA, Parker (1982) found that 33.3 percent of his patients fell in the 50-59 year group, 31.4 percent in the 60-69 year group, 23.3 percent older than 70, and 12 percent younger than 50 years. The youngest reported case was that of a 15 years old Korean boy who developed carcinoma following corrosive stricture of the oesophagus (Kinnman et al, 1968).

SEX

Males are more commonly affected than females. The ratio is higher in low risk regions than in high risk regions. In one series of 743 patients, in France, the male/female ratio was found to be 18 : 1 (Tuyns et al, 1982). This ratio is exceptionally high. Rensburg (1981) reports a male/female ratio of 3.11 in low risk regions, a 2.37 in moderate, and

1.53 in high risk regions. This is possibly because males are more subjected to alcohol and tobacco in low risk areas, while the dietary factor in high risk areas is shared by both sexes.

ALCOHOL

The role of alcohol in the causation of oesophageal cancer has long been known. This is particularly true in the western world.

Tuyns (1982), reports a relative risk of 2.72 for alcohol consumption. In Brittany, the alcoholic and heavy smoker has a risk 44 times as that of the non drinker and non smoker. Alcohol may be responsible for the breakdown of normal mucosal barrier to carcinogenic agents, (Bremner, 1985).

Alcohol may also act by precipitating a deficiency of one or a few critical protective nutrients that are taken in marginally adequate amounts of population. Alcohol intake essentially lowers the vitamin status by reducing vitamin intake, absorption, and metabolic activation. It may also cause a deficiency of protective elements. It has been found that patients with alcoholic cirrhotic livers, and non cirrhotic alcoholics have low serum levels of zinc together with an increased excretion rates, (Rensburg, 1981). Mellow et al, (1983), found that the mean level of plasma zinc in an alcoholic control group was 72.4 microgram/dl, compared to a normal mean level of 80. He also found that the level of zinc in patients with cancer oesophagus was 65.7 microgram/dl.

Moreover, it has been found that severe zinc deficiency increased the incidence of methyl-nitrosamine-induced oesophageal cancer in rats.(Fong et al, 1978).

In South Africa, the 'amount' of alcohol consumed does not correlate well with the incidence of oesophageal cancer, it the type of alcoholic beverage that make the difference. It has been found that the distribution of beer made from maize is in many ways similar to the distribution of oesophageal cancer. Maize is an introduced crop in Africa, and the spread of its use as an ingredient of beer seems to coincide with the rise in the frequency of oesophageal cancer in recent years. Contamination of alcoholic drinks by carcinogens as lead or polycyclic hydrocarbons during fermentaion and distillation has been suggested, (Cook, 1971).

Ziegler, (1986), investigated the relation of alcohol consumption and the increased incidence of oesophageal cancers among men particularly Washington DC black men. Apart from finding a definite correlation between the amount and type of beverages used and the incidence of cancer he proposed some possible mechanisms for alcohol associated carcinogenesis. These include the following:

1- Specific beverage may contain naturally occurring constituents or contaminants that are carcinogenic like fusel oils (which are produced during the distillation process) polycyclic aromatic hydrocarbons, or nitrosamines. 2- Alcohol may irritate the mucosal lining and increase the number of

rapidly dividing susceptible cells. 3- Alcohol may facilitate the transport of carcinogens across the muocosal lining (as tobacco-associated carcinogens). 4- Alcohol may damage the liver's ability to detoxify certain carcinogens. 5- Alcohol may affect the nutritional status by reducing the intake or absorption of essential protective materials as zinc and vitamins. 6- Alcohol may suppers the immune response.

TOBACCO

The relative risk of cancer oesophagus among smokers was estimated at 2.61 by Tuyns, (1982). La Vecchia et al, (1986), studied the risk of smoking in the production of cancer of the oesophagus and compared the difference between low-tar and high-tar cigarettes. He found that the relative risk for those who smokes less than 15 cigarettes per day was 2.61, which rose to 4.61 for those who smokes more than 15 cigarettes per day. As for the duration of smoking, he found that with less than 20 years smoking the risk was 2.39, between 20 and 29 years it was 4.81, and more than 30 years it was 5.61. As for the tar yields, he found the relative risk with tar yield less than 22 mg was 2.89, as compared to 8.9 in smokers of 22mg or more cigarettes.

OPIUM was put in consideration as a possible cause of cancer, in Iran. Hewer et al, (1978) reported a geographical association between the use of opium as a pain killer or for pleasure and the incidence of oesophageal cancer. It has been suggested that pyrolyzed products of opium are carcinogenic,

and that opium decreases the oesophageal peristalsis by the direct action of papaverine on the smooth muscle. It also inhibits the relaxation of the lower oesophageal sphincter by the action of morphine. The resulting stasis allows prolonged contact of a potential swallowed carcinogen, with the oesophageal mucosa. This is particularly true if the oesophageal mucosa is already vulnerable by associated chronic malnutrition, (Dawlatshahi and Miller, 1985).

It was found that in Iran, addicts ingests opium dross which remains in the pipe after smoking, it is locally called `sukhteh´. Although crude opium is not carcinogenic, it was found that `sukhteh´ is mutagenic, and it was suggested that mutagenic pyrolysis products are formed during opium smoking, and that they may be responsible for the increased incidence of oesophageal cancer in Iran, (Hewer et al, 1978).

