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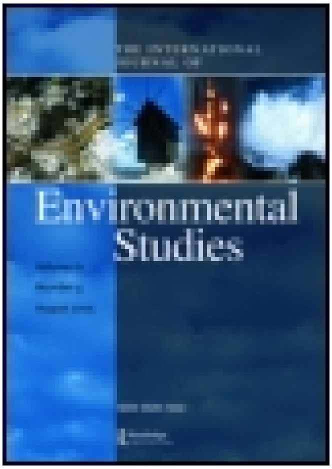

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MEDICAL GEOCHEMISTRY OF NITRATES AND HUMAN CANCER IN SRI LANKA

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A study of the incidence of various types of human cancer in relation to nitrate concentrations in Sri Lanka revealed a significant positive correlation for stomach, small intestine, oesophagus and liver cancers, as well as total malignant cancer incidence and benign tumours. The Northern and Western Provinces of Sri Lanka showed the highest total cancer rate. The abundance of nitrates in the groundwater of certain provinces of Sri Lanka has been attributed to use of nitrogeneous fertilizers, human and animal wastes in densely populated regions and nitrates produced as result of atmospheric electric discharges and precipitation. Even though the correlation of nitrate abundance and cancer rates is significant, nitrate cannot necessarily be considered as being causative in view of the biological intricacies involved in the complicated mechanism of cancer inducement.

KEY WORDS: Cancer, human, nitrates, geochemistry, Sri Lanka.

INTRODUCTION

Recent evidence indicates that cancer, after heart disease, is the leading killer in many industralized societies and is largely due to environmental factors. A large number of causative factors which have been isolated are in one way or another environmental. Research into the causes of cancer is now based on the hypothesis that all cancers are environmentally caused until the contrary is proved.[1] The relationship between cancer and the environment has been known since 1775, when Pott[2] observed a correlation between scrotal skin cancer and heavy exposure to soot among chimney sweepers.[3] Since then, many environmental pollutants have been shown to produce cancer in various parts of the body. Whereas the carcinogenicity of many laboratory synthesized chemical compounds have been the subject of intensive study, the effect of the natural environment on cancer has often been somewhat neglected. Epidemiological studies have indicated the importance of the quality of the potable waters, the chemistry of the soils and the plants growing on them in geographically separated areas, quality of the air we breathe, etc. in human cancer. In view of the fact that correlations by themselves rarely justify mechanistic interferences and are well recognized as weak instruments in the study of causality,[4] evidence from epidemiology cannot often be used to draw conclusions on biological mechanisms. Yet, epidemiology has its own virtues and if used intelligently, bearing in mind the intricacies involved in biological mechanisms, valuable preliminary information may be obtained. The very fact that certain areas of the world have anomalous incidences of certain diseases, cancer being one of them, clearly indicates some special features that are unique to that environment. The very high incidence of

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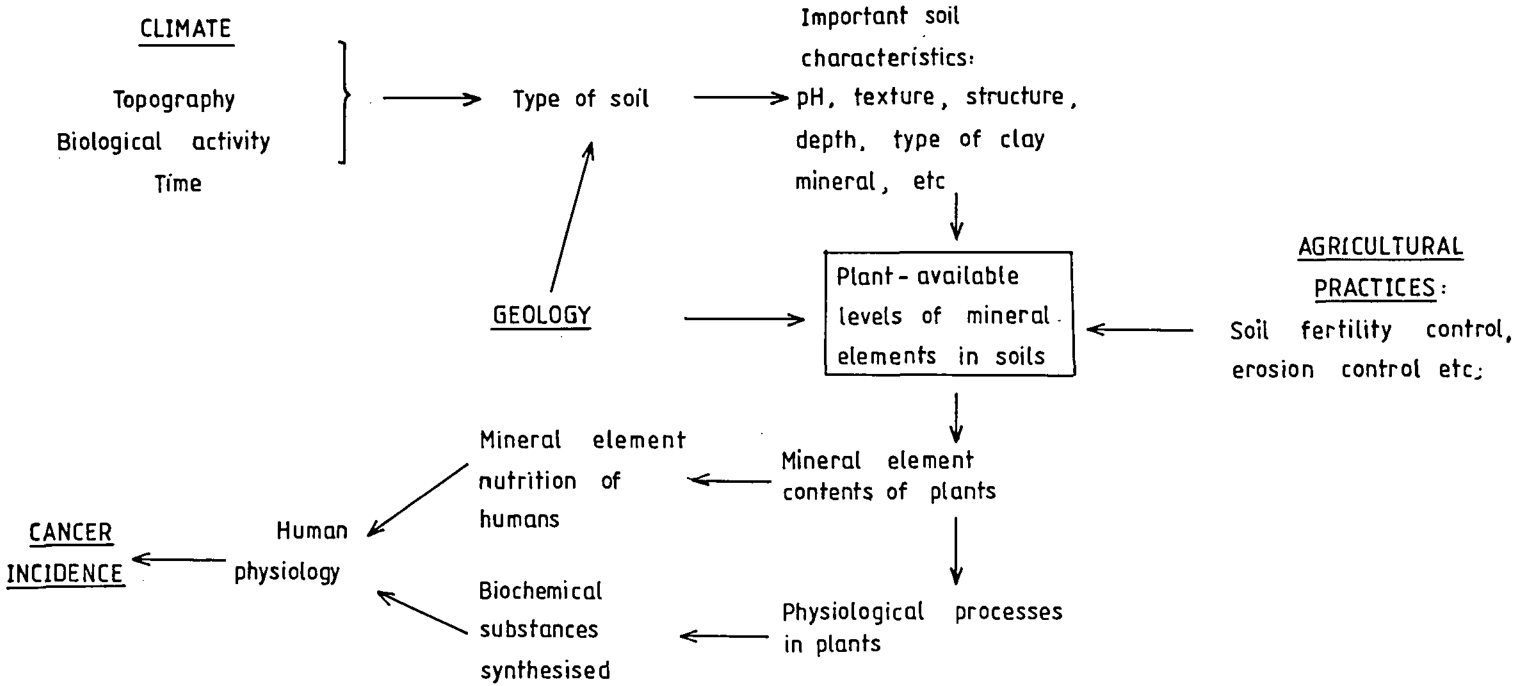

