Most of the developments reported here result from efforts at Bell Laboratories to improve its information apparatus for research and development tasks. The seven systems described are taken from over 30 computer-aided technical information services and functions currently in operation and indicate the wide applicability and utility of computers in information systems. Throughout the account there is ample evidence of the hospitality one computer system offers to another. Modules of existing systems may be used in new systems. Another common feature is the multiple information purposes served by each system. Figure 1 is an attempt to graphically display these relationships.

There has been only minimum reliance on several recently offered national and international computer-based information services. The value of these new services as a substitute for in-house information systems is still unclear. Adjustment of ongoing in-house systems to exploit the national systems will be explored carefully during the next few years and efforts to achieve compatible intermixing will, of course, be made. There is now an inadequate coordination of standards, formats, and other factors among the new computer-aided services being offered (*3*). This incompatibility, plus the tendency of national systems to cover only specific disciplines, poses problems for organizations that want to use these large-scale data files. By the end of the decade, there may be some light at the end of this particular tunnel. Despite these problems, the computer will continue to strengthen its kinship with information systems and may prove to be the most important development for dissemination of information since the time of Johann Gutenberg.

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Esophageal Cancer in the Caspian Littoral of Iran: Initial Studies

Detailed studies of geographical pathology are opening new vistas in cancer epidemiology.

Janez Kmet and Ezattollah Mahboubi

This article deals with a peculiar pattern of distribution of esophageal cancer in the ecologically diverse regions of the Caspian littoral of Iran. However, the deciphering of the complex extrinsic and intrinsic factors that are most likely responsible will require highly sophisticated research techniques and are not dealt with here.

Whereas large parts of the world have changed from the simple soil-man relationship to very complicated systems, there are, nevertheless, still vast areas in which entire population groups depend heavily on the food grown or found locally. It is here that we should seek the clues to understanding those basic conditions that lead to well-established disease patterns in the indigenous population. If a given cancer site in the body in a given area of the world could be linked with environmental characteristics, new ways of understanding this particular cancer site might open.

The esophagus is a case in point; the distribution of the incidence of esophageal cancer seems to be particularly promising for pointing out those areas of the world in which special studies should be carried out. This site has many advantages. First, it has a peculiar pattern of incidence, with 100-fold differences between the highest and the lowest rates, and even 200-fold differences in men from the ages of 35 to 64 (*1*). Second, the incidence may vary markedly in areas that are only a short distance apart (*2*). Third, the male-to-female ratio varies greatly throughout the world (it is, for example, 20 to 1 in France and near equality in Liverpool), and a high incidence is not invariably associated with a high male-to-female ratio (*1*). Fourth, in some areas of the world the incidence seems to have risen greatly very recently (*2*).

Background Information

From the available hearsay information on the incidence of esophageal cancer in Iran, it appears that the disease is common in most parts of the country, particularly Khorasan, Iranian Azerbaijan, and the Gorgan plain, to the east of the Caspian coast. The probable high incidence in Iran is not isolated, but represents part of a vast area of high incidence that extends from the Middle East to China and includes, besides Iran, Afghanistan, and Soviet central Asia, parts of Siberia, Mongolia, and northern and western China (Figs. 1 to 3).

That the frequency of the disease is

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high in Soviet central Asia, Kazakhstan, Uzbekistan, and Turkmenia (*3*), as well as in northern China (*4*), is relatively well documented. Information from Mongolia is less precise (*5*). During a visit to Afghanistan in 1966, one of us (J.K.) observed several major hospitals there and was impressed by the relatively high frequency with which esophageal cancer occurred in northern Afghanistan. In the vast Siberian areas, esophageal cancer seems to be a common disease in several ethnic groups of Mongolian origin, such as the Buriato-Mongolians, or the Yakutians (*6*).

The ecologically varied areas of the Caspian littoral in Iran attracted our attention as the most likely place to look for sharp differences in the incidence of esophageal cancer. We were particularly interested to find such differences in neighboring areas of the littoral. During the first exploratory visit to the region in November 1966, we had little difficulty in confirming the high incidence of esophageal cancer in the eastern portions of the province of Mazandaran (the Gonbad and Gorgan districts), particularly in the desert and semidesert areas settled by Turkomans. When proceeding westward, we got the "clinical" impression that the prevalence of esophageal cancer is still relatively high in the central parts of the Caspian coast (in the districts adjoining Sari and Babol), but low in the west, particularly in the province of Gilan. The hypothetical borderline between the high- and the low-incidence areas seemed to be on the coast—approximately on the Teheran meridian, where the coastal strip becomes very narrow. Our impression was that the distribution of esophageal cancer closely reflected the broad climatic divisions of the area.

Low incidence seemed to be confined to the western part of the Caspian region, often referred to as the Caspian rain belt, which has a very special climatic regime. Being located under the northern slopes of the Elburz Mountains and near large expanses of water, which cause a depression "storm track" to be formed, the region has a very high rainfall. Humidity is high throughout the year, with a slight peak in winter. A hot, but not torrid, summer, a winter milder than in the adjacent areas of Iran, and abundant rainfall well distributed throughout the year are the climatic characteristics of the Caspian rain belt—the hothouse of Iran—with its tea estates and paddy fields giving a somewhat subtropical tang to the area.

Preliminary inquiries about alcohol intake in Iran, particularly in the Caspian littoral, pointed against its having an etiological role there.

