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AETIOLOGICAL FACTORS IN MOUTH CANCER AN APPROACH TO ITS PREVENTION

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History has always been one of man's best teachers, a truism which applies also to man's quest to comprehend the nature of disease. We call to mind Snow's classical study on cholera through the use of epidemiological techniques. Through his observations a disease was curtailed and the mechanism of an illness more closely understood at a time when its exact pathogenesis was unestablished. To be learned from this historical study, too, is that one does not need to understand the mechanism of a disease completely in order to accomplish a reduction of its incidence.

This point is stressed because it represents the basis of current epidemiological studies in the field of cancer. While many factors may induce cancer and the basic mechanism of cancer is still beyond our reach, we know factors which do play a part in the development of cancer whose removal or reduction will lead to a decrease in incidence of this disease. This is the primary goal of the epidemiologist in his fight against any disease. If a given factor is found to contribute to a disease it is of little importance to the patient whether this factor was of causative or of catalytic nature. What matters to the population is whether the removal of a given factor will reduce the incidence of a given disease. The present investigation on aetiological factors of cancer of the oral cavity was designed to serve towards this end. This report, to be presented in greater detail elsewhere, will outline some of the factors which influence the development of cancer of the mouth and whose control can lead to a drastic reduction in this type of cancer (Wynder, Bross, and Feldman, 1957).

Incidence Pattern

One reason why environmental factors are thought to play a part in certain types of cancers is that these cancers have a varying incidence distribution. Environmental factors found to be statistically significant in an epidemiological study must, at least in part, account for variations in incidence patterns in any given cancer. Some interesting features of the incidence pattern of cancer of the oral cavity are as follows: (1) Cancer of the oral cavity in males has not increased during the last two or three decades, and even may have slightly decreased (Public Health Service, 1950-2). (2) A small increase has been noted in cancer of the oral cavity among women (Public Health Service, 1950-2). (3) Can-

cer of the oral cavity is predominantly a male disease, with sex ratios for different sites ranging from 2:1 to 10:1. (4) Cancer of the oral cavity is relatively common in Swedish women. In Sweden cancer of the tongue, gum, and buccal mucosa is about as frequent in women as in men (Wynder, Hultberg, Jacobsson, and Bross, 1957). (5) Cancer of the oral cavity is common in India, where it accounts for 40% of all male cancer admissions to the Tata Memorial Hospital (Khanolkar, 1950). (6) Cancer of the lip is more common in southern than in northern areas. Cancer of the lip is very uncommon among negro patients (Public Health Service, 1950-2). (7) At the Memorial Center for Cancer and Allied Diseases, New York, mouth cancer occurs relatively more often among Catholic than among Jewish men.

Methodology

The method was similar to that used in our previous studies (Wynder, Bross, and Day, 1956). We obtained information from a series of study-group and control patients through trained interviewers. The questions related to environmental, medical, and social background. This study sought to investigate all of those factors that at one time or another had been suspected to be associated with cancer of the oral cavity (Table I).

TABLE I.—Factors Suspected to be Related to Cancer of the Oral Cavity

1. Tobacco smoking	7. Dentures
2. Tobacco chewing	8. Dentures irritation and sharp teeth
3. Betel-nut chewing	9. Nutritional deficiencies (iron, riboflavin)
4. Sunlight	10. Hot beverages and foods
5. Alcohol consumption	
6. Syphilis	

With the exception of data on tobacco and syphilis, however, none of the factors had hitherto been based upon statistical analysis of data (Martin *et al.*, 1940; Moore, Bissinger, and Proehl, 1953; Sadowsky, Gilliam, and Cornfield, 1953; Sanghvi, Rao, and Khanolkar, 1955).

Upon completion of the interviews, the information was coded on International Business Machine (IBM) cards and the controls and the cancer cases were matched for age, religion, hospital status, and socio-economic background. The study cases were analysed separately for each specific site as well as for the whole group.

All cases had microscopical diagnosis and represented epidermoid cancer. The statistical analyses were carried out by one of us (I. B.), with the assistance of R. Feldman.

If a given factor was found to differ significantly, it was tested against other variables to determine possible interdependence.

