A study is reported of 2,177 men with cancer of the lip, oral cavity, or pharynx discharged in a five-year period from Veterans Administration hospitals. Except for cancer of the lip, geographical distribution of cases was generally similar to controls. A marked association was seen between cancer of the floor of the mouth and cirrhosis of the liver. No association was found between cancer and diabetes, arteriosclerosis, alcoholism, and syphilis.

THE EPIDEMIOLOGY OF LIP, ORAL, AND PHARYNGEAL CANCERS, AND THE ASSOCIATION WITH SELECTED SYSTEMIC DISEASES

Andrew Z. Keller, D.M.D., M.P.H.

THERE is abundant evidence that many diseases of the oral cavity are related to more generalized systemic diseases.[1] This is no less true of cancers.[2-7] This study investigates the hypothesis that there is an association between cancers of the mouth, pharynx, and lip, and the following systemic diseases: (a) diabetes mellitus; (b) liver cirrhosis; (c) chronic alcoholism; (d) generalized arteriosclerosis; and (e) syphilis. Moreover, it will characterize these cancers in males as to age, race, anatomical sites, and geographical distribution.

Only a few studies have been devoted to the epidemiology of lip, oral, and pharyngeal cancers. Notable among these are a study of oral cancer in Bombay, India, and a study of lip carcinoma in the United States.[8,9] Generally, reports are small case series, limited by inadequately defined sampling procedures, which emphasized the lip, tongue, and otherwise combined sites.

Lip cancer is most common among white males from the South and West; the mean age of cases is 62 years.[9,10] The lower lip is usually affected.[11] Salivary cancers are more prevalent among Negro males than white males; the major salivary glands, principally the parotids, are affected in about 90 per cent of the cases.[10,11]

The proportion of cancers involving the tongue, regions of the pharynx, and other parts of the mouth are similar for white and Negro males.[13] These cancers are commonly diagnosed after the age of 40.[14,15]

Blood glucose levels are elevated in carcinomatosis, and frank diabetes is reported with unusual frequency in cancer patients.[16] Altered carbohydrate metabolism in tumor tissues results in low glycogen content.[17,18,19,20] Moreover, leukoplakia, a precancerous condition in which tissue glucose is atypically metabolized, is a common finding in patients who eventually develop oral cancers.[11,21-23] These observations suggest the possibility that diabetics may

develop cancers with a greater frequency than nondiabetics.

Inanition and deficiency syndromes have been associated with a high incidence of mucous membrance cancer.[2,4] Among the pathological conditions seen in malnourished individuals are glossitis, mucous membrane atrophy, abnormal keratinization, and the Plummer-Vinson syndrome.[25,26] A true deficiency becomes evident when nutrients are poorly absorbed by the villi of the gastrointestinal tract or when the liver inadequately stores, metabolizes, and excretes nutrients and their products. Accordingly, the diagnosis of liver cirrhosis or chronic alcoholism might identify individuals who tend to have poor nutrition.

Possible factors in the etiology of lip cancer are tobacco, syphilis, and radiations.[27,29] Reportedly associated with tongue cancers are syphilis, leukoplakia and its precursors, tobacco, chronic alcoholism, and hepatic cirrhosis.[2,3,5,6,11,25,26] The etiology of floor of the mouth cancer is decidedly more obscure than other forms of oral cancer; there is little evidence of an association between this cancer and trauma, the use of tobacco, poor oral hygiene, or chronic alcoholism.[11,30,31] Factors thought to be associated with cancer at other oral sites and the pharynx are reviewed elsewhere.[2,11,32]

Nature of the Veterans Administration Material

The Veterans Administration Central Office receives information concerning the characteristics and diagnoses of a systematic 20 per cent sample of patients discharged from 171 VA hospitals throughout the country. The quality of medical care, the training and qualification of doctors, and diagnostic indexing of records in the VA are generally regarded as high, and fairly uniform. Furthermore, all pathological diagnoses are checked by the Armed Forces Institute of Pathology. Thus, for comparative and epidemiological purposes, these data present distinctive advantages.

