CANCER OF THE OESOPHAGUS IN TRANSKEI

An investigation into the dietary and social habits of the people of Transkei with the intention of casting light on the aetiology of cancer of the oesophagus within the region

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SUMMARY

Transkei is a region of very high incidence of Cancer of the oesophagus (CO). Enquiry within the community revealed an unusual number of potential causes of injury to the oesophagus, the prevalence and extent of which were confirmed in opportunistic studies by questionnaire.

The statistical relationship between CO and a large nunmber of potentially important factors in dietary and social habits was determined by iterative development of questionnaires for both CO patients and controls, culminating in a case-control study of 100 pairs.

In the case-control study the following were significant:- smoking, consumption of Solanum nigrum, consumption of Chenopodium album and use of traditional medicines were positively associated with CO; number of sheep kept, and total bought dietary fat were negatively associated with CO.

Conditional logistic regression analysis of significant factors revealed relative risks of 3.6 for consumption of Solanum nigrum and 2.6 for smoking, both risks being significant. The wild vegetable Solanum nigrum has been identified as a probable carcinogen in Transkei, and a theory of pathogenesis is described which involves nutritional predisposition due to the staple diet, and carcinogenesis by substances which include tobacco and Solanum nigrum.

CHAPTER 1

INTRODUCTION

The geographical position of Transkei is shown in Fig.1. It has a coastline of 250 km. and an area of 45,000 square km. It is a region of rolling grasslands extending from the Drakensberg mountains to the Indian ocean coast. Lying between 30 and 33 degrees South of the equator, it has a subtropical climate. The rainfall of 815 mm. per year is nearly all in the summer months from October to March.

The soils are red and yellow laterites, with podosolic and rarely solonetzic soils. In the higher regions the soil depth is poor.

Part of the Cape Colony and then of South Africa, it was granted local self-government in 1963, and then independence by South Africa in 1976. This independence has not received international recognition.

The population of about 2 million people is predominantly (95%) Xhosa, who owe their origin to the East African migration of Nguni peoples, with some intermarriage with Hottentots and Bushmen. Sotho speakers make up 4% and Zulu speakers 1% of the population, with a very small number of caucasians.

Migrant labour, subsistence farming, and limited industry are the main employments. A large number of men undertake contract work

in "white" South Africa for one or two year spells to earn money. At some time each year there are twice as many females as males in Transkei in the 15 to 64 year age group because of migrant labour.

The main crop is maize. Beans and pumpkin are also grown and together with maize form the staple diet of Transkeians. Maize is eaten as whole kernels, stamped, or ground. Bread and margarine also provide a significant proportion of the calories of the diet. Meat is eaten occasionally but then often in large quantities. Cattle are kept for wealth and status. They are milked and the milk used either fresh, or more commonly after it has been soured with tartaric acid or with a herb. Goats are used for food and for religious rites. Sheep are raised for meat and wool. Pigs are kept to deal with nightsoil and are sometimes eaten. Some garden vegetables are grown. A very rich variety of wild plants is harvested as food and used as vegetables or relishes.

Traditional beer is a major constituent of many rural Transkeian diets. It is a mildly alcoholic drink brewed from either maize or millet. Herbal medicines are widely used as self-medication or as prescribed by traditional healers.

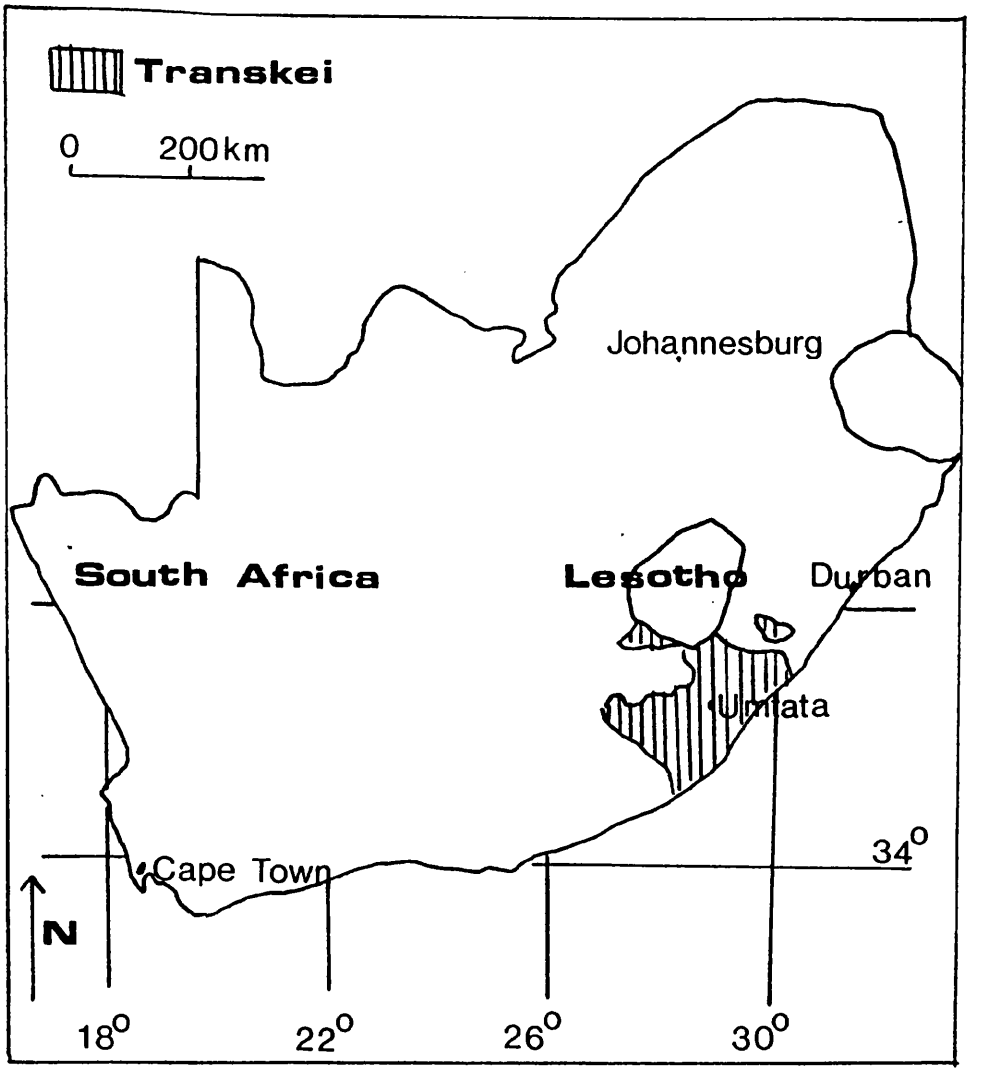


FIGURE 1 — SOUTHERN AFRICA AND TRANSKEI

The average per capita income has been assessed as US$200 per year. Despite this there is still considerable protein-calorie malnutrition of children. Tuberculosis is common but becoming less so, perhaps due to naturally changing disease patterns as well as to treatment and prevention programmes.

Pellagra was and is common, one doctor reporting an incidence of 14.4% of unselected patients as having the disease in 1952(1).

CHAPTER 2

FIRST IMPRESSIONS AND OBSERVATIONS

The author, during seven years clinical work in Transkei noted the following:-

1 Cancer of the oesophagus(CO) appears to occur in a specific socio-economic group who are poor, but not the very poorest of the community. The majority are uneducated but some have modest education.

2 There is a very high incidence of heartburn in Transkei, to the extent that it is accepted as a normal happening, and medical advice is not commonly sought about it.

Extensive preliminary enquiries were carried out by the author into the local dietary and social habits, particularly with respect to heartburn, and into factors which were prevalent in Transkei, and might cause injury to the oesophagus.

There are five apparent causes of oesophageal trauma in Transkei:-

2.1 Foods that cause heartburn

2.2 Self-induced vomiting

2.3 Tobacco usage

2.4 Alcohol consumption

2.5 Vitamin deficiency

2.1 Heartburn

Heartburn is very common in Transkei, and follows ingestion of a variety of foodstuffs. The most commonly blamed are maize/pumpkin mash (*umqa wethanga*), and fermented maize drink (*amarewu*), and these are consumed by nearly all Transkeians.

Umqa wethanga is prepared as follows:- the skin is removed from a flat white pumpkin (which may be fresh or have been stored for up to six months), the seeds are discarded and the remaining pumpkin boiled in water with a little salt or sugar until it is soft. Maize meal is then poured in and mixed well until the mixture is stiff. The maize meal may be either commercially ground or ground by hand in the homestead. The mixture is set aside for about one hour then eaten.

Amarewu is made as follows:- lukewarm water is added to roughly ground maize meal and set aside for about seven hours. The liquid is squeezed out, strained, and the resulting fluid put in a pot. The solid matter from which the fluid has been squeezed is ground fine, added to the pot, and boiled for two hours, then set aside. A cup of old *amarewu* or Traditional beer is then added and mixed in, along with a cup of wheat flour. The mixture is set aside overnight and is strained in the morning when it is ready to be drunk. It is not alcoholic.

2.2 Self-induced vomiting

This habit is widespread in Transkei (and much of Southern Africa) and is a traditional way of dealing with, or "cleaning" from a variety of problems. Indications for self-induced vomiting include nausea, protection from witchcraft, and seeking popularity with the opposite sex. Many people use emesis regularly, often more than once a week. A number of local herbs or medicines is used, or just local stimulation of the throat, usually on an empty stomach. Regurgitation of bile is common.

2.3 Tobacco usage

Tobacco is used in Transkei as cigarettes, in pipes, as snuff and for chewing. Scrapings from the pipe bowl are used as a paste (*isixhaxha*), which is packed between the teeth where it remains for some time. The inside of the pipestem is scraped with a piece of grass which absorbs fluid in the pipestem. The grass (*intshongo*) is then placed and left in the buccal pouch. Commercial and home-grown tobaccos are both used in Transkei.

2.4 Alcohol consumption

Many rural Transkeians drink *umqombothi* (traditional beer). When prepared by the traditional method it is an unadulterated drink of relatively low alcohol content. It is prepared as follows:- Maize corn is placed in water in a pot and left for eight days. The water is sieved off and discarded. The corn is allowed to dry and is then ground roughly. This is called *nkuduso*. More maize corn is soaked for two days in water and then ground fine. The next day it is ground very fine, thrown into boiling water

and a porridge made. It is left for twenty minutes, then cold water, and some of the previously prepared *nkoduso* added. It is left for 24 hours then boiled. When it is cool more *nkoduso* is added. It is set aside for one or two more days, then is ready for drinking. Previously millet was used in making traditional beer, but now maize is the sole constituent. A generation and more ago, beer was often made with millet, but this is now rare.

2.5 Vitamin deficiency

Pellagra is common in Transkei from August to November, when there is little in the way of vegetables or "*imifino*" (wild vegetables). In some areas it may affect a large proportion of the population in late winter and spring. Other vitamin deficiencies are rare.

In pellagra there is an acute inflammation of the oesophagus with loss of epithelium, leading to chronic inflammatory changes(2). The mouth lesion of pellagra is known in Transkei as "*ikhelebha*"(3). It is likely that mild forms of the disease are unrecognised.

These initial observations prompted the literature review and research which follows.

CHAPTER 3

REVIEW OF THE LITERATURE

A: Demography of carcinoma of the oesophagus

3.1 General

There is a high incidence of CO in the following countries:-

Iran

South Africa

Kazakhstan

Linxian,China

the very highest incidences being in Transkei, the Caspian littoral areas of Iran and USSR, and Linxian in China.

The disease is common in the following countries:-

India

France

Switzerland

Central and Southern America

Non-white USA

Worldwide incidences are shown on table 1.(4,5,6)

For example, in Linxian, 20% of all deaths are caused by CO. A sample of 10,264 people over the age of 30 found 118 with CO, equivalent to a prevalence of 379/100,000. The incidence in people over 60 was 800/100,000.(7)

3.2 Local variations

Worldwide, there is a very remarkable variation between highest and lowest incidences. The Guriev region of Kazakhstan had a reported annual incidence of 547 per 100,000 males age 35-64, Africans in Durban South Africa an incidence of 98.9, while the Netherlands equivalent figure was 2.5, and Uganda 6.0. Within endemic areas a great variation in incidence may occur, often over short distances. High risk and low risk areas or populations may exist in close proximity. Some of these high/low variations have existed for generations, as in China; North China has 1.43 deaths per 100,000 (lowest), and the highest in China is 139.8/100,000 (7). Table 2 demonstrates local variations in six areas. CO varies in incidence more than any other tumour in Africa (8).

TABLE 1

INCIDENCE OF CANCER OF THE OESOPHAGUS IN DIFFERENT POPULATIONS
Annual rates per 100,000 males aged 35-64, standardised for age

Population		Incidence of cancer of the oesophagus
Mozambique	Lourenco Marques	11.8
Nigeria	Ibadan	2.6
South Africa	Coloured	28.0
	White	6.1
Durban	African	98.9
	Indian	14.7
Johannesburg	African	21.8
Jamaica	Kingston	26.6
USA	Non white	20.5
	White	5.8
Hongkong		23.0
India	Bombay	21.3
Israel		4.2
USSR	Armenia	9.1
	Kazakhstan	64.9
	Kazakhstan, Guriev region	547.0
	Turkmenistan	510.5
England	Birmingham	4.8
France		25.5
Greece		2.5
Switzerland		15.1
Australia		5.0

Adapted from a compilation by Warwick and Harington, 1973 (4)

3 Sex Ratios

Table 3 shows the sex ratios of CO incidence in different countries. It can vary from M:F 15:1 in one county of Hungary to M:F 0.4:1 for non-Jews in Israel. Within countries it varies between ethnic groups as in South Africa where the ratio for Africans is 3.8;1 (M:F) but 0.5:1 for Indians. There are also differences in USA in the ratio of the white and negro populations, and in New Zealand between the people of European and those of Maori origin. There is a much greater incidence worldwide of CO in males(9). Differential use of tobacco, alcohol, and betel are likely to explain most of the sex differences and the variations in ratio.