The study is based upon 543 male cases of cancer of the oral cavity compared with 207 male control patients who had benign diseases of the head and neck, lymphomas, benign diseases of the thoracic region, or cancer

TABLE II.—Number of Cases by Site and Sex (Whites)

Site	Male	Female	Total
Lip	74	2	76
Floor of mouth .. .	86	8	94
Gum	41	18	59
Buccal mucosa .. .	40	12	52
Tongue	180	57	237
Palate	41	7	48
Tonsil	57	7	64
Pharynx	24	5	29
Total	543	116	659
Controls	207	246	453

of the lower gastro-intestinal tract as well as of the skin. The female group includes 116 female patients with cancer of the oral cavity who have been matched against 246 female control patients* (Table II). All cases studied—male and female, study and control—have been matched for the same background factors.

Results in Males

Tobacco

Smoking was found to be an important factor in the development of cancer of the mouth. Three per cent. of the study group were non-smokers, in contrast to 10% of the controls.

FIG. 1.—Incidence of mouth cancer according to number of cigarettes smoked daily.

FIG. 2.—Incidence of cancer in relation to predominant types of smoking in males.

*Initially 123 female cases were matched, each case for two control cases. Then seven cases of nasopharyngeal cancer were removed from the study group without removing a comparable number of control cases. This accounts for the uneven number of study and control groups, though they were matched case for case.

TABLE III.—Diagnosis by Type of Smoking (Percentages Males)

Site	None	Cigarette	Cigar	Pipe	Mixed, With Cigarettes	Mixed, Without Cigarettes
Lip (74) .. .	4	51	18	15	8	4
Floor of mouth (86) .. .		67	16	12	2	2
Gum (41) .. .	2	54	20	15	7	2
Buccal mucosa (40) .. .		43	30	18	10	
Tongue (180) .. .	4	63	18	7	4	4
Palate (41) .. .	2	54	22	12	7	2
Tonsil (57) .. .	4	56	21	14	2	4
Pharynx (24) .. .	4	50	25	13	4	4
Total (543)	3	59	20	12	5	3
Controls (207)	10	63	13	5	6	2

TABLE IV.—Percentage Distribution of Male Patients with Different Cancer by Predominant Type of Tobacco Smoked

Predominant Type of Tobacco	Lung (132)	Intrinsic Larynx (107)	Extrinsic Larynx (93)	Oral (543)	Control (207)
None .. .	1	1	0	3	10
Cigarette .. .	93	90	82	63	69
Pipe .. .	1	2	9	20	13
Cigar .. .	5	7	9	12	5

ance. The percentage of cigar and pipe smokers among patients with cancer of the mouth is higher for all sites than for the controls. Twenty per cent. among the study cases smoked predominantly cigars, 12% predominantly pipes, and 3% cigars and pipes equally. The respective percentages for controls were 13, 5, and 2 (Fig. 2). This again was uniform for the total study group. The group with the fewest predominant cigarette smokers was the buccal mucosa cancer group containing 43% predominant cigarette smokers. The highest group of predominant cigarette smokers were patients with cancer of the floor of the mouth, 67% (Table III).

It was of interest to compare the type of smoking against the data previously determined for cancer of the lung and larynx (Table IV). These data show the percentage of pipe and cigar smokers to increase as one moves upward in the respiratory tract. A comparison between the group with lung cancer and the group with oral cavity cancer is particularly remarkable, with the former including only 5.4% pipe and cigar smokers.

Seventeen per cent. of the study group chewed tobacco, compared

with 8% of the controls. With one exception, however, a patient with cancer of the gum, all the tobacco chewers were also tobacco smokers. In cases of lip and gum cancer the lesion was usually found at the site where the tobacco was held. No relationship of tobacco chewing

FIG. 3.—Risk of oral cancer in males in relation to amount of tobacco smoked.

FIG. 4.—Risks of smoking 35+ cigarettes a day relative to pipe and cigar smokers, by cancer site.

was found to cancer of the pharynx, floor of the mouth, and tonsil. The highest percentage of tobacco chewers was among patients with cancer of the palate, 22%, and buccal mucosa, 20%. Among the 17% tobacco chewers in the total study group, 11% had chewed for more than 10 years, the remainder having chewed less than 10 years. Though tobacco chewing appears to have some influence on the development of some cancer sites of the mouth, it is less important than tobacco smoking.

The relative risk of smokers developing cancer of the mouth rises with the amount of tobacco consumed (Fig. 3). This risk among cigarette smokers, however, does not appear to the same degree as that found for cancer of the lung, while the relative risk among cigar and pipe smokers of developing mouth cancer is greater than that of cigarette smokers (Fig. 4).