Some problems have been explored in previous publications which drew upon the record system of the Veterans Administration. The geographical distribution of sarcoidosis, multiple sclerosis, ulcerative colitis and regional enteritis have been delineated with VA data.[33-35] An association between ulcerative colitis, regional enteritis, and ankylosing spondylitis was shown from data on U.S. veterans.[36] Similarly, the relationship of the distribution of multiple sclerosis to latitude, solar radiation, and other variables was provided from a study by Acheson, Bachrach, and Wright.[37]

Materials

Case Series

Cases were selected from the systematic 20 per cent sample of patients on whom information is received routinely by the Veterans Administration Central Office. A case was defined as a male veteran, discharged from a general medical and surgical hospital during 1955-1959, whose claim number terminated in one or five, and whose neoplasm corresponded to the International Classification 140 through 148. Selected data as entered on punch cards were analyzed.

In the original sample were 2,695 discharges from tuberculosis, neuropsychiatric, and general medical and surgical hospitals, consisting of white males and females, and males who were Negro, brown, and unspecified as to race. Patients discharged from tuberculosis and neuropsychiatric hospitals were excluded. Duplicate discharges were also excluded so that a person was counted only once regardless of the frequency of readmission. Duplicates were checked for consistency against previously tabulated data on the original sample. A total of 2,177 general medical and surgical (GM&S) first admissions remained in

the study population, including 2,018 white males and 159 Negro males.

Selective Factors

Each year, 171 Veterans Administration hospitals discharge about 400,000 patients who are drawn from a population of 22.5 million veterans. The cancer patient load in the Veterans Administration, like the veterans' population, is 99 per cent male.

The proportion of veterans with cancers who obtained care in a VA hospital varied with the place of residence, years of school completed at entry into service, broad classes of occupation, the veteran's age, and with the primary site affected by the neoplasm.[38] The details of these selective factors were set forth in "A Report on the Utilization of VA Hospitals by Veterans Dying of Cancer in 1950-54."[39] A summary of these factors is presented here.

The study showed that rates of hospitalization in VA hospitals were lower in the Middle Atlantic States than in the South and West. Taking education with occupation as indexes of socioeconomic status, it was found that hospitalization for neoplasms in VA hospitals was far more frequent among those of low socioeconomic status than those of higher levels. This would be expected from the policies governing admission to such hospitals for nonservice-connected disability. Thus, veterans hospitalized for cancer in these hospitals are not a completely representative sample of all veterans with cancer. However, of all veterans who died of cancer of the buccal cavity and pharynx during the years 1950-1954, 85 per cent of all World War I veterans and 79 per cent of all World War II veterans had been seen in a veterans hospital for their fatal cancer at some time prior to death.

Comparison Group

The cases are derived from a well-defined closed population; one choice of denominator might be the total number of veterans living. But data are not available on the characteristics of the living veterans population. Moreover, such a denominator will not take into account the selective factors which determine whether a veteran will seek hospitalization in a VA hospital.

To minimize selective factors which might introduce bias, the control disease to be studied should require services similar to the case series, the chronicity of the control disease and the urgency of the need of treatment for it should be comparable to the case series, and should produce a similar degree of economic distress. Any disease could be used as a control, provided that the selected systemic diseases (liver cirrhosis, chronic alcoholism, diabetes mellitus, generalized arteriosclerosis, and syphilis): (1) are equally likely to be entered in the clinical records as associated conditions in both the case series and controls; (2) would not increase or decrease the likelihood of admission to the hospital any more for the cancer patients than for the control patients; and (3) are not etiologically related to the diseases to be used as controls.

Bronchitis and emphysema, and rheumatoid arthritis were chosen as controls because they approximate more closely the requirements for controls than any other disease groups considered. Neither disease group meets all of the requirements set forth above; the effects of these deficiencies will be analyzed later. Those selected are believed to reflect the characteristics of the population from which the cancer group was drawn in that they are drawn by a similar process from the same population as the cases; and they share the selective processes as to age, race, sex, geographical pattern, socioeconomic status and hospital type, by which the cases came to our attention. These diseases, however, do not require surgical services as does oral cancer.

Methods

The cancer distributions by site were analyzed by race, age, hospital size, and geographical factors. Cases were compared with controls. Single and combined cancer site distributions were analyzed for an association with diabetes mellitus, liver cirrhosis, chronic alcoholism, generalized arteriosclerosis, and syphilis.