Figure 1 Relationship between environmental factors and cancer incidence.

oesophageal cancer in parts of Transkei[5] provides a good example. Oesophageal cancer which is considered as a progressive and normally fatal disease occurs in parts of the Transkei and Ciskei, Iran, Soviet Central Asia and Northern China.[6] In these regions, it is a more important cause of death than coronary heart disease in Europe and the United States. During the last 35 years, substantial evidence has accumulated a relationship between geology, soils and climate and the occurrence of widespread oesophageal cancer. As pointed out by Laker,[7] such an integration of environmental factors leads to distinct soil properties, and it has proved possible to identify certain soil types as common to areas of high incidence. Figure 1 illustrates the relationship between environmental factors and cancer incidence.

ROLE OF NITRATES, NITRITES AND N-NITROSO COMPOUNDS IN THE INCIDENCE OF CANCER

In spite of the usefulness of nitrate and other nitrogeneous compounds as essential elements in the life processes of plants and animals, nitrate is potentially hazardous when present in drinking water at sufficiently high concentrations. Although nitrate in itself is relatively non-toxic, it can be reduced bacterially to nitrite in the intestines of new-born infants and may result in the disease methaemoglobinemia. Infant mortality from methaemoglobinemia is rare where nitrate-nitrogen concentrations in drinking water are less than 10 mg/l, but its incidence increases with increasing concentrations.[8] Nitrite can also react with other substances, such as amines, in the stomach or lungs to form N-nitrosoamines, which have been found to induce tumours in laboratory animals. Although human tumours are not directly linked to these compounds, exposure to the compounds may pose a risk of human cancer.[9]

An N-nitroso compound can be formed whenever there is an interaction between a secondary nitrogen group and nitrite. The secondary nitrogen group may be in an amine (giving an N-nitrosamide), an amide (giving an N-nitrosamide), an alkyl urea (giving an N-nitrosourea) or a peptide bond. Tertiary and quaternary amines will often react with nitrite with the elimination of alkyl groups to give N-nitroso-compounds.

N-nitroso compounds can be formed endogeneously in humans. They have been identified *in vivo* in the normal stomach[10,11] in the achlorhydric stomach,[12] in the infected urinary bladder,[13–15] in saliva[16] and in faeces.[17] As noted by Fraser *et al.*,[18] the conditions in the achlorhydric stomach (high nitrite concentration, large numbers of bacteria and adequate amounts of amine or amide) are ideal for the formation *in vivo* of N-nitroso compounds, and their formation has been demonstrated in the gastric juice of such patients.[12] Jones *et al.*[19] have shown that there is a histological progression from normal gastric mucosa through intestinal metaplasia and dysplasia to carcinoma and a concomitant increase in the mean nitrite concentration in the gastric juice.

