

ORAL CANCER

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INTRODUCTION

Like malignancy in other parts of the body oral cancer is a public health problem because co-ordinated community efforts and resources are required in the prevention and control of this disease. In any cancer control programme, research is an integral and important part of the programme, for it is only through research that knowledge is acquired which makes possible more effective control measures. Research is centred primarily on the nature and causation of the disease, its early detection, and improvement in the current methods of treatment.

Total prevention of oral malignancy cannot be attained at present because the etiology of this disease is still not clearly understood. However, partial prophylaxis may be achieved by removing suspected factors which act as chronic irritants in the mouth.

The early detection of this disease is so vital because on it may depend the life of the patient. In recent years, oral exfoliative cytology has been extensively promoted in the United States as an aid in the early detection of oral malignancy. However, specific diagnosis must still be made on

the basis of microscopic examination of tissue obtained by biopsy.

In the treatment of patients with oral cancer, rapid strides have been made in the realm of surgery and radiotherapy. The use of anti-cancer drugs represents another advance made in the management of patients with this disease, although at present chemotherapy is used mainly on a palliative basis.

Oral cancer is perhaps the most serious disease the dentist will encounter as far as the welfare of the patient is concerned. Members of the dental profession must share the responsibility with their medical colleagues in the fight against intraoral malignancy. The opportunity to detect an early lesion is very likely to present itself in the dentist's surgery, because the early symptoms of this disease are mild and are frequently interpreted by patients as minor dental disorders. The function of the dentist when he finds an abnormality in the oral cavity is not necessarily that of diagnosis but that of suspicion and referral. The task of referring the patient to a competent specialist for further examination and biopsy, if indicated, is the fundamentally important duty and responsibility of the dentist.

Cancer of the mouth is a global problem and, like malignancy in other parts of the body, its incidence and distribution vary from country to country. Environmental factors and racial susceptibility are believed to be responsible for such variations. Among the millions of people in South East Asia, oral cancer is a much greater problem than in Australia and other western countries. The peak incidence of this disease is seen in countries like Ceylon and India. According to Pindborg,²⁵¹ the percentage of oral cancer (expressed in terms of all cancers) in these two countries are 41 per cent. and 45 per cent. respectively. As compared to Australia in which oral malignancy constitutes about 4.8 per cent.* of all cancers, the magnitude of this problem in Ceylon and India is about ten times greater than in Australia.

In other South East Asian countries, the prevalence of this disease is also greater than in Australia, though not quite as high as in Ceylon and India. Thus according to Pindborg,²⁵¹ the percentage of oral cancer in Indonesia is 12 per cent., in Malaya 15 per cent., in South Vietnam 15.1 per cent., and in Thailand 21 per cent. These are percentages expressed in terms of all cancers.

At present, it is not possible to give exact figures for the incidence of oral cancer in the

* For Victoria 1959 - 1964, *Victorian Central Cancer Registry*.

majority of Asian countries, since in most of these countries there are no cancer registries. Hence, the morbidity of this disease is not easily assessed, and in countries where the system of death reporting and registration are not compulsory, or are inadequate, reliable mortality data are also difficult to come by.

At present, Australia has no national cancer registry and, therefore, morbidity data of oral cancer for the whole country as such are not available. However, accurate and reliable mortality figures for this disease can be obtained from the Commonwealth Bureau of Census and Statistics. The only state in Australia which has a central cancer registry at the moment is Victoria. Until such time as accurate statistics are available from a national cancer registry, or from cancer registries in all the states, data regarding oral cancer morbidity can only be obtained from institutions engaged in cancer diagnosis, treatment, and research.

In the preparation of the second part of this thesis, the author has visited the major hospitals in all capital cities - Sydney, Melbourne, Brisbane, Adelaide, Perth, and Hobart (for Darwin and Canberra, the information obtained is through correspondence) - in an attempt to collect information relating to the morbidity of oral cancer in Australia by age, sex,

intraoral sites (lip, tongue, floor of the mouth, buccal mucosa of the cheek, gingiva, palate, and salivary glands - according to the International Classification of Diseases, these sites are covered by the coded number from 140 to 144, and 191.0)

histologic type of cancer, treatment, and prognosis.

The information collected are from a personal examination of the case histories of patients with this disease first seen in these hospitals during a six-year period from 1959 to 1964 inclusive.

The first part of the thesis is an extensive review of the literature on the subject of oral cancer, its etiology, methods of detection and diagnosis, its metastatic capacity, and the general treatment of the disease. With perhaps the exception of the histopathology of oral malignancy, the various aspects of this disease and its occurrence in the different intraoral sites have been covered in detail. The section on oral sarcomas is included to make the review more complete and is treated only very generally.

ORAL CANCER

PART ONE

REVIEW OF LITERATURE

DEFINITION OF TERMS

Throughout this thesis there will be certain basic terms which will be used repeatedly. A definition of these terms, as given by Castigliano,⁵¹ will be appropriate here:

TUMOUR A tumour is an abnormal growth, growing independently of the rest of the body and serving no useful purpose. A tumour may be benign or malignant.

NEOPLASM Neoplasm is a synonym for tumour and, therefore, may be benign or malignant.

CANCER Cancer is a generic term encompassing all malignant tumours or neoplasms.

CARCINOMA Carcinoma is a malignant tumour of epithelial origin - example, carcinoma of the skin, lip, tongue, stomach, thyroid gland, rectum, etc. This form of malignancy constitutes 95.6 per cent. of all cancers.

SARCOMA Sarcoma is a malignant tumour of mesodermal origin - example, malignant tumours originating from connective tissues such as bone, cartilage, fibrous tissue, muscle, fat, etc. This type of malignancy makes up only 3.5 per cent. of all cancers.

METASTASIS Metastasis is a secondary focus of a malignant growth. Malignant cells may invade lymphatic channels or blood vessels, and may be carried to other parts of the body where they may live or die. If they live, the small nidus of cells grow as an independent tumour which is known as a metastasis.

ORAL CANCER Oral cancer is a term used to describe malignant tumours originating from epithelial or mesodermal structures of the oral cavity. Epidermoid carcinoma of the squamous type constitutes about 90 per cent. of all oral malignancies.

In the study of oral cancer in Australia, malignancy of the following intraoral sites is being considered - lip, tongue, salivary gland, floor of the mouth, buccal mucosa of the cheek, gingiva, and palate. According to the International Classification of malignant diseases,⁷⁶ these sites are covered by the coded numbers from 140 to 144, and 191.0 (skin of lip).

ORAL CANCER, A PUBLIC HEALTH PROBLEM

When a given problem of health and disease can no longer be solved by the unassisted effort of the citizen and the unco-ordinated resources of the community, it becomes a public health problem. The emphasis here is on the necessity of organised co-ordinated community effort and resources to solve problems of such a nature.

Oral cancer is a public health problem which goes beyond the unassisted efforts of the individual and requires the co-ordinated efforts of the entire community. Many intraoral cancer patients require extensive and expensive treatment, lengthy hospitalization, and special rehabilitative programme which call for assistance from outside the family circle. Like malignancy in other parts of the body, oral cancer is dreaded by all because of its shattering impact upon the health of the victim, the morale of the patient and his family, and the financial resources of those in the average income bracket.

The prevention and control of oral cancer embraces all the aspects in the fight against this disease. It involves research into the nature and causation of the disease, research into better methods and techniques of detection, diagnosis and treatment, the control of carcinogenic hazards encountered in the ordinary pursuits of daily life, the dissemination of

scientific knowledge at various levels in the community, the provision of adequate facilities for the detection and treatment of the disease, and the establishment of centres and clinics for such purposes.

Prevention is based primarily on the complicated and complex subject of the etiology of oral cancer and those lesions in the oral cavity that possess the potentiality of undergoing malignant degeneration.

Although much research has been done in this field, the basic causes of this disease are still not clearly understood. Hence, total prevention cannot be obtained at this stage. Partial prophylaxis can be obtained by reducing or removing any suspected irritants that might contribute to this disease. The dentist can aid materially in the prevention of oral malignancy by searching for evidence of chronic irritation in the mouths of patients, by cautioning them regarding the excessive use of tobacco and alcohol, by referring them for treatment in instances of suspected vitamin B deficiency disease or syphilis, by persuading them to discontinue such social habits as the chewing of betel nut and the practice of reverse-smoking, and by being on the alert for lesions which are potentially precancerous.

Much research has been done to improve methods and techniques in the detection, diagnosis, and

treatment of this disease. In recent years, the utilization of exfoliative cytology in the oral cavity as an aid to the diagnosis of intraoral malignancy has been extensively promoted, especially in the United States. Apart from the well established value of biopsy and oral exfoliative cytology, other methods of oral cancer detection and diagnosis are still on an experimental basis.^{31, 53, 229, 298} In the treatment of this disease, advances have been made in the field of radiotherapy in the last decade as are reflected in the use of super-voltage irradiation which has many advantages over conventional X-ray therapy.^{87, 274, 341, 396} In the realm of surgery, with the advent of endotracheal anesthesia, refined transfusion procedures, and a combination of sulfa drugs and antibiotics, the results of radical surgery have been elevated.^{41, 72, 73, 410} Research into the use of anti-cancer drugs has been fruitful and promising, although at present chemotherapy is mainly used on a palliative basis in the treatment of oral cancer patients.^{104, 133, 171, 173}

One of the aims of a cancer control programme is to make available to the medical and dental profession the information acquired from research. To this end, programmes for professional education regarding oral cancer have been developed and extended to members of the dental profession and undergraduate dental

students.^{110, 146, 147, 358} Education of the lay public is as important as professional education in a cancer control programme. Lay educational activities are designed to alert the public to the threat of this disease, and to motivate individuals to seek instruction upon the appearance of suspicious signs and symptoms that warrant examination. With this object in view, a great deal of time, effort, and money have been expended on lay propaganda in an attempt to improve the laymen's knowledge of this disease.

Dalitsch⁸¹ indicates that the promotion of a public educational programme for teaching self-examination of the oral cavity could be valuable, and this should be directed to the public in general, especially to middle and older age groups. This suggestion is based on the success of a similar self-examination programme in the early detection of breast cancer.

Facilities should exist for the detection, diagnosis, and treatment of oral cancer. There should be centres and clinics adequately equipped which would facilitate the management of patients with this disease, for without such facilities a highly trained group of personnel will not be able to give the best service to a well educated population in the control of oral malignancy. As can be seen from this, the

prevention and control of this disease requires a programme of immense magnitude, depending for its success on the co-ordinated resources and efforts of the community.

The control of oral cancer should be carried out on an international level besides local, state, and national efforts. Through the World Health Organisation, a meeting of investigators from different countries was arranged in New Dehli in 1963 as a first step toward the international control of this disease.^{415*} In this meeting, the epidemiology and pathology of oropharyngeal tumours were discussed with the view of establishing a standard histologic classification of such tumours.

As a result of the meeting, an International Reference Centre for the Histopathological Definition and Classification of oral and pharyngeal tumours has been established in Agra, India, under the direction of Professor P. N. Wahi. Six co-operating centres have also been established, one in each of the following places: Alma Ata in the Soviet Union, Boston in the United States, Colombo in Ceylon, Copenhagen in Denmark, Durham in South Africa, and Singapore.

In the meeting, the investigators recommended the establishment of reliable systems of death registration and the setting up of cancer registries in countries that have not got them. They also recommended further research into the etiology of this disease.

FREQUENCY OF ORAL CANCER

The study of the geographical distribution of oral cancer is important because an understanding of the variation in the incidence of this disease in different countries may help to elucidate the etiology of the disease and, therefore, make it possible to plan and institute practical preventive measures. The frequency of oral cancer may be expressed as a relative incidence, that is, the percentage of oral cancer to all cancers, or it may be expressed in terms of morbidity rate per 100,000 population or mortality rate per 100,000 population. Pindborg²⁵¹ states that the ideal procedure is to express it in terms of morbidity rate per 100,000 population.

However, such an estimate cannot be determined in the majority of Asian countries because of the absence of cancer registries in these countries at present. Therefore, the frequency of oral cancer is frequently expressed as a percentage of oral cancer to all cancers seen in large medical institutions.

From a review of the literature, Table 1 is presented to show the sharp geographic variation in the frequency of oral cancer, and cancer of the oral cavity and pharynx (W.H.O. Classification, 140-148) in different countries expressed either in terms of the percentage

TABLE 1

MORBIDITY DATA OF ORAL CANCER, AND CANCER OF THE ORAL
CAVITY PLUS PHARYNX (140-148) IN SELECTED COUNTRIES

Country	Cancer of the oral cavity			Cancer of the oral cavity and pharynx				
	%			%			Rate per 100,000	
	M	F	Total	M	F	Total	M	F
AUSTRALIA ⁴¹⁴ (VICTORIA) 1948-60				8.4	3.1			
BELGIUM ⁴¹⁵ 1963				4.4	1.5			
BURMA ¹²¹ (RANGOON)	22.9	5.6	13.3					
CANADA (REF. 414, 415)								
BRITISH COLUMBIA 1963-64				4.4	1.5			
MANITOBA 1963				5.4	2.3			
NEW BRUNSWICK 1964				8.8	1.6			
NEWFOUNDLAND 1963				1.9	1.0			
ONTARIO 1962				11.4	1.9			
PRINCE EDWARD IS. 1962				3.3	1.6			
QUEBEC 1963				10.5	2.4			
SASKATCHEWAN 1962-63				8.3	1.5		29.6	3.1
CHILE ⁴¹⁴ 1962				4.6	2.6			
CHINA ⁴¹⁷ (COMMUNIST)			6.2					
CEYLON (REF. 43, 55)			40.0 to 53.5					
CZECHOSLOVAKIA ⁴¹⁴ 1960-61				5.7	1.6		13.2	3.6

	M	F	Total	M	F	Total	M	F
DENMARK ²⁴⁷	4.0	1.2						
EUROPE ³⁷¹			5.0					
FINLAND ⁴¹⁵ 1960-61				5.1	5.2		12.3	4.3
FORMOSA (REF. 370, 417)			2.7 to 5.5					
FRANCE ⁴¹⁵ 1962				38.4	5.1			
GERMANY								
DEMOCRATIC REP. ⁴¹³ 1957-58				2.8	0.9		7.8	2.5
FEDERAL REP. (REF. 413, 415) 1963				2.9	1.4		8.9	4.6
HONG KONG ⁴¹⁷			2.9					
HUNGARY (REF. 371, 415) 1964			6.6	10.5	1.9		18.7	3.6
INDIA (REF. 27, 241, 242, 253, 268, 317)						26.6 to 48.0*		
INDONESIA (REF. 92, 266, 417)						8.5 to 11.9		
ISRAEL ⁴¹⁵ 1962-63				3.9	2.1		8.5	4.4
IRELAND ⁴¹⁵ 1963				29.4	6.2			
JAPAN (REF. 42, 268, 370, 417)						2.1 to 2.8		
MALAYA (REF. 207, 260)			6.9 to 15.0					
NETHERLANDS ⁴¹⁵ 1964				4.0	1.6			

*Oral cavity and oropharynx

	M	F	Total	M	F	Total	M	F
NEW GUINEA ⁷	23.0	10.8	17.8					
NEW ZEALAND ⁴¹⁵ 1963				3.6	1.4		7.0	2.5
NORWAY ⁴¹⁵ 1962				4.3	1.4		9.8	3.4
PHILIPPINES (REF. 42, 266, 285)			6.0, 10.5 23.8					
POLAND ⁴¹⁵ 1963				7.2	1.3		7.7	1.5
PORTUGAL ⁴¹⁵ 1964				26.2	3.9			
SINGAPORE ²²⁶			8.0					
SOVIET UNION (REF. 224, 268, 370)			4.6 to 7.1					
SWEDEN ⁴¹⁴ 1960				3.3	1.8		8.5	5.1
THAILAND (REF. 42, 254, 260, 417)			14.1 to 21.1					
UNITED KINGDOM ⁴¹⁵ (ENG. & WALES) 1962				3.6	2.0		9.7	4.8
UNITED STATES (REF. 47, 106, 107, 111, 182, 358, 395*)			4.0 to 5.0					
VIETNAM, SOUTH ²⁶⁰			15.9					
YUGOSLAVIA ⁴¹⁴ (SLOVENIA REP.) 1959-60				5.3	1.6		11.3	2.8

*Rate per 100,000

M = 19.4
F = 5.2 (oral cavity)

of oral cancer to all cancers or the morbidity rate per 100,000 population. Table 2 shows the different frequency distribution of oral and pharyngeal cancer (140-148) in 24 countries expressed in terms of mortality rate per 100,000 population, and this is further illustrated in figure 1 which depicts in descending order of magnitude the frequency of the disease in these countries.