TABLE 2

REGIONAL VARIATIONS IN THE INCIDENCE OF CANCER OF THE OESOPHAGUS

Area	High Incidence Zone	Low Incidence Zone	Distance Apart (miles)	Ratio of rates high/low
Southern USSR	*Kazakhstan (547)	Georgia (8)	500	70
Northern Iran	N.E.Gonbad (516)	N.W.Gilan (49)	400	10
Northern China	N.E.Honan (237)	N.Shansi (4)	300	60
Southern Africa	S.Transkei (181)	N.Transkei (26)	150	7
East Africa	Kenya (106)	*Uganda (6)	200	20
West Europe	W.France (41)	Netherlands(2.5)	500	16

* Part only

From van Rensburg 1979 (6)

TABLE 3

SEX RATIOS OF CANCER OF THE OESOPHAGUS PATIENTS
male to female

Population		Ratio of crude rates
Nigeria		2 : 1
Zimbabwe, Bulawayo		7.6 : 1
South Africa, Natal	African	3.8 : 1
	Indian	0.5 : 1
USA, California	Negro	3.1 : 1
	White	2.1 : 1
India, Bombay		1.2 : 1
Israel	all Jews	1.3 : 1
	non-Jews	0.4 : 1
Japan, Miyaga		2.6 : 1
England, Birmingham		1.3 : 1
Hungary, Szaboles-Szatmar		15.0 : 1
New Zealand	Maori	8.5 : 1
	European	1.7 : 1

From Doll et al 1970 (9)

4 Geographical spread and change

A Feature of CO in Africa is a rising incidence over a period of several decades and a pattern of geographical spread. Cook(10) has written of the spread within Africa, involving Southern Africa, Malawi, Zambia and Kenya, and Oettlé (see fig.4)(11) has documented the spread within southern Africa. Cook draws a parallel between this and the change to using maize as a staple. Oettle speaks of an 'epidemic' spreading from an epicentre in Butterworth, Transkei, proceeding northwards towards Mozambique in the 1950's and 60's.

5 Transkei

The disease in Transkei is 97% sqamous carcinoma, predominantly of the middle third, and nearly all patients present too late in the course of their disease for treatment other than palliative (12). It affects males and females equally.

The tumour was not apparently seen before the 1940's in Transkei(13). Since then its incidence has risen rapidly, and was reported as 357/100,000 black persons in 1965-69. This exceeded the incidence rate in all other parts of the world except for the Guriev region of Kazakhstan, where it was 547 (6). It has been estimated that as much as 20% of the men up to the age of 75 would be affected by the disease in the absence of other causes of death (6). This is against a background of high incidence in neighbouring regions. Durban has an incidence of 99 and Bulawayo an incidence of 158/100,000 (4).

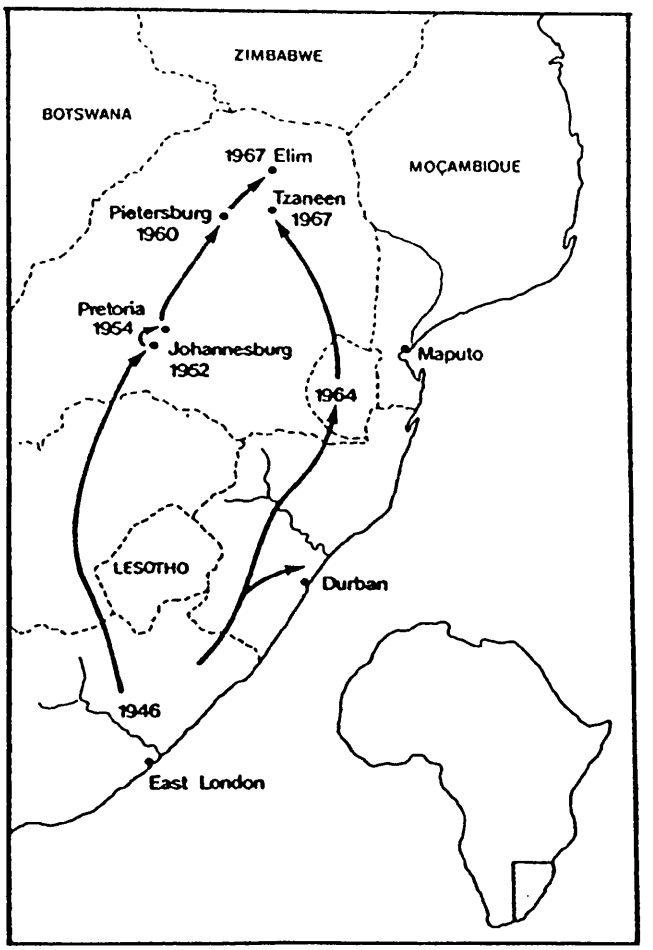


FIGURE 2 SPREAD OF CANCER OF THE OESOPHAGUS IN SOUTHERN AFRICA

from oettlé et al (11)

Within Transkei, in the 1960's, there was a wide difference in incidence between the low-incidence areas of Bizana and Lusikisiki and the high incidence area of Butterworth, areas separated by only 150 miles, but having a sevenfold difference in CO incidence.

Burrel et al.(14), working in high incidence areas, reported a marked variation in incidence even from one valley to the next, and significant evidence of spatial clustering has been demonstrated (6). This clustering of cases is independent of time.

CHAPTER 4

REVIEW OF THE LITERATURE

B: Observed associations

4.1 geographical and climatic

4.2 social

4.3 diet

4.4 alcohol

4.5 tobacco

4.6 oesophagitis and mechanical irritation

4.7 carcinogenic

4.8 infective

4.1 Geographical and climatic

Two associations have been established which link high incidence areas in the world:-

i) low annual rainfall and

ii) soil characteristics.

i) Low Annual Rainfall

Transkei, and the high incidence areas of Iran and China all have a low annual rainfall.

In the Caspian area of Iran, the five high incidence areas have an annual rainfall of 300mm to 800 mm rain per year and all areas which have a rainfall of more than 800mm per year are moderate to low incidence areas (15). In Transkei, where the average annual rainfall is 815mm, a similar pattern has been shown by

Rose (16). Neither of the two quoted papers attempts to explain this finding, but possibilities include effects on the type and quality of vegetation, the economy, and the types of employment available.

ii) Soil Characteristics

The soil characteristics which have become strongly associated with CO are those of a low potential for rainfed cropping and a high subsoil pH. This has been demonstrated in Transkei (17) where comparisons were made between high and low-incidence areas for CO. Multiple samples were taken in both the low incidence and the high incidence areas.

Humic soils were found in none of the high incidence areas but in one fifth of the low incidence areas. Many highly weathered and highly leached soils were found in the high incidence areas, but none in the low incidence areas. Whereas the high incidence areas have predominantly low potential (for rainfed cropping) soils, the low incidence areas are dominated by high to moderate potential soils for rainfed cropping.

The same study showed the subsoils from the high incidence areas to be dominantly alkaline in contrast with a majority of strongly acidic subsoils in the low incidence areas. Subsoil ph is not a clear discriminator between high incidence and low incidence areas, however. In this study by Laker only 16% of the samples from high incidence areas had low pH values, with 54% of samples from high incidence areas having a pH higher than 7, whereas the

vast majority of subsoil samples from low incidence areas were strongly acidic.

In this study Beaufort sediment and dolerite soils were the only soils found in the high incidence areas, and in the low incidence areas Beaufort sediment soils were absent.

In Iran a similar study (18) demonstrated a relationship between low CO rates and high potential soils with high organic matter and low subsoil pH. The high CO incidence areas included moderate and low potential soils similar to those dominant in the high incidence regions in Transkei. Both subsoil and topsoil pH's were alkaline in the high incidence areas, ranging from 7.5 to 8.1. The researchers concluded that there is a marked similarity between the main kinds of soils in the high incidence areas of Transkei and Iran. The soils in Transkei have been shown by Laker (19) to be generally deficient in minerals, However in this study boron, cobalt and manganese were all more frequently low in the low incidence areas. This study is not presented with a statistical analysis, and mineral levels do not give a consistent discrimination between the high and low incidence areas.
pH measurement of topsoil and subsoil showed no consistent difference between the groups, but there were slightly more acidic soils amongst the high incidence areas tested.

Laker's study in Iran (18) demonstrated an association between CO and low available manganese levels in the soil. However, one high incidence area for CO had moderate manganese levels and one

low incidence area for CO had low manganese levels. By contrast, boron levels were high in most of the high CO areas, but nearly all low in the low CO areas.

Studies on the soil do not come out with a consistent picture of specific mineral deficiencies, but rather of poor quality soil with a low mineral content. Such associations may be assumed to mediate any causative effect through their action on the quality and variety of plant life which grows in the endemic areas.

Associated studies on plant mineral content were carried out in Transkei (19,20). Maize was selected as the indicator crop, since it is the predominant staple crop in all of Transkei, almost to the exclusion of other crops. Multiple samples were taken from each representative site, both in high incidence areas and low incidence areas. Low nitrogen and copper levels in plants were associated with high incidence areas. Other minerals were significantly different in the first half of the study in 1976 :- Aluminium(low in high incidence areas), Iron(l in h),phosphorus(l in h),potassium(l in h),manganese(l in h),and zinc(h in h), but were not significantly different in the 1977 study and so cannot be taken as established associations. Plants from high incidence areas were also found to be significantly lower in iron (19), and to have a significantly lower K/Mg ratio and lower potassium and manganese and higher magnesium content (20).

The author of this paper concluded from his study that plant mineral levels were a better indicator of possible relationships

between mineral element levels and oesophageal cancer incidence rate than soil analysis in Transkei, and named the following as possibly causally related factors:-

low nitrogen in maize leaves

low potassium concentration in maize leaves

high magnesium concentration in maize leaves

low K/Mg ratios in maize leaves

low manganese concentrations in maize leaves

The possibilities that soil type might favour growth of harmful plants, or render harmful plants that in normal circumstances were safe to consume were not discussed.

Burrell et al (14), reporting from Transkei in 1965 state "within the memory of elderly people still living, grass grew to knee height over the entire Transkei. The largest area that still has this tall grass remains free of esophageal cancer".

The land surrounding the home of a Transkeian family is normally used for growing vegetables and maize. Burrell et al compared 29 "cancer gardens" i.e. gardens of homes where there was or had been a case of CO with controls. These controls were selected apparently without being seen beforehand by the researchers and it was reported that the cancer gardens were all obviously much less productive than those which were tumour free. They reported intense molybdenum deficiency in the plants of gardens where present or previous inhabitants had had CO, but "less intense" molybdenum deficiency in gardens in the same area where there had been no CO. The plants of cancer gardens were also reported to

be suffering from a complex trace-element deficiency. No accurate chemical sampling was carried out, and visual signs were used for the diagnosis of molybdenum deficiency. Molybdenum supplement of these gardens greatly improved the quality of the crop, so that molybdenum deficiency was felt to be a major factor in the general deficiency problem. They mention the fact that owners of cancer gardens depend more on pumpkin vine tips and edible weeds than do occupants of better gardens, and mention Solanum nigrum as one weed known to be poisonous. They failed to identify high soil pH as a related factor per se, but felt that there may be an interrelationship with some other relevant factor. This is a paper of great interest but suffers from lack of scientific measurement of molybdenum levels, and of controls. They state that molybdenum deficiency renders maize cobs prone to fungal attack.

The concept of the 'cancer garden' has been widely used in discussion of the aetiology of CO, but this paper which first used this term can only be said to raise the possibility rather than prove any association with individually poor gardens for CO victims. Similarly the authors did not consider whether a poor garden might be associated with a greater reliance on maize or a lower socio-economic status with different social habits.

Warwick and Harington (4) stress the recent changes in Transkei's fertility, mentioning systematic deforestation, erosion, and overstocking with sheep and cattle.

Spatial clustering has been shown to occur, with uneven distribution of the disease within high-incidence areas, and a higher than expected occurrence of CO close to the home of other CO victims.(6)

In summary, the main associations shown are with soils with low potential for rainfed cropping which are highly weathered and leached. The dominant type is Beaufort sediment. There are wide variations between districts, and also within districts, where there is spatial clustering. Consistent mineral associations are with low manganese and high boron in the soil. In plants, associations are low nitrogen, a low potassium/magnesium ratio, and low manganese.

Rose (21) states that the disease is found most often in Transkei between 1000 and 3000 feet of altitude. This may be a spurious association, or may be related to type and quality of vegetation.

4.2 Social

Burrell et al (14) describe in detail the changes that have occurred in Transkei society in the first half of the 20th century, with migrant labour resulting in bad land usage, followed by deterioration of fertility, poor crops and malnutrition. This has occurred at the same time as the massive rise in incidence of CO in Transkei.