TABLE V.—*Diagnosis by Quantity of Alcohol (Percentages) (Males)*

Site	Rare and Occasional	Units			Sporadic Binges
		1-2	3-6	7 or More	
Lip (74)	36	26	23	15	1
Floor of mouth (86)	26	6	24	42	2
Gum (41)	34	24	17	24	—
Buccal (40)	48	18	18	18	—
Tongue (180)	21	19	22	34	3
Palate (41)	14	20	32	35	—
Tonsil (57)	18	11	30	37	5
Pharynx (24)	12	17	25	42	4
Total (543)	26	17	24	31	2
Controls (207)	46	27	15	12	—

Alcohol

Heavy alcohol consumption, particularly that of whisky, was found to be a significant factor among patients with cancer of the oral cavity. Forty-six per cent. of the controls were occasional drinkers or non-drinkers compared with 26% among the study group (Fig. 5, Table V). In contrast,

FIG. 5.—Incidence of mouth cancer relative to amount of alcohol consumed per day (males).

FIG. 6.—Risk of oral cancer in relation to amount and type of alcohol consumed.

while 26% varied in type of alcohol consumed, roughly the same distribution as found for the controls. Among the study cases the percentage of people who drank whisky straight was 44%, which is greater than found among the controls, 26%, a difference which is probably associated with the fact that

the patients in the study group were heavy drinkers. Analysis for relative risk shows heavy alcohol consumption to significantly influence the development of cancer of the oral cavity. Whereas this relative risk increases in the moderate drinker, it rises very sharply among the heavy drinkers. The increased risk of developing oral-cavity cancer is significantly greater among people who drink whisky predominantly than among those who drink wine and beer predominantly (Fig. 6).

It was again of interest to compare the alcohol intake among patients with cancer of the oral cavity with patients with cancer of the lung and larynx (Table VI). Alcohol intake is significantly greater among patients with cancer of the mouth than among patients with cancer of the lung,

TABLE VI.—*Percentage Distribution of Male Patients with Different Cancer Types by Amount of Average Daily Alcohol Consumption*

Alcohol Consumption (Units)	Lung (132)	Intrinsic Larynx (107)	Extrinsic Larynx (93)	Oral (543)	Control (207)
Less than 1 a day	36	35	22	26	46
1-2 a day	26	18	15	17	27
3-6 "	25	21	20	24	15
7 plus or sporadic	14	24	42	33	12

and also, though to a less extent, among patients with cancer of the vocal cords. The alcohol intake for patients with cancer of the extrinsic larynx is slightly (but not significantly) higher than for the oral-cavity series. This effect may be in part due to the lip-cancer cases in the oral-cavity series, where there is little, if any, influence of alcohol.

Syphilis

A history of syphilis or positive serology was found more common among patients with cancer of the mouth, 11%, than among the controls, 5%. The only sites, however, which showed statistically significant differences were lip, 17% (at the 1% level) and tongue, 12% (at the 5% level). Dividing the results for the tongue into anterior two-thirds and posterior one-third showed that among 86 cases of cancer of the anterior two-thirds of the tongue 22% had a history of syphilis, whereas among 89 cases of posterior one-third only 3% gave such a history. A relationship of syphilis to cancer is therefore particularly significant among those with the anterior two-thirds of the tongue affected. We attempted to determine what effect, if any, therapy might have on this association. Forty-three per cent. of those patients who could recall the type of therapy employed stated that they had received arsenical treatment. This, however, is roughly the same percentage as that found in the controls, since a majority of these patients were treated at a time when arsenical therapy was in vogue. We are thus unable to determine what influence, if any, arsenical therapy has on cancer of the tongue in man.

Dental Conditions

Edentia was more prevalent among male patients with cancer of the oral cavity, 44%, than among the controls, 28%. Edentia did not appear to be related to the tobacco and alcohol consumption of the two groups. Sixty per cent. of the study group wore dentures, compared with 63% among the controls. Eleven per cent. among the denture-wearers in the study group gave a history of irritation from the denture compared with 7% of the controls, a difference which was not significant. Six per cent. among the study group complained of sharp teeth compared with 4.7% among the controls. There were a few instances (especially in two cases involving cancer of the buccal mucosa and one case of cancer of the tongue) where a sharp tooth present for many years was in direct line with the lesion; however, no definitive conclusions can be drawn from such isolated cases. Dental hygiene was somewhat poorer among the study group, a finding not related to alcohol and tobacco consumption.