Environmental Approach

As a first step in our environmental studies, we organized an ad hoc cancer registry covering the eastern part of the Caspian littoral (the province of Mazandaran) in June 1968; the registry was extended in June 1969 to cover the western part of the Caspian coast (the province of Gilan). In brief, technicians have made regular visits at intervals of 4 to 6 weeks to the 500 or so doctors in the area to collect forms that give details of all cancer patients diagnosed since the previous visit. A pathologist has been stationed in the study area to improve the standard of diagnosis and to stimulate interest in the registration scheme by providing a service to the local doctors.

It was then planned to plot the incidence patterns on the characteristic environmental patterns. We hoped in this way to eliminate the irrelevant elements and to concentrate on those factors which showed a real association and would fit into our biological knowledge of esophageal cancer. The main reason for this approach was that there were hardly any indications of what the underlying causes might be, and consequently it was difficult to formulate questions that might be used in a case-control study to identify differences among risk groups. It seemed unlikely that comparisons of dietary and smoking habits, alcoholic intake, and social customs between individuals with and without esophageal cancer would be the best way to obtain new information on the cause of the disease. A better approach seemed to be to search for working hypotheses by making broad-based comparisons of the environment and way of life of those who lived in areas where esophageal cancer was either a common or a rare disease. A particular advantage of such an approach is that it permits a very large number of factors to be examined simultaneously. It was planned that the present study should include features of the physical environment, such as climate and soil; biotic characteristics, such as the flora and fauna, and disease patterns in man, animals, and plants; and cultural characteristics, such as the social and economic structure, diet, habits, and customs.

In the Turkoman area we expected to find an ecosystem typical of those in other high-incidence areas of central Asia, whereas we expected a substantially different ecological pattern in the Caspian rain belt.

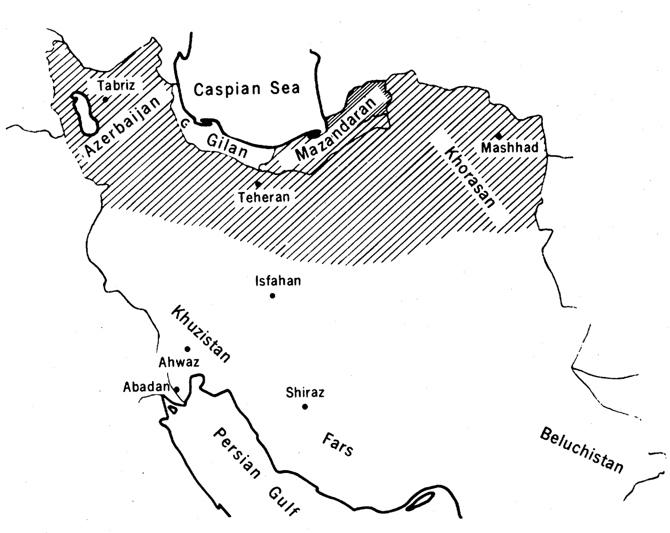

Fig. 1 (left). Esophageal cancer belt in Asia.

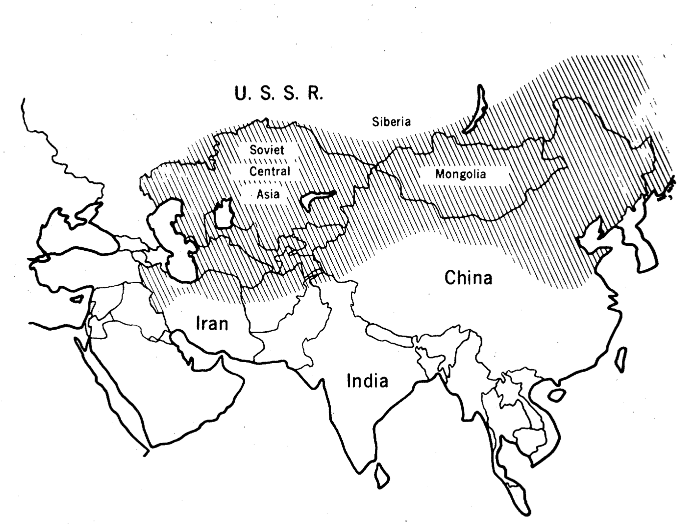

Fig. 2 (right). Iran and its location in the esophageal cancer belt in Asia.

Initial Observations

"For Iran, as for the Middle East as a whole, the Koranic: 'We made from water every living thing' is as true today as ever" (*7*).

Figure 2 shows Iran relative to the Asian "esophageal cancer belt." However, the only relatively well-documented evidence of incidence is based on the Caspian cancer registry for the provinces of Mazandaran and Gilan. There is hospital evidence, as well as pathological evidence, in Tabriz and Mashhad and in the Cancer Institute in Teheran that this cancer occurs with high frequency in northern Khorasan and western Azerbaijan. There is evidence of high incidence in the district of Ardebil in eastern Azerbaijan (based on the experience of radiologists) and in the district of Shiraz (based on the records of the Shiraz Medical School's pathology laboratory) (*8*).

Table 1 gives the age-standardized incidence rates of esophageal cancer in the Caspian littoral, by district, based on the population figures of the 1966 census of Iran (Table 2). For those districts with the highest incidence (Gonbad and Gorgan), figures are given by subdistrict, in order to define more precisely the differences in the frequency of cancer between the various ecological zones. One of the most outstanding features is the much higher incidence in females in areas of highest risk. The level of medical care and the method of registration are such that the figures shown in Table 1 must represent minimum rates of incidence, but there is no evidence that regional variations in the level of medical care within the study area are responsible for the pattern of regional variations observed in the frequency of cancer of the esophagus. Indeed, there are fewer doctors per capita in the areas of highest frequency.