Pindborg^{247, 248} indicates that in recent years, there are changes in the mortality rates of oral cancer in certain countries. This change is markedly seen in men where there is a decrease in the mortality rate, whereas in women there is an increase or no change in the mortality rate. He²⁵¹ presents the following table which summarises the findings of this significant change by various investigators. (Table 3) Further evidences of the change in mortality rate of cancer of the oral cavity and pharynx (140-148) in different countries are contained in the table prepared by Segi et al.³⁵⁵ (Table 4)

Pindborg^{247, 248, 251} indicates that the decrease in oral cancer mortality rate has been attributed to an elevation of oral hygiene standard, a reduction in the number of jagged teeth and ill-fitting dentures, and an elimination of other traumatic conditions that may predispose to the development of oral malignancy. Other factors which bring about this decrease according to

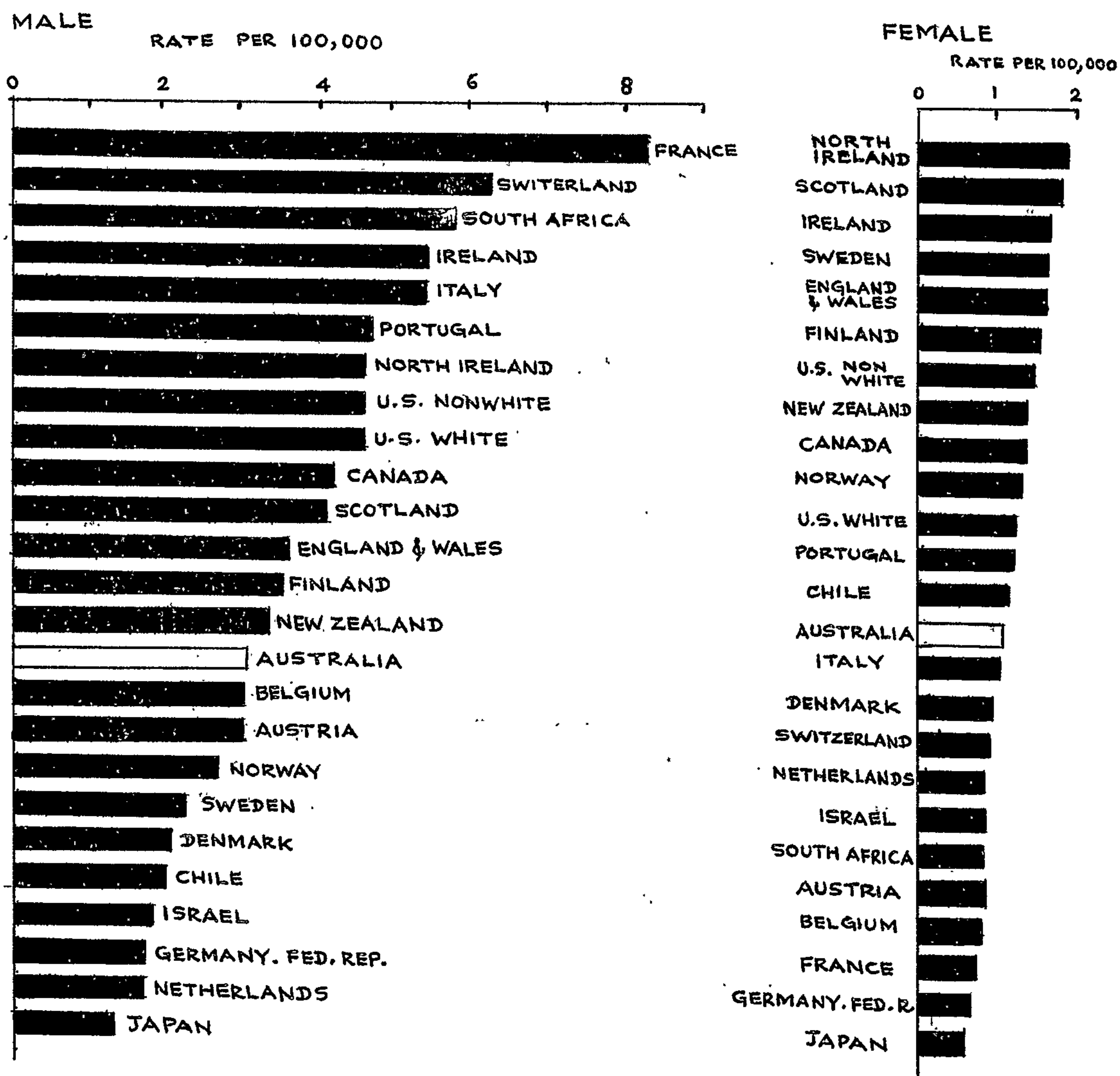
TABLE 2

AGE-ADJUSTED DEATH RATES PER 100,000 POPULATION FOR
MALIGNANT NEOPLASM OF THE ORAL CAVITY AND PHARYNX IN
24 COUNTRIES

COUNTRY	1960-1961	
	CANCER OF THE ORAL CAVITY and PHARYNX	
	Rate per 100,000	
	Male	Female
AUSTRALIA	3.08	1.06
AUSTRIA	2.98	0.80
BELGIUM	3.01	0.79
CANADA	4.16	1.29
CHILE	2.00	1.10
DENMARK	2.08	0.91
ENGLAND and WALES	3.58	1.57
FINLAND	3.51	1.50
FRANCE	8.32	0.72
GERMANY, FED. REPUB.	1.70	0.62
ISRAEL	1.85	0.83
IRELAND	5.44	1.65
ITALY	5.40	0.92
JAPAN	1.32	0.59
NETHERLANDS	1.68	0.83
NEW ZEALAND	3.37	1.34
NORTHERN IRELAND	4.60	1.88
NORWAY	2.63	1.28
PORTUGAL	4.68	1.15
SCOTLAND	4.12	1.83
SOUTH AFRICA	5.76	0.82
SWEDEN	2.25	1.63
SWITZERLAND	6.24	0.89
UNITED STATES (NON-WHITE)	4.59	1.46
UNITED STATES (WHITE)	4.58	1.26

SOURCE: SEGI et al.³⁵⁶

Figure 1



AGE-ADJUSTED DEATH RATES FOR MALIGNANT NEOPLASMS
OF THE ORAL CAVITY AND PHARYNX, 1960-61

Source: SEGI et al.³⁵⁶

TABLE 3

INVESTIGATIONS REVEALING CHANGES IN THE FREQUENCY OF ORAL CANCER

AUTHOR	COUNTRY	YEARS COMPARED	CHANGES IN FREQUENCY
BHANSALI	England	1936-45 vs 1946-55	M: 49% decrease F: 16% increase (oral cancer patients in Royal Marsden Hospital, London)
DALITSCH and VAZIRANI	U.S.A.	1943-47 vs 1953-57	M: 19% decrease F: 15% increase (oral cancer patients in Cook County Hospital, Chicago)
FREUDENBERG	West Germany*	1936 vs 1956	M: 50% decrease F: 33% decrease (mortality rate per 100,000)
HORAK	Australia	1934 vs 1961	M: 66% decrease in mortality
PHILLIPS	Canada	1941 vs 1957	M: 38% decrease in mortality F: no change
RUSSELL	England	1935-39 vs 1945-49	M: 40% decrease in morbidity rate F: 30% increase in morbidity rate
WOOD	England	1942 vs 1952	M + F: 31% decrease in mortality

*Includes oral cavity, pharynx and oesophagus.

Source: PINDBORG²⁵¹

PER CENT. CHANGE IN AGE-ADJUSTED DEATH RATES FOR MALIGNANT
NEOPLASM OF THE ORAL CAVITY AND PHARYNX FROM 1952-53 TO
1958-59 IN 21 COUNTRIES

COUNTRY	Per cent. change	
	Male	Female
AUSTRALIA	-22#	+15*
AUSTRIA	-24#	-18
CANADA	-15*	-10*
DENMARK	-12	-11
ENGLAND and WALES	-18#	-4*
FINLAND	-20	-12
FRANCE	+35#	+28#
GERMANY, FED. REPUB.	-0	-2*
ISRAEL	-43	+62
IRELAND	-18	+19
ITALY	+6#	+2
JAPAN	-8	+0
NETHERLANDS	-11	-4
NEW ZEALAND	-2	+15*
NORTHERN IRELAND	-9	-2
NORWAY	+14	+16
SCOTLAND	-27#	+4
SWEDEN	-2	-24#
SWITZERLAND	+3	-24
UNION OF SOUTH AFRICA	+26	+5*
UNITED STATES (NON-WHITE)	+22*	+3*
UNITED STATES (WHITE)	+3*	+6*

SOURCE: SEGI et al.³⁵⁵

Figures with mark #: Continuous increase or decrease

Figures with mark *: Almost continuous increase or decrease

Figures without mark: Irregular trend

him are a decrease in syphilitic glossitis, early diagnosis of oral malignancy, and improvement in surgical techniques in the treatment of this disease. He adds that the increase in frequency of the disease in women has been attributed to an increase in the use of tobacco.

THE DENTIST AND ORAL CANCER

THE ROLE OF THE DENTIST

The dental profession has other responsibilities to the community apart from the restoration of teeth or the fabrication of dental appliances. One of such responsibilities is his participation in the prevention and control of oral malignancy. The dentist is required to share the responsibilities in the fight against oral cancer with his medical colleagues for the following reasons:

1. Members of the dental profession can contribute significantly in the detection and diagnosis of intraoral malignancy and prophylaxis against this disease by virtue of the fact that the public is educated to visit their dentists for regular dental check-ups. This provides the dentist with an excellent opportunity to examine the oral cavity at periodic intervals.
2. In many instances, the dentist has been consulted first by patients with intraoral lesions. Boyle,¹⁸ Handy,¹³¹ and Gardner et al.¹⁰⁵ indicate that about one third of all patients with oral malignancy consults a dentist first, and this is especially true in the case of gingival cancer. To illustrate this point, the following

table, prepared by Castigliano,⁵¹ shows the percentage of patients with cancer at the different intraoral sites and adjacent regions who consulted a dentist first before consulting a physician. (Table 5)

TABLE 5

PATIENTS WITH ORAL CANCER SEEN BY DENTIST BEFORE REFERENCE TO PHYSICIAN AND PROPER TREATMENT

	Percentage of Patients consulting Dentist Before Physician	
	H. Martin Series*	Castigliano Series ⁵¹
Lip	-	5.0
Tongue	-	7.7
Tonsil	35	20.8
Buccal Surface of Cheek	35	27.9
Palate	45	32.2
Floor of Mouth	27	40.0
Gum	65	49.2
Maxillary Antrum	-	52.6
Oropharynx	-	00.0
Nasopharynx	-	00.0
Parotid Tumour	-	00.0

* - Memorial Hospital (597 cases)

⁵¹ - Oncologic Hospital (530 cases)

SOURCE: CASTIGLIANO⁵¹

3. The oral cavity is familiar ground to the dentist, and his knowledge of this region of the body and constant contact with it SHOULD enable him to

distinguish competently what is normal and what is not normal in the mouth. The important thing is for the dentist to be able to detect any suspicious abnormal growth or lesion within the oral cavity, diagnose it perhaps, or AT LEAST refer the patient to more competent authorities who can establish a correct diagnosis in the shortest possible time so that treatment can be instituted.

All this does not infer that the medical profession has a less significant role in the early detection and diagnosis of oral cancer. The fact is that a well developed programme in the detection of this disease could be made available to members of the profession and undergraduate dental students whose main interest is the oral cavity.

The treatment and rehabilitation of patients with extensive oral and facial growths has become a formidable and complicated problem. In order to ensure that the patient receives the best possible treatment, there must be a concerted and conscientious effort of a carefully selected group acting in perfect accord. This group, functioning harmoniously as a co-ordinated team, should include all medical and dental specialists with adequate training in this type of surgery and rehabilitation.

The oral surgeon, the prosthodontist, and the general dental practitioner should all be an integral part of this team. Each of them should be consulted routinely prior to radical surgery in order that replacement of lost structures can be planned accurately, and the oral cavity be made to simulate the normal. . . . Spilka, Cole and Malson³⁰⁷ indicate that in many instances the dental specialist is the 'forgotten man' when surgery is being planned for extensive oro-facial growth. Frequently, it is not until when reconstruction and rehabilitation are being considered that the dental specialist's help is sought. . . . They indicate that this is unfortunate since the eventual restoration of function and appearance is as important to the patient as the eradication of the disease. . . . Prevention of disfigurement can be attained by a proper and accurate prosthesis inserted at the optimal time.

The dentist may aid the team in preparing the patient for treatment, in the treatment period, and throughout the post-treatment of the patient. The institution of good oral hygiene, removal of calculus and all sources of irritation, and the extraction of teeth in regions which will be subjected to radiotherapy are the responsibility of the dentist. The extent of the extraction of teeth and the appropriate

time must be established in collaboration with the radiotherapist. In the event of surgery, extensive defects and deformities may be created, and impressions for study casts may prove invaluable in the rehabilitation of the patient later on.

In the rehabilitation of oral cancer patients, the dentist may prove to be a valuable member of the cancer control team by virtue of his experience and knowledge in the specialised branch of prosthetics. The contribution of the prosthodontist in this field is of great significance. Treatment of patients with cancer of the head and neck often necessitates extensive and radical surgery in which the ear, nose, eye, palate, mandible, or cheek may be removed completely or in part. The prosthodontist's knowledge of materials used in the fabrication of prostheses and his skill in the manipulation of splints and moulds to hold epithelial grafts (or radioactive sources) make him the most qualified person in the health team to construct such artificial substitutes. He should examine the patient during the pre-treatment evaluation and be present when the overall plan of management is being developed.

Protheses used in the rehabilitation of patients with head and neck cancer may be broadly categorized into three groups³⁵⁹ - (1) facial or

external prostheses, (2) intraoral prostheses, and (3) implants. Facial prostheses, which are made of flexible materials and are removable, are used primarily for aesthetic reasons. The intraoral prostheses, on the other hand, are used for both functional and cosmetic reasons. Their purpose is to replace portions of the maxilla, the palate, or the mandible, to help in speech and/or deglutition. Implants are artificial replacements of parts of bone.

Flesch⁹⁴ indicates that the dentist can create prostheses for the patient, but the task of using them is the patient's and not the dentist's. To this end, the patient can be assigned a series of small exercises or duties related to the use of the prosthesis, thus keeping the patient from falling into helpless passivity or dependency because of his illness. Bard¹³ reports that many patients have wrong ideas about prostheses and it is the dentist's responsibility to present the facts to the patient in a reassuring but realistic manner.

From such a consideration of what the dentist can and has contributed significantly to the welfare of the oral cancer patient, it can be seen that he is a valuable member in the oral cancer team. A team approach is essential in the treatment and subsequent rehabilitation of all patients with oral cancer. It

is this group approach which yields the best treatment for the patient with a minimal loss of time.

THE NEED FOR EARLY DETECTION AND DIAGNOSIS

Oral cancer is perhaps the most serious disease the dentist will encounter as far as the patient's welfare is concerned. The need for a high index of suspicion and the importance of early diagnosis and treatment in the management of this disease cannot be overemphasized.

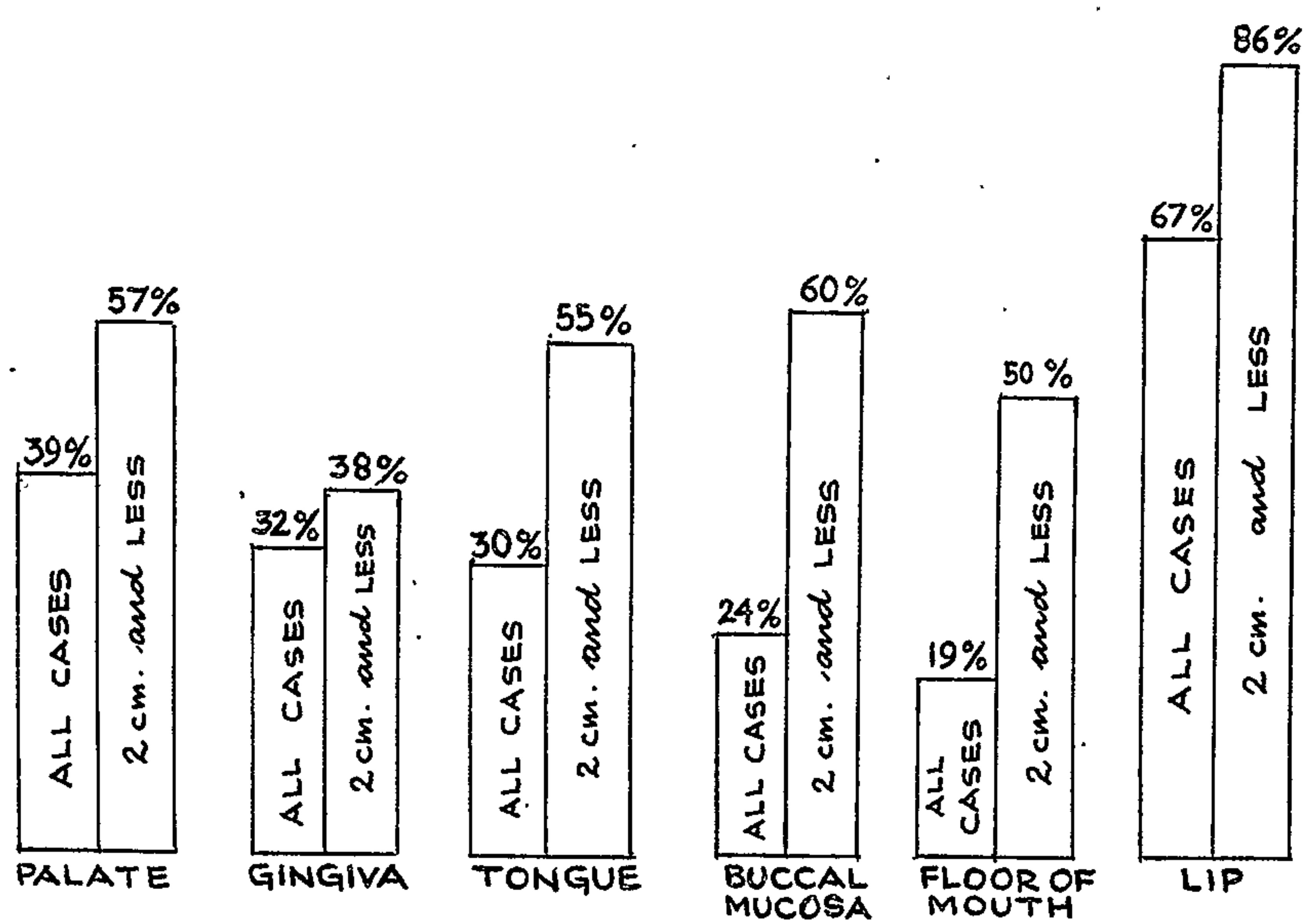
Cancer of the oral cavity is a more deadly disease than are many other malignancies occurring in different anatomical sites of the body.^{47, 106} Castigliano⁵¹ states that epidermoid carcinoma of the oral cavity is a more vicious and fatal disease than is cancer of the breast and cancer of the rectum. He claims that 80 per cent. of patients with neglected and untreated oral cancer die within eighteen months after the discovery of the disease, while Welch and Nathanson,⁴⁰³ on the basis of a very extensive survey of 2,923 intraoral cancer patients, report that the median life expectancy of untreated cases is ten months.

The physician and dentist should be alerted to a consideration of cancer first in any suspicious lesion in the oral cavity, and such a possibility should be ruled out before another diagnosis is

considered. A biopsy is mandatory in any suspicious lesion which persists in the oral cavity. Husted,¹²⁶ Donaldson,⁷⁹ Boyle,¹⁸ and Castigliano⁵¹ are of the opinion that any lesion which does not respond completely to treatment within a week to ten days should be considered as possibly cancerous until a correct diagnosis is established by biopsy.

The appraisal of the results of treatment in early detected cancer of the oral cavity has been a prime factor in postulating and supporting the thesis that early diagnosis and prompt treatment of this disease can effectively reduce its appalling mortality. Salley²⁸⁸ indicates that the five year cure rate for oral cancer can be doubled (from 33 per cent. to 66 per cent.) if lesions in the mouth are detected prior to an increase in size of 2cm., while Lloyd¹⁶⁹ and Odenheimer²³⁵ report that with early detection and treatment, at least 50 per cent. of intraoral malignancy can be cured. To illustrate this point, the following diagram (Figure 2) prepared by Taubenbaus³⁵⁸ shows distinctly the favourable five year survival rates of cancer in various intraoral sites when the lesions are detected early enough and are still small.

Figure 2



ORAL CANCER: FIVE YEAR CURE RATES

Source: TAUENBAUS³⁵⁸

Further evidence of the importance of early detection and diagnosis before the lesions grow to a point of hopelessness is contained in the following tabulation prepared by Handy¹³¹ based on more than 5,000 cases of intraoral malignancy from the National Cancer Institute (Table 6).

TABLE 6
FIVE YEAR SURVIVAL RATES OF PATIENTS WITH OROPHARYNGEAL CANCER

Types of Cancer	Five Year Survival Rates: Percentage			
	Early Cases		Late Cases	
	Male	Female	Male	Female
Cancer of the lip	92	83	65	24
Cancer of the Tongue	52	58	18	31
Cancer of other parts of the mouth includ- ing Buccal Mucosa	63	60	23	38
Cancer of Pharynx includ- ing Tonsil, Naso- pharynx, & Hypotharynx	29	45	13	18

SOURCE; HANDY¹³¹

Data of such a nature should provide an impetus to the dentist and physician to seek out early cases of oral cancer so that prompt and effective treatment can be instituted. Castigliano⁵¹ indicates that metastases generally occur, or at least become clinically manifested, only after the primary cancer in the oral cavity has been present for some

time. Hence, the longer the delay the greater is the chance for metastases to develop. Metastasis is the cause of many failures in cancer therapy. It is for this reason that early detection and prompt treatment are so important if success is to attend therapeutic efforts.