Figures 2A and 2B illustrate the sources, movement, reaction of nitrogen in soils, groundwater and heterotrophic conversions and Figure 2C illustrates the sources of nitrite and nitrosatable amines and some sites of formation of carcinogenic nitrosamines. The simplified process of cancer induction can be thought of as initiation, promotion and progression.[20] Initiation consists of an irreversible lesion in the DNA that can lead to a cancer if further attack on the DNA occurs. Promotion is a biochemical process that can accelerate the progression of an initiated cell to cancer. If, however, a promoter attacks a "normal" (uninitiated) cell, the damage is thought to be reversible. What governs these steps and the eventual progression to a tumour

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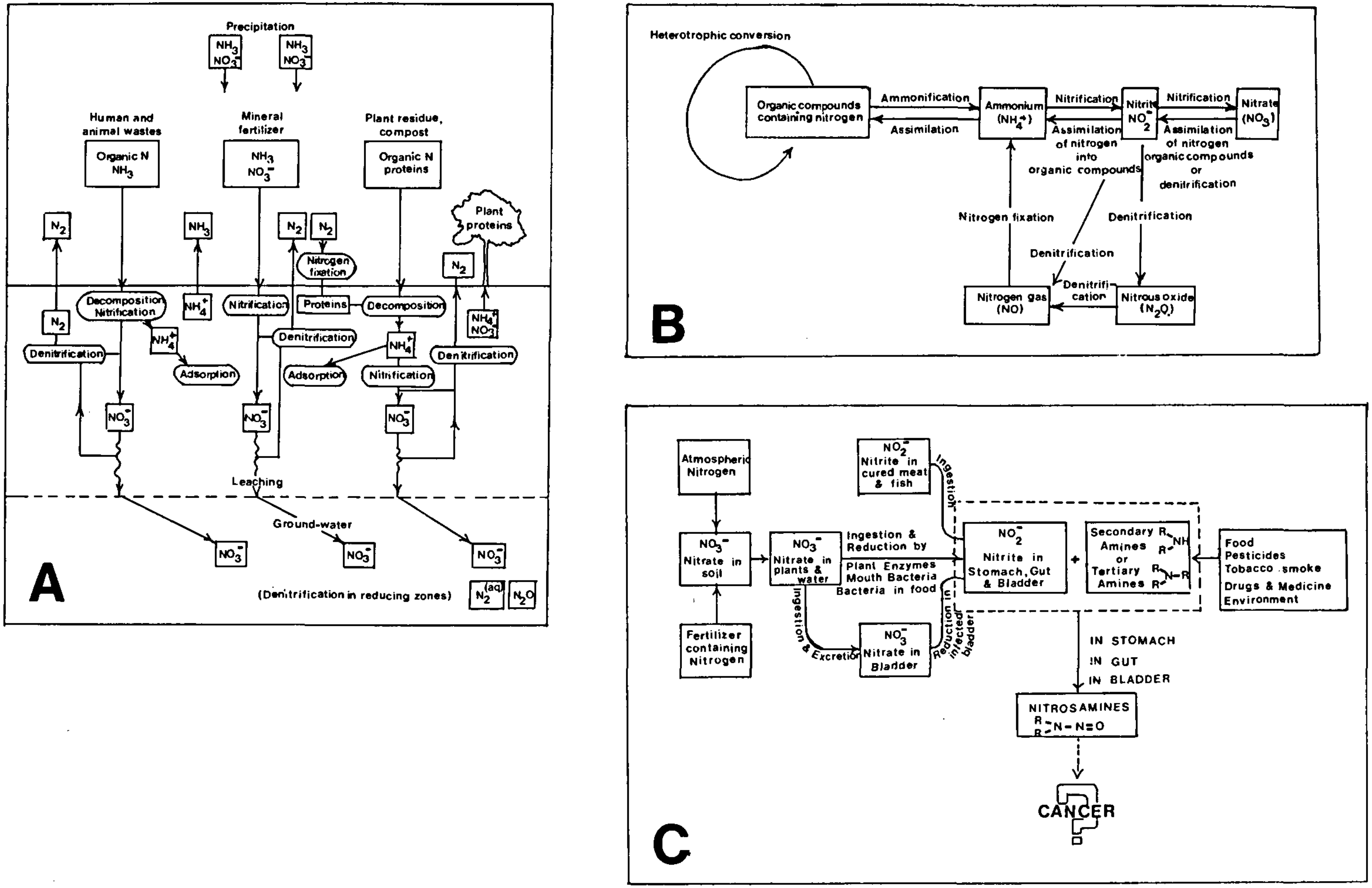

Figure 2A Sources, movement and reaction of nitrogen in soils and groundwater. **2B** Simplified biological nitrogen cycle showing some environmentally important reactions. Source: National Research Council.[9] **2C** Sources of nitrite and nitrosatable amines and some sites of formation of carcinogenic nitrosamines. Source: Fishbein.[21]

or cancer is not clear. The occurrence of the nitrosamines, whether as direct emissions of N-nitroso compounds or via localized release of large amounts of precursor compounds (eg. secondary amines, nitrogen oxides, nitrate, nitrites), effluent discharges from sewage treatment plants or runoff from feedlots or croplands treated with amine pesticides, ammonium fertilizers or nitrogenous organic materials or accidental products in food processing and use, tobacco smoke or via the body burden contributed by *in vivo* nitrosation reactions, has resulted in extensive investigations dealing with potential sources, mechanism of *in vitro* and *in vivo* formation, body burdens, as well human health risk assessment.[21]

This paper deals with the incidence of certain types of human cancer in Sri Lanka in relation to the geochemical distribution of nitrates. It was felt that a study of this nature would provide useful information to the epidemiologist in view of the following reasons.