Figure 3 summarizes visually the data set out in Table 1 for the incidence of esophageal cancer in northern Iran. It is evident that the figures, based on the cancer registry, confirm our initial impressions. An area of very high incidence exists in the easternmost districts of Mazandaran (in Gorgan and particularly in Gonbad), and it has become clear that the highest incidence—one of the highest ever recorded—occurs in the northern part of both districts, on the borders of Soviet Turkmenia.

A moderate incidence occurs in the southern part of the Gorgan and Gonbad districts, in the piedmont region of the eastern Elburz mountain range. A still lower incidence was reported from central Mazandaran, extending from the Behshahr district to the Amol district, and relatively low figures were reported from the two westernmost districts of Mazandaran, Nowshahr and Shahsavar. Low incidence, but still not very low relative to the rest of the world, extends from there throughout the province of Gilan. The evidence for this finding is based on the material of the cancer registry for 2 years of registration in Mazandaran (22 June 1968 to 21 June 1970) and for 1 year in Gilan (22 June 1969 to 21 June 1970).

Figure 4 shows the mean annual precipitation on the Caspian littoral. When compared with the incidence of esophageal cancer, it is obvious that there is a negative correlation between the two—the areas of lowest precipitation being the areas of highest incidence.

Figure 5 shows the details of the types of soil in Mazandaran and the general soil patterns in Gilan. The analyses were performed at the Soil Institute in Teheran, with the help of experts from the United Nations Food and Agriculture Organization (FAO), in the course of a systematic "land evaluation project" (*9*). The coincidence of saline soils with the highest prevalence of cancer is almost complete in the eastern part of Mazandaran; in central Mazandaran, several patches of marshy saline

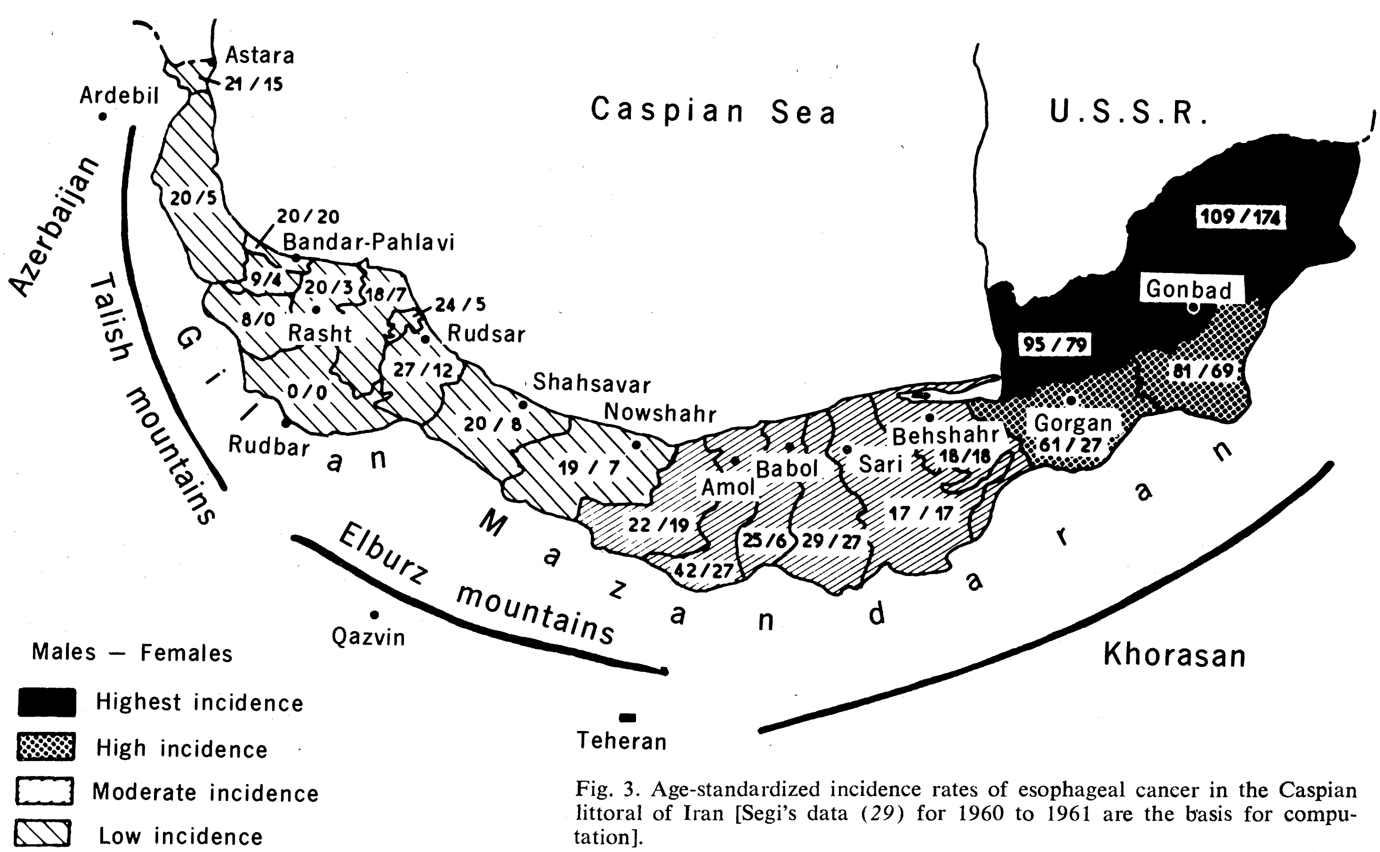

Fig. 3. Age-standardized incidence rates of esophageal cancer in the Caspian littoral of Iran [Segi's data (*29*) for 1960 to 1961 are the basis for computation].

lands are present, and the incidence of esophageal cancer is moderate. The heavily leached soils in the western corner of the province are on the border of the low-incidence area. Unfortunately, detailed soil analyses for Gilan were not available during the preparation of this article, but the general information shows nonsaline, heavily leached soils covering the Caspian rain belt (*10*).