The sites considered are the lip, tongue, floor of the mouth, salivary glands, nasopharynx, mesopharynx, hypopharynx, parts of the pharynx unspecified, and the "other mouth." In the "other mouth" are malignant neoplasms of the alveolar process, buccal mucosa, palate, uvula, and maxillary gingiva. The characteristics of a "special group" of cancers is defined to include tissues exposed to the oral environment and those anatomical portions of the pharynx which are direct continuations of the tongue. Within the "special group" are the tongue, floor of the mouth, other mouth, mesopharynx, and the hypopharynx. The mesopharynx embraces the pillars of the fauces and the posterior third of the tongue; and the base of the tongue is located in the hypopharynx.

Hospitals were classified into four size categories and nine geographical areas. The geographical distribution of cases and controls was compared with the regional pattern of hospital utilization, of veterans living June 30, 1958, and of the U.S. white male population of July 1, 1960, aged 21 years and older.

Random samples of clinical folders for cancer cases (12.5 per cent) and bronchitis and emphysema cases (3.7 per cent) were abstracted to ascertain the completeness of data entered on the punch cards, to determine the extent to which diagnoses had been histologically confirmed, and to evaluate other variables. In the 12.5 per cent random sample of cancer cases, stratified for the floor of the mouth, were 18 per cent of the tongue cancers and 26.2 per cent of the floor of the mouth cancers, plus cancers involving other sites. Randomization was effected by selecting indi-

Table 1—Discharge of White Males with Cancer of the Mouth and Adjacent Sites, Bronchitis and Emphysema, and Rheumatoid Arthritis, by Size of Hospital

Bed Capacity of Hospitals	All Cancers of the Mouth and Adjacent Sites		Special* Cancers		Cancers of Floor of Mouth		Bronchitis and Emphysema		Rheumatoid Arthritis	
	No.	%	No.	%	No.	%	No.	%	No.	%
Totals	2,018	100.0	1,183	100.0	214	100.0	2,217	100.0	1,494	100.0
Less than 200 beds (35 hospitals)	167	8.3	57	4.8	9	4.2	410	18.5	279	18.7
200-349 beds (36 hospitals)	521	25.8	292	24.7	50	23.3	607	27.4	483	32.3
350-499 beds (21 hospitals)	527	26.1	296	25.0	47	22.0	466	21.0	270	18.1
500 beds and over (19 hospitals)	803	39.8	538	45.5	108	50.5	734	33.1	462	30.9

* Special Cancers: Tongue, floor of the mouth, other mouth, mesopharynx, hypopharynx.

Table 2—Place of Residence of Cases and Controls, Contrasted with that of Population, and Utilization of VA Hospitals*

	U.S. White Male Population 7-1-60 (1)	Veterans Living 6-30-58	All Cancers of the Mouth and Adjacent Sites	Special Cancers†	Floor of Mouth	Tongue	Salivary Glands	Other Mouth	Lips	Hypopharynx	Mesopharynx	Nasopharynx	Other Parts of Pharynx	Bronchitis and Emphysema	Rheumatoid Arthritis	Rates of VA Hospital Utilization (3)
Totals	46,160,050	22,434,000	2,018	1,183	214	364	176	257	458	156	192	106	95	2,217	1,494	35,270
Percentages	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
New England	6.6	6.4	5.6	6.9	7.4	8.5	5.1	5.4	2.2	7.7	4.7	5.7	8.4	6.5	5.5	5.0
Middle Atlantic	20.8	20.6	13.2	17.6	16.8	22.5	16.5	17.9	1.5	11.5	13.5	12.3	9.5	16.8	13.0	16.8
East North Central	21.2	20.8	18.6	22.7	20.1	22.0	15.9	20.2	10.5	28.2	25.5	15.1	15.8	13.6	13.7	16.0
West North Central	9.4	8.7	11.1	8.8	8.9	9.4	14.8	7.8	17.5	9.6	8.3	7.5	6.3	10.3	10.9	9.9
East South Central	5.8	6.1	9.1	7.5	8.9	7.1	6.8	9.0	11.5	7.1	5.2	12.3	19.0	7.7	8.8	7.2
South Atlantic	12.7	13.2	12.1	11.7	8.4	9.1	12.5	16.3	11.8	10.9	14.7	15.1	14.7	13.8	17.4	15.1
West South Central	8.8	8.9	11.5	8.2	9.8	6.3	10.8	9.3	19.9	9.6	7.3	13.2	10.5	12.9	12.6	11.5
Mountain	3.8	3.6	3.7	1.9	0.5	2.5	2.8	1.6	9.0	1.9	2.6	2.8	3.2	6.9	6.8	5.6
Pacific (2)	11.0	11.7	14.6	14.1	18.7	11.5	14.8	12.1	15.7	12.2	18.2	16.0	12.6	11.0	11.2	12.9
Puerto Rico	—	—	0.5	0.6	0.5	1.1	—	0.4	0.4	1.3	—	—	—	0.5	0.1	—