1. A very high percentage of the population of Sri Lanka literally live close to the soil, depending on the natural environment for their food, shelter and most necessities. The geochemical status of the soil and groundwater therefore governs the general health of the community to a great extent.

2. The bulk of Sri Lanka's health problems is deeply rooted in the environment. It is estimated that only 15–20% of the 16 million population have access to safe water. The fact that very few people use piped water, the rest depending on small unprotected wells, presents the epidemiologist with an almost ideal situation in which to study the relationship of the natural environment and incidence of diseases.

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DISTRIBUTION OF NITRATES IN THE GROUNDWATER OF SRI LANKA

Figure 3A illustrates the distribution of nitrates in the groundwater of Sri Lanka and 3B, the maximum nitrate levels observed in the districts of Sri Lanka. In general, the average nitrate levels are below the danger level of 50 mg/l specified by the World Health Organization. In Jaffna, however, these levels are exceeded.[22] The nitrate concentrations appear to show a marked increase in areas of high population density, extensive fertilizer usage and in areas of the wet zone where atmospheric electric discharges are frequent. The type of farming practice and fertilizer use is an important facet in any research study concerning the regional distribution of nitrates. Oakes *et al.*[23] state that during the period 1975–1980, research in UK has produced a large and possibly unique body of data on the distribution of solutes derived from agricultural land in the major British aquifers. Unsaturated zone pore water quality profiles demonstrated a clear relationship between the concentration of certain solutes, especially nitrates and farming practice. High concentration of nitrates, often in excess of WHO recommended limits, are characteristic of arable farming, whilst low concentrations are generally found beneath permanent grass woodland.

In Sri Lanka, highly nitrogeneous fertilizers such as urea are used in abundance, and farming practice and agriculture influence the abundance of nitrates in the water. As shown in Figure 3A, the Jaffna peninsula has the highest nitrate contents in the groundwater of Sri Lanka. Geologically, the Jaffna Peninsula is underlain by highly fractured and karstified limestone. There is a thin soil mantle of the red/yellow latosol type, and in the southern part of the peninsula are 10–20 m of fine sand which lie over the limestone formation. According to Gunasekaram,[24] 80% of the groundwater of Jaffna peninsula is being extracted from the limestone aquifer and utilized for drinking, domestic, agricultural and industrial purposes, the rest being