DIETARY FACTORS

The dietary factor seems to play a very important factor in aetiology of oesophageal neoplasms especially in high risk areas.

One interesting natural experiment occurred in northern China. Rural families in the Henan province breed chicken and give them scraps of their own food. It was found that chicken owned by families in high cancer risk areas in Linxian developed carcinoma of the gullet, more than those in low incidence areas. Moreover it was found that chicken bred by

immigrants from high incidence areas still developed carcinoma at a nigher rate than chicken bred by native inhabitants. This observation shows that soil and water are not apparently important as a contributing factors in this example, The high cancer incidence of the chicken as well as of their breeders appears to be due to eating habits which the immigrants have brought along with them.

Whatever the dietary factor might be, **nitrosamino compounds** seem to be commonly implicated as a carcinogenic agent in the majority of cases. Its excretion in urine and saliva in high incidence areas is higher than in low incidence areas. It has been shown to induce carcinoma in different experimental animals. They are formed when nitrates are converted to nitrites and combine with amides or secondary amines. Nitrosamines are either performed in the diet or endogenously formed from its dietary precursors.

In north China, rain water is collected and stored in man-made ponds called dry wells. In houses water is kept in ceramic jars and pots, called `gang´. It was found that both dry wells and the gang are heavily contaminated by microorganisms, as well as human and animal refuse. The water content of nitrates and nitrites was found to higher especially during summer and after storage or heating, (Yang, 1980).

In addition, the Chinese eat plenty of pickled vegetables,

as well as mold fermented food, particularly pickled cabbage, turnips, and sweet potatoes. In some families these are eaten daily for as long as 9 to 12 months a year as an important part of the diet. Various fungal organisms were found in this moldy fermented or pickled food; these included Asperigillus, Fusarium, and Penicillium. All these fungi were found to reduce nitrates into nitrites; moldy food was also found to contain an excess of secondary amines and nitrosamino compounds. The relation between the rate of consumption of moldy and fermented food and the incidence of cancer oesophagus was well established in China (Yang, 1980).

Molybdenum deficiency in the soil may contribute in the aetiology of cancer of the oesophagus in some high risk areas as South Africa. Molybdenum is a cofactor for nitrate reductase enzyme which affects the nitrite and nitrate content in the plants, it was also found that molybdenum content in hair, serum and urine of males in high incidence areas was lower than in low incidence areas. (Burrell et al, 1966).

The **diet staple** in high and low incidence areas was studied by many workers. It was found that cancer of the oesophagus was more prevalent among people whose main dietary staple was corn or wheat. Rensburg, (1981) compared the incidence in different areas in relation to the dietary staple and found that people whose main dietary staple was wheat, corn or maize (indian corn), were at highest risk, as compared to medium risk for rice and lower risk for millet, sorghum,

cassava, or yams (these are kinds of grass like millet or corn, and tuberous plants used for making bread). Rensburg attributed this correlation to the depletion of zinc, magnesium and vitamin A, from the flower of wheat and maize during its procession. These three elements appear to play a protective role against oesophageal carcinogenesis.

In support of this view is the South African example, before the introduction of maize cultivation cancer oesophagus was virtually unknown. As high yielding maize, and to a lesser extent wheat were introduced into the country and replaced other crops the incidence started to rise until it became one of the highest in the world in the past 40 years (Cook, 1971). It was also found that those people who continued to subsist on sorghum, millet or yams which were the traditional crops before the introduction of maize retained their resistance to cancer of the oesophagus (Rensburg,-1981).

In Iran it was found that wheat flour was contaminated by fine **silica fibers** derived from seeds of some common mediterranean weeds of the genus `Phalaris´. These fibers had the length of 50-150 microns and the diameter of 1-10 microns. The seeds of this grass has the same size of wheat and are ground with them. These silica fibers were found to stimulate the proliferation of fibroblasts of tissue cultures more than 100-folds. The possibility that these fibers actually contributed for the increased incidence of cancer oesophagus in northern Iran has been raised but not proven, (O´Neill et

al, 1980).

Deficiency of certain protective elements from the diet was studied as contributary factors, among these are zinc, vitamin A, magnesium, vitamin C, and riboflavin.

Mellow et al (1983), reported decrease level of both zinc and **vitamin A**, in patients with cancer oesophagus. He reported zinc levels in plasma of 65.7 micrograms/dl as compared to 80 micrograms/dl in controls. As for vitamin A he found mean plasma levels of 32.6 micrograms/dl in cancer oesophagus patients as compared to 60.2 in controls. Vitamin A and related retinoides were found to suppers tumour progression in animal models.

As mentioned before, zinc deficiency was found to promote oesophageal tumour induction by chemical carcinogens in experimental animals, (Halstead and Smith, 1970, and Fong, 1978).

Magnesium content of the diet was found to correlate well with risk of oesophageal cancer. Patients with cancer of the oesophagus are reported to have lower content of magnesium in their hair and lower urinary excretion than normal, (Yang, 1980).

Vitamin C content of the diet in high risk areas was found to be low. This vitamin inhibits the endogenous formation of