Van Rensburg (22), in a study of 211 Zulu men with Cancer of the oesophagus and the same number of hospitalised patients matched

for age and urban-rural background, concluded that those most affected were in a transitional state between tribal subsistence farming and western living. A rural mud home, ownership of agricultural land, a cash income, and better than average education are indicators of high risk. Within the tribal context, the most susceptible to CO were the better educated and wealthier. He interpreted the important characteristics of this state as excess smoking and a diet having a low vitamin and mineral density. This is a carefully researched and documented study, in which he seeks to support his long held view that CO is caused by vitamin deficiency and carcinogen(s).

Rose (23) reported that in Transkei semi-westernisation was an apparent risk factor.

CO patients in Durban were found to have more schooling and be more likely to speak English than either lung cancer patients or control patients with no malignancy (24).

4.3 Diet

Diet has been the major area of research for CO, reasonably so in view of the oesophagus's intimate relation to food. Diet is very closely linked to soil characteristics in societies which live mostly by subsistence farming.

The major, and well established association is with use of maize as a staple diet in high incidence areas for CO. van Rensburg (25) demonstrated that high incidence areas for CO throughout the world all used either maize or wheat as the staple. Paula Cook showed that in Africa, the distribution of maize and the distribution of CO are similar (10). Wheat use as a staple is also a risk factor(25).

Van Rensburg (22) showed a relative risk of 5.7 in Natal for CO for those buying maize meal daily against those buying weekly in Zulu households. He took this to indicate more reliance on commercial maize, and therefore more exposure to deficiencies in magnesium, zinc, nicotinic acid and riboflavin. It would have been reasonable to consider that daily buying of maize might be due to convenience of access and therefore proximity to a store, this being consistent with his finding of CO victims being semi-westernised.

In a high incidence area of Transkei for CO, over 90% of meals were found to be maize based, and a greater use of maize kernels was found than in low incidence areas of Transkei (26). Bradshaw, Mc.Glashan and Harington (27) report an ever-increasing use of maize as a staple foodstuff in Transkei.

The association is with long term use of maize as a staple, CO appearing up to fifty years after the introduction of the crop. Paula Cook (see above) showed convincingly in her study (10) that the incidence of CO closely parallels the use of maize as a staple. She links CO with beer consumption on the grounds that alcohol has been implicated elsewhere, but fails to observe that in endemic areas no strong link has been demonstrated with alcohol. She brings forward no evidence to implicate beer as the medium through which maize exerts its carcinogenic effect on the oesophagus.

Bradshaw, Mc Glashan and Harington (27) state that in Transkei traditional beer used to be brewed from maize, with sorghum providing the malt, but over the course of time two thirds of those brewing beer have come to use maize as the malt-starting material.

Van Rensburg (26) showed that meals in high risk areas of Transkei more often contained beans, pumpkin and melon, and less often wild vegetables.

Diet may have a causal association with CO due to either the presence of some noxious agent or due to a deficiency.

van Rensburg (28) has postulated deficiency of micronutrients in a maize based diet as a causal factor. He has described a marked decrease in commercial maize meal (as opposed to whole maize) of magnesium, zinc, nicotinic acid and riboflavin. This relative

deficiency is in addition to the marginal deficiency he postulates for all those who use maize as a staple (25).
van Rensburg (22) mentions that during the past 50 years Zulus, whose incidence of CO has also risen greatly and who are neighbours to the Xhosa of Transkei, have moved from their diet of millet and sorghum to high yielding maize, animal products and wild fruits and vegetables, then more recently to overdependence on maize.

Bread consumption and rice consumption have also been shown to have an association with incidence of CO.

A study of household water in Transkei (29) revealed a significantly lower pH (7.065 + 0.407) in the high incidence areas than in the low incidence areas (7.381 + .651). This is in contrast to the findings above of a more alkaline soil in high incidence areas.

Pellagra is said to have emerged as a common disease in Transkei in about 1930, 25 years before CO became common. In Linxian, China, a study of 105 subjects undergoing endoscopy found 96% deficient in riboflavine (30). Yang (7) also reports from Linxian that symptoms of riboflavin deficiency, e.g. cheilosis, have been observed among the population in winter.

Yang (7) reports on a paper in Chinese where an inverse relationship is demonstrated in Northern China between CO mortality and food and drinking water content of molybdenum,

manganese, zinc, magnesium, silicon, nickel, iron, bromium, iodine, chlorine, potassium, sodium, phosphorus and bicarbonate. A similar inverse relationship was found for hair content of magnesium, molybdenum and zinc.

Other dietary associations are with a low fruit and green vegetable intake (31), with a low intake of wild vegetables,and with an increased consumption of beans and pumpkin (26). The joint Iran study (15) identified a 'severely limited' diet as a high risk association, particularly low intake of vitamin A, vitamin C, riboflavin and good quality protein .

Where the human diet has been shared with chickens the chickens have also shown an increased incidence of CO (7).

A reduction in risk (RR=0.51) was demonstrated by van Rensburg (22) for those using butter or margarine daily in his study of Zulu men.

The association with achalasia (32) may be partly due to the malnutrition that is a feature of longstanding achalasia.

The association between anaemia and CO is at least uncertain (33,34) and will not be discussed further.
The possibility that dietary content rather than deficiency is the source of the problem is supported by work by Jaskiewicz et al (35), although they did not themselves draw such a conclusion. They studied cytological changes in the oesophageal

mucosa in Transkeians. Changes of folic acid deficiency, cellular atypia, dysplasia, and carcinoma were found. A six month course of vitamins and trace elements did not change the cytological appearances, nor did a higher dose six month course of riboflavin, nicotinic acid, folic acid, molybdenum, and zinc. However they reported slight improvement in cellular atypia after the summer months, when the diet is different from winter.

Purchase, Tustin and van Rensburg (36) tested Transkei diets on rats. The first group were fed a diet of maize, beans and salt, and a second group receieved maize, beans, salt, and two wild vegetables, *umsobo* (Solanum nigrum) and *irwabe* (which they identify as Sonchus oleraceus but other authorities identify as Sonchus asper). The addition of two wild vegetables to this diet resulted in epithelial cell dysplasia of the oesophagus, and an increased incidence of tumours of various types. They concluded that some toxic factors were present in this "Full Transkei diet" which caused the epithelial cell dysplasia and that the wild vegetable may contain the carcinogen. They extrapolated to suggesting that the same factors may contribute to the high incidence of CO in man in Transkei. No nitrosamines or aflatoxins were present in the samples of Solanum nigrum and Solanum oleraceus analysed. This is carefully researched and written, and it is surprising that no published follow-up is available to this work.

Rose and Guillarmod (37) state that Solanum nigrum may be dried and kept for winter use as well as being eaten fresh. Solanum

nigrum is indigenous to Southern Africa and is used widely. It is a nitrate accumulator, particularly where there are deficiencies of molybdenum and manganese. Drought and frost also increase the nitrate concentration. Dollahite et al (38) state that nitrate poisoning is worse when a large quantity of a nitrate accumulating plant is eaten over a short period. Rose et al say "if the oxidation reductase enzyme system cannot function due to some deficiency of trace elements in the soil, these accumulated products may possibly unite with secondary and tertiary amines to form nitrosamines which are highly carcinogenic substances".

Solanum nigrum was grown on normal and molybdenum deficient soil by Schutte (39) and produced luscious growth in the molybdenum deficient soil, and a smaller and straggling plant on the normal soil.

4.4 Alcohol

Alcohol use has an established association with CO (40,41,42), and a linear relationship with dose has been established (31,42,43,44). Pottern et al (31) who researched among black men in Washington D.C. showed a relative risk of 6.4 for those who consumed alcohol.

However, no role of alcohol abuse has been shown in the main endemic areas of Transkei, (12,21) Natal (22), the Caspian littoral area (15), or Linxian in China (30), despite suggestions by Cook(10) and Wynder and Bross (45) that maize based beer may be implicated (see above).

Bradshaw, McGlashan and Harington (27) found a highly significant difference in preparation of traditional beer between high and low incidence areas, in that high incidence areas were more likely to use maize for the malt, and low incidence areas more likely to use sorghum. While this could be a significant, causal association, another interpretation is that sorghum is not a normal dietary component in high incidence areas, and this is a facet of a diet highly dependent on maize.

Xhosa beer has been raised as a possible factor by Bradshaw et al (27) who showed a high prevalence of beer drinking in Transkei, and an increased prevalence of beer drinking in areas with a high incidence of CO. Adulterated traditional beer has also been suggested as a rich source of carcinogens. Burrell (14) wrote of " illicit Bantu beer" prepared in discarded metal drums

after containing petroleum-asphalt, with a thick residual coating of the probably carcinogenic contents on the inside; also added to the brew were carbide, liquid metal polish, etc., to give it an additional 'kick'."
However van Rensburg (22) showed no association between CO and use of Traditional beer in a controlled study in Natal.

'Indiginous alcoholic spiritous concoctions' have been shown to be less common in high incidence areas in Transkei (27). Three studies have demonstrated a sizeable percentage of abstainers among CO victims (12,22,24), the last study quoting 10.2% of CO victims as total abstainers. An association, however has been shown by Segal et al (46) in Soweto, between CO and traditional beer.

A synergistic effect has been shown with smoking and alcohol consumption (43). Wynder and Stellman believe that alcohol causes nutritional deficiencies which predispose to carcinogenesis by tobacco. This conflicts with the apparent rise in incidence of CO in a linear fashion as alcohol intake rises, i.e. a moderate alcohol intake, which would not be expected to compromise nutrition, does in fact increase the risk of CO. McSween (47) suggests a direct effect on the oesophageal mucosa causing dysplasia, also raising the possibility of contaminant carcinogens in alcoholic drinks, and the effect of alcohol as a solvent for other carcinogens and as a co-carcinogen.

Another posssible mechanism is that of promoting gastro-oesophageal reflux and thus damaging the oesophagus (48).

Bradshaw, McGlashan and Harington (27) showed that both amongst men and women in Transkei, the combination of drinking and smoking is significantly more common ($p<.001$) in high incidence areas for CO.

4.5 Tobacco

A strong and undeniable association with tobacco use has been shown in many studies, (22,40,42,44) the risk increasing as personal tobacco use rises (44). They also showed commercial cigarettes to be important in aetiology in non-endemic areas. Wynder and Stellman showed a relative risk for CO of 1.7 for snuff users.

van Rensburg (22) showed a relative risk of 2.6 for those currently smoking commercial cigarettes, and a relative risk of 2.1 for pipe smokers in Natal, and Bradshaw and Schonland (24) also demonstrated an association between CO and pipe smoking, but also pointed out that 15% of CO patients had never smoked. Cotton and Sammon (12) found about 30 % non-smokers amongst CO victims in Transkei.

In Transkei, three forms of tobacco are used. Commercial cigarettes, commercial pipe tobacco and homegrown tobacco. Significantly more tobacco is grown in the high incidence areas than in low incidence areas (27) and smoking in general, pipe smoking in particular, are more prevalent in high incidence areas, in both sexes.

The mutagenicity of homegrown Transkei tobacco pyrolysate has been demonstrated to be considerably higher than that of commercial tobacco (49).

Auerbach et al (50) described a hyperplastic response of the oesophageal mucosa in cigarette smokers, which was remarkably similar to those found in the trachea and bronchus.

Three facts prevent posulation of tobacco as the sole or main factor in CO causation in Transkei and other endemic areas. Firstly that smoking has been common for very many years (51), certainly for over a century, yet the disease is apparently new as a major cause of death. Secondly, studies (12,22,24) have shown a persistent percentage(30%, 19% and 15.3% respectively) of non-smokers in those afflicted. Thirdly, van Rensburg in Natal states that the mean total quantity of tobacco used is considerably less than used by many rich western communities where CO is rare (25).

4.6 Oesophagitis and mechanical and irritant associations

Oesophagitis has been found to be widespread in endemic areas. Munoz et al (30) found an incidence of 84% of chronic oesophagitis in a study of 527 subjects in Linxian, China. 10% of these had epithelial atrophy and 8% dysplasia. Reexamination of 20 of those with oesophagitis showed one year later that 4 individuals had dysplasia, and 4 had frank cancer. Clear cell acanthosis was the commonest lesion (80.8% of men and 72.4% of women and chronic oesophagitis with papillomatosis, lymphocyte and plasma cell infiltration and blood vessel dilatation of submucosa and epithelium were present in 65% of men and 63.5% of women.

Oettlé et al (11) examined endoscopically 119 consecutive patients presenting to them with foregut symptoms in Johannesburg and found oesophagitis in 78. 55% was distal oesophagitis, 3% proximal, and 42% panoesophagitis. The oesophagitis was diffuse and largely non-ulcerative. Candida were found in 30% of cases, but only one third of these had endoscopic evidence of candidiasis. They also noted that hiatus hernia and lower oesophageal sphincter incompetence were 'not uncommon'.

Hamilton and Isaacson (52) examined the oesophagi of 28 unselected children between the ages of 2 years and 18 years who had died in Johannesburg. They found chronic non-specific oesophagitis in 15. Similar changes were not found in children under two years. The oesophagitis was characterised by atypical basal cell hyperplasia.

Crespi et al (53), investigating in Northern Iran, a high incidence area for CO, studied 430 volunteers, and found a prevalence of 80% of chronic oesophagitis, mainly of the middle and lower thirds. The oesophagitis was normally accompanied by acanthosis, dilatation and proliferation of blood vessels in the epithelium and submucosa, and superficial necrosis. There was a very low incidence of incompetent cardiac sphincter and hiatus hernia.

Rose (21) mentions finding chronic inflammation of the oesophagus in cases negative for CO as well as at post mortem in a high risk population in Transkei. This finding is not described in detail or in numbers and is insufficient evidence on which to base any conclusion.