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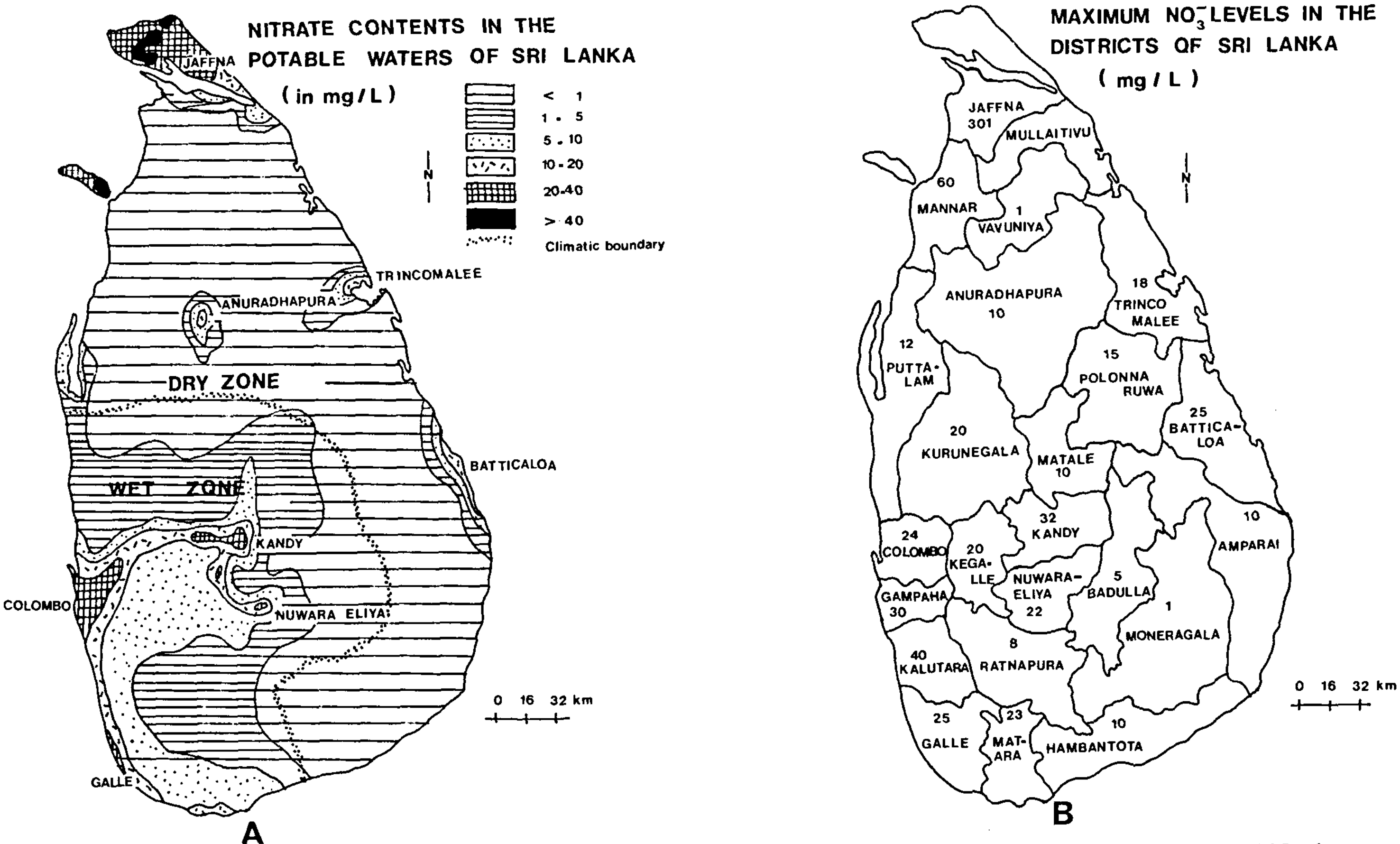

Figure 3A Distribution of nitrates in the potable waters of Sri Lanka. **3B** The maximum nitrate levels recorded in each district of Sri Lanka.

obtained from the sand aquifer. The water table in the Jaffna peninsula is very shallow on account of the surface aquifiers.

Gunasekaram[24] in his detailed study of the groundwater contamination and case studies in the Jaffna peninsula found that 80% of the water wells yielded water of unacceptable bacteriological quality contaminated with faecal coliform. Among the major factors responsible for the poor water quality in the Jaffna peninsula area are:

1. Discharge of human excreta in the form of soakage pit/septic tank effluents directly underground within densely populated urban areas. In some cases due to limitations of available land, the distance between soakage pit and water well is only 6 m.

2. Abundant use of agricultural fertilizers, mainly urea which contains 46% N. Excessive use of urea on crops such as chillies and onions is prevalent. In addition, cattle manure is commonly used.

3. The easy solubility of urea enables it to reach the very shallow groundwater table and under normal conditions about 75% of the nitrates applied reach the groundwater.

The fact that Jaffna has nitrate levels exceeding the WHO limits by 100–150% is thus mainly due to the abundant nitrogeneous waste matter in the form of human excreta and synthetic and animal fertilizer reaching the shallow groundwater table aided by the surface limestone aquifer. The geological conditions are therefore ideal for the excessive accumulation of nitrates. The poor sanitary conditions are mainly caused by improper planning of soakage pit and latrines and this aids in the serious contamination of the groundwater by nitrates.

The dangers associated with drinking water wells being placed very close to the septic tanks have been highlighted in many case studies from other countries. Hutton and Lewis[25] in their study of nitrate pollution of groundwater in Botswana found nitrate levels as high as 603 mg/l in several water supplies providing drinking water to many villages. A lithium chloride tracer injected into a pit latrine was detected in the supply borehole 25 m away after only 235 mins. The steep hydraulic gradient between the latrine and the borehole had obviously induced the rapid movement of nitrates occurring in open fissures.

The situation in Jaffna can even be worse bearing in mind the very short distance of 6 m from the pit latrine to the water well as observed in some cases. Brooks and Cech[26] in their study on the nitrates and bacterial distribution in rural domestic water supplies in Houston County, east Texas found that wells with the highest observed concentration of nitrates were those located in close proximity to the septic tanks, animal feedlots and barnyards. Keller and Smith[27] studied the groundwater contamination by dissolved nitrate in the USA. More than 5000 water samples in Missouri, mainly from water-table wells, ranged from 0–300 ppm nitrogen from nitrate. The main contaminating source, both in distribution and concentration, was nitrogeneous waste matter at sites of animal habitation. Excessive application of nitrogen fertilizers in certain soils also contributed to the nitrate concentration. The problem becomes acute when the nitrates that accumulate below the groundwater table are not metabolized into innocuous compounds by the inability of the microorganisms to do so.