Miscellaneous

Analysis of previous disease showed no significant differences between study and control groups with the exception of a high level of leucoplakia, 19%, present in the study group. The two sites with the least history of leucoplakia among the study group were tonsil and pharynx, 4% each, and the highest buccal mucosa, where 45% of the patients gave a history of leucoplakia. We cannot make a comparison here with the control group because an individual with leucoplakia could not enter the control series. Fifty-nine patients with cancer of the mouth gave a history of multiple primary cancers. In 60% of these cases the second or third cancer occurred in the upper alimentary or respiratory tract. The alcohol consumption and the history of syphilis were similar among patients with multiple primary cancers, but the percentage of excessive smokers among the cases with double primaries was twice as high as in the remaining study cases.

Evaluation of nutritional intake of the patients showed no significant differences. This does not necessarily mean, however, that no differences exist. It would be surprising if there were no nutritional differences among people who drink more heavily than those who drink moderately. However, it is difficult to obtain accurate nutritional histories by interview technique, particularly in a country with such variations in dietary patterns as in the United States.

Outside exposure was suggestively, but not significantly, higher in the lip series than in the controls. However, the proportion of outdoor labourers was significantly higher in the group with lip cancer. The 3 non-smokers among 74 patients with cancer of the lip were all outdoor workers.

A certain group of occupations, though not more prevalent for the entire study group, were more commonly affected at specific sites. These included plumbers among patients with cancer of the tonsil, 12%, and pharynx, 16%, compared with 6% for the controls; cold-metal workers among those with the gum lesion, 17%, in contrast to 4% among the controls; painters among those with cancer of the pharynx, 13%, in contrast to 2% among the controls; and labourers among those with cancer of the lip, 15%, compared with 4% among the controls.

Among the factors studied which did not give significant findings were food temperatures, a history of general trauma to the oral cavity, and family history of cancer.

Results in Females

The study included 116 cases of cancer of the oral cavity and 246 controls. In general, the female data confirm the previous findings for the male cases. Forty-seven per cent. of the female study cases were non-smokers compared with 70% of the controls. Thirty-four per cent. of the females smoked more than 16 cigarettes per day for at least 20 years compared with 11% of the controls, a significant difference.

No differences were found for the individual study sites, some of which of course contained too few cases to permit statistical analysis. All of the smokers were cigarette smokers (Fig. 7).

There was also a slightly greater amount of heavy alcohol consumption among the female study cases than among the controls. Ten per cent. among the

FIG. 7.—Incidence of oral cancer relative to number of cigarettes smoked by females.

former drank more than two "shots" of whisky a day compared with 3.4% among the controls. Obviously, a much smaller group admitted alcohol consumption than was demonstrated for the males.

A history of syphilis was found in five patients in the study group (including two with tongue cancer), compared with three of the controls (3.8% and 0.8% respectively).

Forty-nine per cent. of the study cases gave a history of edentia compared with 29% among the controls, and 14% among the study cases had lost their teeth prior to the age of 40 compared with 8% among the controls. The variable of edentia was analysed against the variable of pregnancy.

TABLE VII.—Per Cent Edentulous by Number of Pregnancies—Study and Control Groups

No. of Pregnancies	Study Group (116)	Control Group (246)
None	29	22
1-2	44	30
3-4	70	24
5+	71	62
Total	49	29

A significant association exists between the number of pregnancies and edentia (Table VII). In the study group, among the women who had never been pregnant 29% were edentulous, those with three or four children 70%, and those with five or more children 71%. A similar phenomenon, though to a less marked extent, was noted among the controls. These data therefore indicate that pregnancies have a marked influence on the loss of teeth, particularly among patients with cancer of the mouth.

Study of the history of dental irritation or trauma due to sharp teeth showed that, in general, women tend to recall such histories more often than men. But again, with the exception of a few isolated cases, the histories of site and duration of irritation were not particularly impressive.

As to previous disease, no differences were found, with the exception of a slightly higher proportion of women with glossitis, 8%, as compared with the controls, 3%, and with oral fissures, 5%, against the control, 2%. The study includes only one case of Plummer-Vinson disease that could be verified by x-ray studies of the hypopharynx; the patient was a 64-year-old woman with cancer of the gum who was born and raised in Scotland. Leucoplakia was again found to be more common among women in the study group, 30%, and the largest proportion was again found for the buccal mucosa, 58%. Nutrition-wise, there was again no remarkable difference with the exception of tongue cancer cases, whose intake of citrus fruit was deficient among 38% of the study group compared with 25% among the controls.