Figure 6 shows the natural vegetation of the Caspian littoral. Wherever the natural vegetation has not been replaced by cultivation, the areas of highest incidence are characterized by vegetation of the halophylic, *Artemisia*, and *Astragalus* associations (*11*). These associations cover most of the surface of Iran and comprise a great number of species, among them *Artemisia herba alba* and several *Astragalus* species (*12*).

Areas of moderate incidence are covered mostly by remnants of *Quercus*, *Carpinetum*, and *Fagetum hyrcanum* associations. Querco-Buxetum forests (*13*) are found in the western parts of Mazandaran, beginning close to the borderline, where the incidence of esophageal cancer diminishes, and are widespread throughout the lowlands from Gilan to Astara, on the borders of Soviet Azerbaijan. Querco-Buxetum forests represent the typical forest of the Caspian plain; they exist in a maritime climate, growing on sandy soil and blown by winds saturated with moisture from the Caspian Sea. It is a dense, two-level forest, the crown level consisting of tall trees. This association is rather like a humid, subtropical forest; many of its species, and even genera, have their close relations in the Indian tropical forests (*12*).

In the upper part of Fig. 6, the main features of the agricultural patterns of the Caspian provinces have been plotted relative to the natural distribution of vegetation. The changing patterns of agricultural practices parallel the declining incidence of esophageal cancer, from the high-incidence areas in the east, to the low-incidence areas in the west. Somewhat schematically, the following outstanding features can be outlined: very high incidence—dry and irrigated (wheat, barley, and cotton); high incidence—mostly dry farming (wheat, barley, and cotton); moderate incidence—dry farming (wheat, cotton, melons, vegetables, citrus and other fruits, rice, and beans); low incidence—wet paddy, citrus fruits, other fruits, and tea.

Table 1. Age-standardized incidence rates of esophageal cancer (per 100,000 per annum) in the Caspian littoral of Iran. [Standardized to the world population, see Segi's data (*29*) for 1960 to 1961.]

District	Males		Females		Age-standardized rates (male-female)
	No.	Rate	No.	Rate	
*Mazandaran province**					
Northern Gonbad	83	108.8	106	174.1	0.6
Northern Gorgan	44	94.5	36	79.2	1.2
Southern Gonbad	61	81.1	45	68.5	1.2
Southern Gorgan	51	61.0	18	26.7	2.3
Behshahr	11	17.9	12	18.1	
Sari	20	17.3	18	16.9	
Shahi	30	28.8	29	27.3	
Babol	33	25.0 } 25.4	9	5.7 } 18.0	1.4
Amol	36	41.6	28	27.4	
Nur	6	22.4	4	19.2	
Nowshahr	12	18.5 } 19.4	3	7.3 } 7.8	2.5
Shahsavar	14	20.2	6	8.0	
Gilan province†					
Rudsar	11	26.7	3	12.4	
Langarud	4	23.9	1	5.1	
Lahijan	11	17.9	6	7.3	
Rasht	17	20.3	4	2.7	
Bandar-Pahlavi	3	19.6 } 17.2	4	20.3 } 5.5	3.1
Sowma-Eshara	2	8.6	1	3.8	
Fowman	3	7.9	0	0.0	
Rudbar	0	0.0	0	0.0	
Tavalesh	6	19.7	2	5.4	
Astara	2	21.0	1	14.7	

* July 1968 to June 1970. † July 1969 to June 1970.

Special research will be necessary to study in detail the environmental and population characteristics of the Caspian littoral. There is good detailed information based on the last census taken in the autumn of 1966.

Discussion

"Due to the specific physiographic conditions of Iran . . . to a perpetual and effective interference of five important and ruling factors of atmosphere, soil, physiography, living creatures and time, microecological conditions have developed in every part of the country, thus creating a very interesting and valuable area of activity for today's research men as well as those of tomorrow" (*14*).

There are very favorable conditions for epidemiological research in cancer in Iran because of the existence of such well-supported, specialized institutions as the Cancer Institute and the Institute of Public Health Research, Teheran, with its field research stations in several provinces. General medical services are well developed and are supplemented by

Table 2. Age structure of the population in the Caspian littoral of Iran.

District	Sex	Age groups				Total
		0–19	20–39	40–59	60+	
Mazandaran province						
Northern Gonbad	M	40,290	21,852	10,768	3,469	76,379
	F	38,147	19,980	8,073	3,064	69,264
Northern Gorgan	M	24,814	10,886	5,917	2,743	44,360
	F	25,233	10,499	4,835	2,437	43,004
Southern Gonbad	M	41,420	17,854	10,082	3,362	72,718
	F	38,191	17,735	7,585	2,983	66,494
Southern Gorgan	M	64,272	30,006	16,298	5,768	116,344
	F	60,045	27,507	13,002	5,416	105,970
Behshahr, Sari, Shahi, Babol, Amol, Nur	M	290,978	121,789	68,482	26,808	508,057
	F	285,493	122,980	59,488	31,881	499,842
Nowshahr, Shahsavar	M	69,157	30,002	17,136	6,129	122,474
	F	66,512	29,979	13,910	6,340	116,741
Gilan province						
Entire province	M	364,087	158,605	89,544	37,105	649,341
	F	358,286	160,933	90,885	40,797	650,901

the Army Health Corps in the remote parts of the country. On the one hand, the population in many rural parts of the country is still exposed to the traditional natural environment, and the disease patterns could be considered the product of the local environment. On the other hand, a quickly expanding economy is able to provide sophisticated research institutions and detailed statistical surveys. Such a combination is very rare, since developing countries are usually not able to provide good statistics, and life in rural areas in developed countries has practically lost its "natural" characteristics.