INCIDENCE OF HUMAN CANCER IN SRI LANKA

Panabokke[28] in a five year study on the geographical pathology of malignant tumours in Sri Lanka presented data on investigations on 24,029 biopsy specimens. Accord-

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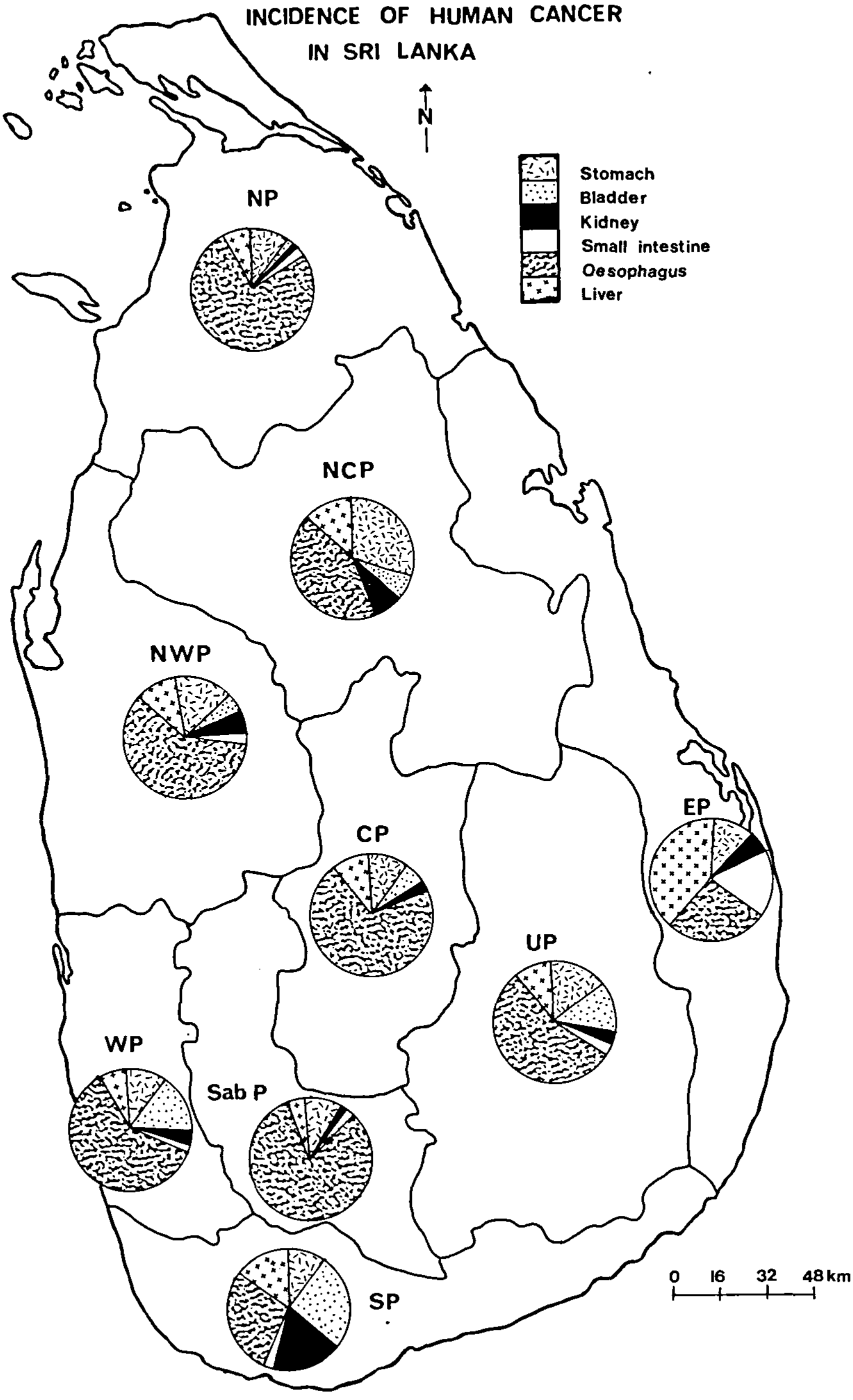

Figure 4 The incidence of different types of human cancer in the provinces of Sri Lanka. NP – Northern Province; NCP – North Central Province; NWP – Northwestern Province; CP – Central Province; EP – Eastern Province; WP – Western Province; Sab. P – Sabaragamuwa Province; SP – Southern Province, UP – Uva Province.