* Each heading pertains to white males only, except veterans living June 30, 1958, which includes Negroes.
† Special cancers: Tongue, floor of mouth, other mouth, mesopharynx, hypopharynx.
(1) Persons 21 years of age and older.
(2) Pacific excludes Alaska and Hawaii.
(3) The differential rates of hospital utilization, based on a 20 per cent random sample of patients remaining in GM&S hospitals on November 30, 1958.

viduals with certain combinations of digits in their claim numbers, and their clinical records were obtained for study. All cancers were histologically confirmed.

Results

The patient distribution within hospitals having different bed capacities is seen in Table 1. The oral cancer cases were much less frequently treated in small hospitals (fewer than 200 beds) than were the control cases. There is a corresponding excess of cases treated in hospitals with over 500 beds. This is presumably due to the smaller hospitals having inadequate facilities for specialized surgical care, including the services of oral surgeons.

The geographical pattern of cases and controls by place of residence is seen in Table 2. These are contrasted with the living veterans population of June 30, 1958, and the U.S. white male population of July 1, 1960, and the rate of hospital utilization based on a 20 per cent systematic random sample of records for patients remaining in GM&S hospitals on November 30, 1958.

Hospitals were utilized principally, by cases and controls, in the North Central and South. Only cases with tongue cancers utilized hospitals principally in the Northeast and North Central. Over-all, hospitals were utilized least in the West and most in the South.

The distribution of cases with cancers of the floor of the mouth, salivary glands, other mouth, the special group, and the U.S. white male population of July 1, 1960, were highly correlated with the general regional pattern of living veterans. Except for a low expected number of tongue cancers in the South, this high correlation prevailed for the tongue cancers as well.

The geographical pattern of cancers involving the lip, pharynx, and all oral and adjacent sites, was also compared with the regional distribution of living veterans. Lip cancers showed a great relative variation. They were high in the West North Central, East South Cen-

Table 3—The Relative Frequency Distribution of Cancers by Anatomical Sites, Based on All Cancers of the Mouth and Adjacent Sites

	Whites		Negroes	
	No.	%	No.	%
Cancer of the mouth and adjacent sites	2,018	100.0	159	100.0
"Special group"	1,183		111	
Tongue	364	18.1	44	27.6
Floor of mouth	214	10.6	19	12.0
Mesopharynx	192	9.5	16	10.1
Hypopharynx	156	7.7	11	6.9
Other mouth	257	12.7	21	13.2
Nasopharynx	106	5.3	11	6.9
Other parts of pharynx	95	4.7	4	2.5
Salivary glands	176	8.7	31	19.5
Lips	458	22.7	2	1.3

Table 4—Age Distribution of Lip Cancers Among White Males

Age in Years	Upper Lip		Lower Lip	
	No.	%	No.	%
25-34	1	1.8	16	4.7
35-44	8	14.0	57	16.7
45-54	6	10.5	35	10.2
55-64	14	24.6	128	37.4
65 and over	28	49.1	106	31.0
Total	57	100.0	342	100.0

tral, West South Central, and Mountain regions; and surprisingly, they were not high in the South Atlantic. Moreover, there were significantly fewer lip cancers than expected in the Northeast and more lip cancers than expected in the South and West. Except for a significantly high proportion of cancers classed as "other pharynx" in the South, the proportions of pharyngeal cancers were unremarkable. Cancers involving all oral and adjacent sites were significantly low in the Northeast, and correspondingly high in the West and South, due principally to the lip cancers, and partly to the "other pharynx" in the South.