One would not suspect much alcohol intake in a Moslem country such as Iran, and all the available evidence so far has confirmed this conjecture. Preliminary evidence from a case-control study has revealed only 10 alcohol drinkers among 100 patients with esophageal cancer, and the same proportion among 160 control subjects. In view of evidence from other parts of the world (*15*), it is particularly pertinent to stress that so far we have not been able to find any evidence of illegal alcohol production in the areas with the highest incidence of cancer. There is some illegal distilling of arak on the Iranian plateau, particularly in Qazvin, which is one of the wine-making centers of Iran; however, there is no wine made in Mazandaran. Preliminary information indicates that relatively more alcohol is consumed in the low-incidence area of Gilan, which, because it is linked with Russia by the Caspian Sea, was influenced in the past by the West.

Our findings in Iran indicate a relationship between esophageal cancer and climate, soils, vegetation, and agriculture. The correlation between saline types of soils and a high incidence of esophageal cancer is particularly striking; in areas with the highest incidence, large patches of solonchak and solonetz soils are found (solonchak soils contain large quantities of soluble salts and little organic matter; solonetz soils are the product of the partial leaching and alkalization of solonchak soils. Solonchak soils are usually formed on alluvial sediments brought by water; in many cases, these soils had originally contained uniform amounts of salt, having been part of a lake or a sea at one time).

Solonchak soils are, in general, unsuitable for agricultural use, although measures can be employed to reclaim them. Such land is principally used as range for livestock. In some areas in Iran, notably around Lake Rezaiyeh, in Azerbaijan, sheep and goats that normally graze on soils of less salinity are brought to graze on salty vegetation in solonchak areas about once a week. It might be that the local shepherds have thus ensured a balanced diet (including trace elements) for their sheep and goats (*10*).

It is interesting to note the differences in the availability of micronutrients (trace elements) to plants in different types of soils. Truog (*16*) has analyzed the influence of soil *p*H on the availability of plant nutrients. The availabilty to plants of iron, manganese, boron, copper, and zinc is seriously inhibited in alkaline soils. While this holds true for plants, it might also have repercussions on the balance of trace elements in human beings.

Among the almost unexplored roles of trace elements in cancer etiology, the role that zinc plays deserves particular attention in Iran. Prasad *et al.* (*17*) have found a deficiency of zinc to be the main etiological factor, in southern Iran and Egypt, in a syndrome of dwarfism, hypogonadism, hepatosplenomegaly, and iron-deficiency anemias. The factors most likely to be responsible for the iron and zinc deficiencies observed in these patients were poor dietary intake of these elements and blood loss through parasites, since red blood cells contain large quantities of iron and zinc. In addition, patients lost these elements through sweating, and their diet was found to consist mainly of bread and beans, with very meager quantities of animal proteins. Prasad *et al.* (*17*) suggested that a high intake