Patient's procrastination, either through ignorance, fear, financial problems, etc., could cost the patient his life. However, professional delay on the part of the physician or dentist to arrive at a correct diagnosis and, hence, a delay to corrective therapy also play an important part in the low salvage rate in this disease. Martin¹⁸⁰ points out that in many instances where a patient with oral cancer consults a dentist, the malignant character of the disease is not recognized, and in such cases, some form of dental treatment is usually given over a considerable period of time, and the patient is reassured that his complaint is not serious by the non-committal attitude of the dentist. This sort of approach frequently results in the loss of valuable time which can lead to a fatal outcome.

A more specific analysis by Martin¹⁸⁰ shows that when the dentist did not recognize the malignant nature of the patient's complaint, extraction of teeth was performed in 70 per cent. of cases. The

patient is entitled to the best possible care and through ignorance, indecision, incompetence, and a negative action on the dentist's part may deprive the patient of a good chance of a cure.

THE CASE HISTORY AND CLINICAL EXAMINATION

In order that the dentist (or physician) may play his part effectively in the detection of oral cancer, he must be acquainted with the early signs of this disease, learn the technique of examining the oral cavity, and establish a routine for examining the entire mouth.

The first step in obtaining necessary knowledge about the patient and his disease is the taking of a detailed history which should include his chief complaint, present illness, and past medical and dental history. The case history could prove to be a valuable aid to diagnosis and, therefore, systematic and thorough questioning is advisable. The case history should include detailed information regarding events leading to the development of the lesion, the initial character of the lesion, and any changes which occurred as it develops. It should also include any symptoms which attended the development and progress of the lesion.

Following the case history, a detailed examination of the face, neck, and oral cavity is carried

out. This should be accomplished in an orderly procedure of inspection, palpation, percussion, and sometimes auscultation.^{116, 159} Palpation is important and, whenever possible, bimanual palpation should be employed and bilateral inspection should be done to compare the right side with the left.

The clinical examination must be carried out under proper and adequate illumination. Finger cots, mouth mirror, tongue blades, and sponges may be used. To ensure a complete examination, these procedures should progress in an orderly and routine manner so that all areas are examined. A systematic and thorough procedure, as advocated by Gans¹¹⁶ and Kerr,¹⁵⁹ is as follows:

1. The face and neck is examined for symmetry, blemishes, rash, warts, ulcers, and pigmentation followed by palpation of each group of cervical lymph nodes, major salivary glands, and thyroid glands for evidence of enlargement or firmness.

2. The lips are inspected for persistent ulcers, encrustations, deep fissures, white plaques, swellings, atrophy, colour, and texture, plus palpation for induration using the index finger and thumb.

3. The cheeks are retracted so that both

sides can be clearly visualized and palpated for masses. Bimanual palpation should be used. The vestibular fold and openings to Stenson's duct are also inspected.

4. Next, the palate is examined for any alteration in contour, evidence of swelling, or areas of softening due to bone destruction.

5. All four surfaces of the tongue are carefully examined. Inspection and palpation of the lateral and dorsal surfaces of the tongue can be facilitated if the tongue is pulled forward with the tip held with a gauze sponge and then moving the tip from side to side. The patient may then be instructed to elevate his tongue to close scrutiny of the ventral surface.

6. The floor of the mouth is examined as the patient's tongue is elevated. Palpation of the floor of the mouth for any lesion located deep in the tissues should be bimanual. The procedure further enables observation as to the patency of the submaxillary and sublingual ducts and the quality of secretion.

7. The gingivae and their associated structures are next examined for spontaneous haemorrhage, purplish discolouration, and interdental papillary enlargement (this may reflect a malignant process).

Spontaneous loosening of teeth in the absence of odontogenic reasons, either periodontal or caries, should be viewed with suspicion.

8. Inspection of the oropharynx and nasopharynx necessitates the use of a laryngeal mirror. In occasional patients, topical anesthesia may be used to prevent gagging. Holding the patient's tongue with one hand and the laryngeal mirror with the other, the posterior surfaces of the tonsillar pillars, the vallecular, base of the tongue, pharyngeal wall, and larynx may be visualized. Then, by depressing the tongue with a tongue blade and reversing the laryngeal mirror, the nasopharynx may be inspected.

After the clinical examination, the jaws should be examined by full mouth periapical X-ray films and, whenever necessary, this could be supplemented by lateral jaw or occlusal films. X-rays are particularly valuable when detecting bony involvements.

The diagnosis of lesions in salivary glands may be facilitated when a sialogram is employed using a contrasting medium.

When a lesion is detected in the mouth, it should be examined in detail to determine its nature and cause if possible. If a positive diagnosis cannot be made by clinical examination, it may be necessary to carry out various laboratory procedures

such as haematologic, bacteriologic, and histologic studies. When such special investigation is warranted, the dentist should make positive and immediate arrangements for the patient to see a competent specialist. The dentist is not fulfilling his responsibility by casually suggesting further investigation in an off hand fashion. The dentist must take the initiative and make all the necessary arrangements and make sure that the patient follows his instruction. The task of placing the patient in proper hands for further examination and biopsy is the fundamentally important duty and responsibility of the dentist.

It is important that this should be done as tactfully as possible without alarming the patient unnecessarily and at the same time without loss of valuable time. Boyle¹⁸ points out the importance of the careful choice of words when informing the patient of the necessity for a further investigation. He feels that the term cancer should be avoided and words such as growth or lesion be used instead. However, Stehlin and Beach³⁰⁸ differ markedly from this view, and believe that the word cancer should be used. They indicate that terms such as tumour, growth, mass, or malignancy are less meaningful to the layman and should be avoided.

Bard¹³ is of the opinion that the dentist

should be prepared to spend considerable time with the patient, interpreting the need for biopsy and encouraging the patient to express his feelings and fears freely so that misunderstandings and misconceptions may be clarified.

BIOPSY

The word Biopsy is derived from the Greek word bios, which means life, and opsis, meaning sight or vision. Perhaps the best definition of the term is that of Stoopack,³³⁸ who defines it as the removal of a piece of tissue from a lesion on a living patient for direct histological examination as an aid to correct diagnosis and treatment.

Early correct diagnosis is imperative in malignant disease. At present, diagnostic confirmation of any malignant lesion can only be achieved by the microscopic examination of the tissue involved. The histologic diagnosis, invaluable though it may be, is only a diagnostic aid, and its limitations have to be realised. To arrive at a correct diagnosis, one may have to utilise other diagnostic aids such as case history, clinical examination, radiographic examination, and relevant laboratory tests.

Castigliano⁵¹ indicates that microscopic examination should not only be confined to lesions obviously malignant. Rather, a biopsy should be used to rule out malignancy in seemingly significant lesions. He adds that it should not be regarded as a waste of time if the majority of the lesions biopsied prove to be non-malignant. In fact, this

should be so as it underlines the principles of preventive medicine.

Besides being a diagnostic tool, biopsy is employed for other purposes. These include the assessment of whether a relatively benign lesion has malignant tendencies as in leukoplakia, the determination of the degree of malignancy after the diagnosis of a lesion has been established, and the evaluation of the degree of radiosensitivity, which will help in the treatment planning.^{16, 338} Also, biopsy can be employed to identify specific infectious processes, reactive lesions, and certain metabolic disorders.¹⁵⁹

Although there is unanimous agreement that for a definitive diagnosis of a lesion the biopsy is indicated, there is less agreement as to who should perform this procedure in lesions of the oral cavity. The question has often been raised as to whether the dentist is competent enough to obtain a representative sample of the involved tissue for microscopic examination. Castigliano⁵¹ feels that the average dentist will not be qualified to perform a biopsy. He emphasizes that the purpose of the biopsy is to establish a diagnosis in the earliest possible time in order that curative treatment may be instituted and, therefore, it is best to refer the patient to a specialist.

Cooke^{56, 75} is of the opinion that the person performing this surgical procedure must be familiar with oral pathology; but in the best interest of the patient when malignancy is suspected the patient should be referred to a specialist. Boyle^{18, 19} shares the opinion that the biopsy should be performed by a trained and experienced specialist who will assume the full responsibility of treatment as well.

On the other hand, Shira and Reed³²⁴ stress emphatically that biopsy procedures must become an integral part of the dental practice if the practitioner is to fulfil his obligation in the early diagnosis of oral lesions. Kerr and Hayward¹⁵⁹ indicate that the dentist is amply prepared in anatomy and basic surgical principles of the oral cavity to perform biopsy procedures in this region of the body. Cahn and Slaughter⁴⁷ are of the opinion that the dentist, through his close and constant association of working in the mouth, is competent to obtain an adequate and representative piece of tissue for histologic examination. However, they add that unless the dentist has had special training, he should probably confine his biopsy efforts to superficial mucosal lesions of the epidermoid carcinoma variety. For biopsy of a vascular sub-

mucosal bone tumour or angioma, the dentist must be aware of the possibility of creating a sudden haemorrhagic emergency and, in this regard, the biopsy procedure may be best performed in a hospital operating room rather than in a dental office.

Donaldson⁷⁹ indicates that in the case of a small lesion requiring excisional biopsy, the dentist may perform the biopsy if he wants to, but if the clinical impression is that of malignancy, or if the lesion is gross, then perhaps it would be better to leave it to a specialist.

In biopsy procedure, another issue which frequently has been raised is that relating to the possibility of disseminating malignant cells, especially in incisional biopsy. The general consensus of opinion today is that the likelihood of this happening is fairly remote. Castigliano⁵¹ and Thoma³⁶⁸ suggest cauterizing the wound after the biopsy has been performed so as to seal off exposed blood vessels, lymphatics and tissue spaces to minimise this remote possibility.

Cooke⁷⁵ and Slaughter³²⁸ indicate that although the risk of metastasis is not great, there is still the need for gentleness at all times when performing a biopsy. Stoopack³³⁸ is of the opinion that there is very little risk in surface lesions if sectioning

is done carefully, but in deeply situated tumours such procedure may modify the clinical setting and cause a breakdown of the natural local barrier to the spread of the disease, thus favouring early metastasis in some cases.

Bernier¹⁶ indicates that careful planning so that surgery follows immediately, or previous irradiation, will eliminate the possibility of spreading cancer cells. He advises caution in sarcomatous lesions since they are usually quite vascular and the risk of disseminating tumour cells is greater in these cases.

On the other hand, Boyle¹⁹ claims that the possibility of promoting metastasis through injudicious palpation of a lesion is very real, and quotes the impressive work performed on experimental animals by many investigators to substantiate his claim.

INDICATIONS FOR BIOPSY

It has generally been agreed by numerous authorities^{16, 19, 47, 51, 75, 126, 159, 252, 288, 324, 338, 398} that any lesion which cannot be diagnosed with certainty as non-malignant should be examined histologically. These include ulcers which persist for two to three weeks without evidence of healing, definite persistent hyper-keratotic changes on the surface tissues, any persistent visible or palpable

tumescence beneath relatively normal surface tissues, inflammatory changes which persist for prolonged periods, and any bone lesions of unknown etiology.

CONTRAINDICATIONS TO BIOPSY

Castigliano⁵¹ states that there is no contra-indication to biopsy. However, some authorities^{16, 19, 228, 338} are of the opinion that pigmented lesions such as nevi and melanomas should be handled with extreme care and gentleness because of their tendency to metastasize. They indicate that such lesions should not be cut into but removed by complete excision. The same applies to hemangiomas because of ensuing haemorrhage which is always severe and at times has proved fatal. Bernier¹⁶ further suggests that well encapsulated tumours should not be subjected to surgical incision since perforation of the capsule may interject some of the content, which may be dangerous, into the surrounding tissues. He is also of the opinion that lesions in extremely inaccessible places should not be approached twice.

Nepola and Allenby²²⁸ feel that mixed tumour and salivary gland tumours should not be incised, while Cooke⁷⁵ finds this hard to understand. He indicates that biopsy of any sort is contraindicated in patients thought to be suffering from blood dyscrasia, and that in such a case, smears of the peripheral blood stream

must be made first to exclude such a possibility.

SELECTION AND PREPARATION OF THE BIOPSY SITE

The area selected should be representative of the lesion in question. Numerous authorities^{75, 159, 253, 338, 368} believe that it is desirable, and at times essential, to include a portion of the normal adjacent tissue in the biopsy.

On the other hand, Castigliano⁵¹ does not share this opinion, and indicates that normal tissue should be avoided whenever possible. This is because he feels that to obtain normal tissue will break the natural barrier which the body is attempting to build as a defense against the invading carcinoma. Boyle¹⁹ is of the opinion that it is unnecessary to include normal tissue as long as an area of the tumour growth is selected for biopsy.

Tissues taken from only the necrotic centre of the lesion may prove to be useless due to lack of cellular detail. Instead, the actively growing portion of the tumour, usually near the border of the lesion adjacent to normal tissue, should be biopsied.

Adequate depth is extremely important as a shallow specimen does not represent a cross-section of the lesion. If the lesion is very large and exhibits variation in different parts, or if there are several lesions with different characteristics, more than one

biopsy is recommended. Castigliano⁵¹ indicates that generally areas nearest bone, cartilage or teeth, blood vessels, and necrotic sites should be avoided.

Aseptic precautions should always be observed in the preparation of the site prior to biopsy. However, the use of highly coloured antiseptics such as iodine, mercurial preparations, or any chemicals which may alter the staining properties of the tissue is to be avoided. Antiseptics used should be colourless, although solutions with a slight amount of colour such as metaphen may be permissible.³³⁸ The Oral Surgery Department in the United Dental Hospital, Sydney, recommends the use of 70 per cent. alcohol, or 0.5 per cent. solution of Hibitane in 70 per cent. alcohol.

Slaughter³²⁸ feels that gentle mechanical drying with a gauze sponge is all that is necessary as an aseptic precaution.

ANESTHESIA

The injection of anesthetic solution into the lesion, or its immediate vicinity, is to be avoided. If anesthesia is indicated, the solution should be injected widely around and beneath the base of the lesion, so as not to distort the tissue for histologic examination.

Thoma³⁶⁸ feels that if there is considerable danger of haemorrhage, or if an exploratory biopsy is

planned, general anesthesia is preferred. However, in most biopsy, local anesthesia will suffice. Cahn and Slaughter⁴⁷ indicate that there are no nerves in cancerous tissue and, therefore, in many instances anesthesia is not required, but if needed, surface anesthesia may be used. This opinion is shared by Sharp, Bullock and Hazlet,³²³ but they indicate that for tender lesions complicated by inflammation, and for non-ulcerated growth and bone tumours, regional nerve blocks are desired.

BIOPSY TECHNIQUES

There are several methods by which a biopsy specimen may be obtained.

I. SURGICAL TECHNIQUE

When the lesion is superficial or readily accessible, this is the method of choice. The surgical technique is most frequently used in the biopsy of intraoral lesions.

An incisional or excisional biopsy is performed, depending on the size and accessibility of the lesion, its relation to important structures, and the provisional diagnosis. It is important to use a sharp, pointed scalpel to ensure maximum efficiency of removing the specimen without distortion.

Castigliano⁵¹ recommends the use of the No.15 Bard-Parker blade, while Cooke⁷⁵ advocates the use of the

No.11 Paragon blade plus scissors to free the specimen. The use of instruments is really a matter of personal preference and convenience of handling.

When forceps are being used, great care should be exercised in handling the piece of tissue so as not to crush or distort the cellular architecture of the specimen obtained. Cooke⁷⁵ avoids the use of forceps in biopsy procedures.

Haemorrhage can usually be controlled by gauze pressure applied for a few minutes or by sutures. Sharp, Bullock and Hazlet³²³ indicate that dessication or cautery should not be used to control bleeding, while others^{51, 75} feel that the use of such procedures is of no consequence.

1. EXCISIONAL BIOPSY: Excisional biopsy, or the removal of the mass in toto with a border of normal tissue, is to be preferred whenever possible.^{328, 338, 368} This is feasible only if the lesion is small and easily accessible.

Slaughter³²⁸ points out the advantage of an excisional biopsy in that, if successful, only one procedure is required for both diagnosis and treatment. Stoopack³³⁸ indicates that in a lesion of extreme vascularity, it is advisable to place sutures widely and deeply to the lesion before removing it by this procedure.

2. INCISIONAL BIOPSY: Incisional or sampling biopsy is indicated when the lesion is extensive, somewhat inaccessible, or complicated by its involvement of important structures, or when the lesion appears to require extensive surgery or irradiation.

Cooke⁷⁵ emphasizes the importance of obtaining a specimen of uniform thickness, while Stoopack³³⁸ indicates that thin, deep sections are preferred to broad, shallow ones. Particular design of the specimen in an incisional biopsy - that is, whether triangular, elliptical, or rectangular - is a matter of personal choice and convenience.³²⁸ Most authorities^{51, 368} favour the cauterization of the wound following biopsy to minimise the possibility of disseminating malignant cells.

A representative sample of the lesion should be incised, including a portion of normal adjacent tissue, bearing in mind that there will be some shrinkage of the specimen after fixation. The piece of tissue obtained should be placed immediately in a wide mouthed bottle containing at least ten times the tissue volume of 10 per cent. formalin (4 per cent. formaldehyde). If excess blood is present, it may be advisable to gently

rinse the specimen using cold water prior to immersion in the formalin solution. Alcohol should not be used as the fixative unless specifically advised.

II. ELECTROSURGICAL TECHNIQUE

According to Stoopack,³³⁸ this technique is unsuitable because of severe distortion of the cellular structure in the specimen obtained through "cooking the tissues", even when handled by an experienced operator. The minor advantage lies in its haemostatic qualities in dealing with vascular tumours.^{221, 318}

III. PUNCH BIOPSY

This is a procedure whereby special punch instruments are used to secure biopsy specimen. Stoopack³³⁸ describes two types of punch biopsy procedures and their usages. In the first type, the desired size punch is selected, and the instrument is applied to the tissue and rotated back and forth until it reaches a depth of five to seven millimetres. This frees the specimen from the surrounding tissue, except at the base, which is subsequently freed using a scalpel. The second type employs the use of a forcep sort of tissue cutter in such a manner as to snip off representative samples of the lesion.

Punch biopsy is frequently used in biopsying lesions in inaccessible regions, such as those occurring

at the base of the tongue, the pharynx, the larynx, and the nasal cavity.^{51, 328, 338} Its use in the oral cavity is fairly limited.³²⁴

IV. DRILL BIOPSY

This technique, devised by Ellis, is mainly used for securing tissue specimen from central lesions of the jaws when employed intraorally.⁷⁵ According to Cooke,⁷⁵ the drill consists of a hollow tube which can be fitted to a straight hand piece. The cutting edge of the drill consists of two pointed teeth-like structures which are most satisfactory for fibro-osseous lesions. The specimen obtained will measure 1 to 2 cm. in length and 1.4 mm. in diameter, and could give approximately 100 sections when carefully embedded and sectioned.

V. ASPIRATION BIOPSY

Aspiration biopsy is indicated for tumours which lie below the surface of normal tissue, and this applies to both soft tissue tumours, and tumours within bone.^{315, 338, 368} Castigliano⁵¹ indicates that the technique requires special skill, and it finds its greatest use in the diagnosis of lymphnode metastasis.

