SALIVARY GLAND TUMOURS
WITH SPECIAL REFERENCE TO MALIGNANCY

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PATHOLOGICAL ASPECTS
AND THERAPEUTIC IMPLICATIONS

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PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR IN DE GENEESKUNDE AAN DE RIJKSUNIVERSITEIT TE LEIDEN, OP GEZAG VAN DE RECTOR MAGNIFICUS DR. J. DANKMEIJER, HOOGLERAAR IN DE FACULTEIT DER GENEESKUNDE, TEN OVERSTAAN VAN EEN COMMISSIE UIT DE SENAAT TE VERDEDIGEN OP WOENSDAG 23 FEBRUARI 1966 TE 14.00 UUR.

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Dit proefschrift is bewerkt op de chirurgische afdeling van het 'Dijkzigt' Ziekenhuis te Rotterdam (Hoofd: C. van Staveren), het Centraal Pathologisch Laboratorium te Rotterdam (Hoofd: Dr. H. E. Schornagel) en het Rotterdamsch Radio-Therapeutisch Instituut (Hoofd: Prof. Dr. K. Brem en Mevr. S. den Hoed-Sijtsema).

To my invalid father

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HISTORICAL INTRODUCTION

Tumours arising from salivary glands have always been of immense interest to the clinician and especially to the pathologist, who through the ages has been fascinated by the widely varied histological features and who has sometimes found it difficult to distinguish between possibly malignant and probably benign types.

Toward the end of the 18th century, parotid tumours were described as 'squirrhous tumours' and considered malignant (Ch. G. and J. B. Siebold 1793—1797). The first brief reports on attempted surgical therapy appeared at the beginning of the 19th century. The terminology was still 'scirrhous cancer' or 'induration' or 'hypertrophy' (Kyll 1822, Duguied 1829, Braamberg 1829). Berard's 1841 thesis: 'Des opérations que réclament les tumeurs developpées dans la région parotidienne' was a great step forward. He was the first to make a classification of the enlargements commonly found in the parotid area. He distinguished abcesses, enlarged lymph nodes, cysts, benign salivary gland tumours and carcinomas. Lebert and Broca (1845, 1857) introduced the term 'adenoma' for benign tumours and brought to light differences between common enlargements and cancer. Lebert (1845) published the first case of 'sarcoma' of salivary gland origin.

According to Richard (1856) and Dolbeau (1859), the tumours arising from salivary glands were called 'enchondromas' and were considered to be usually benign. Billroth (1859) gave a good description of the macroscopic and microscopic structure of these 'enchondromas'. He was the first to detect carcinomatous structures in one case of 'enchondroma' after the seventh recurrence.

Virchow (1863) gave the first presentation of the histological structure of these tumours. He found different types of tissue in different areas of these enchondromas and, on the basis of the type of tissue dominating the structural pattern, he looked upon these tumours as myxomatous enchondromas or myxomas, myxochondromas, fibro-myxomatous enchondromas, etc.

For the enchondromas with an extremely divergent structural pattern Virchow used the designation 'Gemischte — oder Kombinations-Geschwülste'.

Despite the enlightened descriptions of Billroth and Virchow, there still was confusion regarding the most comprehensive terminology.

With the development of embryology and under the influence of different

doctrines (endothelial, branchiogenic, mesenchymal and epithelial), an avalanche of names appeared for these salivary gland tumours, e.g. endothelioma, enclavoma, branchioma, myxoma, chondroma, sarcoma, epithelioma, adenocarcinoma, myxo-chondro-sarcoma, etc. The significance of salivary gland sarcoma and endothelioma declined as the epithelial theory became more generally accepted. But still there was no uniform opinion among pathologists as to which tumours are benign and which malignant. Most authors concerned themselves with the benign and malignant so-called mixed tumours, often without making any clear distinction between them.

The question as to whether a mixed tumour can undergo malignant transformation became an intriguing one. This explains Masson's (1924) introduction of the term 'semi-malignancy' in an attempt to solve the difficulties of distinguishing the benign from the malignant tumours.