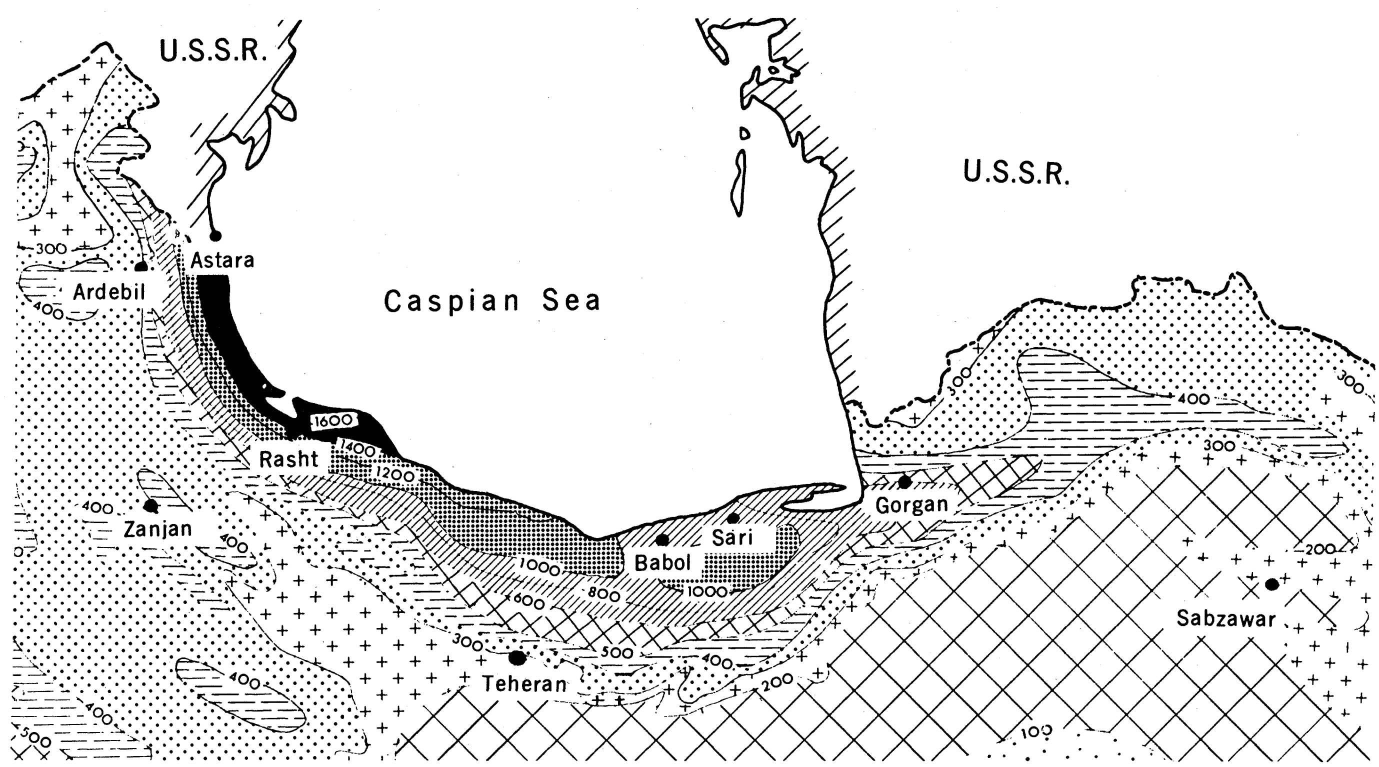

Fig. 4. Mean annual precipitation in the Caspian littoral of Iran (measured in millimeters), from 1951 to 1960 (*30*).

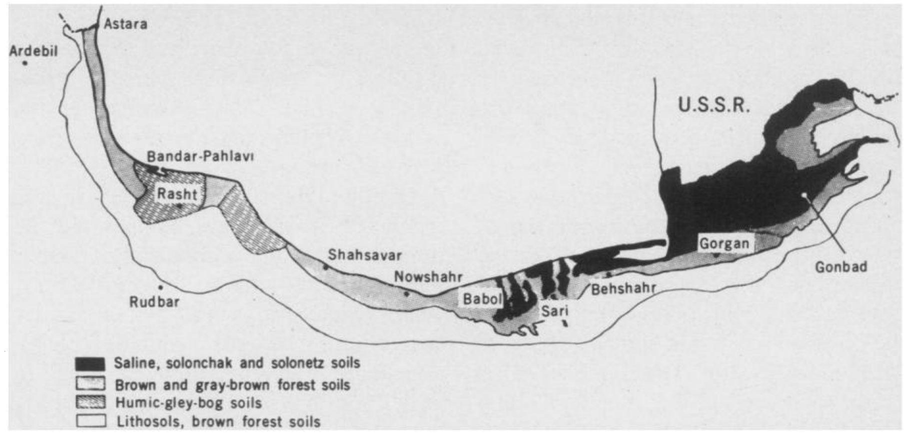

Fig. 5. Types of soil in the Caspian littoral of Iran. Brown and gray-brown forest soils: soils of deciduous forests in temperate climate; humic-gray-bog soils: continually or intermittently moist soils; Lithosols: thin stony soils, shallow over bedrock.

of cereal might decrease the amount of available zinc, since heavy metals form insoluble complexes with phosphates and phytates. The patients improved very much after zinc therapy.

The general conditions of life in the high-incidence areas in the Turkoman semidesert seem to be similar to those in southern Iran.

Zinc is an essential trace element for the proper functioning of the human body, and many essential enzymes have now been identified as zinc proteins. Vitamin A–resistant night blindness and alcoholic cirrhosis were found to be linked with primary or secondary zinc deficiency (*18*). Pories *et al.* (*19*) have treated men and experimental animals with zinc to promote the healing of wounds, thus indicating the role of zinc in stimulating protein synthesis.

As far as the possible role of intrinsic characteristics in the etiology of esophageal cancer is concerned, Plummer-Vinson syndrome is the only relatively well-established factor, although even this is far from being completely understood (*20*). It is not clear that glossitis, angular stomatitis, and dysphagia, as the main features of Plummer-Vinson syndrome, are the direct results of iron deficiency. They seem to decrease in some communities where iron deficiency remains prevalent, and may therefore be caused by associated deficiencies, chiefly of the vitamin B complex (*21*). Although sideropenic dysphagia has been associated with cancer of the upper esophagus in Sweden, it may be that similar deficiencies play a role in the etiology of cancer of the middle and lower esophagus (the most common sites of esophageal cancer in Iran). It is interesting to note that epidemiological studies of the etiological role of Plummer-Vinson syndrome were not continued after alcohol and tobacco had been found to be implicated in the etiology of esophageal cancer.

A higher incidence of esophageal cancer in women than in men in the areas of highest risk (in northern Gonbad) points to the possibility of a dietary deficiency in this economically deprived, semidesert region. One would expect that women would be much worse off than men in a region where the conditions of life are difficult, where both agriculture and homemaking are traditionally women's work, and where it is still the custom for women to be more or less permanently pregnant and to breastfeed numerous children during the major part of their reproductive life.

In trying to find common denominators between the situation in Iran and that in the Transkei, where a recent "epidemic" of esophageal cancer has been described (*22*), it is possible to speculate on some similarities between the traditionally poor soil in the high-incidence area of Iran and the very recent depletion and impoverishment of soils in the Transkei. Burrell *et al.* (*22*) comment on the drastic impoverishment of the soil in the Transkei, where in 1933, after 2 years of the worst droughts in recorded history, there were winds of gale force, followed by torrential rains. This devastating sequence of events took a heavy toll of the land, especially those exposed areas that had been cleared for cultivation.

Further variations on the same theme are given by Rose (*23*), who mentions that the Bantu in the Transkei, who were originally cattle herders, have turned to agriculture through necessity. The game is scarce and the cattle of poor quality, thus meat and milk are rarely consumed and proteins are supplemented by edible weeds. People are closely bound to the soil, which, in spite of some more sophisticated goods from the trading stores, still supplies their basic needs.