The special instruments required for aspiration biopsy include a 16-18 gauge needle measuring 5 to 10 cm. in length, and a 20 to 50 c.c. syringe.

In this procedure, a stab wound is made on the

mucous membrane to facilitate inserting the needle without contamination of the aspirated material by the surface epithelium. If the tumour is within bone, a small round bur is used to penetrate the bone prior to inserting the needle.

The technique described by Stoopack³³⁸ utilizes a vacuum effect, created by the piston in the syringe, to aspirate the materials. Hardin¹³⁴ uses a continuous twisting motion such as in coring an apple, to obtain the desired specimen with the needle. In both techniques, the materials are then transferred to a clean glass slide, which is then gently smeared by drawing another glass slide across it using firm, flat pressure. It is then immediately stained, air dried, and sent to a pathologist for examination. Sometimes a small portion of the material is transferred on to a small piece of Gelfoam, which is then fixed in formalin and sectioned.

Katz¹⁴⁸ and Thoma³⁶⁸ describe a modification of this technique employing a non-aspirating Vim-Silverman needle, and they claim it is superior over the ordinary method. Katz,¹⁴⁸ in a study on 100 consecutive biopsies made on the cheek, neck, and salivary glands, claims a 92 per cent. efficiency employing the Vim-Silverman needle technique. He indicates that the advantages of this method are that

it is easy to perform, simple, safe, and accurate in most instances. However, Thoma³⁶⁸ is of the opinion that a negative result is often unreliable in all needle biopsies.

VI. SPONGE BIOPSY

Bolla and Dusi²¹ describe the use of this technique in the mouth, and conclude that it is a reliable method for establishing the diagnosis of oral tumours. They indicate that this method cannot be used for tumours situated in inaccessible sites.

Gladstone,¹⁰⁸ in a study of 38 sponge biopsies of the oral cavity claims that the technique is useful and reliable. Of the 38 cases studied, he reports that ten revealed malignancy using this technique, and these were subsequently confirmed by surgical biopsy. In the remaining 28 negative sponge biopsies, nine were followed by surgical biopsy technique with confirmatory negative results. The rest of the 19 sponge biopsies were not followed by surgical biopsy; however, none of these showed any subsequent evidence of cancer.

Sponge biopsy depends on the procurement of tissue particles from accessible ulcerative lesions by means of a suitable sponge. If the surface of an ulcer is covered by a thick layer of necrotic debris, or by a scab or crust, these should be removed with a

dry cotton gauze before the cellular sponge is rubbed on the surface. The sponge and absorbed material is placed in a small bottle of formalin (10 per cent.) and sent to the pathologist for microscopic examination after it has been prepared in the usual manner.

FURNISHING AN ADEQUATE HISTORY

A history and description of the tumour should accompany the specimen sent to the pathologist. This should include the following information -

1. the patient's age, sex, and nationality;
2. the location, size, and colour of the lesion;
3. the nature of its attachment, whether pedunculated or sessile;
4. the duration and rate of growth of the lesion;
5. whether there are secondary changes such as ulceration, inflammation, necrosis, or haemorrhage;
6. whether the regional lymph nodes are involved;
7. any previous treatment, whether it be surgery, irradiation, or chemotherapy;
8. whether the lesion is primary or a recurrence.

The pathologist should also be provided with any available radiographs and results of any laboratory tests.

SIGNIFICANCE OF THE BIOPSY REPORT

A prompt report on the part of the pathologist is

essential. The patient should be immediately informed whatever the outcome of the result is.

A negative biopsy means only one thing - the slide or slides examined fail to reveal evidence of malignancy. It does not automatically rule out the possibility of cancer, although this is usually the case with a properly performed biopsy. If in the clinician's judgement the lesion in question is suspicious enough to warrant a second biopsy, he should not hesitate to do so.

Castigliano⁵¹ indicates that sometimes typical carcinoma may be found deeper in the paraffin block and, therefore, one should not be afraid to ask the laboratory for results of the block.

ORAL EXFOLIATIVE CYTOLOGY

VALUE OF EXFOLIATIVE CYTOLOGY

It has been known for more than a century that exfoliated cells from certain tissues of the body could provide a valuable clue to the diagnosis of cancer.²⁹⁵ However, its full potential as a diagnostic aid in cancer detection was not realised until Papanicolaou^{225, 256} published his classical studies. Since then exfoliative cytology has been extensively studied, promoted, and widely adopted as a standard method in the detection of cervical cancer. Its introduction to the oral cavity in the detection of oral malignancy is relatively new.

Besides its application to the detection of cervical and oral carcinomas, cytologic examinations of such materials as sputum, bronchial secretions, gastric secretions, pleural and ascitic fluids, cerebrospinal fluid, urine sediment, and nipple discharge have been carried out to assist in arriving at a cancer diagnosis in these specific sites.^{23, 29, 48, 292, 399} Though the emphasis in the application of exfoliative cytology has been in cancer detection, this technique also has potential value as a diagnostic aid in the examination of non-neoplastic conditions. These include herpes simplex and variella-

zoster, pemphigus, pernicious anemia, hereditary benign intraepithelial dyskeratosis, white sponge nevus of Cannon, and Darier-White's disease.^{59, 115, 369}

To the present, more than a hundred articles have been published in the various journals pertaining to oral exfoliative cytology, many being repetitious.³¹ A review of the literature shows the considerable enthusiasm in the United States to employ this technique in screening oral cancer, but British and other authorities are more reserved and cautious at present. Although sharp differences of opinions prevail concerning its diagnostic value in oral cancer detection, its general acceptance is reflected in the wide-spread establishment of new projects in the United States, and the increasing number of favourable published reports.

The feasibility of utilising exfoliative cytology as a reliable method in the detection and diagnosis of oral malignancy is well documented in the publications of Sandler,^{293, 294, 304, 305} Sandler and Stahl,²⁹⁷ Sandler et al.,²⁹⁵ Stahl,³³⁴ Umiker et al.,³⁷⁶ Silverman, Becks and Farber,³²⁵ Alling and Secord,¹ Montgomery and von Haam,¹⁹⁶ Pomeranz and Stahl,²⁵⁷ Helsper, Sharp and Bullock,¹²⁴ Tiecke, Kendrick and Calandra,³⁶² Scheman,^{300, 315} Goldsby,¹¹⁵ Tiecke and Blozis,³⁶⁹ Cohen,⁵⁹ and Watanabe et al.³⁸⁹ Numerous other authorities^{320, 22, 38, 149, 236, 245, 252, 316,}

342, 368, 392 feel that exfoliative cytology has a place in oral cancer detection, especially in malignant lesions so innocuous clinically that a biopsy is unwarranted.

The Veterans Administration Co-operative study²⁹² on oral cytology is particularly interesting in this regard. Out of 2,758 oral lesions examined cytologically, there were 315 primary mouth cancers. Of these, 87 were considered to be clinically benign on initial examination. In 25 of these a biopsy was recommended and performed. The remaining 62 lesions were so benign in clinical appearance that a biopsy was not contemplated. All these lesions were scraped for cytologic examination, and the cytologic findings led to a diagnosis of cancer. Thus 62 of 315 cancers, or nearly 20 per cent., would have remained undiagnosed if the study protocol did not call for cytologic investigation of early lesion no matter how benign its appearance.

The study of Silverman, Becks and Farber,³²⁵ on a smaller scale, also demonstrates the usefulness of oral cytodiagnosis. In this study there were 60 patients in whom a biopsy was unwarranted because of the innocuous appearance of the lesions. Exfoliative cytology was applied to this group of patients and the smears from four of them indicated malignancy

which was confirmed subsequently by biopsy.

Alling and Secord,¹ in their study, detected three unsuspected early oral carcinomas out of 146 cases using the smear technique. Further evidence to substantiate the value of exfoliative cytology in early cancer detection is summarised by Tiecke and Blozis³⁶⁹ in an analysis of eighteen studies conducted by various authorities. They report that of 2,070 patients on whom smears were performed (and subsequently followed by biopsy confirmation), 105 had malignant lesions that were totally unsuspected by the dentist or physician at the time of clinical examination. They indicate that these were the very early harmless looking lesions that probably would not have been biopsied. Thus in this group of 105 patients, as a result of smears taken, early carcinomas were detected soon enough to assure that these patients would be treated early before metastasis occurred.

Comparative studies of biopsy and oral exfoliative cytology in most cases reveal a high degree of correlation between the two.^{49, 245, 292, 295, 297, 325, 334, 342, 362, 376, 389} Williamson and Shapiro,³⁹⁹ in an extensive review of the literature, have tabulated the results of such studies. They point out that with lesions diagnosed as cancer, the findings show 52 (6.5 per cent.) negative smears among 803 lesions

identified as cancer by biopsy. On the other hand, in 30 instances that smears suggested malignancy, initial biopsy was negative, and further biopsy confirmed the existence of cancer.

Sandler,³⁰⁵ in an investigation of 592 patients in whom smears were taken plus biopsy confirmation, reports that there were eight false negatives and seven false positives in the smears, giving a total of 15 instances of error (2.5 per cent.) In the same study, he indicates that there were also 22 instances of error of histologic diagnosis, that is, the cytologic specimens revealed malignancy, but the first biopsy was negative. Of these 22 cases, 17 required two biopsies to give a confirmatory diagnosis of cancer, three required three biopsies, one required four biopsies, and another required five biopsies. Thus in this study there was also an overall error of biopsy diagnosis of 3.7 per cent.

The accuracy and sensitivity of oral exfoliative cytology, as reflected by the number of false positive and false negative smears, are further demonstrated in an excellent tabulation prepared by King¹⁴⁹ (Table 7)

A similar, but more detailed, table (Table 8) prepared by Tiecke and Blozis³⁶⁹ from a review of eighteen studies conducted by various authorities further substantiates the value and reliability of

TABLE 7

PUBLISHED RESULTS OF INTRAORAL CYTOLOGY

		Pat- ients	Pos.*	Neg.	False Pos.*	False Neg.
MORRISON and OTHERS	1949 (1)	22	10	12	0	0
GLADSTONE	1951 (2)	38	10	28	0	0
WAHI and GUPTA	1954 (3)	50	41	9	0	0
HOPP	1958 (4)	25	24	0	0	1
PETERS and RISSINGHANI	1956 (5)					
PETERS	1954, 1958 (6,7)	893	252	609	13	11
SANDLER and STAHL	1958 (8)	151	34	13	0	4
CAWSON	1960 (9)	40	29	8	0	3
SANDLER and OTHERS	1960 (10)	239	131	88	5	15
TIECKE	1960 (11)	150	43	100	0	7
UMIKER and OTHERS	1960 (12)	160	100	48	6	6
KING	1962 (13)	179	51	127	0	1
		2,048	789	1,071	27	53

Neg. = Negative

Pos. = Positive

* Includes those listed as 'suspicious'

Source: KING¹⁴⁹

TABLE 8
MAJOR CYTOLOGY STUDIES

Study	Number of Patients					Number of		
	With SM & BIO FU*	With can- cer	With +ve or Susp. Cyt. /	With- out can- cer	With -ve Cyt. ^θ	False +ve	False -ve	Un- Suspd.
CHICAGO	90	62	51 11 P	28	26 9 N	2	11	28
FROST	29	16	5 I	13	4 I	0	0	
HOPP	25	25	24	0	1	0	1	
INGRAM	71	27	23				4	
KING			51		82		1	
PETERS	114	114	100	0	4	0	4	
PETERS	194	194	186	0	8	0	8	
PETERS	263	263	252	0	11	0	11	6
POMERANZ	8	8	7	0	1	0	1	
SANDLER	51	38	34	13	17	0	4	
SANDLER	592	315	322	277	285	7	8	62
SELBACH	93	93	90	0	3	0	3	2
SILVERMAN	75	19	18	56	57	0	1	4
SILVERMAN	100	7	7	93	93	0	0	
TIECKE	75	53	46	22	29	0	7	3
UMIKER	160	106	100	54	48	6	6	
UMIKER	80	80	77	0	3	0	3	
WAHI	50	41	41	9	9	0	0	

ABBREVIATIONS: P = POSITIVE; N = NEGATIVE; I = INCONCLUSIVE

* WITH SMEAR AND BIOPSY OR FOLLOW UP

/ WITH +ve OR SUSPICIOUS CYTOLOGY FINDINGS

^θ WITH -ve CYTOLOGY FINDINGS

Source: TIECKE and BLOZIS³⁶⁹ (slightly modified)

exfoliative cytology in the detection and diagnosis of oral cancer. They report that of 2,070 smears plus biopsy confirmation or follow up, there were 73 false negatives, or 3.5 per cent. error, and 15 false positives, or 0.7 per cent. error, to give a total error of 4.2 per cent.

The advantage of oral exfoliative cytology, as pointed out by various authorities,^{47, 49, 149, 292, 293, 296, 304, 368, 398} over traditional biopsy procedures is that the method is simple, quick, painless, atraumatic, harmless, and can be performed without arousing unnecessary fear or needless concern in the patient. Furthermore, no special or expensive armamentarium is required and the procedure can be easily repeated.

The evaluation of the criticisms directed towards the application of this technique in the detection and diagnosis of oral malignancy by certain authorities^{49, 51, 55, 56, 320, 399} is appropriate at this juncture. Apart from its controversial diagnostic role, most of these authorities,^{49, 56, 320, 399} however, agree that the technique has other uses in the oral cavity such as in the selection of appropriate sites for biopsy, and in instances in which a patient refuses to have a biopsy done, a positive smear may induce him to change his mind.

Dr. Kramer,⁵⁵ Castigliano,⁵¹ and Cawson⁴⁹ are

of the opinion that in an accessible region such as the oral cavity, there is absolutely no point in doing anything less than a biopsy. Cooke⁵⁶ states that in the diagnosis of early cancer it is not the appearance of any one cell alone, but the disturbed relationship of each cell to the other that is so important, and since a biopsy must be performed in all suspicious lesions, whether or not a smear is negative or positive, it is difficult to see the rationale for taking routine smears.

Shapiro, Gorlin and Jordan,³²⁰ and Williamson and Shapiro³⁹⁹ are of the opinion that the recognized advantages and applications of cytologic screening in the uterine cervix cannot be properly applied to the oral cavity. They indicate that this is because cervical carcinomas usually originate at the junction of the columnar and stratified squamous epithelium, the so-called squamo-columnar junction which is a relatively small zone, whereas in the mouth any region of the mucosal surface may be susceptible to malignant degeneration. Yet still another limitation is pointed out by them and Cooke.⁵⁶ They are of the opinion that the method is not applicable to lesions such as nodules and lumps in which the cancer does not involve the surface. This is substantiated by Cawson's⁴⁹ study in which he could not find malignant cells in the

smears from four cases of a deeply situated neoplasm in which the mucosal covering was apparently intact. They further indicate that scrapings from heavily keratinized or encrusted lesions may fail to demonstrate malignant cells which are present in the deeper layers.

Sandler,²⁹² Umiker et al.,³⁷⁶ Waldron,³⁹⁸ and Helsper, Sharp and Bullock,¹²⁴ who are strong supporters of oral exfoliative cytology, appreciate the existence of such a limitation. Other advocates^{1, 48, 325, 398} of this technique recommend the removal of the keratinized or encrusted coverings of such lesions prior to scraping for exfoliated cells. King,¹⁴⁹ not disputing the existence of this rather serious limitation, indicates that since squamous cell carcinoma comprises about 90 per cent. of all intraoral malignancies, and he claims that since they normally ulcerate, the value of this cytological technique is not significantly altered by the fact that some lesions may be covered by a keratinized or encrusted surface.

Concern has been expressed by certain authorities^{56, 320} that because of the simplicity of the technique and its widespread promotion, clinicians may fail to realise the limitations of oral cyto-diagnosis and use it in place of biopsy. However, the advocates of oral exfoliative cytology have repeatedly stressed the importance of biopsy for a confirmatory

diagnosis and that cytodiagnosis is not meant to substitute biopsy, and should never be used as such.

A few have even indicated that the use of oral exfoliative cytology has stimulated interest and a greater use of biopsy, because lesions which once might have been dismissed casually or ignored completely because of their harmless clinical appearance could now be detected by the smear technique and confirmed by biopsy. They stress the potential value of oral exfoliative cytology as a diagnostic aid supplementing and complementing biopsy, but never supplanting it or good clinical judgement.

A number of investigators^{115, 245, 297, 375, 376, 398} have reported favourably on the use of this cytological technique in following the natural development of premalignant lesions in the mouth such as leukoplakia. Other authorities^{325, 342} are not convinced of its value in this field. Montgomery and Von Haam,¹⁹⁴ in a study of ten patients with oral leukoplakia, report that there were no cytologic characteristics in the smears to suggest premalignant or malignant change. On the other hand, Peters²⁴⁵ comments on the increased number of keratinized squamous cells from patients with oral leukoplakia using the smear technique, and grades the leukoplakia lesions into three types according to the degree of atypism.

Umiker et al.³⁷⁶ noted that smears from oral white patches were characterized by many bright yellow-orange or red squamous cells, whose nuclei were frequently pyknotic or absent. These cells represent keratotic scales, the opacity of which is reflected in the white patches seen clinically. In a study of 45 patients with white oral mucous plaques, they indicate that the smears from nine cases showed some nuclear atypism, enlargement, hyperchromasia, thickening and wrinkling of the nuclear membranes, and disturbance of the nucleo-cytoplasmic ratio, or abnormal nucleoli in addition to hyperkeratosis. Although Umiker and his associates³⁷⁶ are convinced of the diagnostic value of intraoral cytology for studying potential premalignant lesions, they are concerned about the frequent sparsity of atypical cells in oral leukoplakic smears, and the minor degree of atypism in these cells when compared to those observed in vaginal or cervical smears.

The value of oral smears in both the preoperative and postoperative management of malignant oral lesions have been extensively investigated.^{326, 347, 375, 376, 378} The studies of Umiker and his co-workers^{375, 376, 378} and Seydel³⁴⁷ indicate that exfoliative cytology provides an excellent atraumatic method for screening the oral mucosa after irradiation

to exclude a recurrence or a new primary lesion.

Umiker and his associates^{375, 376, 378} in their studies report that generally there were fewer malignant cells from recurrent or residual neoplastic smears than from pre-treatment smears. A numerical increase in malignant cells was seen during the first or second week of irradiation, probably indicative of a greater exfoliation of cells during this period. They observed that patients whose smears contained abundant malignant cells consistently were more prone to develop lymph node metastases, and this usually proved to be a more resistant form of cancer. They indicate that the presence of malignant cells in smears, taken at the completion of treatment, does not necessarily indicate failure of radiation therapy, nor does the absence of such cells in the smears rule out the existence of residual neoplasm. However, the sudden appearance of pus cells in post-treatment smears, from patients whose previous smears contained no such cells, is indicative of recurrence of the lesion or the development of radionecrosis.

They indicate that the presence of atypical epithelial cells, not associated with inflammatory processes, was usually related to radiation induced epithelial hyperplasia of the non-malignant mucosa. Cytologic change from positive to negative smear was

not seen by them after the eighth week from the beginning of treatment, and this probably would be an appropriate time to commence post-irradiation screening. Caution must be exercised when interpreting smears because irradiation may occasionally give rise to epithelial atypism resembling cancer cells.