The relative frequency distributions of cancers by anatomical sites between whites and Negroes are seen in Table 3. These relative frequencies are based on the total cancer of the lip, oral cavity, and pharynx. The deficit of lip cancer in Negroes is gross and unquestionable. When lip cancers are excluded from the relative frequency distribution, as they properly should be, the percentage difference in tongue cancers and salivary gland cancers is reduced. On adjusting the number of tongue or salivary gland cancers to the age distribution of males in the total sample (from which lip cases were excluded), the observed and expected values do not differ significantly. Accordingly, only cancers of the lip were selective for race.

Anatomically, lip cancers were distributed as follows: Upper—12.4 per cent; lower—74.7 per cent; both—6.6 per cent; and unspecified—6.3 per cent. The age distributions of cases of lip cancer are seen in Table 4. A significantly higher proportion of upper lip cancers occurred in persons aged 65 years and older.

Salivary gland cancers were anatomically distributed as follows: Parotid glands—79.5 per cent; other major and minor salivary glands—16.5 per cent; and salivary glands, unspecified—4 per cent. The median ages of cases with parotid and other major and minor salivary gland cancers were 60 years and 40 years, respectively.

The age distribution of cases of cancer at individual sites among white males is seen in Table 5. A bimodal age distribution of some cancers will be noted, since, due to the large number of men recruited during World War I and World War II, the age pattern of veterans eligible for VA care is bimodal.

The median ages of all cases with cancers of the mouth and adjacent sites were around 60 years, and ranged from 55 to 62 years. The median ages of cancer cases were as follows: Salivary glands (total)—55 years; nasopharynx and other pharynx—59 years; lips (total)—60 years; floor of the mouth, mesopharynx, and other mouth—61 years; tongue, hypopharynx, and the "special group"—62 years. Bronchitis and emphysema, and rheumatoid arthritis cases had median ages of 63 and 47

Table 5—Distribution, by Age, of Cancers Involving the Mouth and Adjacent Sites, for White Males

	Total		Less than 25		25-34		35-44		45-54		55-64		65 and Over	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
All cancers of the mouth and adjacent sites	2,018	100.0	8	0.4	74	3.7	209	10.3	274	13.6	815	40.4	638	31.6
"Special group"	1,183	100.0	—		11	0.9	83	7.0	164	13.9	536	45.3	389	32.9
Tongue	364	100.0	—		4	1.1	18	4.9	48	13.2	175	48.1	119	32.7
Floor of mouth	214	100.0	—		2	0.9	20	8.9	43	20.2	79	37.1	70	32.9
Mesopharynx	192	100.0	—		1	0.5	11	5.7	25	13.0	97	50.5	58	30.2
Hypopharynx	156	100.0	—		—		9	5.8	14	9.0	79	50.6	54	34.6
Other mouth	257	100.0	—		4	1.6	25	9.7	34	13.2	106	41.3	88	34.2
Nasopharynx	106	100.0	4	3.8	9	8.5	16	15.1	13	12.2	32	30.2	32	30.2
Other parts of pharynx	95	100.0	—		—		10	10.5	20	21.1	44	46.3	21	22.1
Salivary glands	176	100.0	4	2.3	29	16.5	28	15.9	27	15.3	44	25.0	44	25.1
Lips	458	100.0	—		25	5.5	72	15.7	50	10.9	159	34.7	152	33.2

(Age in Years spans the columns Less than 25 through 65 and Over.)

years, respectively. The median ages of Negroes with cancers of the mouth and adjacent sites (while cited with less confidence owing to fewer cases being represented), were comparable to whites, except that for the salivary glands the median age was 45 years.

The frequency of diabetes mellitus, liver cirrhosis, chronic alcoholism, generalized arteriosclerosis, and syphilis among cancer cases, as entered into the clinical summaries, was recorded. This was contrasted with the corresponding frequencies of these conditions among the controls. A positive association between a particular cancer and one of the five other diseases was said to be present if the disease were more often found in cancer cases than in the controls.

No association was found between any cancers and diabetes mellitus, generalized arteriosclerosis, or syphilis. Moreover, no association was found between liver cirrhosis and cancers of the tongue, mesopharynx, or hypopharynx, alone or in combinations.

An association, which is not considered genuine, was found between a history of chronic alcoholism and tongue cancers in the age group 55-64 years. A review of the random sample of cases with tongue cancers and bronchitis and emphysema buttressed an a priori impression that the association was spurious. Hence, the association is rejected, due to the use of variable definitions of chronic alcoholism, to the lack of reproducible histories, and to related biases.