The pattern of iron-deficiency anemias in the Transkei is not clear. There are many reasons to believe these deficiencies to be a common feature, particularly in women. Oettlé (*24*), on the contrary, believes that the rarity of hypopharyngeal and upper esophageal cancer suggests that iron deficiency is not a factor in the etiology of esophageal cancer in the South African Bantu and that the habit of keeping drinks in iron containers results in a high intake of iron. Hemosiderosis was often seen

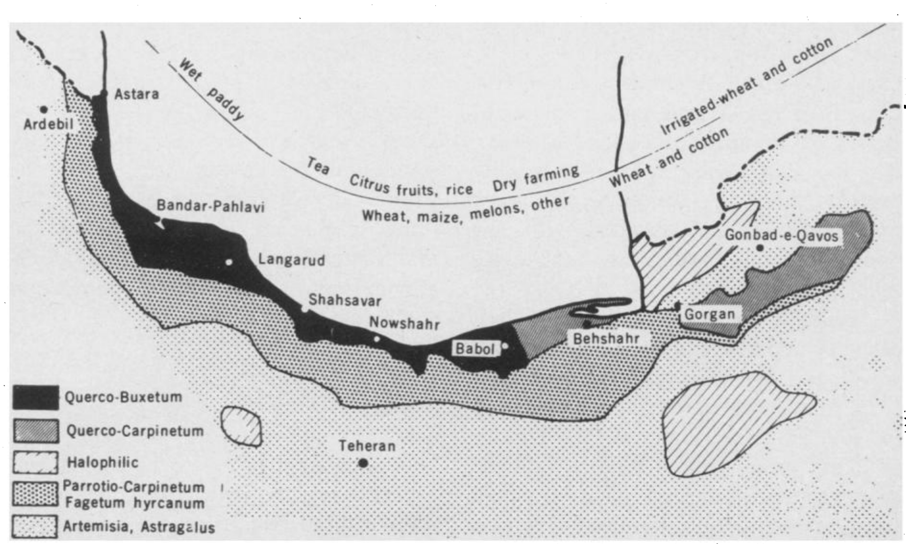

Fig. 6. Natural vegetation and main agricultural practices in the Caspian littoral of Iran.

in Bantu women, and anemia in pregnancy was rare (*24*). It is, however, difficult to rule out iron deficiency in the Transkei, since in some areas tin-plated containers are used, and even lead plating of kerosene containers has been introduced (*25*). As to the site-specific effect within the esophagus of the potential carcinogenic stimuli, Oettlé pointed out that, in many cases, sections taken from sites remote from the carcinoma have shown areas of carcinoma in situ. The evidence of a systemic effect on the esophagus suggests that, because of the specific conditions of life, the entire mucosa is damaged and that additional factors determine exactly where the cancer will develop first.

In a survey of dietary habits in Mazandaran, organized by the FAO and the Institute of Food and Nutrition, Teheran (*26*), the worst conditions of food intake were observed in two villages in the Gonbad district (which has a high incidence of esophageal cancer). The diet there was found to be adequate in calories, total proteins, and, to some extent, in calcium from cereals, but greatly deficient in animal proteins, vitamin A, riboflavin, and vitamin C; in addition, the quality of the dietary proteins was low. Villages in the nearby, lower-risk districts of Gorgan had a substantially better diet.

Other areas of the world that have a high incidence of esophageal cancer also have much the same nutritional status that the villages of the Iranian high-risk areas have. One such situation was described by Martinez (*27*) in Puerto Rico, an area with a moderate incidence of esophageal cancer. The majority of the 400 esophageal cancer patients in his study were grouped in occupations with the lowest salaries, and their diets were deficient in fruits, vegetables, milk, eggs, and meat. A similar pattern had been found in several earlier studies of rural communities in Puerto Rico, where a diet deficient in good quality proteins, calories, vitamin A, riboflavin, and calcium was associated with low concentrations of vitamin A and carotene in serum.

Although we have found the highest rates of incidence among Turkomans, we do not feel that the disease is confined to any one particular ethnic group in central Asia. Among the Turkic-speaking groups, the Khirghiz, in their mountainous homeland of Tien Shan, seem to be exempt. However, there is a high incidence among Uzbeks, Kara-Kalpaks, Kazakhs, and Uighurs. It is interesting to note that Persian-speaking Tadjiks, in the Pamirs, seem to represent a relatively low-incidence group, whereas Iranians on the plateau are a high-risk group.

Our finding sharp contrasts in the incidence in Iran does not seem to be unique in distribution patterns of esophageal cancer—at least not in central Asia, where in a few places similar correlations between climatic conditions and disease distribution seem to exist. The highest incidence of esophageal cancer in Soviet central Asia was observed in Ghuryev, Kazakhstan, which is located on the northeastern shore of the Caspian Sea. The crude incidence there was estimated to exceed 150 cases per 100,000 population (*28*). Since a much lower incidence was observed both in the region of the Ural Mountains and in the central Russian plains bordering the Ghuryev district, we can suppose that there are pronounced borderlines similar to the one identified in the southern coast of Iran. There are other areas in Kazakhstan where similar borderlines seem to exist, notably between the very high-incidence areas on the shores of Lake Balkhash and the lower-incidence areas in the mountainous regions of Tien Shan, around Alma-Ata (*28*). In all of these areas, a lower incidence of esophageal cancer seems to be connected with high precipitation rates.

One would expect that similar ecological conditions would be reflected in similar disease patterns of the population in many parts of the world, and it is intriguing to realize that high esophageal cancer incidence areas in northern China are located in cotton-growing districts.