Seydel³⁴⁷ indicates that acridine orange stained smears may be of value in predicting the effects of radiation therapy upon primary tumours. In a study of exfoliated cells taken from 27 patients undergoing radiotherapy for malignancies of the uterus and the oral cavity employing this method, he reports that most patients whose smears exhibited more than 40 per cent. of damaged cells, following 4000r radiation dose, showed evidence of recurrence eight to twenty-six months after radiation therapy.

Several other authorities^{49, 56, 245, 295, 315, 320, 342, 399} have indicated the usefulness of cytological smears in evaluating the effects of radiation therapy, especially when biopsy is not advisable in such cases because of poor healing and the tendency to infection in irradiated tissues.

Monte et al.¹⁸⁷ indicates the possible value of intraoral cytology in studying toxic oral manifestations in cancer patients receiving chemotherapy. They are of the opinion that this technique may serve as a guide in

the administration of cytotoxic drugs such as anti-folic acid derivatives, anti-purines, and other oncolytic agents. Cancer chemotherapy results in the disturbance in nuclear and cytoplasmic metabolism in the cells, which may be reflected morphologically. A study was made by them of the exfoliated cells of the buccal mucosa in patients receiving chemotherapy, but further evaluation of the results is necessary.

THE BASIS OF EXFOLIATIVE CYTOLOGY

The stratified squamous epithelium lining the mouth is composed of different layers of cells in various stages of differentiation. Progressing from the innermost layer adjacent to the connective, and working outwards toward the surface, the cells become more and more differentiated.

The basal cells of the oral epithelium divide by mitosis continuously to give rise to further basal cells. As a result of this process, pressure is exerted on neighbouring cells, pushing some of them upwards into the para-basal layer, the intermediate layer, and ultimately onto the surface where they desquamate. Bertalanffy²² is of the opinion that the effects of differentiation and the increase in size of the cells as they move upwards contribute markedly to the ultimate migration of these cells onto the surface. Thus the oral epithelium is being renewed

continuously by cell division and exfoliation.

Bertalanffy²² states that cell desquamation likewise occurs from superficial abnormal and malignant lesions. He indicates that several factors promote the exfoliation of neoplastic cells. These include cell pressure due to rapidly proliferating new cells which crowd out older tumour cells, absence of an adequate supply of nutrient due to the diminished vascularity of the lesion resulting in cellular degeneration, necrosis and shedding, the lack of cohesiveness in certain types of tumour cells which thus readily dissociate and, finally, mechanical abrasion facilitates the exfoliation of these cells.

Cahn⁴⁸ is of the opinion that whereas in normal epithelium, only superficial cells exfoliate, in squamous cell carcinoma, the cells of all layers lose their intercellular adherence and, as a result, basal and acanthotic cells are seen in addition to the superficial cells.

Through such an exfoliative process, both normal and abnormal exfoliated cellular elements may be obtained from the mouth of a patient with oral malignancy and, hence, a representative sample for cytodiagnosis may be collected.

TECHNIQUE OF OBTAINING EXFOLIATED MATERIALS

The preparation of slides for cytological examination is a relatively simple procedure. The types of instruments, as used by different authorities,^{22, 47, 48, 149, 362, 399} for collecting the exfoliated materials include the wooden tongue-blade, dental cement spatula, double-ended metal spatula, and the cotton swab applicator, the choice mainly depending on individual's preference. In his study, Cawson⁴⁹ utilised a sterile nickel chemist's spatula of the Chattaway pattern. He indicates that the wooden tongue blade, popularly used, is absorbent and this makes it difficult to transfer the material on to the slide. Alling and Secord¹ prefer using a No. 7 wax spatula, or a No. 15 Bard-Parker scalpel for collecting the exfoliated cells. Schēman^{300, 315} has developed an instrument, called the Scheman-Molomut Cytoaspirator, which is designed to collect cells from surface lesions, in addition to probing the depths of fissured lesions or the bases of ulcers. He indicates that the instrument is useful in obtaining specimens from tooth sockets and from the centres of bony cavities.

Usually, the process of scraping the mucosal surface for exfoliated cells is relatively painless, but for lesions which are tender or sensitive, a topical or regional anesthesia may be used.^{1, 399} If

there is excessive debris or exudate on the lesion, it should be irrigated with a lavage of normal solution,¹ or wiped gently with a piece of gauze^{149, 315, 399} to ensure a clean surface prior to scraping. In cases where a heavy cornified surface is present, this should be removed with suitable instruments before scraping.^{1, 48, 325}

The entire lesion should be scraped if possible, and a new instrument used each time in scraping a different site. Bleeding is generally avoidable, but a little blood is of no consequence. The material obtained is then spread evenly and thinly on a clean, dry, glass slide. It is usual to prepare two slides for the same area, and it is imperative that the slides be placed immediately in the preservative and fixing solution, which usually is 95 per cent ethyl alcohol.^{1, 47, 291, 342}

The jar of fixative must not be shaken as this might detach the cells from the slides. Slides with smears taken from different patients should never be placed in the same fixing bottle to avoid the risk of transferring exfoliated cells from slides of one patient to another. If the fixing solution is to be re-used, it must be filtered and placed in a new clean bottle.

The slides should be left in the fixing solution for at least thirty minutes, then air dried,

wrapped singly in soft paper or plastic sheet, packed carefully in a mailing tube to avoid breakage, and despatched to the pathologist. Adequate data should accompany the mailed specimen. In addition to the identifying data, the following information should be made available to the pathologist - location of the lesion, the patient's history, clinical description of the lesion, and a provisional diagnosis if possible.

CYTOPATHOLOGY: CRITERIA FOR ESTABLISHING
MALIGNANCY IN CYTOSMEARS

The epithelial cells removed by scraping are studied microscopically for nuclear and cytoplasmic changes. The clinical simplicity of oral exfoliative cytology does not mean that the laboratory procedures are equally simple. On the contrary, the actual diagnosis of exfoliative smears is a very complex procedure requiring the greatest of skill, experience, training, and interest on the part of the cytopathologist.^{22, 23, 56, 292, 293, 296}

Smears derived from carcinomatous lesions contain, in addition to many normal cells, recognizable aberrant epithelial cells which meet one or more of the commonly accepted criteria of malignant cellular changes. In his classic atlas, Papanicolaou²⁵⁵ summarized the criteria for determining the malignancy of a smear into five broad headings as follows:

I. NUCLEAR CHANGES

1. Change in the nuclear to cytoplasmic ratio in favour of the nucleus.
2. An increase in the chromatic content, causing hyperchromasia.
3. Aberrant chromatin patterns and changes in morphology.
4. Enlarged or increased number of nucleoli.
5. Multinucleation.
6. Abnormal mitotic activity.
7. Thickening of nuclear membrane.

II. CYTOPLASMIC CHANGES

1. Altered staining reaction.
2. Atypical vacuolization.

III. CHANGES IN THE CELL AS A WHOLE

1. Enlargement of cells beyond their normal changes.
2. Atypical cell-forms, such as 'fibre' cells, and 'tadpole' cells.

IV. CHANGES IN THE RELATIONSHIP OF CELLS

1. A lack of uniformity in the orientation of cells and their nuclei.
2. Anisokaryosis and anisocytosis of cells within the same cluster.
3. Loss of distinct cell boundaries.
4. The formation of characteristic patterns such as the 'rosette'.

V. INDIRECT CRITERIA

1. An excess of histiocytes and blood elements, for example.

A smear does not have to satisfy all the preceding changes listed to be labelled as malignant. The aberrant characteristics suggestive of malignancy found in oral smears, as listed by Sandler et al.,²⁹⁵ in their approximate order of frequency, closely parallel to that of the above list.

Cawson,⁴⁹ in a study of 40 oral smears, states that the commonest change seen in malignant cells was an enlarged, hyperchromatic nucleus with a reduced amount of cytoplasm. He reports that 'fibre' cells and 'tadpole' cells were uncommon, multinucleated cells were moderately common, and cells exhibiting vacuolated cytoplasm or nuclei were frequently seen in those cases receiving radiotherapy treatment.

SIGNIFICANCE OF THE SMEAR REPORT

Pathologists utilise different systems of classifying smears and it is important for dentists to know the systems that are used. Alling and Secord¹ present a classification system which is basically the same as that described by Papanicaloau.²⁵⁵

CLASS I. Normal

CLASS II. Atypical cytology, no evidence of malignancy.

CLASS III. Suggestive of, but not conclusive of malignancy.

CLASS IV. Strongly suggestive of malignancy.

CLASS V. Malignant.

Sandler²⁹² states that a cytology report of 'normal' (Class I) does not rule out the possibility of malignancy, but the chances are small. A report of 'atypical' (Class II) increases the probability that the lesion is from a cancer to about six in a hundred. He indicates that in such a case, close clinical follow up is desirable. An 'indeterminate' (Class III) report should alert the clinician to the possibility of cancer since two out of three of these usually prove to be malignant, whereas 'strongly suggestive of malignancy' (Class IV), or 'positive cancer' (Class V) are presumptive of malignancy. He is of the opinion that biopsy is indicated in Class III, Class IV, and Class V reports and, if necessary, repeated to establish a definitive diagnosis.

Other authorities' interpretation of the report,^{48, 392} although not in such details, is the same basically.

THE MOUTH WASH TECHNIQUE

This, in essence, is a modification of the conventional oral cytology technique. The difference lies in the collection of exfoliated material.

Scheman,³⁰⁰ and Helsper, Sharp and Bullock^{124, 136} claim that this method can be used as a mass screening procedure for patients with oral cancer. They indicate that it is superior over the conventional method, because it is feasible and practical to obtain a truly representative cell population of the entire oral mucosal surface. This is substantiated by Scheman's experiment³⁰⁰ using specific dyes to stain the oral mucosa of eight patients at seven different intraoral sites in each case, and in every instance, cells stained with the different dyes were recovered, indicating that all the surfaces were represented. The accuracy and sensitivity of this method is reflected in the high correlation with biopsy results in the study conducted by Helsper and his associates.^{124, 136} However, they indicate that non-ulcerative carcinomas, although rare, could not be diagnosed by this technique.

Scheman³¹⁵ indicates that since it is not economically feasible to screen a total population, it has been suggested that screening be limited to those populations for which the epidemiologic factors for high oral cancer rate are more apparent. He states that these populations would include heavy smokers, especially pipe and cigar smokers, tobacco chewers, excessive alcohol drinkers, persons who habitually

eat hot and spicy food, persons with a syphilitic background, and those who suffer from severe nutritional deficiency states.

In this mouth wash technique, cytologic specimens were obtained by having the patient rinse his mouth with isotonic saline solution (in Scheman's study), or Gey's solution (in Helsper's study). The solution was then centrifuged, the supernatant fluid decanted, and the sedimented cells transferred to a slide which was then processed for microscopic examination.

Blozis³¹ is of the opinion that the mouth wash technique probably offers the only true screening procedure, but further investigation of the method is indicated before it can be accepted as totally reliable. He quotes the work of Schlegel and Uttermark who used the mouth wash technique to obtain cytologic samples following the administration of dimethylchlortetracycline. The cells recovered were then placed on a filter paper and examined under ultraviolet ray, and the presence of bright fluorescence was interpreted as evidence of malignancy. Of thirteen patients studied by this method eleven had a positive finding indicative of oral malignancy.

ACRIDINE ORANGE WITH FLUORESCENCE MICROSCOPY
IN CYTODIAGNOSIS

Fluorescence microscopy (FM), utilising fluorochrome acridine orange (AO), has been studied extensively and has proved useful in the detection of malignant cells in cytologic smears.^{23, 24, 54, 318, 377, 379} The work of Umiker and his associates^{377, 379} on smears from lesions of oral carcinomas, leukoplakia, or ulcers, are well documented, and have clearly demonstrated the value and sensitivity of this technique.

The application of AO-FM to exfoliative cytology is based upon the affinity of the metachromatic fluorochrome acridine orange for nucleic acids, the deoxyribose nucleic acid (DNA) of the nuclei fluorescing bright green to yellow, and the ribonucleic acid (RNA) of the cytoplasm and the nucleoli fluorescing brown, reddish-brown, orange, or bright red, depending on the amount of RNA present.^{23, 24, 377, 379} Non-dividing or infrequently dividing cells contain little or no RNA and show a green to brown fluorescence, whereas a reddish brown fluorescence is seen in those cells dividing at a physiological rate and containing a moderate quantity of RNA. Malignant cells, possessing a high content of RNA for protein synthesis during rapid formation of daughter cells, exhibit a bright orange

to flaming red fluorescence.

In general, malignant cells in smears prepared by this technique exhibit various shades of brilliant colours when viewed under low magnification, thus attracting the immediate attention of the examiner. Under higher magnification, the fluorescent colours greatly enhance the contrasts to provide an excellent evaluation of morphological criteria. These staining characteristics make possible the employment of personnel of ordinary technical competence for the initial survey examination of the smears. When the findings are positive, a skilled and experienced cytopathologist can then be consulted to examine and evaluate the significance of the brilliance in the smears. Besides this advantage, another recognized advantage is that the acridine orange may be removed by immersing the smear for a few minutes in 50 per cent. alcohol²³ or 1 per cent. acetic acid,²⁴ and the same smear may be processed with the standard Papanicolaou technique for comparison purposes.

Smears are prepared for fluorescence microscopy in the following manner.^{23, 24} The smears taken from a lesion are immediately fixed in equal parts of 95 per cent. alcohol and ether for at least an hour. They are then passed through successive

changes of alcohol - 80 per cent., 70 per cent., and 50 per cent., washed in distilled water, rinsed in one per cent. acetic acid, re-washed in distilled water, stained for three minutes with acridine orange, and transferred to a phosphate buffer ($1/15$ M KH_2PO_4 and $1/15$ M Na_2HPO_4 at pH 6) for at least one minute to remove any excess stain. They are then placed in 0.10 CaCl_2 for one or two minutes to bring out the differentiation between the RNA and DNA, and finally rinsed with a phosphate buffer. For the microscopic examination, a fluorescence lamp with a high pressure mercury burner (e.g. HBO 200) and proper filters, which can be attached to any laboratory microscope, are required.

OTHER DIAGNOSTIC METHODS

Apart from the well established value of biopsy and, more recently, oral exfoliative cytology in the detection and diagnosis of intraoral malignancy, other methods of oral cancer detection are still in the experimental stage.

Advances in the histochemistry of oral cancer has led some investigators^{20, 53, 298, 348} to evaluate the possibility of a histochemical diagnostic aid in the detection of oral malignancy. One of the many activities in this research field is the application of the Periodic Acid Schiff stain technique (PAS) in the study of the basement membrane.

Cahn⁵³ is of the opinion that the PAS stain may make it possible to distinguish potentially malignant epithelium. Santis and Shklar,²⁹⁸ in an investigation of 200 cases of epidermoid carcinoma using this technique, report that there is a lack of correlation between the presence of the basement membrane and invasive carcinoma, but there may be a general correlation between anaplastic carcinoma and defects of the basement membrane. They indicate that this method may also be used in the study of the distribution of glycogen in normal epithelial cells and in cancer cells.

The use of methyl-green pyronin stain, which brings out the ribonucleic acid of cells, has been evaluated by Cahn⁵³ as a potential diagnostic tool in oral cancer detection and diagnosis. He states that the presence of ribonucleic acid is indicative of cellular proliferation and, in normal epithelium, this is found rather abundantly in the germinative layers, but not in higher strata. However, in epithelium with malignant potential, the cells in all the strata are rich in ribonucleic acid, and this is brought out by the use of methyl-green pyronin stain.

Another staining technique which seems to hold promise of being a useful diagnostic tool employs the use of a dye. In-vivo staining of oral lesions with toluidine blue has been carried out by Niebel and Chomet²²⁹ on 20 patients, and they claim that the method is accurate and will stain intra-epithelial neoplasms. However, they point out that when used as such, this technique reflects only changes of the epithelial layer, and not the underlying tissues.

In this technique, a cotton swab saturated with one per cent. aqueous solution of acetic acid is used to clean the lesion and surrounding mucous membranes. The mouth is rinsed with water and the area to be stained is dried. Next, a one per cent. aqueous solution of toluidine blue is applied to the

lesion. After several minutes, the mouth is rinsed and saturated acetic acid is swabbed over the lesion. The intensity of the stain is correlated with the nuclear density which gives a rough indication of malignancy.

Niebel and Chomet²²⁹ indicate that the technique is of considerable value in biopsy procedures as it delineates the extent of the lesion.

The Schiller's iodine test has also been used to clinically identify intraoral lesions suspected of malignant change.^{53, 229} This test is based on the absence of glycogen in cancerous tissue, in contrast to normal squamous epithelium which is rich in glycogen. When the iodine solution is applied to normal tissue, a mahogany-brown stain appears, while in actively proliferating epithelium, the lesion remains poorly stained or unstained. It has been pointed out that unfortunately, certain benign neoplasms may fail to take the stain, while certain keratinizing malignant tumours may contain glycogen and stain faintly.

Another technique, which has been used in an attempt to detect early oral malignancy, utilises the property of tetracycline drugs which impart a fluorescence to malignant tissue. This method is used by Schlegel and Uttermark (quoted by Blozis³¹), and it involves giving the patient dimethyl chlortetracycline

and collecting a sample of exfoliated cells using the mouth-wash technique. The cells recovered are then placed on a filter paper and examined under ultraviolet light, the presence of bright yellow fluorescence being indicative as evidence of malignancy.

In a study of 13 patients with oral cancer using this method, they report that 11 cases gave a positive result.

In another method utilising tetracycline-vitamin B₁₂ solution, Navarro and Childress²³² report that the technique seems to be of potential value as a screening test for oral neoplasm. In this test, the patient is seated in a dark room. The lesion is dried, painted with the tetracycline-vitamin B₁₂ solution and dried again. The Wood's light is then focussed on the lesion after darkening the room, which gives a yellowish-green fluorescence. The lesion is then swabbed with the 'challenge' solution, consisting of a 4.9 per cent. solution of trichloroacetic acid.

If the fluorescence disappears immediately, the test is regarded as negative. If the colour persists over a ten second interval, it will appear as fluorescent specks or granules and, in this instance, the test is ruled as positive. After the test, the lesion is swabbed with a saturated solution of sodium bicarbonate.

Of the patients tested using this technique, a relatively large number of false negative and false positive results were elicited.

Other histochemical studies^{20, 348} of oral cancer which may be of value at a diagnostic level in this disease are centered on the distribution, qualitatively and quantitatively, of the various enzymes present in normal and malignant cells.

EXPERIMENTAL ORAL CARCINOGENESIS

Levy¹⁶⁷ defines carcinogenesis as the process by which normal cells or tissues become transformed into cancer. He states that in experimental carcinogenesis, a direct causative relationship between the agent employed and the neoplasm produced is not implied. All that can be said is that, in animals which are injected with certain agents or exposed to certain procedures, tumours arise in significantly higher incidence than in untreated animals.

Kolas¹⁶⁰ states that various factors are influential in the production of experimental tumours such as species of the animal, type of carcinogen, solvent, site of application, mode of application, frequency of application, trauma, infection, and period of life following application. He adds that, moreover, the cell "unit" would contribute in part through such inherent factors as genetics, age, nutrition, and endocrine function.