An association between liver cirrhosis and floor of the mouth cancer was found. This is presented in Table 6, where the expected values are age-adjusted to the prevalence of liver cirrhosis among the controls. In comparing the frequency of cirrhosis in a group of cancer patients with the frequency of cirrhosis in another disease group, as the controls, it

Table 6—The Frequency of Cirrhosis of the Liver as a Coexisting Disease Among Patients Discharged with a Diagnosis of Cancer of the Floor of the Mouth, with Expected Frequencies Based Upon Age-Adjusted Proportions Among Controls

		Age in Years						
	Totals	Less than 25	25-34	35-44	45-54	55-64	65+	X^2 (Totals)*
Floor of mouth	214	—	2	20	43	79	70	
Liver cirrhosis	21	—	—	5	6	5	5	
Expected (1)	4.0			0.7	0.7	1.7	0.9	73.6
Expected (2)	1.3			0.2	0.4	0.4	0.3	300.4
Per cent with cirrhosis	9.81			25.00	13.95	6.33	7.10	
Bronchitis and emphysema	2,217	9	88	197	259	863	801	
Liver cirrhosis	40		1	7	4	18	10	
Per cent with cirrhosis	1.80		1.14	3.55	1.54	2.09	1.25	
X^2(Yates correction)	40.0			12.1	14.1	3.8	10.0	
				Degrees of Freedom = 4, $p<0.00001$				
Rheumatoid arthritis	1,494	18	232	375	233	381	255	
Liver cirrhosis	10		2	3	2	2	1	
Per cent with cirrhosis	0.67		0.86	0.80	0.86	0.52	0.39	
X^2(Yates correction)	83.6			44.5	17.7	11.1	10.3	
				Degrees of Freedom = 4, $p<0.00001$				

* One degree of freedom, $p<0.00001$.
Expected (1): Based on the frequency of cirrhosis among bronchitis and emphysema cases.
Expected (2): Based on the frequency of cirrhosis among rheumatoid arthritis cases.

is desirable to adjust for any differences in the age distribution of the two groups, lest cirrhosis appears more or less frequently only because the age distribution of one group more closely resembles the age distribution of cirrhotic patients. Chi-square computations, employing Yates Correction, were used as a measure of discrepancy between observed and expected frequencies.

The differences between the observed and age-adjusted expected number of cases has an extremely low probability of chance occurrence. Aside from chance, biases from variables not controlled by chance might account for the differences. Outstanding among these are hospital size, geographical location of hospitals, place of residence, differential rates of VA hospital utilization, and the prevalence rates of liver cirrhosis in hospitals grouped by size in accord with administrative practices. Some of these have been considered already. Now the pattern of hospitalization for cirrhotics by geographical location and sizes of hospitals reporting cirrhosis will be analyzed; also, the prevalence of cirrhosis in the hospitals grouped according to size will be applied to the cases and controls at risk to delineate differences in observed and expected values.

Table 7 presents the geographical location of hospitals in which liver cirrhosis was diagnosed as a coexisting disease among cases and controls, and of hospitals from which a 20 per cent sample of cases with cirrhosis was discharged in 1957. The 20 per cent sample provides a reference distribution of patients with liver cirrhosis. Most cases with both cancer of the floor of the mouth and liver cirrhosis were in the Northeast; these cases and bronchitis are similarly distributed. Otherwise, the "special group" and the 20 per cent sample have similar distributions. The

Table 7—Geographical Location of Hospitals in Which Cirrhosis of the Liver Was Diagnosed as a Coexisting Disease Among Cases and Controls, and of Hospitals from Which a 20 Per cent Sample of Cases of Cirrhosis Was Discharged in 1957 (1)