We hope to be able in the future to use our findings in Iran to open a new ecological chapter in cancer epidemiology. While the traditional, relatively simple search for carcinogenic substances in the environment should be continued, we hope to employ additional ecological tools, following the multifactorial, multidisease, multidisciplinary approach, in broad population studies in the future.

Summary

A peculiar distribution of esophageal cancer was observed in the Caspian littoral of Iran, where an ad hoc cancer registry has been in operation since 1968. A very high incidence, among the hghest recorded in the world, with a higher incidence in women than in men (male: 108.8 cases per 100,000 population; female: 174.1 per 100,000), was recorded in the northeastern corner of the region; this sparsely populated, semidesert area of the central Asian type, with predominantly saline soils, was settled by Turkomans. A lower incidence with a change in the male-to-female ratio was observed in the southeastern and central parts of the region, which are located in the piedmont area of the Elburz Mountains; these areas have more abundant rainfall and nonsaline soils, and are densely populated by Iranians. A steady decline in the incidence with an increase in the preponderance of male cases was observed toward the west, reaching the lowest figures (male: 17.2 cases per 100,000 population; female: 5.5 per 100,000) in the Caspian rain belt, with its heavily leached soils and somewhat subtropical characteristcs. Changes in the natural vegetation and in the agricultural practices parallel the changing features of the climate.

A multidisciplinary, multidisease, and multifactorial study is in preparation. By plotting the detailed physical, biotic, and cultural characteristics of the selected ecological regions on the intrinsic characteristics of the population groups experiencing different esophageal cancer risk, new and profitable working hypotheses as to the etiology of esophageal cancer might be produced.

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11. Halophylic: flourishing in a salty environment; *Artemisia*: a large genus of aromatic herbs, abundant in arid regions; *Astragalus*:

a large genus of the pea family, common in steppe regions (for example, milk vetch in the United States).
12. "Map of the natural vegetation of Iran" (University of Teheran, Iran, 1970).
13. *Quercus*: oak; *Carpinetum*: hardwood, deciduous trees with beech-like bark; *Fagetum hyrcanum*: a Caspian beech; *Buxetum*: belonging to the boxwood family.
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Ion Microprobe Mass Analyzer

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The ion microprobe mass analyzer is an instrument that has been developed to provide an in situ mass analysis of a microvolume of the surface of a solid sample. It accomplishes the analysis by bombarding the surface with a high-energy beam of ions, which causes the atoms at the surface to be sputtered away. A fraction of the sputtered particles is electrostatically charged, and these sputtered ions are collected and analyzed according to their mass-to-charge ratio in a mass spectrometer. The instrument complements other microanalytical techniques, such as the electron microprobe x-ray analyzer, by providing information about the concentrations and distribution of the isotopes of the elements in the surface of the solid. The technique permits isotope ratios to be measured, makes it possible to detect the very light elements, and generally extends spatial microanalysis into the range of trace elements. In addition, a highly sensitive analysis can be made of the sample in depth as successive atomic layers of the surface are eroded away by the impinging ion beam.

The general concept of producing a spatially resolved mass analysis of the surface of a solid by bombarding it with a beam of primary ions and analyzing the secondary ions sputtered from the sample was introduced by Castaing and Slodzian (*1*). Their work has resulted in the production of an ion microanalyzer, which has been described by Rouberol *et al.* (*2*) and Socha (*3*). Other sputtering-ion mass spectrometers with varying degrees of microanalytical capability have been described by Barrington *et al.* (*4*), Tamura *et al.* (*5*), and Nishimura and Okano (*6*). An ion microprobe design was proposed by Long (*7*), and a scanning ion microscope based on the design was built and demonstrated by Drummond and Long (*8*). The present article deals with the ion microprobe mass analyzer basically designed by Liebl (*9*). This instrument is parallel in design concept to the electron microprobe x-ray analyzer in that a heavy-ion beam has been substituted for the electron beam and a mass spectrometer for the x-ray spectrometer. This analogy permits a similar microanalytical methodology to be applied in both instruments.

Instrumentation

Figure 1 is a schematic diagram of the instrument. The ions used for sample bombardment are generated in a hollow-cathode duoplasmatron ion source that is capable of producing ions of a wide variety of gases, including those of a highly electronegative character. The ions, which can be either positively or negatively charged, are accelerated to energies ranging from 5 to 22.5 kilovolts and passed through the primary mass spectrometer. This spectrometer permits the analyst to select and purify by mass separation a specific chemical species from those produced in the ion source. The purified ion beam is focused to a small probe in an electrostatic lens column consisting of a condenser lens and an objective lens and allowed to impinge on the surface of the sample. The diameter of the ion probe can be varied continuously from about 2 to 500 micrometers. The sample and the point being analyzed can be viewed through an optical microscope while under bombardment.

The sputtered ions are collected and their masses analyzed in a double-focusing mass spectrometer generally similar to the Mattauch-Herzog type, in which the velocity dispersions of the magnetic and electric sectors are matched to permit the acceptance of a wide range of initial energies of the sputtered ions. No entrance slit is used, and the bombarded area is stigmatically focused directly onto the resolving slit. A retrofocal lens is used before the mass spectrometer to increase the solid angle of acceptance of the instrument. Because of the stability of the duoplasmatron ion source and the resulting continuous generation of sputtered sample ions, electrical detection and mass scanning can be used to good advantage.

The ion beams are then detected with a high-gain device of the Daly type (*10*) that permits single-ion counting. Both positive and negative sputtered ions can be detected when the potentials of the conversion electrode and the scintillator are suitably arranged. Sputtered ions from the sample eject secondary electrons at the conversion electrode, and

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