Discussion

It is pertinent to determine how different variables found to be significant in the development of cancer of the oral cavity act and interact, and to ascertain to what extent their reduction or modification can lead to a decrease in the incidence of cancer of the oral cavity.

Tobacco

Smoking, as in previous studies of lung and larynx cancer, was found to be an important factor in the development of cancer of the mouth. This applies to all sites of mouth cancer and to women as well as men. Of particular interest is the fact that the relative risk of a cigar and pipe smoker developing cancer of the mouth appears greater than for a cigarette smoker, which is in contrast to the pattern encountered in lung cancer, where the risk of developing this type of cancer is far greater for the cigarette smoker than for the pipe and cigar smokers.

One can only speculate on why cigar and pipe smoking carries a greater risk for mouth cancer than cigarette smoking. One must consider the fact that inhalation is practised more commonly among cigarette than among cigar and pipe smokers. We found 90% of the former and only

15% of the latter to claim that they inhale intentionally. The smoker who does not consciously inhale perhaps keeps the smoke condensate in his mouth longer than those who inhale it into their lungs. It is also possible that the cigar and pipe smoker who tends to keep the cigar and pipe in his mouth longer than a cigarette smoker is exposed more extensively to the tobacco juices.

The fact that the relative risk of a cigarette smoker to develop lung cancer is greater than the corresponding relative risk for mouth cancer might be due to a greater susceptibility of bronchial epithelium compared with oral mucosa. It is also likely that in the smaller confines of the bronchial tree tobacco condensate tends to accumulate more extensively than on the wider and smoother surfaces of the oral mucosa. Furthermore, the constant washing of the oral mucosa through salivation and mastication may prevent the settling of tobacco condensate on its surfaces.

Experimental work has demonstrated that cigarette tar extracted with hexane from unsmoked cigarettes is far less carcinogenic than cigarette smoke condensate (Wynder and Wright, 1957). This demonstrates that the carcinogens in tobacco smoke are largely formed through combustion. These data are compatible with the present data that tobacco chewing plays a lesser part in the formation of cancer of the oral cavity than tobacco smoking.

It has been stated that tobacco could not be a major cause of cancer of the oral cavity because no increase has been noted in males for mouth cancer though there has been a sharp increase in cigarette consumption. U.S. Census data show that, although there has been an increase in cigarette consumption during the past two or three decades,

FIG. 8.—Consumption of tobacco during the twentieth century. (From Haenszel and Shimkin, 1956.)

the total number of smokers has not increased very much, and, in fact, for cigar and pipe smokers there has been a marked drop (Haenszel and Shimkin, 1956) (Fig. 8). In other words, the principal change has been for cigar and pipe smokers to become cigarette smokers. In view of the fact that cigar and pipe smoking involves greater risk for cancer of the mouth than cigarette smoking, we would not expect an increase in cancer of the oral cavity. On the other hand, we would anticipate a slight increase in women because they never smoked cigars and pipes, but are now beginning to have an increased cigarette consumption, which should increase their risk of developing cancer of the mouth.

In a separate report a study of environmental factors of cancer of the mouth in India is presented (Wynder, 1957). The results of this study are in line with those recently reported by Sanghvi and his associates (1955) in that they show cancer of the mouth to be significantly related to bidi smoking and betel-nut chewing. The association of the latter seems to be limited chiefly to cancer of the lip, gum, and buccal mucosa. We attempted to determine whether tobacco was a necessary ingredient of the betel-nut quid among patients with mouth cancer. This was difficult to determine, because there were very few patients with mouth cancer who chewed betel-nut quid without tobacco and were at the same time non-smokers. There is a suggestion, however, based primarily upon female data, that the person chewing betel-nut quid containing tobacco has a greater risk of mouth cancer than the person using one that does not contain tobacco.

Alcohol

Alcohol has a marked influence on the development of cancer of the mouth. As in previous studies on larynx cancer, we were unable to effect a simple separation of

tobacco and alcohol effects, since there were few heavy drinkers who are not at the same time heavy smokers. However, it was possible to obtain some estimate of the separate effects of each factor by a rather complex analysis (Wynder, Bross, and Feldman, 1957). The effect of alcohol on mouth cancer occurs primarily, though not exclusively, in patients who are heavy whisky drinkers. One can only speculate on how alcohol increases the risk of oral cavity cancer. This could be due to a direct effect of the alcohol on the tissues. It could be due to a decrease of protective saliva from the mucosa, which would tend to make it more susceptible to the effect of tobacco. A third possibility is an indirect action due to nutritional deficiencies. Though we were unable to determine significant nutritional differences between study and control groups, it is generally accepted that a majority of people who drink heavily will none the less have certain nutritional deficiencies. In reviewing the literature we were surprised at the lack of detailed studies in this respect. However, available data suggest that alcoholics have deficiencies in ascorbic acid, thiamine, riboflavin, and, upon liver involvement, also vitamin A (Jellinek and Jolliffe, 1940).