Possibly the most common abnormal irritation of the oesophagus is acid reflux from the stomach, and this has been raised as a possible cause of CO. Regular use of emetics causes a similar assault. Gastroduodenal reflux is a much more abnormal event for the oesophagus, bringing bile salts and trypsin as irritants that the oesophagus is less able to deal with.

An increased risk of CO has been demonstrated after gastrectomy (54), with reflux of alkaline duodenal juices containing bile, and/or nutritional deficiency as possible reasons. 8 of 92 patients with CO had previously undergone partial gastrectomy or gastroenterostomy. Maeta et al (55) similarly reported 12 of 129

patients with CO as having undergone previous partial gastrectomy.

Prolonged duodeno-oesophageal reflux resulted in a thickened collagenous oesophagus in rats studied by Mud et al (56). After the reflux had been stopped the collagen continued to increase. Kuylenstierna and Munck-Wikland in Sweden (57) found a strong link between reflux oesophagitis and CO of the lower oesophagus, 95% being squamous. 13 of 51 patients with lower oesophageal cancer had a history of preceeding hiatus hernia and reflux oesophagitis, in most cases for several years. There was no link between reflux oesophagitis and cervical or upper thoracic CO. Salo and Kivalaakso (58) demonstrated that the combination of gastric acid, pepsin, lysolecithin and conjugated bile salts causes a severe oesophagitis.

Asbestos, soot, and metal dust all probably owe their association with CO to simple irritant effects on the mucosa. Oesophagitis has been demonstrated to be a precursor of CO and to be highly prevalent in areas of epidemic CO.

Lye has been put forward by Hurst as a potent cause of CO. He showed a high incidence of CO in Eskimo women who use wood ash containing lye to cure animal skins, and in the process ingest lye. Eskimo men are not subject to the same high incidence of CO, having only two CO victims as against seven female victims in Hurst's study (59).

Drinking water in the high incidence areas of Transkei has been shown to be corrosive (29).

Achalasia has a long-known association with CO, at least 7 of 85 patients with achalasia followed up by Ellis (32) dying from CO. There is a component of local damage from abrasion from obstructed foodstuff in the oesophagus, but possibly also a nutritional component from the malnutrition associated with longstanding achalasia. With modern treatment this may no longer be a risk (34).

Bradshaw and Schonland (24) found that patients with CO and patients with lung cancer in Natal were more often regular users of emetics than controls, but they did not describe the emetics. van Rensburg (22) failed to find any association in his case-control study, also in Natal.

4.7 Carcinogenic

The list of chemical carcinogens blamed is relatively small. Tobacco is discussed in 4.5 above

Aflatoxin B1 was found in 18.8% of food samples from low incidence areas of Transkei, but in 28.5% of high incidence area samples. The same study showed higher levels of two other mycotoxins, deoxynivalenol and zearalenone in food samples from high incidence areas (60).

A study of nitrosamines in food in Transkei failed to show any conclusive picture (61).

Traditional medicines have been postulated as carcinogens, but no clear association demonstrated. van Rensburg (22) found no association between CO and herbal medicines, emetics, purgatives and the use of various wild plants.

Similarly opium has been suggest as a causative factor in Northern Iran (53), but evidence implicating it has been lacking.

Betel users are known to have an increased incidence (62). This is a habit which is common in India and other eastern countries and may be of betel alone, or mixed with tobacco and/or lime.

The chewing of *naas* is common in the high incidence areas for CO in Iran. This is 20 parts tobacco, 4 wood ash, 1 lime and about 1 water (4).

4.8 Infection

A high incidence population for CO has been shown to have increased antibody to cryptantigenic T structure of autologous cell membranes, which is normally related to bacterial action, and evidence of increased viral infection rates (63,21). The significance of this is not clear according to those who reported this finding, but might be either related to viral carcinogenesis or reduced immune surveillance of potentially malignant cells. It is much more likely related to the poorer nutritional state common to all the epidemic areas.

A much clearer association is emerging between fungi and CO. Fungus infection of maize kernels is very common in Transkei, the commonest species being Fusarium and Diplodia. The resulting mycotoxins are referred to in 4.7 above.

Fungal invasion of the oesophagus and fungal contamination of maize consumed (64) have both shown a significant association with CO incidence. Mararsas et al (64) Studied 12 households from each of two areas of Transkei :-Centane, a high risk area for CO and Bizana, a low risk area for CO. Brush biopsies of oesophageal mucosa, and mycological examination of good household maize was carried out. Fusarium moniliforme infestation of maize was significantly more common in the high incidence area, but there were no differences in incidence of cytological abnormalities of the oesophagus.

Papillomavirus has been suggested as a causal agent by Brooks et al (65). This virus has been shown to induce alimentary tumours in cattle in Scotland (66). Brooks et al failed to support this suggestion with experimental evidence.

CHAPTER 5

REVIEW OF THE LITERATURE

C: Postulated causal mechanisms

Postulated causal associations may be classed in three major groups:-

Oesophageal insults

Carcinogens

Nutritional deficiencies

Postulated aetiological mechanisms may be classified as follows:-

5.1	Single Mechanism	5.11 Oesophageal insults
		5.12 Carcinogens
		5.13 Nutritional deficiencies
5.2	Compound Mechanism	5.21 Oesophageal insult + Carcinogen
		5.22 Oesophageal insult + carcinogen + nutritional deficiency
		5.23 Carcinogen + Nutritional deficiency

5.11 Oesophageal insults

Hurst (see 4.6) postulates that alkaline wood ash, ingested in the process of hide tanning causes CO in Eskimo women (59). His evidence is good.

Shearman et al (54) postulate gastric and duodenal content reflux into the oesophagus, this also implying a component of alkaline injury.

Cook (10) suggests that CO is caused by the use of maize based beer. She does not specify the mechanism involved, nor does she put up a convincing case for this causation (see above).
Alcohol as a sole cause for CO in Transkei has been proposed by Burrell (67) and supported by Wynder and Bross (45), and the consumption of traditional beer has been proposed by Cook (10) as an important factor.

5.12 Carcinogens

Tobacco carcinogenesis is supported as an adequate single cause by many, and the evidence is overwhelming that tobacco is a carcinogen and is involved in the aetiology of CO in many places.

Similarly strong evidence implicates alcohol, but in a role as a co-carcinogen with tobacco rather than as an independent agent (44,48). Tuyns (42) has proved a strong association in the absence of tobacco.

Fungal mycotoxins, and viral infection have both been shown to have a strong association with CO, and have been postulated as possible sole agents (64), but the evidence so far is circumstantial, and may well be spurious. Burrell et al (14) observe that cancer garden produce, being deficient in many ways, may be much more prone to fungal attack.

An unidentified carcinogen in the full Transkei diet was postulated by Puchase, Tustin and van Rensburg (37). The evidence is good that a carcinogen exists in the full Transkei diet.

Nitrosamines in food have been suggested by Burrell et al (14). The evidence is circumstantial and may be spurious.

Munoz et al (30) postulate that a single agent may cause both the precursor lesions of oesophagitis, atrophy and dysplasia found in the endemic areas of Iran and China as well as providing the

final carcinogenesis. They suggest opium tar as a possible cause in Iran, but cannot identify a possible agent in China.

5.13 Nutritional deficiencies

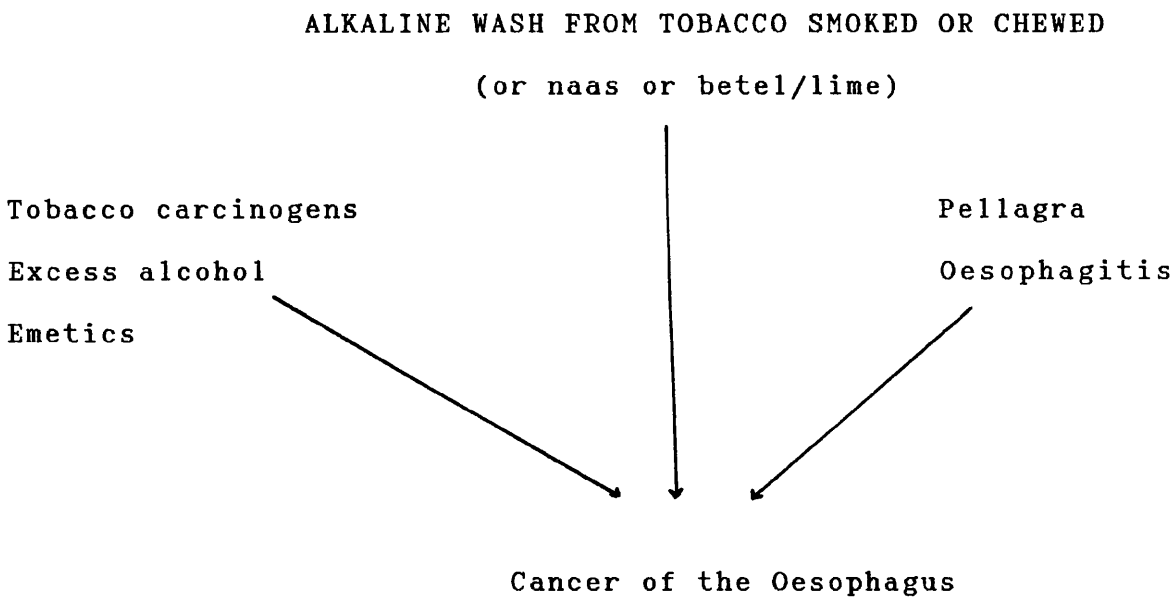
Nutritional deficiency on its own has been suggested by Shearman et al (54) as a possible mechanism, because of the increase in CO noted in patients who have had a gastrectomy. Most of their patients had a low serum iron and one a low serum B12. This theory is overshadowed by their alternative theory of damage to the oesophagus by reflux.

5.21 Oesophageal insult plus carcinogen

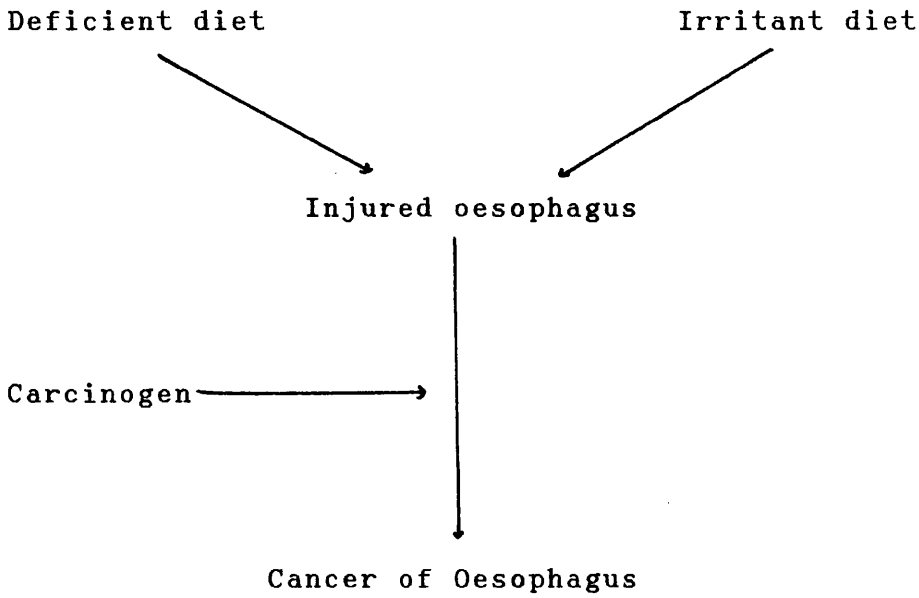
Tobacco plus alcohol is the best documented causal combination, and the evidence is convincing that they work synergistically (47). Tobacco has been established as a carcinogen in its own right. Alcohol may act as an oesophageal irritant, a solvent for the carcinogens of tobacco or as a true co-carcinogen (47). van Rensburg (51) and Wynder and Stellman (43) believe its effect is to cause or to aggravate deficiencies of minerals and vitamins. The combination of tobacco and alcohol is well established in non-endemic areas as the major causal association of CO, but the same has not been demonstrated in endemic areas.

5.22 Oesophageal insult plus carcinogen plus nutritional deficiency

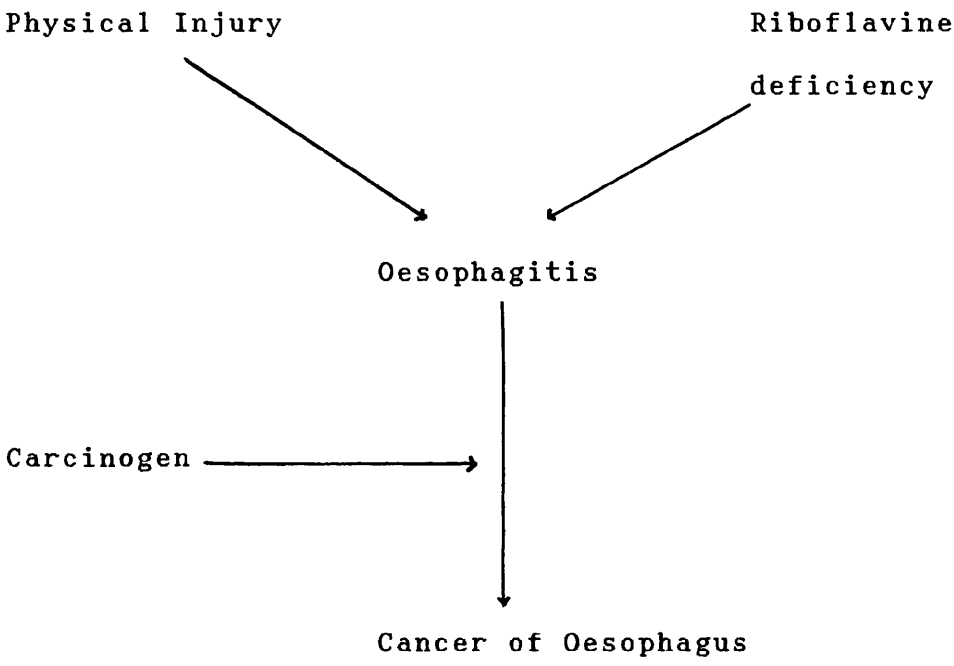
Three studies from endemic areas have come out in favour of this multifactorial initiation of CO. Warwick and Harington (4) reviewed exhaustively the evidence for Transkei and suggested the possibility of an alkaline wash from tobacco use combining with nutritional deficiency, particularly pellagra, and other physical insults including excess alcohol and plant emetics, as responsible for CO, with or without the effect of carcinogens in the local tobacco. They point out that naas is alkaline, as is betel and lime mixture.