Geographical Location of Hospitals	Floor of Mouth		Bronchitis and Emphysema		Special Cancers*		20% Sample of Cirrhosis (1)		Rheumatoid Arthritis	
	No.	%	No.	%	No.	%	No.	%	No.	%
Totals	21	100.0	40	100.0	39	100.0	1,571	100.0	10	100.0
New England	1	4.8	3	7.5	3	7.7	109	6.9	—	
Middle Atlantic	8	38.0	13	32.5	10	25.6	336	21.4	1	10.0
East North Central	3	14.3	6	15.0	5	12.8	334	21.3	3	30.0
West North Central	1	4.8	6	15.0	7	18.0	161	10.2	—	
East South Central	—		2	5.0	—		73	4.7	1	10.0
South Atlantic	2	9.5	4	10.0	5	12.8	187	11.9	2	20.0
West South Central	3	14.3	1	2.5	4	10.3	132	8.4	1	10.0
Mountain and Pacific	3	14.3	5	12.5	5	12.8	225	14.3	2	20.0
Puerto Rico	—		—		—		14	0.9	—	

* Special cancers: Tongue, floor of mouth, other mouth, mesopharynx, hypopharynx.
(1) Age 35 years and older.

Table 8—Bed Capacity of Hospitals Reporting Cases and Controls with Cirrhosis, and the Corresponding Prevalence of Cirrhosis

Hospital Bed Capacity	Patients Having Both Liver Cirrhosis and:								20% Sample of Cirrhotics, 1957 (2)		All GM&S Discharges (3), Cirrhotics and Noncirrhotics		Prevalence Rates of Cirrhosis
	Special Cancers (1)		Floor of Mouth Cancer		Bronchitis and Emphysema		Rheumatoid Arthritis						
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
Total	39	100.0	21	100.0	40	100.0	10	100.0	1,571	100.0	378,502	100.0	0.0208
Number of beds:													
200	2	5.1	1	4.8	1	2.5	1	10.0	200	12.7	56,104	14.8	0.0179
200-349	9	23.1	2	9.5	13	32.5	3	30.0	422	26.9	108,910	28.8	0.0200
350-499	9	23.1	4	19.0	10	25.0	2	20.0	324	20.6	86,742	22.9	0.0187
500 and over	19	48.7	14	66.7	16	40.0	4	40.0	625	39.8	126,746	33.5	0.0247

(1) Special cancers: Tongue, floor of mouth, other mouth, mesopharynx, hypopharynx.
(2) Age 35 years and older.
(3) All GM&S discharges from July, 1957, to July, 1958, who were cirrhotics and noncirrhotics.

differences in proportions observed between each group similarly distributed are not statistically significant.

The bed capacity of hospitals reporting liver cirrhosis, and the corresponding prevalence of cirrhosis, are seen in Table 8. Cases and controls with liver cirrhosis are compared with a 20 per cent sample of cirrhotics. Prevalence rates are based on the latter sample, and all GM&S discharges from July, 1957, to July, 1958, among whom were cirrhotics and noncirrhotics. Liver cirrhosis was more commonly diagnosed in the larger hospitals. Fewer than 50 per cent of all cases with liver cirrhosis were diagnosed in hospitals with more than 500 beds, except cases with floor of the mouth cancer as a coexisting disease. Sixty-seven per cent of the cases with floor of the mouth cancer and liver cirrhosis were diagnosed in hospitals with more than 500 beds.

The frequency of cirrhosis of the liver as a coexisting disease among cases and controls in relation to size of hospitals is presented in Table 9. The expected numbers are computed from the prevalences in Table 8. These rates are applied to the appropriate group at risk, which are retabulated in Table 9 from Table 1. The total difference in the observed and expected number of cirrhotics among the bronchitis cases is not significant. The differences noted in the "special group" results from the inclu-

Table 9—Frequency of Cirrhosis of the Liver as a Coexisting Disease Among Cases and Controls, in Relation to Size of Hospital

Hospital Bed Capacity	Special Cancers*		Floor of Mouth Cancer		Bronchitis and Emyphysema		Rheumatoid Arthritis	
	Observed	Expected	Observed	Expected	Observed	Expected	Observed	Expected
Less than 200 beds	2	1.0	1	.2	1	7.3	1	5.0
200-349 beds	9	5.8	2	1.0	13	12.1	3	9.7
350-499 beds	9	5.5	4	.9	10	8.7	2	5.1
500 beds and over	19	13.3	14	2.7	16	18.1	4	8.6
Total	39	25.6	21	4.8	40	46.2	10	28.4
X^2(total difference)(1)	7.2		55.2		0.9		12.1	
Probability of chance occurrence	0.007		<0.00001		0.34		0.005	

Cases at Risk in Hospital

Bed Capacity	Special Cancer*	Floor of Mouth Cancer	Bronchitis and Emphysema	Rheumatoid Arthritis
Less than 200 beds	57	9	410	279
200-349 beds	292	50	607	483
350-499 beds	296	47	466	270
500 beds and over	538	108	734	462
Total	1,183	214	2,217	1,494

* Special cancers: Tongue, floor of mouth, other mouth, mesopharynx, hypopharynx.
(1) One degree of freedom.

sion of the floor of the mouth cancers. The greatest significant difference was found with the floor of the mouth, which has an extremely low probability of chance occurrence.