The elucidation of the mechanism of the alcohol effect would seem to be a problem for laboratory investigation.

Plummer-Vinson's Syndrome

It is interesting to speculate how nutritional deficiencies associated with alcoholism may tie in with the nutritional deficiencies of Plummer-Vinson disease. In a separate investigation we have demonstrated that Plummer-Vinson disease in Sweden is responsible in large part for the relatively high rate of cancer of the mouth in Swedish women (Wynder, Hultberg, *et al.*, 1957). In addition to a chronic iron-deficiency state, Plummer-Vinson disease probably also involves other nutritional deficiencies, notably vitamins C and B. Future laboratory studies in Sweden and in the United States may determine what common basis there may be in nutritional deficiencies of alcoholism and Plummer-Vinson disease, and from the possible finding of a common denominator much may be learned about some of the intrinsic factors that regulate the formation of cancer of the oral cavity.

Dental Conditions

Dental hygiene and dental irritation have often been stressed as important factors in cancer of the mouth. There is some evidence for this in the present study, though these factors do not appear to be major ones. It is possible that in the isolated case a specific irritation may add to the development of a cancer already initiated, which is compatible with laboratory experiments. The most interesting finding about dental conditions is that edentia occurs more commonly among the study cases than among the controls and more commonly among women than among men. It may be theorized that the same type of deficiency which leads to a loosening of the teeth, perhaps through atrophic changes in the gums and mucous membrane, also promotes cancer of the mouth. In studies on Plummer-Vinson disease we had previously emphasized the marked degree of early edentia. It is of interest in that respect that we found a relationship of pregnancy to edentia, particularly among the study cases. This may indicate that some deficiencies promoted by pregnancy may be the same ones which promote edentia and neoplastic changes in the mucous membranes. Deficiencies commonly associated with pregnancy involve especially calcium and iron, but undoubtedly must involve other minerals and vitamins.

Syphilis

Syphilis was shown to be of some importance in the development of cancer of the lip and of the anterior two-thirds of the tongue. It cannot be established whether this relationship is due to syphilitic glossitis or to arsenical therapy, which most of these patients have received. At any rate, with the modern methods for control of syphilis through its early treatment with antibiotics, this factor will be less important.

Other Factors

Other factors of significance in the development of cancer of the lip include excessive exposure to sunlight, a finding in line with the general geographical distribution of cancer of the lip.

A few occupations seemed to influence the development of certain types of cancer, particularly those of cancer of the tonsil and pharynx, which showed a suggested relationship to the type of exposures that confront plumbers and metal workers. It is of interest that the general occupation of metal workers had been under previous suspicion in cancer of the lung. All of these patients, however, were also smokers. There were no single occupations so outstandingly frequent among the study group as to cause particular concern or to be of special academic interest. However, it would be of value to investigate causes of death within these industries to determine whether the present data can thus be confirmed.

Incidence Pattern

We stated, when introducing this report, that variables significant in a given statistical study will gain causative importance if these variables can account for the incidence pattern of a given cancer. We have summarized the incidence variations among different population groups and compared these with the extent of exposure of these groups to variables found to be of statistical significance. In general, there is a close agreement between the degree of exposure of these variables and the incidence of cancer in a given population group.

1. The greater prevalence of male over female cases of cancer of the mouth is consistent with the heavier consumption of tobacco and alcohol among the male population.

2. The fact that cancer of the oral cavity in males has not increased and perhaps has even decreased in some areas is consistent with the fact that the relative risk of mouth cancer is greater for cigar and pipe than for cigarette smokers. During the past decade, although there has been a slight increase in the total number of smokers, there has been a decrease in the number of people smoking cigars and pipes. In view of this fact, we should not expect an increase in mouth cancer as has occurred in lung cancer, a type of cancer predominantly related to cigarette smoking.