The Joint Iran-International Agency for Research in Cancer Study Group concluded (15) that in the high incidence area of Iran the the causes were a deficient diet, probably a locally irritant diet for the oesophagus and exposure to a carcinogenic agent from opium tars or from wheat contaminants.



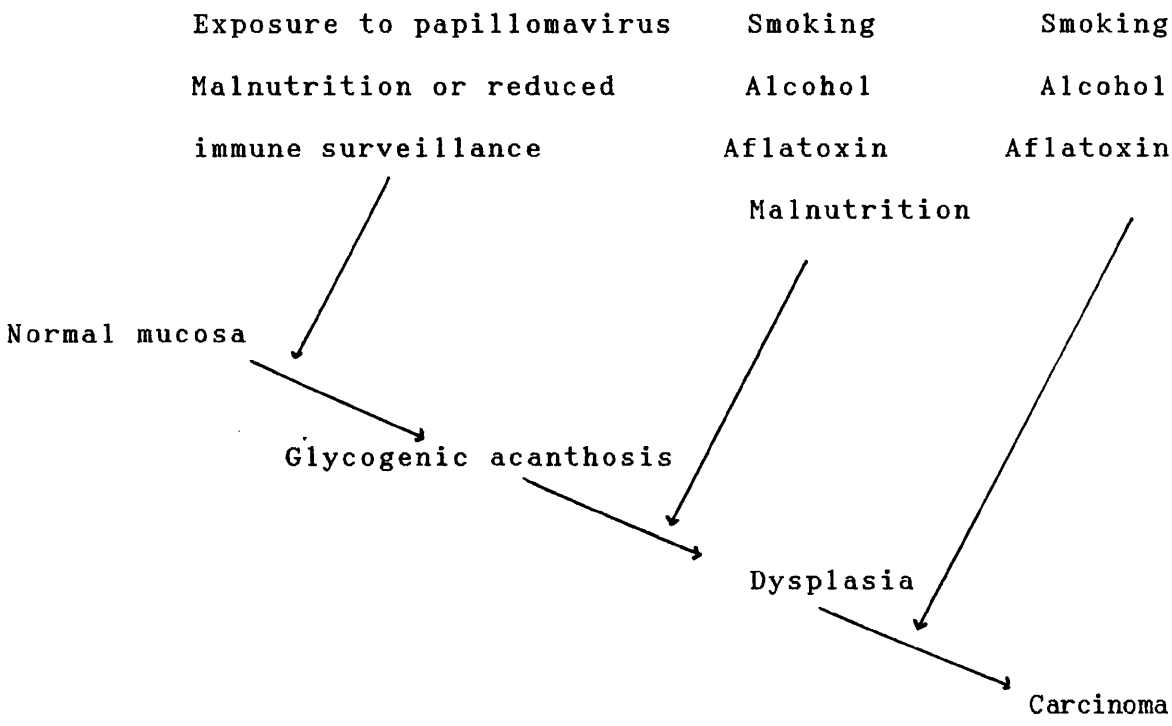
Munoz et al (30), reporting on CO in both China and Iran, postulate precursor oesophagitis, caused by both physical injury due to hot beverages and coarse food, and nutritional deficiency, particularly of riboflavine. A carcinogen then acts on this predisposed oesophagus to produce CO



Bradshaw and Schonland (24) suggest that CO is caused by a variety of oesophageal insults, including smoking, alcohol and emetics, combined with a general state of malnutrition, and possibly an unidentified carcinogen.

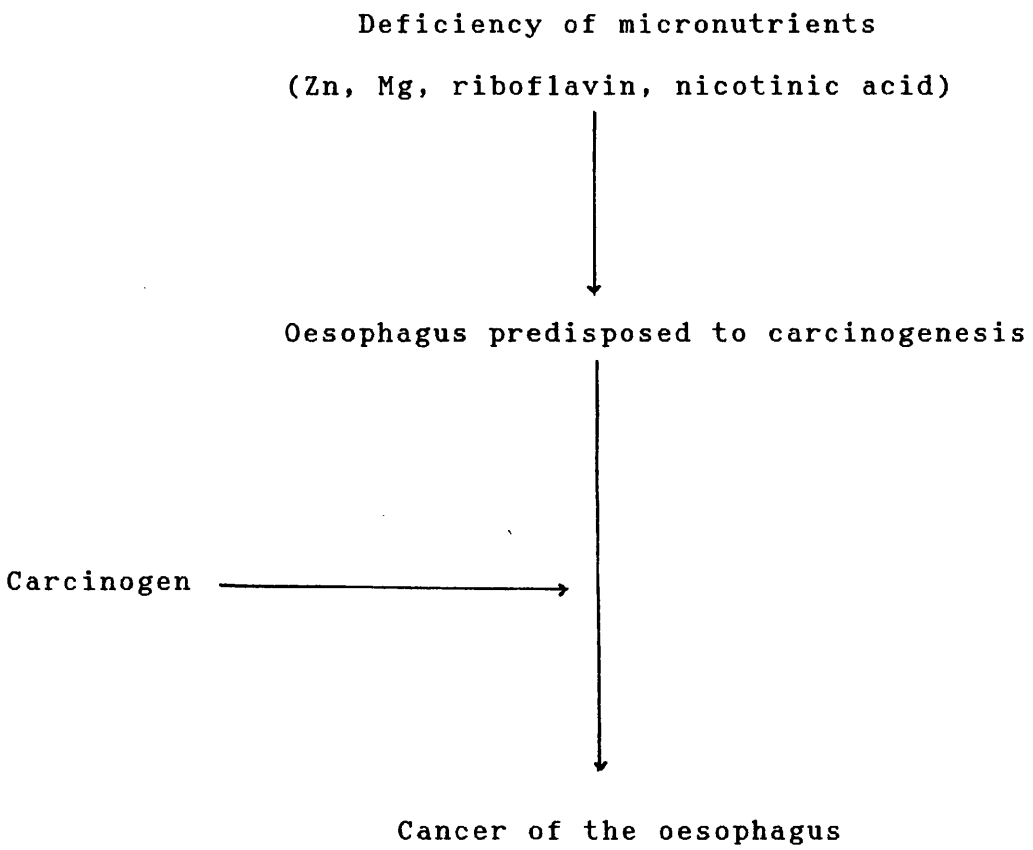
In their paper of 1983, Bradshaw, McGlashan and Harington (27) identify tobacco as the guilty carcinogen.

Morris and Price (68) hypothesise that papillomavirus is an essential part of the carcinogenic process, causing a 'glycogenic acanthosis' or flat, and therefore not easily visible infection of the oesophageal mucosa. This process is favoured by reduction in immune competence such as would occur in malnutrition. Smoking, alcohol, aflatoxins and malnutrition oversee the next stages which are progression to dysplasia and then to carcinoma.



5.23 Carcinogen plus Nutritional deficiency

This theory has been proposed by workers in the major endemic areas of South Africa, China, and Iran. S.J.van Rensburg from Cape Town has consistently supported this theory for many years (25,28,51) and argues that the staple diets of endemic areas are deficient in a range of micronutrients, particularly zinc, magnesium, riboflavin and nicotinic acid, predisposing to carcinogenesis by agents as yet not clearly identified. This mechanism applies equally to 'alcoholics in New York as it does to Iranians, Chinese, or Africans'.



Yang in China (7) proposes a similar causation with low molybdenum and other nutritional deficiencies contributing to carcinogenesis by nitrosamines and other carcinogens. This is also proposed by Laker (69) who blames manganese deficiency in plants for vitamin C deficiency and thereby nitrosamine production and carcinogenesis. Wynder and Stellman (43) also propose the above causation, blaming alcohol for nutritional deficiencies which predispose the oesophagus to carcinogenesis by tobacco.

SUMMARY OF LITERATURE REVIEW

Endemic areas for CO have a low rainfall and a low potential soil for rainfed cropping. Maize and wheat are the staples of the areas where the disease is endemic, and the documented spread of the disease within Africa has accompanied the spread of the use of maize as a staple.

In southern Africa the population at most risk are those in a transitional stage of westernisation.

A carcinogen may be present in Solanum nigrum or Sonchus oleraceus, two wild vegetables present in the Transkei diet.

Alcohol does not have a proven association with CO in endemic regions, but use of tobacco has a very strong association, which is dose-related.

Oesophagitis is very prevalent in endemic areas, including southern Africa.

Associations have been shown between CO and aflatoxins and other mycotoxins, fungal invasion of the oesophagus, and papillomavirus infection of the oesophagus, but the nature of the association is not clear.

Good arguments have been put forward to support the following causes for CO in Transkei:-

Nutritional deficiency plus carcinogen

Nutritional deficiency plus carcinogen plus physical insult

CONCLUSIONS FROM LITERATURE REVIEW

Associations so far demonstrated are almost all with foods and other items swallowed, or strongly related to these (soil and rainfall). A full dietary and social investigation is indicated to cast further light on the relationship between CO and the many items of food and other substances swallowed.

CHAPTER 6

AIMS OF THESIS

1. To investigate dietary and social factors which may affect the oesophagus in Transkei.

3. To seek the statistical relationship between these factors and the incidence of carcinoma of the oesophagus in Transkei.

4. To put forward a theory of pathogenesis of cancer of the oesophagus in Transkei which is in agreement with the facts demonstrated.

CHAPTER 7

METHODS

7.1 STUDIES ON FOODS THAT CAUSE HEARTBURN

7.11 Duration and level of heartburn after ingestion of *umqa wethanga* and *amarewu*.

7.12 Association of regurgitation with heartburn induced by *umqa wethanga* and *amarewu*.

7.13 Effect of aspirin on heartburn induced by *umqa wethanga*.

7.14 pH of *umqa wethanga* and *amarewu*.

7.11 Duration and level of heartburn after ingestion of *umqa wethanga* and *amarewu*.

Method

Fifty healthy Transkeians from among the hospital staff were questioned about heartburn after ingestion of *umqa wethanga* and *amarewu*. All questioning was done by the author in English or Xhosa(in which the author has a university pass). Staff of all grades were questioned in a series of departments until the numbers were made up to 25 male and 25 female.

7.12 Association of regurgitation with heartburn induced by *umqa wethanga* and *amarewu*.

Method

Twenty hospital staff members who suffer from heartburn after *umqa wethanga*, and twenty who suffer from heartburn after

amarewu were questioned. Each was asked " do you ever regurgitate anything into the mouth after *umqa wethanga* (after *amarewu*)?"

7.13 Effect of aspirin on heartburn induced by *umqa wethanga*.

Permission for this study was obtained from the medical superintendent, whose duty it is to give such authority in ethical matters.

Method

Members of staff were questioned, all members in one ward being questioned until a total number of ten was found who :-

a Normally have heartburn after *umqa wethanga*

b Do not suffer from symptoms suggestive of peptic ulcer

c Were willing to participate in the study after full explanation.

Each person was told the following:- "It is not clear why *umqa wethanga* causes heartburn. I know of two possible reasons - either acidity, or by loosening the valve at the top of the stomach. If it is for the first reason, then aspirin will make the heartburn worse. If it is for the second reason, then aspirin may make the heartburn less."

Each subject was given two soluble aspirin tablets and asked to dissolve tham in water and drink the solution twenty minutes before he or she next took *umqa wethanga*.

7.14 pH values of *umqa wethanga* and *amarewu*

Method

Freshly prepared samples were measured in the water laboratory by a trained technician using a pH meter.

7.2 MAJOR QUESTIONNAIRES - Gross study

The data presented was collected over the course of two years. Questions were introduced or deleted from the questionnaire throughout the duration of the gross study as the focus of the investigation became clearer.

The subjects were asked to answer 'yes' or 'no' to each question, except where a quantity or number was required, where the patients' best estimate was requested.

A reply of yes was recorded for any food, medicine or social habit which had been usual at any time during the previous ten years, e.g. even if the patient had stopped smoking nine years ago, the patient was recorded as a smoker.

Cancer of the oesophagus patients

A total of 326 patients were interviewed who had the typical findings on barium swallow of CO. All questioning was done by the author in English or Xhosa. Not all CO patients admitted to the hospital were interviewed, but all patients with CO were included who were admitted to the author's surgical unit, as were many patients admitted to the other two surgical units, each of which admitted similar numbers of such patients with disease of similar severity. On each day when the author had time, all new patients in both other units were interviewed to prevent selection bias by sex or severity of illness. Approximately 60% of all patients with CO admitted to the hospital were interviewed. All patients and controls were Transkeians.