The method by which carcinogenic compounds gain access into oral epithelial cells, subsequent to topical applications, has been a subject of much controversy. Goldhaber¹¹⁸ postulated the necessity of a portal of entry of applied carcinogen in order to effectively act upon mucosal epithelium. This view is

shared by Levy^{166, 167} and others quoted by him. They are of the opinion that a portal of entry such as the presence of epithelial adnexa, or the presence of a pre-existing mucosal ulceration, is necessary for the topically applied carcinogens to enter the oral epithelial cells before carcinogenesis can occur. This interesting postulate is based on the following observations noted by them:

1. The painting of a polycyclic hydrocarbon, dimethyl benzanthrane, on the lip of mice produced changes on the skin side of the lip only and not on the mucous membrane side.
2. The portion of the skin in which superficial wounds have been inflicted and which healed subsequently has no hair follicles and sebaceous glands, and such skin, free of normal appendages, is refractive to methylcholanthrene induced carcinoma.
3. The painting of methylcholanthrene on the skin of new born mice in which the epidermis is thicker, and hair follicles and sebaceous glands are either absent or rudimentary, produced no malignant changes. On the other hand, painting the same agent on the skin of mice five days old, or older, in which epithelial adnexa had fully developed resulted in epidermoid carcinoma.

Renstrup et al.,²⁷² experimenting with hamsters, regard

that ulceration in the oral mucosa, produced by mechanical irritation, is of significance in carcinogenesis. They noted that carcinoma occurred in four weeks when chronic mechanical irritation, capable of producing ulceration in the oral mucosa of hamsters, was combined with the topical application of 9, 10 dimethyl-1,2-benzanthracene, whereas ten weeks were required before carcinoma was induced by the carcinogen alone. The early carcinomas produced by the carcinogenic agent plus chronic mechanical irritation were noted to occur at the margin of the ulcer caused by the latter process.

Similar observations were noted by Goldhaber.^{109, 118} He observed that epithelial malignancies were produced in the labial vestibule of desalivated mice only after collection of debris and resultant ulceration of the mucosa. Goldhaber^{109, 118} compares the breaks in epithelial continuity of mucosa to the portal of entry on skin represented by hair follicles.

Against the theory of the necessity for a portal of entry, Salley^{289, 310} has successfully produced squamous cell carcinoma in the cheek pouch of hamsters using topical applications of 0.5 per cent 9, 10-dimethyl - 1,2 - benzanthrane (DMBA), 3,4-benzpyrene (BP), and 20 methylcholanthrene (MC). The latent period in this investigation before carcinomas developed ranged from seven weeks with DMBA to twenty-five weeks

with MC. The incidence of malignancy was reported to be a hundred per cent. using DMBA, eighty per cent. with BP, and forty per cent. with MC. Salley's work reveals that of the three most commonly employed carcinogenic hydrocarbons, the application of 9, 10-dimethyl - 1, 2-benzanthracene to the hamster cheek pouch epithelium elicited the greatest response. (It has also been shown that mineral oil is the vehicle of choice for that carcinogen.)

In another study, Salley and Krashover³⁰⁹ were able to induce malignant tumours in the palatal mucosae, cheek pouches, and ear epidermis of hamsters. The carcinogenic hydrocarbons used were 9, 10-dimethyl-1, 2-benzanthracene and 3, 4-benzpyrene. Malignant neoplasia was elicited in 54, 100, and 100 per cent. of the respective tissues (palatal mucosae, cheek pouches, and ear epidermis) of survivors when the former compound was used, and in 16, 94, and 100 per cent. with the latter compound. They conclude that the results indicate susceptibility of the intraoral mucosa to chemical carcinogenesis, although salivary flow may have tempered the response somewhat when compared to the incidence of pouch and ear lesions. They further add that the presence of induced carcinoma in the palate and cheek pouch of hamsters, which possess no physiologic or pathologic portal of entry,

leads one to question the importance of this factor in experimental oral carcinogenesis.

In a study of the penetration of carcinogenic hydrocarbons into oral tissues employing fluorescence microscopy, Salley²⁹⁰ was able to demonstrate the presence of the carcinogenic agents in the oral mucous membranes following three to four applications. On the basis of his studies, he postulates that the hydrocarbon is probably brought to the cell by the process of simple absorption through the mucosal surface.

The techniques and observations of Salley are augmented by the work of Morris,²¹¹ who studied age, sex, and concentration of chemical carcinogen in relation to the production of buccal pouch neoplasms. In his investigation, Morris²¹¹ found that:

1. The tissues of the cheek pouch of old hamsters are more resistant to carcinogenic stimuli than those of young hamsters. He thinks that it seems logical that in a tissue (of the cheek pouch of young hamster) undergoing constructive metabolism, biochemical changes and abnormal cells would be produced earlier in response to carcinogenic stimulation.
2. Five-tenths per cent. concentration of 9, 10-dimethyl - 1, 2-benzanthracene is the optimal concentration for the rapid production of malignant

tumours in the hamster cheek pouch. This concentration produces maximum tumour response with minimum latent period, with no loss of animals due to toxicity. (Other concentrations used by him were 1.5 per cent., 0.1 per cent., and 0.05 per cent.)

3. A shorter latent period is required for tumour development in animals exposed to a carcinogen three times per week than in those receiving the carcinogen twice weekly, and that a smaller total dose is required to produce tumours in all animals when the carcinogen is applied twice each week than when given three times weekly.
4. The response of the hamsters to repeated applications of the carcinogen used is not related to the sex of the animals under the conditions of the experiment performed.

While carcinomas can be produced routinely in the hamster cheek pouch by painting the tissue with a carcinogenic chemical, it appears that carcinomas cannot be produced as easily in other oral sites. Thus Levy^{166, 174} was unsuccessful in his attempts to produce oral epithelial malignancies with repeated applications of methylcholanthrene. In one of his experimental series, he painted such a carcinogenic chemical on the labial gingiva of mice and hamsters for varying periods of time up to sixteen weeks, but

gross and microscopic study failed to reveal either cancerous or precancerous changes.

Similarly, Kolas¹⁶⁰ was unable to produce intraoral carcinoma with methylcholanthrene. He states that Salley's productive experiments must be evaluated on the probability that the mucosa of the hamster's pouch is not subjected to the same environmental influences (that is, salivary flow) as is the oral mucosa. This view is also shared by Levy^{166, 167} who also points out that the cheek pouch of the hamster is quite different from the oral mucous membrane, since it is apparently devoid of mucous glands and other appendages found in the oral mucosa.

Kolas¹⁶⁰ has concluded that the failure to develop tumours in the oral cavity was due in part to the continuous diluting and cleansing action of saliva. His attempt to show that saliva per se had an anti-carcinogenic action was unsuccessful. Goldhaber¹⁰⁹ has also investigated the role of saliva in relation to experimental oral carcinogenesis. The experiment conducted by him involved the application of 0.3 per cent 3-methylcholanthrene in acetone dropped on the labial mucosa of mice after the surgical removal of their major salivary and lacrimal glands. His conclusion is that desalivation did not significantly alter the resistance of the labial mucosa to the

topical application of the carcinogen. He states that the chronic ulceration found in association with experimentally produced oral carcinoma in desalivated mice, treated with carcinogen, may contribute to the carcinogenic process by virtue of its action as a co-carcinogen, a portal of entry, or both.

Although Salley and Kreshover³⁰⁹ were able to elicit malignant tumours in the palatal mucosae of hamsters using 9, 10-dimethyl - 1, 2-benzanthracene and 3, 4-benzpyrene, they indicate that salivary flow may have tempered the response in this oral site somewhat when compared to the relatively high incidence of tumours obtained in the cheek pouch and ear epidermis of the hamsters in the same series of the experiment.

Al-ani and Shklar¹¹ were successful in producing carcinomas in the gingivae of hamsters by the tri-weekly application of a 0.5 per cent. solution of 9, 10-dimethyl - 1, 2-benzanthracene in heavy mineral oil for a period of four months. However, they remark that the gingiva is not as susceptible to chemical carcinogenesis as is the buccal pouch, probably because in the buccal pouch the carcinogen is retained longer in apposition to the tissues than on the gingival surface where saliva would tend to remove it.

In an experiment conducted by Levy and Ring,¹⁷⁵ they found that crystals of a carcinogen placed

beneath the gingiva and against the alveolar bone resulted in connective tissue malignancies. Jaw tumours (sarcomas) were produced in eighty per cent. of the hamsters treated with 9, 10-dimethyl - 1, 2-benzanthracene, and these tumours spread by invasion along the periodontal membrane.

Niskamen and Merénmies²³⁰ report that there is substantial evidence from their study to prove that malignant changes in the skin as well as the oral mucosa of mice can be induced by the oral administration of carcinogens in these animals. The morphologic changes were observed to be strongest in the group that received 9, 10-dimethyl - 1, 2-benzanthracene, and weakest in the group receiving ethyl carbonate. They indicate that, even in the latter group, the malignant transformation was convincing.

CO-CARCINOGENESIS

The theory of co-carcinogenic action implies an augmentation of chemical carcinogenic activity by other non-carcinogenic agents or influences. Hence, cancer can be produced by the combined action of a chemical carcinogen too weak to produce a tumour and a co-carcinogen. Croton oil has been demonstrated as an effective agent showing co-carcinogenic activity.²⁶ Co-carcinogenic influences mentioned by Boyd,²⁶ other than chemical ones, include hormone, trauma, diet, age,

heredity, and chronic irritation.

Although a relatively large amount of work has been done in the area of co-carcinogenic action as applied to the skin of experimental animals, little has been done in this field as applied to oral mucosal neoplasms in these animals. Renstrup and colleagues²⁷² demonstrated the co-carcinogenic influence of mechanical irritation on the cheek pouch of hamsters in which a chemical carcinogen had been applied topically. They found that mechanical irritation appeared to hasten the development of hamster pouch carcinoma induced with a carcinogenic chemical.

Silberman and Shklar³¹¹ carried out a series of investigations in relation to chemically induced hamster pouch carcinomas utilizing croton oil for its possible augmentative effect on experimental mucosal lesions. They indicate that croton oil appeared to act as a co-carcinogen in the older animals - carcinomas were produced somewhat earlier in those tissues painted with croton oil and carcinogen than in tissues painted with carcinogen alone. However, in the series of young animals, the mucosal tissue treated with a combination of croton oil and carcinogen developed malignant lesions much more slowly than those tissues treated with carcinogen alone. The croton oil in this series appeared to retard the action of the

chemical carcinogen. They point out that the younger animals reacted to the croton oil with a much greater inflammatory response than did the older animals, and this might account for the retardation of the carcinogenic action in the young animals.

Protzel et al.²⁵⁹ were able to produce oral mucosal tumours in mice following administration of carbon tetrachloride or alcohol to induce liver cirrhosis. The carcinogenic chemicals utilized were benzpyrene and tobacco tar. They conclude that:

1. Induced liver damage in mice significantly decreases the latency and increases the frequency in the production of oral tumours.
2. Alcohol may have a dual role in its contribution to oral malignancy - first, as a promoter or co-carcinogen with tobacco smoke on the exposed mucous membranes and, second, as an agent which interferes with the metabolism of a carcinogen in the hepato-biliary system.

Weathered and Salley,⁴⁰² in assessing the effect of sex hormones on oral carcinogenesis in hamsters, report that oestradiol decreases the induction of experimentally induced carcinoma of the oral mucosa, and that castration prolongs the induction time.

TUMORIGENICITY OF DENTAL MATERIALS

Studies performed on experimental animals in an attempt to determine the tumorigenicity of some dental materials have been carried out by various investigators. Thus Mitchell,²⁰⁹ experimenting with subdermal implants of some twenty-two restorative materials in rats, tried to establish the irritational qualities of these materials. He studied microscopically the tissues around the pellets of these materials after two days, two weeks, and four weeks, and the inflammatory reactions to the various materials were classified as mild, moderate or severe. His findings are as follows:

SUBSTANCES WHICH GIVE RISE TO MILD REACTIONS

- gold foil
- inlay gold
- fused porcelain
- a direct filling resin
- zinc oxide and eugenol and zinc acetate
- a zinc phosphate cement
- a resin cement
- a cavity varnish

SUBSTANCES WHICH GIVE RISE TO MODERATE REACTIONS

- silver amalgam
- a direct filling resin plus sodium fluoride (2 per cent)

- zinc oxide and eugenol plus zinc acetate and calcium hydroxide
- calcium hydroxide
- gutta percha
- silicate cement (implanted wet and set)

SUBSTANCES WHICH GIVE RISE TO SEVERE REACTIONS

- copper amalgam
- copper cement
- a resin plus 5 per cent. sodium fluoride
- a control material of zinc oxide and eugenol plus croton oil.

In another experiment, Mitchell and colleagues¹⁸⁶ placed subdermal implants of small pellets of twelve materials in twelve groups of 120 adult Wistar rats over a period of 27 months. They noted that five of the ten animals developed a sarcoma around a nickel pellet, and nine out of ten animals developed one or more sarcomas around the pellets of a nickel-gallium alloy. No tumours were found to occur around pellets of fused porcelain, silicate cement, an auto-polymerising resin, a denture resin, zinc and eugenol, calcium hydroxide and methyl cellulose, silver wire, silver amalgam, vitallum, and copper.

A study of methyl methacrylate (acrylic resin) by Laskin, Robinson and Weinmann¹⁶² showed that small disks of this dental material, implanted subdermally

in mice, resulted in the formation of sarcomas in 25 per cent. of the animals which survived for 469 days. They state that although it has been suggested by certain authorities that hydroquinone might be carcinogenic, they are of the opinion that the minute quantity contained in a centimeter square of methyl methacrylate film would be unlikely to induce tumour formation. And since cadium oxide has been shown to be non-carcinogenic, they indicate that the tumours were most probably caused by the methyl methacrylate itself.

Methyl methacrylate prostheses have been frequently implanted in humans for reconstructive purposes and no reports of tumour formation have been documented so far.

EXPERIMENTS RELATING TO SMOKING

The evidence which implicate smoking as of etiologic significance in oral malignancy are based almost exclusively on clinical observations. On the experimental side of things, the work of Salley and Kreshover^{154, 291} in this field may be summarised as follows:

1. The muco-cutaneous border of the lip of mice was shown to be unaffected by the daily exposure to whole tobacco smoke over a period of 76 weeks. The difference in the sex and strain of the

animals, and vitamin A and B deficiencies had no apparent influence on this tissue resistance.

2. In contrast, the ears of mice were observed to be noticeably susceptible to daily application of tobacco smoke after a period of 17 months. The severity of the cutaneous changes increased in those animals maintained on a vitamin A and vitamin B complex diet. On the other hand, in the group of mice which had been gonadectomized, prior to smoke application, there appears to be some protective effect on the epithelium of the mice from gonadectomy. The CAF_1 strain of mice were noted to be more susceptible than the Swiss C_{57} strain.

3. In evaluating the effects of temperature in smoking using thermocouples, it was shown that as the cigarette was puffed, the ash temperature arose from 400°C to 650°C , while the temperature at the butt end was recorded as rising only 1.8°C even when the cigarette was smoked down to 2.5 cm in length. Thus, it appears that temperature on smoked tissues is of minor significance as far as any adverse effect goes in relation to smoking.

From the experiments, they conclude that whole cigarette smoke in itself is not a carcinogen when applied in controlled volume to the oral mucous membranes of these animals, and that chronic irritation is the most

likely role that tobacco plays in the production of oral malignancy.

Reddy, Reddy and Rao²⁷⁹ evaluated the role of heat combined with tobacco products in the pathogenesis of cancer experimentally. With proper controls he was able to demonstrate the role of heat as a co-carcinogen in accelerating the development of cancer in the skin of Swiss mice. It was observed that there was not only a shortening of the latent period in producing carcinomatous change, but there was also a marked increase in the yield of tumour in the skin of mice painted with tobacco tar and exposed to heat. They attempt to relate the findings of their experiment with the higher incidence of palatal cancer amongst women who practice the unusual habit of reverse smoking.

Peacock and Brawley²⁴⁶ are of the opinion that it is erroneous to associate epidermoid carcinoma of the oral cavity with the prolonged use of snuff and the chewing of tobacco. They claim that there is insufficient evidence to show a cause and effect relationship. In their experiments, they were unable to produce cancer in the cheek pouch of hamsters using commercial snuff and tobacco during the greater part of the hamster's life span. They report that of the 21 hamsters in which snuff had been implanted in their pouches, none developed neoplasm of any type. Similarly, negative

findings were noted in another 21 hamsters in which tobacco had been implanted in their cheek pouches.

These are but some of the experimental works done on oral carcinogenesis in animals - mainly hamsters and mice. Experimental cancer research of such a nature is of tremendous value, for it contributes significantly to a better understanding of this disease.

ETIOLOGY OF ORAL CANCER

The study of general etiologic factors in cancer of the oral cavity is an extremely difficult task. The mechanism which operates when apparently orderly cells appear suddenly to take on malignant characteristics is unknown. Numerous factors have been implicated in an attempt to determine the causes of oral malignancy, but in many instances a clear-cut, direct, definite causation cannot be established. However, in many instances fairly good correlations have been obtained, but then correlation cannot be equated as causation. Nevertheless, there are certain circumstances that appear too frequently in conjunction with oral carcinomas to be dismissed as mere coincidence. At this stage, it must be conceded that the exact causative agents in oral cancer have not been established.

The most commonly suspected etiologic factors in the development of oral cancer are tobacco, alcohol, syphilis, nutritional deficiencies, solar rays, socioeconomic factors, ionising radiation, lack of protective factors, various dental disorders, hormonal disturbance, and betel nut chewing, which is widely practised in certain parts of Asia and South East Asia.

TOBACCO

The introduction of tobacco into Europe was during the middle of the sixteenth century when it was held by Jean Nicot, the French ambassador to Portugal, that it possessed great curative values.¹³⁷ This opinion was widely accepted at that time, and in his honour the generic name of *Nicotiana* was given to the tobacco herb. Formerly, the species *Nicotiana rustica* was widely used for smoking, but it was supplanted by *Nicotiana tabacum*, which has remained as the chief source of smoking tobacco.

Hammond¹³⁷ indicates that it seems that M. Bouisson, a French physician, deserves credit for the first well-documented clinical study of the harmful effects of tobacco. In 1859, in a study of 68 patients with cancer of the oral cavity, he observed that 66 were pipe smokers, one chewed tobacco, and the other used tobacco in some other form. He was able to establish a correlation between lip cancer and pipe smokers, and suggested that the cancer resulted from irritation of the tissue by tobacco products and heat.

Since then, numerous investigators have attempted to evaluate the ill effects of tobacco in its various forms of usages with regard to oral cancer. Generally speaking, their efforts have produced some substantial evidence to indict tobacco as of etiologic significance.

Wynder, Feldman and Bross,^{394, 395} in an extensive and thorough study of 543 male patients with oral cancer and 207 control patients, report that only 3 per cent. of the oral cancer patients have never smoked, as compared to 10 per cent. of the control group without oral malignancy. Furthermore, 29 per cent. of oral cancer patients were heavy chronic smokers who smoked 35 or more cigarettes, or the equivalent in cigars and pipes per day for at least 25 years, in contrast to 17 per cent. of the controls. They indicate that there is a greater risk for oral cancer to develop in cigar and pipe smokers than in those who smoke cigarettes. This is based on their observations that the study group had a higher proportion of cigar/or pipe smokers (37 per cent.), as compared to the control (21 per cent.) In the same study, they also noted that there was a greater proportion of tobacco chewers in the oral cancer group than in the control, inferring that tobacco chewing is of etiologic significance but not as important as smoking.