3. A small increase of cancer of the oral cavity in women should be expected, because women to-day smoke more cigarettes than in the past and they have never smoked any cigars and pipes. This increase, however, should be small, because there are relatively few women in the cancer age who have smoked extensively for 20 years. Incidence data, of course, are furthermore influenced by some other factors, as suggested by this study and by improved therapy, which makes an exact comparison difficult. However, the present incidence of mouth cancer in men and women is certainly not inconsistent with the relative exposure to different tobacco types and to alcohol.

4. The greater prevalence of cancer of the oral cavity among Catholic men than among Jewish men at the Memorial Center is consistent with the finding that there are three times as many heavy alcohol drinkers among the former.

5. The relatively high rate of cancer of the oral cavity in Swedish women is consistent with the prevalence of Plummer-Vinson disease among this group.

6. The relatively high rate of lip cancer in southern countries is consistent with the greater exposure to sunlight as compared with northern areas.

7. The high frequency of cancer of the mouth in India is consistent with the high rate of bidi smoking and betel-nut chewing.

In addition to the above factors, syphilis and a few occupations influence the rates of cancer of the mouth, particularly for specific sites, but do not seem to have a major influence on the overall incidence.

Preventive Measures: A Summation

The main objective of this communication is to consider possible preventive measures which might effect substantial reduction in the incidence of oral cancer. From this point of view those environmental factors are of special importance which involve a sizable proportion of the general population and which are susceptible to control, either directly or indirectly.

From the point of view of preventive medicine, the main question is whether this study revealed any factors which are susceptible to control and whose control could effect a marked reduction in the nation-wide incidence of oral cancer.

In order to make any prediction of the effect of control of a given factor or factors, it is necessary to make some assumptions. However, if one makes several predictions, each based on somewhat different assumptions, and if these predictions are in general agreement, one can have greater confidence in the prediction. If we assume that control measures are fully efficient and hence the risks for individuals now exposed to an agent would be reduced to the risks of the individuals with little exposure to the agent, we can use the data in this study to predict the potential reduction in incidence rates. Thus, if tobacco and alcohol effects were eliminated by fully effective control measures we would predict that about four out of five male cases of oral cancer could be avoided. If we assume that the inherent susceptibility of males and females to oral cancer is about the same, then if tobacco and alcohol effects were absent the male rates would diminish to the female rates. For example, in New York State (exclusive of New York City) the 1951-3 incidence rates for oral cancer were 15.1 (per 100,000) in men and 4.0 in women. (These data from New York City were supplied to us by Dr. Morton Levin through personal communication.) This would suggest that three out of four male cases of oral cancer are preventable. In view of the fact, as shown by this study, that at least some of the female cases are also related to tobacco and alcohol, the actual lowering of incidence rates that can be achieved should be even more pronounced. We derived a partial check on the assumption of similar inherent susceptibilities of males and females by further analysis of the basic data presented here. While the check is a crude one, we can say that the data seem compatible with this assumption. The Swedish data suggest that, if anything, women may be inherently somewhat more susceptible (Wynder, Hultberg, *et al.*, 1957).

These estimates are, of course, too optimistic, since we would not expect to develop full effective control measures with respect to tobacco and alcohol. Yet, even if the measures were only half effective, there should be a sizable reduction in the incidence of oral cancer in American males.

The question remains, what specific control measures are feasible? From a hypothetical point of view, the individual should reduce or moderate his consumption of tobacco and alcohol. Here it must be emphasized that there is a distinct difference in the use of the term "moderation" as it applies to tobacco and alcohol consumption. Most people will agree that the person who consumes seven or more drinks daily is an excessive drinker, and it is primarily this kind of drinker who carries an increased risk of cancer of the mouth. On the other hand, the person who smokes 20 cigarettes a day or the one who smokes three or four cigars or five or six pipes a day is usually considered a moderate smoker. Yet from the point of view of cancer risk this does not represent smoking in moderation. Only the smoker consuming fewer than 10 cigarettes a day or the equivalent in cigars and pipes has a relatively low risk of cancer of the upper alimentary or respiratory tract. From a practical point of view, voluntary restriction of consumption does not work out effectively. Hypothetically, prohibition of the agents might be a control measure, but past experience with prohibition indicates that this approach is not feasible.