Controls

A total of 683 controls were interviewed. Some were asked the full range of questions. Others were questioned on selected topics only. They comprise:-

Inpatients	212
Outpatients	31
Hospital staff and community	255
Inpatients and outpatients selected for matched pairs	185

57 people included under hospital staff and community self-presented in a village in response to a plea for volunteers for oesophageal brush biopsy.

125 staff and community were interviewed by a research assistant in English with or without an interpreter according to need. All remaining controls were interviewed in English or Xhosa by the author. 185 patients were chosen for their age, sex and educational level as a control pool for the final 100 CO patients.

Comparisons were made

a) between CO patients and all controls

b) between CO patients and inpatients, outpatients, and village volunteers

The latter grouping was felt to provide a more similar control group in terms of educational and social background.

The areas covered by the questionaire were

FOODS

beans	these are usually lima beans
umqa wethanga	a mixture of maize meal and flat white pumpkin cooked together and eaten as a mash
pumpkin	flat white pumpkin
imithwane	a relish made from green pumpkin leaves
holsum	a commercial cooking fat made from 95% fish oil
sunflower oil	bought
margarine	bought
animal fat	liquid fat kept after slaughtering, for later use
sour porridge	maize meal porridge allowed to sour, or actively soured with tartaric acid or herbs

wild vegetables

utyuthu (Amaranthus thunbergii)

imbikicane (Chenopodium album)

This plant contains a large amount of oxalic acid which may cause hypocalcaemia. There is also a photosensitisation effect on the skin(70).

umsobo (Solanum nigrum) Garden or black nightshade.

According to climate, soil and season, there are greatly varying amounts of the alkaloid solanine present. All parts of the plant, but particularly the unripe berries contain it(70). In Transkei the leaves of imbikicane and *umsobo* are used fresh and made into a relish to be taken with maize, or are mixed in with maize meal, and cooked with it to make

a stiff porridge. The leaves may be dried and kept for use in winter.

irwabe (Sonchus asper)

unongotyozana (Centella coriaceae)

amarewu a non-alcoholic drink made by fermenting maize flour and wheat flour

usolontsi a large locally grown pumpkin, proper name unknown

maize meal bought or ground at home

SOCIAL

tobacco

smoking no differentiation was made between cigarettes and pipe smoking

isixhaxha or *intshongo* (use of pipe scrapings as a paste between the teeth, or sucking grass steeped in pipe stem fluid)

snuff

chewing tobacco

traditional beer a home brewed beer, traditionally based on millet, but now made almost exclusively from maize.

education the years of school education are sub A, sub-B, standard 1, standard 2, standard 3, etc to standard 10.

keeping of cattle including number

keeping of sheep including number

age known to patient, or an estimate by ward staff

sex

MEDICAL

use of Traditional Xhosa medicines

self-induced vomiting

frequency

use of Xhosa medicines for emesis

regurgitation of bile

history of "*ikhelebha*" (The mouth lesions of florid pellagra)

7.3 Questionnaire - Case-control study

Cancer of oesophagus patients

100 consecutive CO patients interviewed by the author are included, being the final 100 CO patients of the first gross series.

Controls

All controls were interviewed by the author. Patients were chosen for their age, sex and educational level similarity to the CO patients. Whole wards and outpatient queues were asked about their age and educational level, and each person who matched a CO patient was interviewed fully. No account was taken of Geographical origin within Transkei. As the only national referral hospital it has been assumed that referral patterns are similar for CO and other diseases. The only exclusions from controls were patients suffering from undiagnosed conditions of the upper alimentary tract. Approximately 90% were inpatients, equally divided between medical and surgical wards, the remainder being outpatients of all specialties.

Age groups for pairing were under 31

31-40

41-50

51-60

61-70

over 70

Educational groups for pairing were

Uneducated to two years at school

Three or four years of schooling

Five or six years of schooling

Seven or eight years of schooling

Nine or ten years of schooling

Eleven years of schooling or above

The areas covered by the questionaire were as in the Gross study above

Using minitab (71) pairs were assessed using McNemar's test for qualitative questions. The paired t-test was used for quantitative data (72). Sample calculations are shown in appendix 1.

For further analysis of significant factors, conditional logistic regression analysis for matched case control studies was used.

All comparisons made using t-tests were repeated using the appropriate non-parametric test, with unchanged results.

Population attributable risk was calculated as shown in appendix 2.

7.4 SUPPLEMENTARY STUDIES

7.41 Brush biopsy study

7.42 Water pH study

7.41 Brush biopsy study

In the community of Kambi, a rural village near to Umtata, the local clinic nurses reported a high incidence of CO and named 17 victims in the preceding few years. They asked the author to carry out a study there.

The headman and the elders of the village were approached, and it was agreed that volunteers would present themselves for oesophageal brush biopsy.

Volunteers came to the headman's house, and each was asked to swallow an oesophageal brush biopsy capsule. The attached string was caught at the incisors at a length of 42-45 cm., kept there for at least ten minutes, then withdrawn. Smears were taken and fixed immediately. Fluid from the biopsy sponge was squeezed onto Urobilistix strips and the results read at the appropriate time thereafter.

The slides were examined by an experienced cytologist in the State Pathology laboratory in Umtata General Hospital under the supervision of Professor K.E.Wilson.

7.42 Water pH study

Method

Samples of water were collected by the author in sterile universal containers and delivered to the local water laboratory where the pH was measured using a pH meter.

CHAPTER 8

RESULTS

8.1 Foods that cause heartburn

8.2 Questionnaire - gross study

8.3 Questionnaire - case-control study

8.4 Supplementary studies

8.1 Foods that cause heartburn

All subjects answered the questions put to them.

Heartburn (see figs 3 and 4) is remarkably common in Transkei, affecting 60% of the sample. More were affected by *umqa wethanga* than by *amarewu*. It caused mid-thoracic symptoms in the majority of sufferers, but involved throat symptoms in 30% of sufferers. Its duration was from a few minutes up to 2 days, most symptoms being finished within an hour. It was caused by foods commonly consumed in Transkei. The sample group were predominantly people with some medical education or understanding and of better than average education. This selection bias does not detract from the clear conclusion that an abnormally large proportion of Transkeians suffer from frequent heartburn which may be extensive and prolonged.

The heartburn caused by *umqa wethanga* was predominantly of the middle third, whereas that caused by *amarewu* was fairly evenly distributed from xiphisternum to neck.

Heartburn is very commonly accompanied by a symptom strongly suggestive of gastro-oesophageal reflux, namely regurgitation of fluid into the mouth (table 4). About threequarters of those

suffering heartburn after *umqa wethanga* or *amarewu* complained of regurgitation.

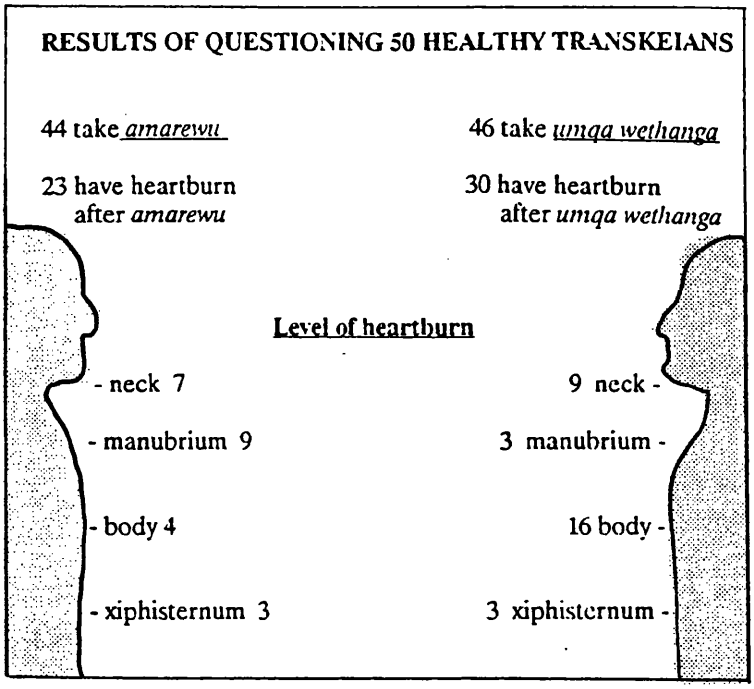
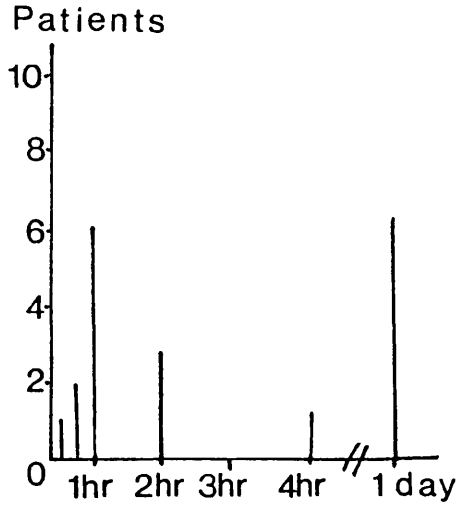


FIGURE 3 — HEARTBURN AFTER *UMQA WETHANGA* AND *AMAREWU*

HEARTBURN AFTER

UMQA WETHANGA



HEARTBURN AFTER

AMAREWU

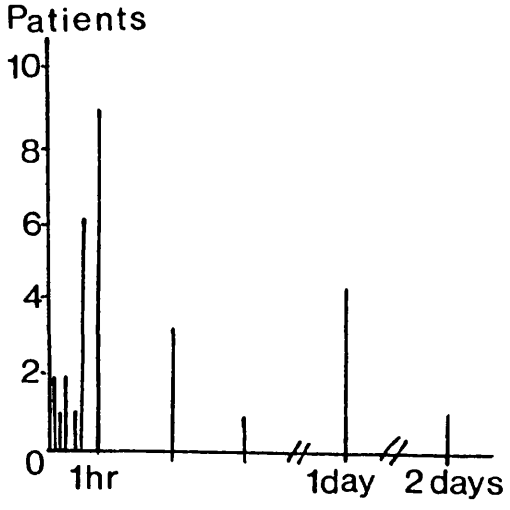


FIGURE 4 — DURATION OF HEARTBURN

TABLE 4

REGURGITATION AFTER *UMQA WETHANGA* AND *AMAREWU*

Number of subjects who have heartburn after *umqa wethanga*	20
Number who regurgitate fluid into the mouth while suffering heartburn	15

Number of subjects who have heartburn after *amarewu*	20
Number who regurgitate fluid into the mouth While suffering heartburn	14

The heartburn was abolished or alleviated by aspirin ingestion in the small experimental study (table 5). All 9 of those completing the test reported that their heartburn was either abolished or reduced after aspirin ingestion. Although small in scale, this study showed a significant effect of aspirin on the food-induced heartburn. The test measured a subjective quality, and is liable to a placebo effect, nevertheless the result was overwhelmingly positive.

The pH of *amarewu* is possibly low enough for its acidity to be a factor in the aetiology of heartburn, but the pH of *umqa wethanga* is neutral, suggesting that the heartburn is not related to acidity (table 6).

7.2 Questionnaire - gross study

All subjects answered the questions put to them. Occasional difficulties in dialect were overcome by inviting the help of a native Xhosa-speaking nurse.

The controls in this series are widely varied socially and geographically within Transkei.

Only one of 240 CO patients did not eat beans, and four did not eat pumpkin (see tables 7 and 8). 96% consumed *umqa wethanga*, and 97 % *imithwane*.

94% used Holsum. Well over half were consumers of several wild vegetables. Only 4% used only home-ground maize.