The bases for rejecting the association of tongue cancer with alcoholism do not hold true for the association between liver cirrhosis and floor of the mouth cancer. The ensuing facts were ascertained when clinical folders were reviewed. The association was significant in all age groups for liver cirrhosis and floor of the mouth cancer. Definitive and reproducible physical examinations, histories and laboratory tests (including biopsies) were employed to diagnose liver cirrhosis. Diagnoses were verified routinely. Under-reporting of liver cirrhosis among cancer cases was twice as frequent as among the controls. Moreover, these cancers were squamous cell carcinomas and came to the patient's attention as either a painless nodule or a nonhealing ulcer near the midline of the floor of the mouth.

Discussion

The geographical distribution of cancers of the floor of the mouth, salivary glands, the "special group," and the "other mouth" was highly correlated with the general regional pattern of living veterans and the U.S. white male population of July 1, 1960. But the relative proportion of lip cancers was high in the South and West. Other studies have related lip cancers in white males to the same geographical regions while emphasizing the deficit of lip cancers among Negroes.[9,10] Moreover, the greater frequency of lower lip cancers and the greater frequency of parotid to other major and minor salivary gland cancers have been cited in other studies.[8,10,11]

The association between liver cirrhosis and floor of the mouth cancer was the most important finding. The difference between the observed and expected number of cirrhotics with floor of the mouth cancer has a markedly low probability of chance occurrence. This was manifest with either control disease or on applying prevalence rates of liver cirrhosis to cases at risk from different sizes of hospitals.

Biases which might account for this finding were considered. For example, it is possible that cirrhosis of the liver occurs in conjunction with floor of the mouth cancer only because the type of hospital that has the greatest probability of receiving a cirrhotic patient, and of recording the existence of his cirrhosis, is also the type of hospital that has the greatest probability of receiving a floor of the mouth cancer patient and of recognizing his cancer, and perhaps less chance of receiving patients having the control diseases. The material presented in Table 8 and Table 9 does not seem to support such an explanation. The 21 patients who had both cirrhosis and floor of the mouth cancer were hospitalized in 19 different hospitals, from which 51 per cent of the cases with floor of the mouth cancer were discharged. These hospitals were not markedly different in size or geographical location from the hospitals that were diagnosing the control diseases. Moreover, cirrhosis does not seem to show an association with other oral cancers. One may, therefore, speculate that the association is dependent upon the pathogenesis of the condition, rather than upon some artifact of the data.

Summary

A study of a sample of 2,177 males with cancer of the lip, oral cavity, or pharynx, discharged in a five-year period from Veterans Administration hospitals, is reported. These cases were compared with the control patients having bronchitis and emphysema or rheumatoid arthritis, and with the living population of veterans, the total dis-

charges from these hospitals, the rates of hospitalization, and the U.S. population of white males.

Cancer cases were discharged mainly from the larger hospitals, which presumably had better facilities for their care. Except for cancer of the lip, which occurred more frequently in the South, the geographical distribution of cancer cases was generally similar to that of the controls. It also appeared that apart from lip cancer, which was extremely rare in Negroes, other oral cancers were not selective for race.

The cases of cancer of the salivary glands had a considerably younger age distribution than that of other oral cancers. Cancer of the upper lip was not only much less frequent than cancer involving the lower lip, but also occurred at an older age.

No association was found between the cancers and diabetes mellitus, generalized arteriosclerosis, chronic alcoholism, and syphilis.

A marked association between cancer of the floor of the mouth and cirrhosis of the liver was seen. It has not been possible to explain this association on the basis of bias or artifacts of the data; it appears to be a genuine association.

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Dr. Keller is associated with the Public Health Research Institute of the City of New York, New York, N. Y.

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