In a parallel study on women with oral cancer contrasted to a control group, they noted that there were twice as many non-smokers among the controls as among patients with oral malignancy, and that there were three times as many chain smokers among the group with oral cancer as there were among the control.

From these findings, they conclude that tobacco seems to increase the risk of oral cancer, and for heavy smokers this risk is at least three times the corresponding risk for non-smokers.

Trieger, Taylor and Weisberger³⁶⁶ were also able to produce substantial clinical evidence demonstrating the significant correlation between oral cancer and heavy smoking. In their study of 68 patients with this disease, they report that 66 of them, representing 97 per cent., smoked twenty or more cigarettes per day, or the equivalent in other forms of tobacco. In another study of 108 patients with cancer of the tongue, Trieger and his associates³⁶⁵ report that about 90 per cent. smoked one pack or more cigarettes, or the equivalent in pipes or cigars per day.

Similar observations were being made by Vincent and Marchetta³⁸³ in their study of 106 patients with cancer of the oral cavity, pharynx and larynx. In this study, the 106 patients were divided into three groups according to the relative amounts of tobacco used. Group one consisted of non-smokers, group two were those who used the equivalent of less than twenty cigarettes per day, and group three those who used the equivalent of twenty or more cigarettes per day. In the control group, that is, patients with no oral

malignancy, the 150 patients were similarly categorized into three groups. They report that it is noteworthy to observe that 83.2 per cent. of the patients with oral cancer were in group three, as compared to 49 per cent. of the controls in group three.

Khanolkar and his associates^{151, 299} conducted an interesting survey of the tobacco habits of Indian patients with oral cancer and tabulated their findings as follows. (Table 9)

TABLE 9
ORAL CANCER IN RELATION TO TOBACCO HABITS (1952-1954)
TATA MEMORIAL HOSPITAL BOMBAY

		Smoking only	Smoking and Chewing	Chewing only	No Habits
No cancer	288	144 (50.0%)	69 (24.0%)	25 (8.7%)	50 (17.3%)
Cancer buccal mucosa	95	18 (18.9%)	42 (44.2%)	28 (29.5%)	7 (7.4%)
Cancer base tongue	191	105 (55.0%)	73 (38.2%)	11 (5.8%)	2 (1.0%)
Cancer oropharynx	85	54 (63.5%)	26 (30.6%)	14 (4.7%)	1 (1.2%)

Source: KHANOLKAR et al.^{151, 299}

On the basis of the data collected, they were able to relate tobacco habits with the sites of malignancy seen in the upper alimentary tract as follows:

1. the habit of chewing tobacco as seen in these

patients was associated with cancer of the oral cavity;

2. the combined habits of smoking and chewing was associated with cancer of the hypopharynx and the base of the tongue;
3. smoking was mainly associated with cancer of the oropharynx and upper portion of the alimentary tract.

Moore,¹⁸⁹ in his follow up series of 78 patients with cancer of the mouth and throat who survived for three years or more after treatment, assigned them to two sub-groups - those who quit smoking and those who continued to smoke after their first cancer. He found that of the 29 patients who stopped smoking, only one developed a second cancer, while in the remaining 49 patients who continued to smoke, 17 developed a second cancer. The average interval between the first and second cancers was 5-7 years.

In another study, Moore¹⁹⁰ reports that of 65 patients with 'cured' cancer of the mouth and throat who continued to smoke, 21 acquired a second cancer within six years in contrast to two patients who developed a second cancer in the same period out of 37 who quit smoking. He is of the opinion that in those patients who acquire cancer of the oral cavity, pharynx, and larynx, tobacco appears to play a causative role in 90 per cent. of cases.

Lemon, Walden and Woods,¹⁶⁸ in a preliminary investigation of Seventh-Day Adventist followers, whose religious convictions would not allow the use of tobacco and alcohol, state that reductions in gross mortality and morbidity from cancer of the mouth and lung are found to be epidemiologically consistent with reports concerning the causes of death among non-smokers. They further remark that Seventh-Day Adventist men who died from epidermoid lung or mouth cancer are usually older adult converts to the religion - and presumably its practices of non-smoking and non-drinking.

An interesting smoking custom which is quite widespread in certain parts of the world is that of reverse smoking. Quigley et al.²⁶⁹ point out that this custom is prevalent in certain parts of India, in the Philippines among the pygmy Negritos of the Bataan Peninsula, in Sardinia, in Jamaica, in Venezuela, in Columbia, in the Panama, and in some South Carribean islands. This social habit is practised mainly by women in these areas. The practice varies slightly from country to country, but essentially it consists of holding the lighted end of the cigarette or cigar in the mouth. Air is supplied to the burning end through the unlighted end of the cigarette or through the mouth. A substantial amount of smoke and

tobacco tar products condense on the teeth and oral mucosal surface, especially on the palate.

Various authorities indicate that this unusual smoking custom is associated significantly with a high incidence of palatal cancer in persons who indulged in its practice. Thus Boyd²⁶ states that the smoking of chotta, a form of cigar, with the lighted end in the mouth is common in Southern India, and addicts show a high incidence of palatal carcinomas. Similarly, Pantangco and Casals²⁶⁶ are of the opinion that the reverse smoking of cigarettes or cigars, as practised by the inhabitants of the Northern Ilocos Provinces and Central Luzon in the Philippines, may explain the cause and effect relationship of some cases of palatal and lingual carcinomas seen in these people.

Paymaster and Gangadharan,²⁵³ in an evaluation of smoking habits and oral malignancy incidence, report that Adda poga, a form of reverse smoking, practised by a minority of the population in Andhra Pradesh in India, is associated with an increased frequency of cancer in this intraoral site. Reddy, Reddy and Rao²⁷⁹ share this view and indicate that the incidence of palatal cancer in men in the same region who smoked the same type of cigars as the women, but in the normal way, is low and comparable to the findings in other parts of the world where this habit is unknown. They

indicate that since the thermal factor is the only difference between the sexes to account for the decidedly preponderant occurrence of palatal cancer in women, heat plays an important role in the production of such cancers in these smokers. In an experiment on mice, they were able to demonstrate the importance of heat as a co-carcinogen in the production of cancer in areas of the skin which were painted with tobacco extracts. However, Quigley and his associates,²⁷⁰ using micro-miniature thermocouples, were able to show that the temperature in the burning zone of the cigarette in reverse smoking is far cooler than that in normal smoking. This may be the case, but the lighted end is much closer to the tissues.

Pindborg²⁴⁸ also shares the opinion that reverse smoking contributes significantly to palatal carcinomas. He indicates that in the Panama, where this custom is widely practised, palatal cancer accounts for 40 per cent. of all oral cancers in sharp contrast to the usual incidence of about 7 per cent. in most other countries.

Quigley et al.,^{269, 271} in an extensive review of the literature, quote similar findings by different investigators in Sardina, Venezuela, Columbia and the Panama. However, in their study of 250 cases of reverse smokers in the Netherland Antilles, who smoked from one

to twenty cigarettes per day, they were unable to substantiate the correlation of this habit and palatal cancer as reported by other authorities. In the series studied by them, about 70 per cent. of the smokers were Negroes and, with the exception of two men, all were women. None of the smokers in the entire group showed any clinical evidence of malignancy. Twenty-one of the 250 smokers were selected for more comprehensive examination. They noted that generally the teeth of these smokers showed heavy tar deposits on the buccal and lingual surfaces, the palatal mucosa was tough, hard and leathery, there was reduction in salivary flow and, in some cases, leukoplakia was seen on the palate and lips. They report that, however, biopsy and cytologic smears did not reveal evidence of dysplasia in the epithelium. They suggest that the low incidence of palatal cancer in the Netherlands Antilles, despite the prevalence of reverse smoking, may result from a factor of ethnic background.

The use of snuff has also been evaluated as of etiologic significance in the production of intra-oral malignancy. Here again the habit is prevalent among women.^{46, 344}

Brown et al.⁴⁶ point out that in the eighteenth century, snuff sniffing was regarded as

fashionable, but today the method of using snuff consists of placing the flavoured powdered tobacco in the gingival buccal sulcus, and sucking on the quid most of the time the patient is awake. This results in severe chronic irritation to the area of the mucosa, and they and Bernier¹⁶ are of the opinion that this would provide an ideal setting for any carcinogen to act.

In a study of 394 intraoral cancer patients with regard to snuff exposure, Brown et al.⁴⁶ were able to demonstrate histologically that in most cases the cancers were of a low grade malignant type and frequently associated with leukoplakia. The same opinion is held by Stecker et al.³⁴⁴ who regard this form of carcinoma as well differentiated and pursuing a slow, progressive course.

Harrison¹²⁸ points out the high correlation between the use of snuff and buccal carcinoma in those parts of the United States where the habit is being practised, and between snuffing and carcinoma of the maxillary sinus in the South African Bantu. He indicates that in the Bantu snuff addicts, the carcinogenic properties of the snuff usually produce a malignancy near the mouth, and among Bantus who practised this habit extensively, cancer of the para-nasal sinuses constitutes about 6 per cent. of all cancers seen in these addicts.

Rosenfeld and Callaway²⁷⁶ claim that 90 per cent. of all women with carcinomas on the alveolar buccal sulcus, in areas where this habit is practised, are habitual snuff dippers, and that these cancers usually develop at the site where the snuff is held. Volger, Lloyd and Milmore,³⁸⁶ in a retrospective study of the etiological factors in cancer of the mouth, pharynx, and larynx, remark that the mortality and morbidity from malignancy of these sites are considerably higher among women of the southern United States, who are habitual snuff users, than among women in other parts of the States.

Bernier¹⁶ indicates that in considering tobacco as a carcinogenic agent, one must evaluate the effects of smoking and the use of tobacco per se. He points out that in the act of smoking, factors such as trauma, heat, smoke, and the combustion products of tobacco have to be taken into account. All these factors vary, depending on whether a pipe, cigar, or cigarette is used, and it also depends to some extent on the habits of the individual. He is of the opinion that the heat from smoking is related somewhat to the volume of smoke generated and, therefore, the pipe and cigar seem more important than the cigarette in this respect. He feels that direct heat to the lips is not important in that both the pipe and the cigars

are well insulated, while the cigarette is not usually kept in contact with the lip mucosa for any appreciable length of time. On the other hand, trauma to the lips resulting from the pipe stem is regarded by him as important, despite the fact that newer materials are used in pipe stems to reduce this effect.

With regards to the combustion end products of tobacco, these substances are brought in contact with the oral mucosa through the smoke and saliva regardless of whether a pipe, cigar, or cigarette is being used. Bernier¹⁶ indicates that in chewing tobacco or snuff, the situation is entirely different. In such instances, tobacco per se comes into direct contact with the oral mucosa, and the seepage of saliva into the mass promotes the opportunity for releasing the potential carcinogenic substances.

Most of the studies which implicate tobacco as of etiologic significance in oral cancer are based mainly on clinical observations. Peacock and Brawley²⁴⁶ contend that such clinical data are insufficient to indict tobacco as being responsible for oral malignancy. They argued that, moreover, there are numerous individuals who use tobacco and yet do not develop oral cancer. On this issue, Martin¹⁸⁰ has aptly pointed out that, not disputing the fact that tobacco does contribute to oral malignancy, in most cases of mouth

cancer, one can find more than one form of chronic irritation and, therefore, it would be erroneous to ascribe the lesion in any given case to tobacco alone simply because the patient smokes. More or less sharing the same opinion, Pindborg²⁵¹ states that the pathogenicity of tobacco chewing depends to a very considerable extent on the condition of the mucosal epithelium, inferring that an atrophic epithelium from other causes is obviously more vulnerable to the influence of tobacco quid of longstanding than is a normal epithelium.

Numerous other authorities^{2, 28, 47, 51, 74, 82, 92, 100, 108, 123, 137, 164, 165, 179, 185, 226, 318, 340} are of the opinion that tobacco, in one form or another, does contribute materially to the development of oral cancer.

ALCOHOL

Alcohol has been indicted by several investigators^{28, 74, 80, 100, 119, 123, 165, 170, 179, 248, 386} as contributing to oral cancer.

Wynder, Feldman and Bross^{268, 271} in their study noted that 33 per cent. of the 543 oral cancer patients drank in excess of six units of alcohol per day, as contrasted to 12 per cent. of a group of 107 patients serving as controls. Furthermore, a greater percentage of the study group was noted to drink whisky

'straight' - this comprised 44 per cent. as compared to 29 per cent. in the control group. From these observations, they conclude that alcohol seems to increase the risk of oral cancer, and this risk is markedly increased for heavy drinkers who consume more than six units per day of either whisky or other various types of alcohol. For them this risk is roughly estimated to be about ten times the corresponding risk for 'minimal alcohol' drinkers.

Trieger et al.,³⁶⁵ in a study of oral cancer and the significance of liver dysfunction, report that of 108 patients with oral malignancy, 75.9 per cent. drank excessively. A minimum of six 'hard' drinks per day, or the equivalent in wine or beer was the criterion established by them for a habitual or excessive drinker. They observed that 48 of the 108 patients, representing 44.4 per cent., had unequivocal evidence of hepatic cirrhosis.

In another study conducted by him and his associates,³⁶⁶ they indicate that 75 per cent. of a series of 68 patients with intraoral malignancy were habitual or excessive drinkers. Forty of the patients exhibited evidence of liver dysfunction at the time when a diagnosis of oral cancer was established. The average age of the cirrhotic patients at the time when a cancer diagnosis was made was 57 years, whereas

in those patients without demonstrable cirrhosis, oral cancer developed on an average age of 70.2 years.

Thus, in patients with hepatic cirrhosis, oral cancer developed 13 years earlier on the average than those without hepatic dysfunction.

They are of the opinion that the local effects of alcohol per se on the oral mucosa is of lesser importance and is secondary to the generalized change in the mucosal substrate. From their findings, they put forward an interesting concept of co-carcinogenesis in oral cancer development. They postulate that a conditional mucosa substrate exists in certain individuals experiencing liver dysfunction, due to a high intake of alcohol, and this substrate then reacts to superimpose carcinogens and irritants such as chronic irritation from tobacco or trauma by malignant degeneration.

Further evidence to substantiate the existence of a relationship between oral malignancy and a high intake of alcohol is provided by the study of Vincent and Marchetta.³⁸³ In this study, 106 patients with malignancy of the oral cavity, pharynx, and larynx are divided into three groups. Patients who never drank, or who drank so rarely that their daily averages were insignificant, were assigned to group one. Group two consisted of patients whose average daily

consumption of alcohol was significant, but less than the equivalent of 2 oz. of 100 per cent. alcohol, while group three was made up of patients whose average intake exceeded the equivalent of 2 oz. of 100 per cent.

alcohol. A control group of 150 patients without malignancy was similarly divided into three groups according to alcohol intake. They indicate that it is noteworthy that in each category of the whole series, over 55 per cent. of the patients with cancer were in group three, whereas only 18 per cent. of the controls were in this group. A similar significant increase in alcoholic consumption was seen among female patients where 30 per cent. were in group three, as compared to only two per cent. of the controls in this group.

Ariel,³ Kreshover and Salley¹⁵⁴ express their doubts on alcohol per se as of etiologic importance in oral cancer, because of the significantly poor status of malnutrition associated with persons who consumed large amounts of alcohol. They are of the opinion that alcohol is of significance only in as much as it might influence the nutritional status of an individual.

SYPHILIS

Most investigators who evaluate syphilis as an important etiological factor in oral cancer indicate that it is of significance only in malignancy of the tongue and the lip.

Gardner, Bowen and Brown,¹⁰⁶ in an investigation of 38 patients with cancer of the tongue, report that four had a history of syphilis, whereas in the group of 68 patients studied by Trieger et al.,³⁶⁶ they report that nine patients had a history of syphilis and a positive serologic test. In a separate investigation conducted by him and his associates,³⁶⁵ they indicate that 20 of the 108 patients with carcinoma of the tongue had a positive history, positive findings, or a positive serology. On this basis they conclude that syphilis is an important factor in cancer of the anterior two-thirds of the tongue.

This opinion is shared by Ariel³ who indicates that a positive complement fixation reaction has been observed in five per cent. of all hospital admissions in a general hospital, and about seven per cent. of all hospitalized patients with oral cancer. Castigliano⁵¹ states that besides cancer of the tongue, syphilis is also significantly related to cancer of the lip, floor of the mouth, and buccal mucosa. He estimates that the incidence of syphilis in the average general white population is approximately three per cent., while that in all male patients with tongue cancer is somewhere between 20 to 30 per cent.

Wynder, Feldman and Bross³⁹⁵ report that five per cent. of a control group of 207 patients had a

history of syphilis or a positive serologic test, in contrast to 11 per cent. of a study group of 543 intraoral cancer patients. In this study, a relationship between syphilis and cancer was found only for patients with malignancy of the lips (17 per cent.) and those with cancer of the tongue (12 per cent.) Among 86 patients with cancer of the anterior two-thirds of the tongue, 19 (22 per cent.) had a history of syphilis, whereas among 89 patients with malignancy involving the posterior one-third of the tongue, only three per cent. had a history of syphilis. They indicate that although there is a high correlation between syphilis and cancer of the anterior two-thirds of the tongue and cancer of the lip, it is difficult to assess the role played by arsenic in the therapy of these cases, but this possibility cannot be dismissed casually.

Martin¹⁸⁰ indicates that in otherwise healthy men in the 55 to 60 year old age group, the general incidence of syphilis is between four to six per cent., as compared to an incidence of 30 per cent. in men of this age group with cancer of the tongue. He adds that although the incidence of syphilis in patients with malignancy of other intraoral sites is less than those with lingual carcinomas, it is still consistently greater than the four to six per cent. figures given for the general population. He is of

the opinion that it is not the spirochete itself, but rather the longstanding chronic irritation which gives rise to malignancy, and that a cure of the syphilitic infection in these instances would not result in a cure for the cancer.

Other authorities who share the opinion that syphilis has a role in the production of oral cancer include Shafer, Hine and Levy,³¹⁸ Chang,⁷⁴ Pindborg,²⁴⁸ Marcial,¹⁷⁹ Farago,⁹² Gladstone,¹⁰⁸ and Dargent and Bertoin.⁸⁰ On the other hand, Volger, Lloyd and Milmore,³⁸⁶ and Vincent and Marchetta³⁸³ indicate that if syphilis is a factor in the development of mouth cancer, it is so in a very small percentage of cases.

NUTRITIONAL DEFICIENCIES

The relationship of oral cancer and Plummer-Vinson syndrome, which is possibly due to nutritional deficiencies, have been firmly established.^{8, 164, 390, 393} However, it is extremely difficult to evaluate the role of nutritional deficiencies as directly contributing to oral cancer, and except for some animal experimental investigations into this field, there is little or no substantial evidence to indict nutritional deficiencies as direct causative factors in human oral malignancy.