TABLE 5

EFFECT OF ASPIRIN ON HEARTBURN AFTER *UMQA WETHANGA* AND *AMAREWU* INGESTION

Number of subjects	10
Number completing test	9
Number whose heartburn was abolished	6 *
Number whose heartburn was reduced	3
Number whose heartburn was the same	0
Number whose heartburn was greater	0

* This is significant at the level of P = .002

TABLE 6

pH OF *UMQA WETHANGA* AND *AMAREWU*

Umqa wethanga	pH	6.93
Amarewu	ph	3.42

TABLE 7

CONSUMPTION OF FOODS AND WILD VEGETABLES

	CO		Inpatients, outpatients and village volunteer controls		All controls	
	Patients	Users	Patients	Users	Patients	Users
Umqa wethanga	307	294	256	230	608	543
Imithwane	293	283	256	244	433	412
Beans	240	239	190	185	367	357
Pumpkin	240	236	149	142	326	309
Holsum	240	225	229	214	406	377
Sunflower oil	240	180	56	43	210	159
Margarine	240	159	56	40	210	145
Animal fat	240	132	56	37	210	125
Amarewu	212	197			483	417
Usolontsi	100	89			154	135
Home ground maize only	181	8	31	3	185	9
Utyuthu	293	261	99	81	401	315
Imbikicane	253	174	62	20	341	177
Umsobo	253	216	99	79	401	315
Irwabe	253	204	99	73	401	286
Unongotyozana	145	100	68	43	370	202

TABLE 8

COMPARISONS OF FOODS AND WILD VEGETABLES

	CO Patients	Inpatients, outpatients and village volunteer controls			All controls		
	% consumers	% consumers	X^2 against CO patients	P	% consumers	X^2 against CO patients	P
Umqa wethanga	96	90	7.6	.001	89	10.9	.001
Imithwane	97	95	0.		95	0.88	
Beans	99.6	97	3.78	.1	97	4.34	.05
Pumpkin	98.3	95	3.07	.1	95	4.87	.05
Holsum	94	93	0.02		93	0.19	
Sunflower oil	75	77	0.08		76	0.03	
Margarine	62	71	1.7	.2	69	2.4	.2
Animal fat	55	66	2.3	.2	60	0.94	
Amarewu	93				86	6.2	.02
Usolontsi	89				88	0.1	
Home ground maize only	4	10	1.5		5	0.04	
Utyuthu	89	82	3.5	.1	79	13.3	.001
Imbikicane	68	32	28.1	.001	52	17.1	.001
Umsobo	85	80	1.6		79	4.7	.05
Irwabe	81	74	9.2	.001	71	20.5	.001
Unongotyozana	69	63	0.7		55	8.9	.01

87% indulged in regular self-induced vomiting. Most kept cattle, drank traditional beer, and used traditional medicines and wild vegetables. A quarter had at some time had pellagra. Compared with all controls CO patients consumed significantly ($p = or < 0.05$) more beans, pumpkin, *umqa wethanga, utyuthu, imbikicane, umsobo, irwabe, unongotyozana, and amarewu.* This includes all the wild vegetables. *Umqa* and three of the wild vegetables are significantly different at the .001 level. When compared with the more similar categories of inpatients, outpatients and village volunteers, differences were much fewer, being significant only for *umqa wethanga, imbikicane* and *irwabe.*

Of the social and medical factors (tables 9 and 10), 61% of CO patients smoked, less than 15% used snuff, *intshongo* or *isixhaxha.* Threequarters drank beer. 87% were regular users of self-induced vomiting, 77% of those regurgitating bile when they vomited. 84% used traditional medicines and almost a quarter had had florid pellagra at some time in the past. Significantly different indices for CO against all controls were smoking, use of snuff and Xhosa beer, keeping of cattle, being male, indulgence in self-induced vomiting, using traditional emetics for self-induced vomiting, use of other traditional medicines, and previous pellagra. Fewer categories of answer were available for comparison against inpatients, outpatients and village volunteers, however again there were less significant indices, with traditional emetics no longer showing up as significant.

The pattern from all the above comparisons is of controls with very many significantly different findings from the CO patients, suggesting different groups of the population. The group of inpatients, outpatients and village volunteers is better matched with CO patients than the wider group and this appears to indicate that the lifestyle of the CO sufferer is more typically that of the rural Transkeian than the educated person working in town. There are still a large number of significantly different indices, some likely to be spurious associations. A closely controlled study is indicated.

TABLE 9

SOCIAL AND MEDICAL FACTORS

	CO cases		Inpatients, outpatients and village volunteer controls		All controls	
	Patients	Users	Patients	Users	Patients	Users
Smoke	224	131	31	6	185	76
Intshongo or *Isixhaxha*	140	15			154	10
Snuff	100	14			154	8
Xhosa beer	248	182	81	32	235	129
Keep cattle	181	139	140	70	317	174
Keep sheep	181	80	140	51	317	142
Male gender	307	164	256	131	608	273
Self-induced vomiting	240	209	206	155	283	281
Traditional emetics	240	95	31	4	185	49
Bile regurgitation	240	161	31	16	185	119
Traditional Medicines	153	128			154	102
Ikheleba(oral pellagra)	167	38			154	16

TABLE 10

COMPARISONS OF SOCIAL AND MEDICAL FACTORS

	CO Patients	Inpatients, outpatients and village volunteer controls			All controls		
	% users	% users	X^2 against CO patients	P	% users	X^2 against CO patients	P
Smoke	61	17	19.3	.001	41	15.4	.001
Intshongo or *Isixhaxha*	11				6	1.7	.2
Snuff	14				5	13.4	.001
Xhosa beer	73	40	30.8	.001	55	22.6	.001
Keep cattle	77	50	25.0	.001	55	23.7	.001
Keep sheep	44	36	2.0	.2	45	0	
Male gender	53	51	0.3		45	5.9	.02
Self-induced vomiting	87	75	10.4	.01	99	16.5	.001
Traditional emetics	40	13	8.4	.1	26	8.0	.01
Bile regurgitation	67	52	2.9	.1	64	0.35	
Traditional Medicines	84	66	12.4	.001			
Ikheleba(oral pellagra)	23	10	8.8	.01			

8.3 Questionnaire - Case-control study

Results are tabulated in tables 11 to 19. No language difficulties were encountered.

One control refused to divulge how much livestock he owned. 15 patients and 28 controls were unable to quantify their intake of fats, otherwise all questions were answered.

97 pairs matched within the groups defined above (Table 11). Three pairs did not match as defined above, but were each within ten years of age and one year's schooling of each other, and were thus regarded as satisfactory controls.

No individual foodstuffs are significantly different between the two groups. *Amarewu* and *umqa wethanga*, both renowned for their ability to cause heartburn, are the same in each group. The use of home-produced maize meal only is as common amongst controls as amongst CO patients.The consumption of beans, and the use of the full staple diet of maize, beans and pumpkin are both higher for CO patients but outwith the 95% confidence interval (Table 12). Consumption of the wild vegetables Chenopodium album and Solanum nigrum are both significantly higher in the CO group (Table 13). Amaranthus thunbergii, Sonchus asper and Centella coriaceae are not significantly different. Amongst the social factors (Table 14) smoking is significantly higher for the CO group with a relative risk of 7.9. The use of snuff is greater, but not significantly so amongst CO patients, but the use of

traditional beer is similar in both groups. Numbers of those who keep sheep and cattle are not significantly different between the groups (but for numbers of sheep kept see below).

TABLE 11

SEX,AGE,AND EDUCATIONAL LEVEL OF SUBJECTS AND CONTROLS

	CE Patients	Controls
Male sex	61	61
Age group under 31	1	1
31 - 40	2	2
41 - 50	20	20
51 - 60	33	31
61 - 70	33	35
over 70	11	11
Education 0 - 2 years	72	70
3 or 4 years	12	14
5 or 6 years	11	11
7 or 8 years	3	3
9 or 10 years	2	2
11 or more years	0	0

IMPERFECT MATCHED PAIRS

CO Patients	100
Controls	100
Correctly matched pairs	97
Imperfectly matched pairs	3

Imperfect matches

		Age	Years of Education
1	CO patient	58	4
	Control	63	5
2	CO patient	56	4
	Control	54	5
3	CO patient	58	4
	Control	68	5

TABLE 12

FOODS

Number who consumed foodstuff regularly within preceding ten years

	CO	Control	2 X	Relative Risk	95% Confidence Interval
Beans	100	96	2.25	4	undefinable
Pumpkin	97	94	0.57	2.5	0.41 to 26.3
Umqa wethanga	93	91	0	1.25	0.41 to 4.66
Imithwane	97	96	0	1.3	0.23 to 9.11
Holsum	91	91	0	1	0.33 to 3.06
Sunflower oil	69	74	0.4	0.8	0.42 to 1.5
Margarine	62	69	0.9	0.7	0.43 to 1.37
Animal fat	52	57	0.3	0.8	0.45 to 1.48
Sour porridge	87	86	0	1.1	0.46 to 2.6
Amarewu	93	92	0	1.14	0.36 to 3.7
Usolontsi	91	86	0	1.5	0.63 to 4.07
Home ground maize only	20	22	0	1	0.32 to 10.7
Diet of maize pumpkin and beans	97	91	2.5	4	0.80 to 38.7

TABLE 13

WILD VEGETABLES

Number who consumed wild vegetable regularly during the preceeding ten years

	CO	Control	2 X	Relative Risk	95% Confidence Interval
Utyuthu (Amaranthus thunbergii)	88	80	2.04	2	0.81 to 5.40
Imbikicane (Chenopodium album)	73	57	5.1	2.1	1.10 to 4.37
Umsobo (Solanum nigrum)	89	77	5.3	2.86	1.16 to 8.00
Irwabe (Sonchus asper)	82	73	2.25	1.77	0.86 to 3.80
Unongotyozana (Centella coriaceae)	68	65	0.2	1.14	0.62 to 2.11

TABLE 14

SOCIAL FACTORS - CASE CONTROL STUDY

	CO Cases	Controls	$2 X$	Relative Risk	95% Confidence Interval
Number of Males	62	62			
Smoke	72	53	7.9	2.73	1.37 to 5.44
Traditional beer	76	71	0.52	1.4	
Intshongo/isixhaxha	10	8	0.05	1.25	
Snuff	14	5	3.37	2.4	.88 to 6.53
Chewing tobacco	7	11	0.56	0.6	
Keep cattle	32	42	2.03	0.6	
Keep sheep	59	57	0.004	1.1	

Table 15 shows only the use of Traditional Xhosa medicines as being significantly different between the groups in the category of medical factors. Self-induced vomiting with or without the use of traditional emetics, and a history of previous pellagra do not carry a risk. CO patients consumed significantly less bought fat per day than controls, and owned less sheep but a similar number of cattle (Table 16).

Logistic regression analysis was carried out for the significant factors of smoking, consumption of Solanum nigrum, Chenopodium album and traditional medicines and showed consumption of Solanum nigrum to have a relative risk of 3.62, and smoking to have a relative risk of 2.36 (both within 95% confidence limits). Chenopodium album was not significant, and the use of Xhosa medicines outwith the 95% confidence limits.(table 17) The population attributable risk for Solanum nigrum is 67% and that of smoking 36%. Crude relative risks for use of Solanum nigrum and smoking were 2.86 and 2.73 respectively.

The groups were shown to be very similar in their use of maize and pumpkin mash (*umqa wethanga*), animal fat, fermented maize drink (*amarewu*), home ground maize, pipe fluid and scrapings (*intshongo* and *isixhaxha*), and in the incidence of pellagra. Table 18 shows that consumption of tobacco or solanum nigrum was associated with a younger age by about ten years at diagnosis of CO than in those who used neither. If both were used then the age

of contracting the disease was 16 years younger than those who used neither. No such pattern is evident in the controls.

TABLE 15

MEDICAL FACTORS - CASE CONTROL STUDY

	CO	Controls	2 X	Relative Risk	95% Confidence Interval
Self-induced vomiting	91	85	1.04	1.6	0.2 to 4.2
Traditional Emetics	32	30	0	1.1	
Regurgitation of bile	63	67	0.4	0.7	
Pellagra	19	16	0.14	1.2	
Xhosa Medicines	85	72	4.36	2.3	1.1 to 4.8

TABLE 16

QUANTITATIVE COMPARISONS - CASE CONTROL STUDY

		Average for CO	Average for controls	P
Sunflower oil	(Gm/day)	9.4	12.9	0.2
Margarine	(Gm/day)	4.6	7	0.36
Holsum	(Gm/day)	10	12.7	0.36
Total bought fat intake	(Gm/day)	24	32.6	0.03
No.of cattle		3.14	3.60	0.79
No.of sheep	(total)	4.56	14.9	0.044

TABLE 17

LOGISTIC REGRESSION ANALYSIS OF STATISTICALLY SIGNIFICANT FACTORS
Adjusted odds ratios

	Relative risk	95% Confidence interval
Smoking	2.36	1.25 to 5.54
Umsobo (Solanum nigrum)	3.62	1.40 to 9.33
Imbikicane(Chenopodium album)	Not significant	
Xhosa medicines	2.01	0.92 to 4.66

TABLE 18

AGE AT ONSET OF CO

	Average age at onset of CO	Case controls
Consumers of both tobacco and Solanum nigrum	57.5 years	59.2 years
Consumers of tobacco	61.8 years	52.8 years
Consumers of Solanum nigrum	61.8 years	58.9 years
Consumers of neither	71.5 years	57.3 years

TABLE 19

POPULATION ATTRIBUTABLE RISK

	P.A.R.
Use of Solanum nigrum	67%
Smoking	36%

The two groups appear to be very well matched. The use of foods, social and medical factors appears to be the same in the two groups. This makes the findings of the logistic regression analysis almost certain to indicate close associations with CO aetiology.

8.4 Supplementary studies

Brush biopsy of the oesophagus (table 20) was successful in 95 % of volunteers. 25 Of 55 resulted in normal smears, and 21 had candida present, but normal cells. 4 had inflammation, 4 had inflammation and candida infection, and one had hyperkeratosis with candida cells present. The median pH was between 5 and 6. 27% had a pH over 6 and 11% a pH over 7. Candida may be present more often in this group because of high pH in the oesophagus. This small sample suggest that there may be a high prevalence of oesophagitis, with or without candida infection in rural Transkei.

Water pH estimation (table 21) showed a neutral pH for spring water at Kambi, but the water from the windmill borehole was alkaline, and river water extremely alkaline at pH 9.17.

TABLE 20

OESOPHAGEAL BRUSH BIOPSY RESULTS

Number of patients	58
Unsuccessful (patient could not swallow capsule)	2
Lost slide	1
Normal smears	25
Normal cells,candida present	21
Candida infection present	4
Inflammation present	4
Hyperkeratosis, candida cells present	1

pH OF BRUSH FLUID

pH 4-5	Number of subjects	9
pH 5-6	Number of subjects	26
pH 6-7	Number of subjects	15
pH 7-8	Number of subjects	6

TABLE 21

WATER pH ESTIMATIONS

pH of Kambi clinic windmill water	8.16
ph of Kambi spring water	6.38
pH of Kambi river water	9.17

CHAPTER 9

DISCUSSION

The controls were matched for age, sex, and educational level. It could possibly have been helpful to match for district of origin. This would have been a much more complex matching without any definite advantage to be gained. The three attributes matched cannot be causal per se, and are therefore appropriate for the choice of control, all having been shown in the past to have a relationship with the incidence of CO.