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ingly, the Northern province showed the highest incidence (184 per 100,000 population) of malignant tumours in biopsy material among the nine provinces of Sri Lanka. In Southern province, the incidence was low (37 per 100,000 population). The commonest sites from which malignant tumours arose were oesophagus (13.9 per 100,000 population), buccal region (12.2) and breast (10.58).

Figure 4 and Table I illustrate the incidence of the different types of cancer in the nine provinces of Sri Lanka. The highest incidence of oesophageal, stomach, liver and small intestine cancer was observed in the Northern province of Sri Lanka, whereas the incidence of bladder and kidney cancer appeared to be low in the same province. The incidence of oesophageal cancer, however, is high in Sri Lanka and is worthy of serious note. An interesting feature of the epidemiology of oesophageal cancer is the accumulation of substantial evidence indicating a relationship between geology, soils and climate with the incidence of oesophageal cancer, particularly in circumscribed areas.[5–7] Epidemiologists have established peculiar uneven distribution patterns for the incidence of oesophageal cancer in less developed rural areas where the average incidence of the disease is high[5], eg. Transkei and the Caspian area of Iran. Laker *et al.*[5] established an integrated model, the main theme of which was the relationship of the cancer incidence rate to the level of some mineral element in humans or in the crops which form their staple diet. An abnormal level of such an element (deficiency or toxicity) is expected to cause physiological abnormalities in the human or the staple food crop, which lead to the production of carcinogenic substances. The mineral element level in the staple food depends on the level of availability of that element in the soil which, in turn, is dependent upon various soil factors, especially pH, determined by environmental factors.

Table I Incidence of human cancer in Sri Lanka (per 10^5 population).

Province	Benign tumours	Malignant tumours	Bladder	Kidney	Small intestine	Stomach	Oesophagus	Liver
Northern	92	184	0.90	0.30	1.30	5.80	37.4	3.3
Northwestern	61	63	0.40	0.40	0.30	1.20	4.6	0.78
Northcentral	35	24	0.20	0.20	0.00	0.90	1.26	0.36
Eastern	24	39	0.00	0.30	0.70	0.50	1.20	1.6
Central	114	84	1.00	0.50	0.10	2.20	13.5	1.9
Western	184	156	5.80	1.70	0.70	4.50	24.1	2.6
Sabaragamuwa	40	57	0.07	0.10	0.30	1.60	12.8	0.6
Uva	46	58	2.40	0.50	0.60	3.00	10.6	1.8
Southern	52	37	1.20	0.80	0.12	0.50	1.30	0.7

Table II Table showing the average values NO_3^-, NO_2^-, Cl^- and TDS in the nine provinces of Sri Lanka.

Province	NO_3^- (ppm)	NO_2^- (ppb)	Cl^- (ppm)	TDS† (ppm)
Northern	12.6	37	1263	1991
Northwestern	5.11	76	481	637
Northcentral	2.54	41	641	856
Eastern	4.98	94	740	816
Central	5.61	148	42	195
Western	9.02	189	58	201
Sabaragamuwa	4.15	212	12	128
Uva	1.75	210	47	346
Southern	5.25	49	321	410