Orr²³⁷ indicates that in the Travancore coastal districts of India where oral cancer is rife, the diet

of the people is extremely poor in vitamins, and that in the Madras Presidency where oral cancer is of lower incidence, the diet of the people is better, while in the North and Central parts of India where this form of cancer is rare, the diet of the inhabitants is better balanced with a higher protein and fat percentage, plus more vitamin-containing substances. He did not arrive at any conclusion from these apparent correlations as there are several other factors involved.

The relationship of alcohol and oral cancer has been discussed and, as pointed out, people who consume large quantities of alcohol, or are chronic alcoholics, have a poor nutritional status. Some authorities^{3, 154} are of the opinion that the poor status of malnutrition in alcoholics is of etiologic significance in oral malignancy.

Many authorities^{47, 92, 106, 112, 154, 180} have pointed out the indirect role played by avitaminosis A and B, acting as predisposing factors, in the production of precancerous lesions and cancer. They comment on the possible epithelial metaplasia arising from avitaminosis A, and on the clinical manifestation of lingual edema, papillary atrophy and glossitis as a result of vitamin A and vitamin B complex deficiencies.

DENTAL DISORDERS

In this miscellaneous group, the factors listed as of possible etiologic significance are ill-fitting dentures, jagged, sharp or carious teeth, oral sepsis, poor oral hygiene, galvanism, and poor dental restorations. All these are capable of producing chronic irritation, and on this basis they are regarded by some authorities as potential predisposing factors in oral precancerous and cancerous lesions.

Gardner, Love and Hamburger,¹⁰⁵ in analysing 189 cases of oral cancer, report that about 43 per cent. of patients were edentulous, and 36 per cent. wore prosthetic appliances. They indicate that of these, one third of the patients developed the cancer within the borders of the appliances. In the same study, they observed that there were only two patients with good oral hygiene, less than twenty per cent. with fair oral hygiene, and more than fifty per cent. with poor oral hygiene.

Boyle¹⁸ and Cahn⁴⁷ are of the opinion that oral carcinoma occurs much less frequently in individuals with good oral hygiene and good dentition that are regularly maintained, and that ill-fitting dentures may have a definite influence in irritating the mucous membranes. This view is shared by Lederer and Skolnik¹⁶⁴ who claim that ragged or irregular

teeth produce superficial erosions, thickening of the regenerating epithelial layer, lymphocytic infiltration, heteropia, followed by a downgrowth of atypical cells.

On the other hand, Lucas¹⁷⁰ indicates that although fibrous proliferation due to pressure from dentures is common, malignant change either in the epithelium or the fibrous tissue itself must be extremely rare. He indicates that it is difficult to obtain statistical proof to show that patients with poor oral hygiene are more prone to oral malignancy than those with properly cared for mouths and, since the presence of sharp broken down teeth, badly fitting dentures, and rough fillings are all quite common, the occurrence of carcinomas may be coincidental.

This view is shared by Martin¹⁸⁰ who states that since dental disorders of some degree are almost universal, their presence in patients with oral cancer can hardly be considered of any particular etiologic significance. He feels that there is an over emphasis regarding the role played by ill-fitting dentures in the production of oral cancer, and indicates that more critical examination frequently reveals that, in a large percentage of cases, the growths will be found to have their origin in the tissues adjacent, but not in direct contact with the dentures.

On the other hand, Ariel³ reports that in 5 to 20 per cent. of patients with lingual cancer, the lesions are found situated at the site in juxtaposition to a malfitting denture or a carious tooth, and that in about half of the cases the oral hygiene of the patients is extremely poor, and severe dental sepsis is seen in about one third of the cases. He makes no definite inference from these observations, but expressed the difficulty in evaluating the significance of these factors in relation to lingual cancer.

Wynder, Bross and Feldman,^{394, 395} in a study of 116 women patients with oral cancer, and an additional 116 with no oral malignancy serving as controls, indicate that for long term symptomatic denture irritation, no significant differences were found between the study and control patients. In comparing the group of female oral cancer patients with a group of male patients with this disease, they found that the former had a history of ill-fitting dentures more often than the latter. They indicate that their findings do not suggest dental hygiene or irritation as playing a major role in the development of oral cancer.

On the other hand, Dargent and Bertoin,⁸⁰ in a study of 580 patients with cancer of the tongue, claim that constant irritation from spicules, untreated carious teeth, and poor fitting dental restorations play

an important role in the causation of lingual malignancy. On the subject of irritation, Pindborg²⁵¹ indicates that he has never been impressed by the significance of this factor in Denmark, but in South East Asia, he is convinced that oral irritation from whatever sources contributes significantly to the development of oral malignancy.

Sharp, Bullock and Hazlet³²³ found a very low correlation between relief chambers of dentures and palatal carcinomas, but they found a rather significant correlation between carcinomas at the junction of the hard and soft palate and an irritating posterior denture border.

Vincent and Marchetta,³⁸³ in an investigation of the etiological factors of 106 patients with cancer of the mouth, pharynx, and larynx report that 62 per cent. of the patients wore dentures, as compared to 65 per cent. of a group of 150 patients with no malignancy who used the same type of dentures. They further indicate that 26 per cent. of the cancer patients had septic or decayed teeth, as compared to 25 per cent. in the controls. However, they observed that all patients with carcinoma of the gingiva had either septic teeth or irritating dentures, or both, and feel that this is significant.

Numerous other authorities^{107, 108, 154, 165,}

273, 337³¹⁸ briefly indicate that dental disorders may be of some etiologic importance, while Shafer, Hine and Levy³¹⁸ regard such factors as of no significance in relation to oral malignancy.

With regards to galvanism produced by dissimilar metallic fittings, Castigliano⁵¹ states that it is of no etiologic significance in oral cancer.

SOLAR RAYS

Sunlight has long been regarded as a causative factor in cancer of the lip and the exposed skin of the body, particularly about the facial region. Most of the evidence is based upon the fact that cancer in these areas of the body frequently develop in Caucasians living in geographical areas with long exposure to sunlight.

Boyd²⁶ indicates that the high incidence of cancer of the lip and skin among field workers in the white population of the tropics, Australia, and the southern United States is due to the carcinogenic components of actinic rays. Cowan (quoted by Ariel²) claims that the high incidence of lip cancer in persons living in the mountainous regions of Utah is the result of prolonged exposure to dry alkaline dusts and actinic rays.

Sharp, Bullock and Hazlet³²³ are of the opinion that in dry, hot areas, where women are habitually

exposed to the sun and wind without the protection from lipsticks, as in more sophisticated communities, the incidence of lip carcinoma in women is proportionally higher and closely parallels the incidence of this disease in men.

Castigliano⁵¹ and others^{394, 395} indicate that excessive exposure to sun-shine accounts for the relatively high incidence of cancer of the skin and lip among farmers, lumbermen, sailors, and other out-door workers. Cahn⁴⁷ and Bhaskar²⁸ also share the view that actinic rays is of etiologic significance in lip cancer.

On the other hand, Shafer, Hine and Levy³¹⁸ regard sunlight as only of minor etiologic importance in cancer of the lip, although they share the opinion with others that this factor is of considerable importance in skin cancer. They point out that from experimental studies, it has been shown that the specific factor in sunlight responsible for carcinogenesis appears to be ultra-violet radiation. However, they indicate that it should not be inferred that ultra-violet radiation is the only important etiologic factor in the production of malignancy.

Other authorities who are of the opinion that actinic rays play a definite role in lip malignancy include Bernier,¹⁶ Ward and Hendrick,⁴⁰¹ and Schreiner and Christy.³⁰²

OCCUPATIONAL FACTORS

Some forms of occupation bear quite a striking relation to cancer in particular sites of the body, and in some patients with oral cancer, the malignancy clearly reflects the hazards of their occupation.

The study of the painters of luminous dials for watches and clocks, who developed cancer after radium ingestion, is of special significance in the history of occupational cancer. Professor Schuchardt⁵⁵ points out that in Switzerland, these workers used little brushes to paint fluorescent markings on the faces of watches, and frequently they used their lips to point their brushes without realising the danger of the radioactive fluorescent substances. As a result, many of them developed carcinomas of the lip. A similar tragic incident in New Jersey is quoted by Sarnat and Schour.³⁰¹ They report that many of these workers swallowed and absorbed sufficient radium to cause osteoradionecrosis of the jaws, bone destruction, loss of teeth, and in many instances death.

Boyd²⁶ indicates that cancer of the lip was noted to be especially common among fishermen on the west coast of Scotland, who, in mending their fishing nets, held the bone needle threaded with tarred twine between their lips, resulting in malignancy in these sites of the oral cavity. Lucas⁷⁰ claims that metal

workers appear to suffer from an increase incidence of oral cancer.

Bruusgaard²⁵ reports the occurrence of certain tumour forms which occurred mainly in the oral cavity, respiratory tract, and urinary tract among gas-workers in Norway. Autopsies performed on 125 gas-plant workers, who died from cancer, revealed 21 instances of malignant tumours in the maxillo-facial region involving mainly the oral cavity, 12 instances of malignant neoplasms in the respiratory tract, 5 instances of primary cancer of the bladder, and 3 instances of malignancy of the oesophagus. He is of the opinion that these malignancies were due, at least in part, to the abundant smoke associated with the manufacture and refining of gas and gaseous products containing tar and pitch which are well established carcinogenic agents. He indicates that these malignant tumours of the oral cavity and the respiratory tract were found to be especially common in the so-called retort-house workers.

In addition, it has already been pointed out that out-door workers such as farmers, lumbermen, and sailors, whose occupations require them to spend a great deal of their time under the sun, have a higher incidence of cancer of the lip and the skin.

SOCIO-ECONOMIC FACTORS

Levin (quoted by Gardner, Bowen and Brown,¹⁰⁶ and Castigliano⁵¹) indicates that a progressive increase

in cancer mortality is associated with each 'lower' socio-economic group, and that this increase is confined mainly to malignancy of the skin, the lip, the oral cavity, the larynx, the oesophagus, and the stomach. In general, the mortality rate is twice as high in unskilled as in professional workers.

In recent years, the World Health Organisation conducted an investigation into the problems of oropharyngeal cancer in India and reveal that the frequency of oral cancer rises significantly with the fall in socio-economic classes. It was noted that patients with this disease appeared to come mainly from the lower socio-economic strata of the community, and it has been suggested that such an association probably operates indirectly through social habits or nutritional status.

The importance of various social habits, as seen in different countries which have an influence on oral cancer, have been pointed out by several authorities.^{7, 92, 207, 237, 241, 253, 269}

IONIZING RADIATION

Cancer of the oral cavity may arise as a long term complication of radiotherapy.¹⁷⁰

Cahan et al.⁷⁰ report of eleven cases in whom osteogenic sarcomas developed in irradiated bones six to twenty-two years after the patients had received

radiotherapy. Of the eleven instances, three involved the bones about the oral region - one in the mandible, one in the maxilla, and one in the ethmoid bone.

Slaughter and Southwick³²⁹ report of nine patients with carcinoma arising in the mucous membranes that were previously irradiated. Of these, six were squamous cell carcinomas involving the hypopharynx (two cases), the tongue (one case), the buccal mucosa (one case), and the anal canal (one case). The other three cases were adenocarcinomas involving other parts of the alimentary tract.

Ariel² indicates that irradiation should seldom, if ever, be used to treat lip cancer in young patients, because of the undesirable late radiation cosmetic effects, and more important, because it may conduce toward the production of a late radiation cancer.

LACK OF PROTECTIVE FACTORS

Castigliano⁵¹ suggests the possibility of a protective index influencing the development of oral malignancy. He indicates that the effects of chronic irritation on the oral mucosa of some individuals may be minimal and, through this protective index, it may take a long period for any strong stimulating force to produce cancer in such individuals. On the other hand, those individuals who possess a low index of protection may develop malignancy readily and without

any prolonged period of stimulation.

From experimental studies, Boyd²⁶ indicates that genetic constitution may be a factor of importance in the development of cancer. He states that the ease with which a tumour may be experimentally induced depends on the genetic make-up of the animal.

HORMONAL DYSFUNCTION

A review of the literature shows that there is very little or no evidence to indict hormonal dysfunction as of etiologic significance in oral cancer, although this factor has been shown to be of considerable importance in other parts of the body, particularly in cancer of the breast, uterus, ovary, and prostate.

Gardner, Lilley and Simmon¹⁰⁷ mention briefly the possible role played by hormones indirectly in the development of oral malignancy.

BETEL NUT CHEWING

In many standard textbooks of oral pathology there is only sporadic mention of this social habit in a discussion of the etiology of oral cancer. Yet this habit, which is so widely practised in certain parts of Asia and South East Asia, is regarded by many authorities as of considerable importance in the etiology of this disease, which has a much higher incidence than in Western countries. Pindborg²⁵¹ states that oral cancer is a global problem, but among

the estimated 700 million people of South East Asia, it is a much greater problem than in the western world. A detailed consideration of the betel nut or areca nut, the betel leaf, its practice as a social habit, and its relation to oral cancer will follow.

Muir and Kirk,¹⁹¹ and Burton-Bradley⁴⁴ point out that the habit of chewing betel nut is of great antiquity, and is widespread in Ceylon, India, Pakistan, Burma, Thailand, Vietnam, Malaysia, Singapore, Indonesia, the Philippines, Formosa, Micronesia, Tanzania, Madagascar, New Guinea, New Britain, New Ireland, certain parts of China, and Southern Tibet. The latter author indicates that this social custom is currently indulged in by some 200,000,000 people in the geographical area mentioned. Balendra³⁶ emphasizes the importance of this social habit among the daily life of the people in Ceylon and India. He indicates that all Indians and Ceylonese, whether they be Hindus or Mohammedans, have chewed betel nut once in their lives, and that more than 50 per cent of the people chew betel nut regularly. This habit is the practice of the poor and rich alike and has been used in various Hindu ceremonies.

Muir and Kirk¹⁹¹ indicate that pharmacologically, the betel leaf contains a fair number of volatile oils, the main one being eugenol, an unsaturated aromatic phenol. Large amounts of potassium nitrate and small

quantities of sugar, starch, and tannin are also present. The areca nut, on the other hand, contains many alkaloids such as arecoline, arecaine, guvacine, arecolidine, guvacoline, 150-guvacine, and choline. They indicate that arecoline is the only one of importance in this group, the dried nut containing about 0.1 per cent. of this substance. This alkaloid is cholinergic and has been shown to exert a sialogogue and diaphoretic action in normal dosage, while very large amounts depress the central nervous system. Tannin, the glycerides of lauric, oleic, and myristic acids, plus some sugar have also been extracted from the nut.

Muir and Kirk¹⁹¹ further indicate that by itself, the areca nut is highly acidic (of dental interest, they quote Riker as saying it may exert a deleterious effect on the enamel of teeth) and astringent, and that the addition of lime neutralises this to a large extent and promotes the appearance of a red dye, which markedly stains the oral tissues. Eisen⁸⁸ indicates that saliva is not essential to bring about this colour change, inferring that the reaction of the mixture to give a red colour will take place outside the oral cavity. He states that the mixture of areca nut, leaf, and lime induces intense salivation and produces certain systemic effects which include

exhilaration and sleeplessness, and if over indulged, ocular disturbances are seen. Pantangco and Casals²⁶⁶ indicate that the addition of lime to the mixture neutralises the bitter taste from the betel leaf. They are of the opinion that lime from lime-stone is less irritating to the oral tissue than the lime preparation derived from shells.

Paymaster²⁴¹ reports that from recent investigation, it has been shown that the chewing of betel nut and leaf, without the addition of other complementary ingredients, play no part in the development of oral cancer. He indicates that a large percentage of the adult population in certain parts of India chew a cheap variety of tobacco with slaked lime and betel nut mixture, and the resulting bolus lodged in the posterior part of the cheek for many hours of the day and, in some instances, throughout the night. He reports that after a lapse of several years, a cancer is seen to develop at the site where the bolus has been retained. Numerous other reports^{55, 244, 253, 317, 340} confirm this observation among Indian patients.

Orr²³⁷ points out that besides tobacco and slaked lime, spices such as catechu, cardamon, and nutmeg are frequently added to the betel nut and leaf preparation. In a study of this habit in Travancore,

he observed the difference in the incidence of oral cancer among the tea-workers in the hills of Travancore and the people in the coastal regions, although both population groups chewed the same betel nut mixture of lime and tobacco. He ascribes this difference to the different socio-economic status of the two groups, the coolies of the tea estates being paid regularly and better, chewed their quid for only five to ten minutes before expectorating the mixture without retaining it in the mouth for long periods, while the poorer coastal Travancoreans, because of poor economic situation, were forced to retain the chew for several hours in the mouth, and some of them even sleeping with it. He further adds that the workers of the tea estates could afford a better diet than the coastal people.

Mardsen²⁰⁷ noted a higher incidence of oral cancer among Indian labourers in Malaya when compared to the Malay and Chinese population of the country. He indicates that both the Indians and Malays chew betel nut, but only the Indians add tobacco in their preparation, while the Chinese do not indulge in this habit at all. Furthermore, he observed that the Indian labouring class retained the same betel quid in the mouth for longer periods before discarding it than those of higher class, and hence the social gradient of the disease.

Mardsen²⁰⁷ indicates that the labourers usually commence to indulge in this habit in their adolescence, and girls tend to acquire the habit earlier than boys, while women chew betel nut for longer periods each day than men. He concludes that as a result, the age and sex incidence of the disease are related to the duration and intensity of the habit.

Atkinson et al.⁷ and Farago⁹² indicate that the incidence of oral cancer in the Territory of Papua and New Guinea is relatively high, as compared to the Australian mainland, and share the opinion that betel nut chewing is of etiologic significance. In a review of 110 patients with oral malignancy, Farago⁹² reports that all, but two, of the patients chewed betel nut since early childhood. Atkinson et al.⁷ point out that in the highlands of New Guinea where this is not practised, the number of oral cancer patients is proportionately smaller than the numbers seen in other parts of the country where the habit is extensively practised by more than 90 per cent. of the population.

They indicate that in New Guinea, betel nut chewers never add tobacco in their preparation in contrast to the chewers in India and Malaya, where many authorities^{151, 207, 237, 241, 242, 244, 317} identify tobacco in the betel quid as the possible

carcinogenic agent. However, like other chewers elsewhere, the New Guinean natives add a lime preparation, which consists of slaked lime and calcium carbonate, to the betel mixture. From this, they are of the opinion that lime plays an important role in the carcinogenic process, while tobacco, not underestimating its carcinogenic potential, enhances the process.

Contrary to the studies of Atkinson et al.⁷ and Farago,⁹² Eisen,⁸⁸ in an investigation of this habit among the natives of New Guinea and the adjacent islands, reports that betel nut chewing does not appear to elicit cancer in the mouth. Maxwell¹⁸⁰ and Balendra⁴³ are also not convinced of the etiologic significance of this social habit in the production of oral malignancy. The former author indicates that in the southern part of Formosa, where betel nut chewing is widely practised with all the essential ingredients as elsewhere, buccal cancer is a rarity. On the other hand, other workers in Thailand,^{192, 254} India,²⁶⁸ Singapore,²²⁶ the Philippines,^{42, 266, 285, 384} Formosa,⁷⁴ and Ceylon⁵⁸ are impressed by the significant role played by betel nut chewing in the development of oral malignancy in the respective countries.