The only clearly established association in endemic areas, which is not solely demographic and which may be causal in Transkei is tobacco usage.

The only clearly established association in endemic areas which is demographic and which may be causal of CO in Transkei is use of maize as a staple.

Low rainfall and soil characteristics cannot be directly causal since they do not have a direct effect on the internal physiology of the human. Trace element deficiency is a common accompaniment of a maize based diet. Low potential soil and low rainfall are also closely associated with maize farming. Fungal invasion of the oesophagus is more common in high prevalence CO areas, but a clear link with CO has not been demonstrated.

This paper has confirmed the association of tobacco and CO in Transkei.

While it is possible that tobacco, particularly home-cured tobacco, acts by promoting an alkaline lower oesophageal environment which damages the mucosa, it is much more likely that its principal action is as a carcinogen.

All people in this study were maize consumers - both the healthy and CO sufferers. The use of maize as a staple causes deficiencies typified by the high incidence of pellagra in the community, and the multiple deficiencies of micronutrients proven to accompany its use may predispose the organs of the body to carcinogenesis. If deficiencies are the reason for susceptibility to carcinogenesis, then why the oesophagus should be specifically so predisposed amongst the organs of the body is not clear.

Beans and pumpkin are used in every rural household, so that their refusal by one person almost certainly indicates a strong personal dislike rather than any lifestyle difference. If this is true, then the finding of a difference in the use of these staples at the 7% level may indicate an association which was not significant because of the small numbers in our study. All CO patients used maize and beans, and 97% of patients used maize, beans and pumpkin, identifying the at-risk group as being users of this staple diet.

The remarkable prevalence of heartburn demonstrated in the community could be due to the nature of the foods which

precipitate the heartburn. Other explanations are that there does exist a high prevalence of oesophagitis which causes 'normal' reflux to become symptomatic, or that the use of maize as a staple has an effect on the lower oesophageal sphincter tone. The high frequency of reporting fluid in the mouth during heartburn suggests reflux above 'normal' in quantity. Aspirin may have its effect by inhibition of prostaglandin E2-mediated relaxation of the cardiac sphincter. The high pH values obtained from the oesophageal biopsy sponges suggest a decreased gastric acid secretion amongst the people in the village tested, which again may indicate an excessive prostaglandin activity. These findings support a hypothesis of maize exerting its effect not by microdeficiencies directly predisposing to local carcinogenesis, but by chronic damage to the oesophagus caused by repeated reflux of gastric or duodenal juices. Against this is the grouping of the majority of the cases in the 'rural poor' group which is more subject to nutritional deficiencies but not necessarily more to the use of maize.

While no clearly premalignant changes were seen on histology of the sponge biopsies of the oesophagus, the significant incidence of candida infestation and infection is of note since fungal mycotoxins have been suspected of involvement in carcinogenesis.

The remarkably high pH of water used for domestic purposes in Kambi lend support to the suggestion of Warwick and Harington (4) that CO may be caused by a chronic alkaline lower oesophageal

milieu, but water tests in high risk areas in Butterworth/Centane (29) did not reveal any consistent pattern of pH.

It would not be reasonable to postulate tobacco as the sole causal agent in Transkei because the incidence in Transkei is far greater than in other societies which use tobacco at least as much. Furthermore there is a very high incidence of CO even among non-smokers, far in excess of expected rates. Nevertheless an acceptable theory of causation for Transkei must account for the high relative risk of tobacco usage.

From the results of this study, another major significant association is added, that of consumption of Solanum nigrum, with a P.A R. of 67%, nearly twice that of smoking.

One may then postulate the following aeiology for CO:-

1) Predisposition to carcinogenesis,
   plus carcinogens, including tobacco

   or

2) Co-carcinogens synergistic with tobacco and with other carcinogens present in the environment

   or

3) One unidentified powerful carcinogen with which tobacco may act as a co-carcinogen.

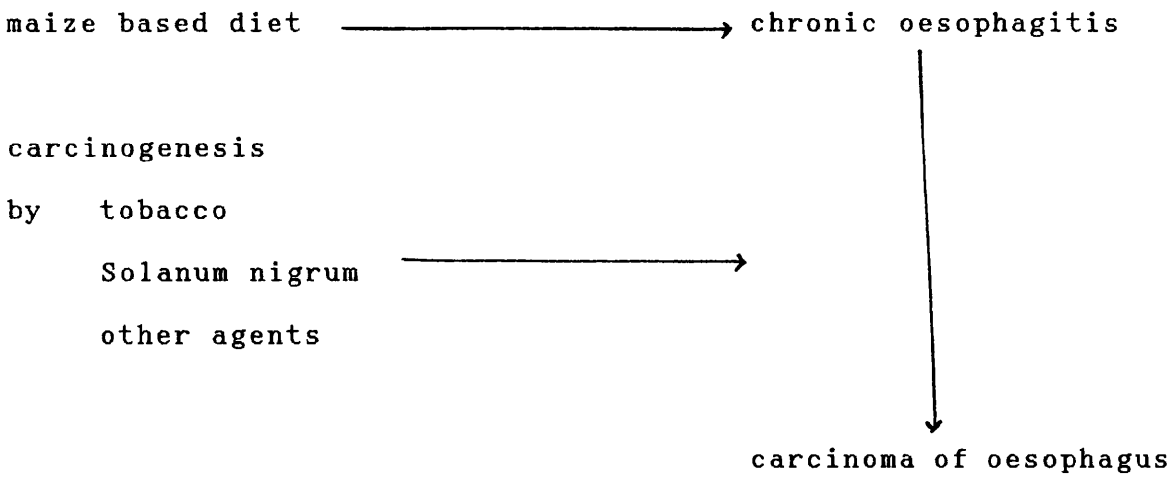
Considering the experimental evidence of Purchase et al, and the significant relative risk attached to the consumption of Solanum nigrum, then this plant may be considered as a carcinogen, or as

a co-carcinogen with some other powerful, unidentified carcinogen.

Published data does not exist for the prevalence of oesophagitis in Transkei, but it is probable that it is high, taking into account the very high prevalence in a nearby area which shares much of the same diet, and almost the same incidence of CO - Soweto.(11,52) In other endemic areas, oesophagitis has been shown to be widely prevalent, and a precursor of CO, and it is reasonable to postulate a similar situation in Transkei. This line of reasoning favours the concept of predisposition of the oesophagus in the chronically inflamed state to carcinogenesis by tobacco, Solanum nigrum, and other carcinogen(s), these acting singly, together, or synergistically.

Much effort and thought has gone in over the past few decades to the search for a single potent carcinogen which is active in Transkei. Failure to find such an agent may be due to lack of adequate investigation, and theory 3 may be true, but it is much more likely that no such agent exists, and that the theory should be abandoned.

The theory which best fits the information available is as follows:-



Transkei has changed its basic diet over the last fifty years to be much more dependent on maize, and less so on sorghum and millet. There is less meat and less milk available, causing a drift towards a much higher consumption of wild vegetables. This is consistent with the rise in incidence seen in the last half-century.

Local and regional variations in incidence can be explained by differences in availability and quality of Solanum nigrum, which in turn will vary with the soil type, angle of incidence of sunlight, and presence of cows and sheep. Poor soil, yielding less staples and vegetables, may cause a greater dependence on use of wild vegetables.

It is interesting that the number of people who kept sheep was the same in patients and controls, but the latter had a

significantly greater number of sheep. This may indicate a greater move to westernisation among control subjects, but it is almost certain that the sheep alter the type, quality, or quantity of wild vegetation available for human consumption.

The significant association with the taking of traditional medicines, some of which are powerful emetics or purges, raises the possibilities, as with Solanum nigrum, of either irritative or carcinogenic actions. There is much secrecy about these potions, and no details of their composition could be found.

The protective influence of increased fat may be due to:-

Improved intake of vitamins and minerals

Better general diet which is associated with higher fat intake

A direct protective effect on the oesophagus - nature uncertain. Marine oil based margarines are known to contain unnatural polyunsaturated fatty acids which may obstruct or compete with utilisation of natural polyunsaturated fatty acids(73) and may in turn interfere with prostaglandin synthesis involved in causing reflux.

If the above theory of causation is correct then it is important to know whether there are other major carcinogens active in Transkei. Table 28 suggests that tobacco and Solanum nigrum may, between them, account for the vast majority of CO cases, in that those in the study who contracted the disease without being

consumers of either tobacco or Solanum nigrum were both few and late. This also suggests that they may act singly, or synergistically on a predisposed oesophagus, and that the small remainder may be caused by carcinogens which are used less often, or are of much lower potency.

The negative findings of the study are of considerable note. Alcohol has again been shown not to have a significant association in an endemic area, 24% of CO patients being non-drinkers.

There was no difference between patients and control subjects for those whose maize meal was home produced and those who were suppplied from the local shop. This casts doubt on the 'cancer garden' concept, which would require that most of the food intake came from the patients' garden.

CHAPTER 10

CONCLUSIONS

Significant associations have been shown between CO in Transkei and consumption of

a) tobacco

b) Solanum nigrum

The 'assaults' of traditional beer, pellagra, self-induced vomiting, and heartburn have not shown a significant association with CO.

A theory of causation has been presented which fits satisfactorily with other published data and with the results of this study, namely predisposition of the oesophagus by use of maize as a staple to carcinogenesis by tobacco and/or Solanum nigrum, or other carcinogens.

To confirm the findings of this study, an incidence study should be carried out which would include investigation of the quality and quantity of wild vegetables and traditional medicines used, with the prediction of again finding a higher incidence of CO amongst users of Solanum Nigrum.

A case-control study could also be instigated, with sufficient numbers to prove or disprove the possible association of CO with the full traditional diet of maize, beans and pumpkin.

Further studies are required into the composition and possible modes of action of Solanum nigrum, and its composition on different soil types in Transkei.

Enough data has been presented here to justify further investigation into the nature of the association between the staple diet and oesophagitis.

There is sufficient evidence for the initiation of a campaign to reduce consuption of Solanum nigrum and tobacco in Transkei. It would be less expensive, and also potentially of more value to have an intervention study in one or two districts only, with control areas well separated geographically from intervention areas.

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APPENDIX 1

Samples of statistical analyses

Group comparisons

	Smokers
CO patients	134 of 221
Total controls	76 of 185

	Smoke		
	Yes	No	
Cancer	134 (a)	87 (b)	221
Control	76 (c)	109 (d)	185
	210	196	406

$$X^2 = \frac{(134 \times 196 - 76 \times 87) \times 406}{(134+76)(87+109)(76+109)(134+87)}$$

$$= 15.4$$

Case control study

McNemar's test

		Controls	
		smoke	don't smoke
CO patients	smoke	42	30
	don't smoke	11	16

$$X^2 = \frac{((30-11)-1)^2}{30+11} = 7.9$$

$$\text{Relative risk} = \frac{30}{11} = 2.7$$

95% Confidence Interval

$$(l,u) = \log_e RR + 1.96\sqrt{\frac{1}{b} + \frac{1}{c}}$$

$$C.I. = e^{l}, e^{u}$$

$$l = 1.003 + 1.96\sqrt{\frac{1}{30} + \frac{1}{11}}$$

$$= 1.6939$$

$$\text{Upper C.I.} = e^{1.6939}$$

$$= 5.44$$

$$u = 1.003 - 1.96\sqrt{\frac{1}{30} + \frac{1}{11}}$$

$$= 0.312$$

$$\text{Lower C.I.} = e^{.312}$$

$$= 1.366$$

APPENDIX 2

Calculation of Population Attributable Risk

$$PAR = \frac{p(r-1)}{p(r-1) + 1} \times 100 \quad \%$$

Where p = proportion of population exposed, and r = odds ratio.

Proportion of population exposed was taken from the figure for all controls in the unmatched series.

APPENDIX 3

Sample questionnaire sheet

Carcinoma of the oesophagus questionnaire

Patient Number

Beans										
Umqa wethanga										
Pumpkin										
Imithwane										
Male/female										
Holsum										
Gram/day										
Sunflower oil										
Gram/day										
Margarine										
Gram/day										
Animal fat										
Education										
Self-induced vomiting										
Once per										
Xhosa medicines										
Other										
Bile regurgitation										
Buy or grind maize										
Cattle - number										
Sheep - number										
Utyuthu										
Imbikicane										
Umsobo										
Irwabe										
Xhosa beer										
Smoke										
Age										
Amarewu										
Usolontsi										
Intshongo/isixhaxha										
Xhosa medicines										
Chew tobacco										
Snuff										
Pellagra										
Unongotyozana										

APPENDIX 4

A CASE-CONTROL STUDY OF DIET AND SOCIAL FACTORS IN CANCER OF THE OESOPHAGUS IN TRANSKEI

Alastair M. Sammon

CANCER 69:860-865,1992

This paper is included in a pocket inside the back binder

APPENDIX 5

Copies of appprovals for research

APPENDIX 6

Extent of collaboration with other workers

The extent and purposes of self-induced vomiting in Transkei were brought to the author's attention by Professors David Mugwanya and Kwami Eshun-Wilson of the University of Transkei.

Professor Wilson supervised the examination of the brush biopsy cytology smears.

Rob Young, a research assistant,undertook questioning of one group of hospital staff and community controls, as requested by the author.

All the remaining work and interpretation were carried out by the author.