The most promising field in respect to tobacco at present appears to be further research to identify the carcinogens in tobacco smoke and to reduce the exposure to the carcinogens by effective filtration or modification of the tobacco in cigarettes, pipes, and cigars. If safer tobacco products can be developed—and current laboratory results are encouraging—then these can be substituted for present products. Such modifications might reduce the incidence of oral cancer and also the incidence of lung and larynx cancer and other cancers related to smoking. Another measure which can be begun now would be the health education of students in high school. One preventive measure, in conjunction with alcohol effects, would be improved nutrition, particularly with respect to possible supplements of iron and vitamins B and C.

These recommendations apply primarily to oral cancer in countries such as the United States. Preventive measures have to be tailored to the particular situation, and therefore the emphasis in other countries might be somewhat different. In Sweden, for example, current preventive measures in respect to dietary supplements are already achieving a reduction in Plummer-Vinson disease, and, we believe, will eventually reduce the incidence of oral cancer in women from Northern Sweden. In India, moderation in the use of bidis and betel-nut chewing should lead to a great reduction in oral cancer. In the warmer regions of the globe protection against excessive exposure to sunlight, particularly among fair-skinned people, represents a preventive measure for lip cancer.

From the point of view of preventive medicine we can avoid many of the semantic tangles and arguments that have hampered the study of environmental agents in cancer. The important question is not whether an agent is "associated with," "increases the risk of," "causes," "initiates,"

or "promotes" cancer at a given site, although this question is of academic interest. The essential question is whether control measures can be devised which will reduce the incidence of the cancer. Similarly, we can avoid the confusion engendered by multiplicity of factors. A disease such as cancer has a complex aetiology, and,

FIG. 9.—Aetiological factors in cancer of the oral cavity.

as this study indicates, there may be many factors operating (Fig. 9). Even if a given factor accounts for a few cases, this is surely no reason to ignore factors which account for the majority of the cases. The viewpoint of preventive medicine enables us to maintain some perspective and to keep us from focusing all of our attention on a handful of highly interesting but very rare case histories.

Finally, we would like to make clear the spirit in which these predictions and recommendations are made. We cannot claim that some assertions are absolutely correct, since they have not been subjected to the final test of experience. Until control measures actually reduce the incidence of disease, we can only employ indirect arguments. The final proof of epidemiological data, however, the reduction of disease, cannot be accomplished until proper control measures have been instituted.

The goal we expect to attain demands that we give this problem our fullest attention. If our conclusions are correct, then perhaps much of the suffering and death from oral cancer can be avoided. We do not believe, as stated at the onset of this discussion, that the development of practical control measures must await a complete understanding of the pathogenesis of a given disease. This holds

as true to-day as it did during the days of Snow. In this concept lies the practical significance of epidemiological research and preventive medicine.

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SEROLOGICAL EVIDENCE OF INFECTION WITH SENDAI VIRUS IN ENGLAND

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The first description of Sendai virus as a possible cause of human disease was given by Sano *et al.* (1953), who investigated an outbreak of pneumonitis among newborn infants in a hospital at Sendai, Japan. Twelve out of 17 patients died. The onset was acute, with pyrexia, cyanosis, and marked dyspnoea. X-ray examination showed opacities in the lung fields of some cases, but there were few physical signs in the chest. Jaundice developed in a few cases. From five of the fatal cases, Kuroya *et al.* (1953) isolated a virus by the intranasal inoculation of mice with lung extracts and adapted it to grow in fertile hens' eggs. These workers also reported that a pyrexial disease with pneumonitis occurred in a human volunteer aged 8 years who had been inoculated intranasally with the virus and from whom it was subsequently re-isolated. Later the virus was found to have the property of agglutinating the red-blood cells of a fowl. Haemagglutination-inhibiting antibodies were found in the residents of the town of Sendai but were not present in residents of three other districts. The properties of this virus were also investigated in Japan by Fukumi *et al.* (1954).

In the course of a serological survey of sera from a variety of illnesses in the U.S.A., Jensen *et al.* (1955) found evidence of infection with Sendai virus in two patients; one had suffered from an atypical pneumonia and the other from a nondescript respiratory illness of two to three days' duration. No virus was isolated by these workers. They suggested that the virus might be termed influenza D.

Serological evidence of infection with Sendai virus was detected in this country in 1956 (Bruce White, Gardner, and Hope-Simpson, 1957), during the investigation of an outbreak of respiratory disease in a hospital for the chronic sick. Additional serological evidence of infection has been found in England in a number of other patients, details of which are the subject of this report.

Materials and Methods

For this investigation use was made of all suitably paired sera sent to this laboratory during 1956 from patients suffering