† TDS: Total Dissolved Solids

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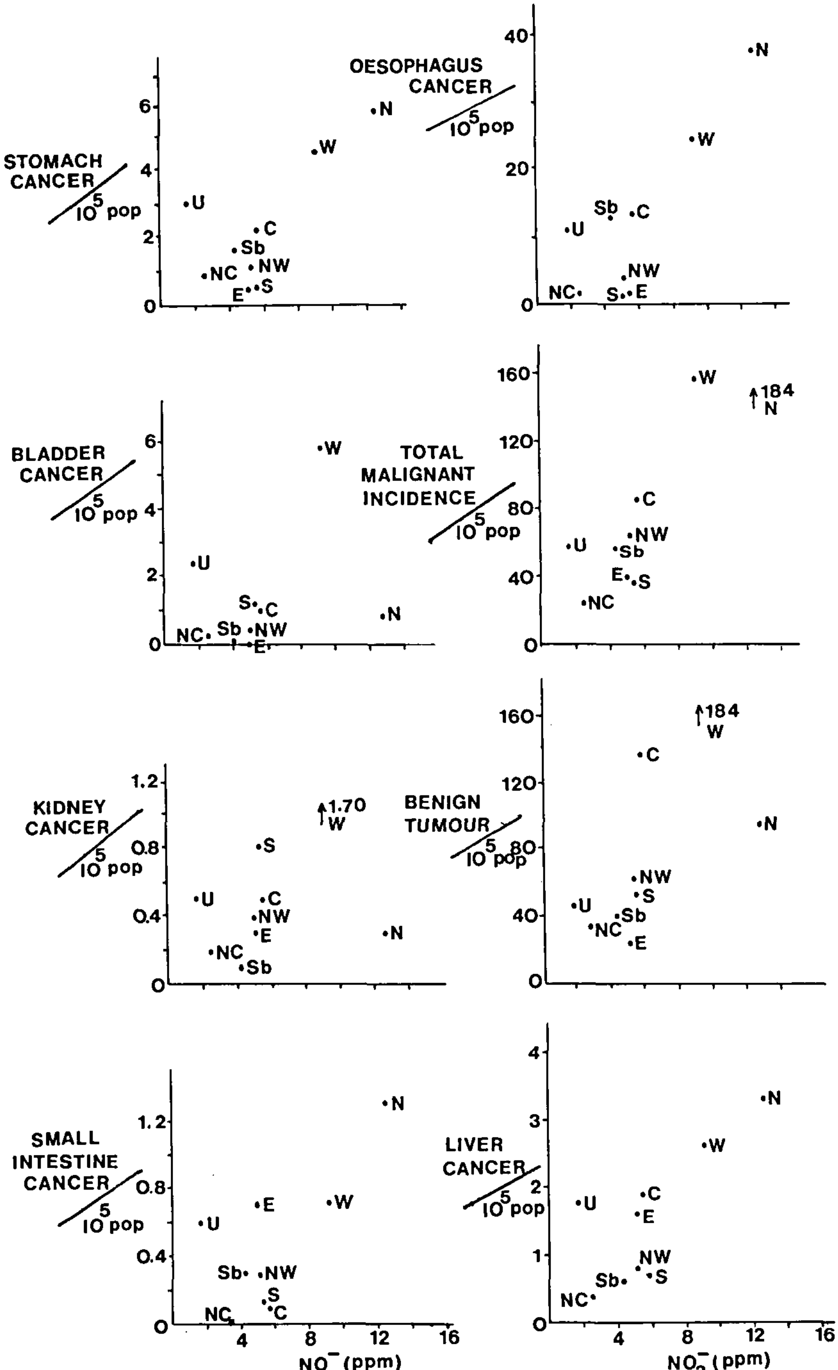

Figure 5 Correlation of nitrate contents of groundwater with the incidence of human cancer in Sri Lanka. The names of the Provinces are the same as for Figure 4.

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Table II shows the average chemical analysis of well water samples of the nine provinces of Sri Lanka. As illustrated in Figure 5, significant correlations are observed for certain types of cancer with the average nitrate concentrations. It is worthy of note that the nitrite concentrations of the water did not show any significant relationship with cancer incidence indicating the predominance of an *in vivo* reaction involving nitrite as against an *in vitro* reaction.

The main source of dietary nitrate are vegetables and drinking water,[29–31] with cured meat products also contributing in Western countries. There is considerable variation between countries both in mean daily intake and in the relative contributions from different sources. As noted by Fraser *et al.*,[18] in the United States, for example, the estimated mean daily intake of nitrate is about 100 mg, 80% of which comes from vegetables and less than ten percent from drinking water. Nitrate intake is much higher in Japan, the estimated mean daily intake being about 300 mg, mostly derived from vegetables and very little from fresh water. In Britain the mean daily intake of nitrate is 60 to 80 mg with vegetables contributing more than 50% of the total. The contribution from drinking water was less than 25% of the daily nitrate intake. In Sri Lanka it is very likely that vegetables contribute the greater part of the daily nitrate intake with a significant percentage from drinking water, particularly in the Northern and Western provinces. As noted by Prescott and Flexer,[32] the minimum possible rate of any particular cancer in the world is defined as an irreducible background rate, higher rates possibly being environmentally caused.

It is necessary at this juncture to emphasize the fact that even though there appears to be a significant correlation between the incidence of certain human cancers in Sri Lanka with the overall nitrate content in the groundwater, causative effects need not be attributed to the nitrate contents. Tannenbaum and Correa[4] commenting on the paper by Forman *et al.*[33] on the nitrates, nitrites and gastric cancer in Great Britain noted that in the case of gastric cancer, the prevailing aetiologic hypothesis calls for a complex interaction of irritants, nutritional deficiencies, mucosal atrophy, bacterial overgrowth, *in vivo* nitrosation and sequential mutations which is so intricate that it represents a special challenge to the epidemiologist. A given dose of nitrate may be harmless to a normal subject but noxious to a patient with atrophic gastritis, especially if the diet contains precursors of N-nitroso mutagens and carcinogens. The study of the geographical distribution of cancer in relation to nitrate concentrations in the geochemical environment must therefore necessarily be viewed in the light of the limitations of epidemiological research in understanding cancer. Forman *et al.*[34] make the point that if nitrate exposure is a *crucial* factor in the development of cancer, epidemiologists can legitimately ask the question of whether populations that experience cancer have a high nitrate exposure, or alternatively whether populations exposed to a lot of nitrate experience cancer.

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