Up to 1935 many authors (Heinike 1924, MacFarland 1926, Stohr & Risak 1927, Benedict and Meigs 1930, Hintze 1934, Stein & Geschikter 1934, Ahlbom 1935) tried to assemble as large a material as possible in order to use it as a basis for a comprehensive clinical and especially pathological treatise.

Ahlbom's material was the basis for the first important classification of a comparatively large series of salivary gland tumours described according to the knowledge available up to 1935. Before him, attempts to divide these tumours into different groups which present predictable clinical behaviour patterns, failed because of an insufficient number of cases and because of the diversity of ill-founded views regarding the nature of these tumours.

After 1940, operations on these salivary gland tumours increased owing to improvements in general anaesthesia and surgical technique.

Collections of operative series between 1945 and 1955 were consequently larger than ever before (Marshall and Miles 1947, Rawson et al. 1950, Kirklin et al. 1951, Gricouroff 1953, Slaughter et al. 1953, Edvall 1954, Foote and Frazell 1954), and possibilities of classifying characteristic histological structures for separate types of tumour were evaluated (Stewart et al. 1945, Quattlebaum et al. 1946, Meza-Chávez 1949, Godwin et al. 1954).

Consequently several types of tumour (e.g. muco-epidermoid carcinoma, oncocytoma, cylindroma, acinic cell adenocarcinoma) could be differentiated from earlier different conceptions, and the group of mixed tumours was more distinctly defined histologically.

On the basis of the histologically defined tumour types up to 1954, Foote and Frazell presented their histological classification of these salivary gland tumours.

This classification, although more differentiated than any earlier ones, includes several types of tumour, e.g. muco-epidermoid tumours and acinic cell adenocarcinoma, which even in some recent classifications are still not regarded as distinct types (Redon 1960, Willis 1960).

Even in today's literature, several types of salivary gland tumour are still surrounded by an attitude of confusion so far as their malignancy is concerned. As to the malignancy of mixed tumours, many authors consider the entire group to be potentially malignant or so-called semi-malignant, e.g. Utendorfer (1955), Agner and Nielsen (1956), Rauch (1959), Gläser (1962), Hellner (1962) and Morehead (1962). Others believe the whole group to be benign (McCune 1951, and Kirklin et al. 1951), or totally malignant (Dockerty and Mayo 1942, Duplessis 1951, Dargent 1952, Perzik 1958).

Low-grade muco-epidermoid carcinomas, acinic cell adenocarcinomas and cylindromas are considered semi-malignant by Morehead (1962).

It is evident that there is still considerable uncertainty regarding the histological classification and consequently the prognosis of these salivary gland tumours. We are therefore in need of a classification based on well-defined types of tumour, from whose microscopic features clinical conclusions can be drawn. A classification into benign, semi-malignant or intermediate or questionably malignant and malignant tumours offers difficulties of interpretation.

For clinical purposes a classification into benign and malignant tumours is to be preferred.

The main object of this investigation is to ascertain which histologically distinct types of salivary gland tumour can be classified as benign or malignant, with special reference to the malignant tumours. A special clinico-pathological study has therefore been made. Furthermore, the apparent variation in the results of surgical and radiological efforts to eradicate these neoplasms permanently, and the uncertainty regarding the ultimate prognosis, prompted us to prepare a detailed analysis of cases of primary salivary gland tumours.

CHAPTER II

HISTOLOGICAL CLASSIFICATION

The salivary glands are of epithelial origin. A better insight into the diversity of the morphogenesis of these tumours can be gained by considering certain biological potencies and histological features of salivary gland tissue.

Microscopically, all salivary glands show tubulo-alveolar structures arranged in lobules. The lobules of the large glands form lobes. Lobules and lobes are supported by strands of loose connective tissue, which contain many blood vessels. The acini are composed of either serous or mucous cells or both. The so-called myo-epithelial cells are located between the secretory cells and the basal membrane, and also between the epithelial cells themselves.

Histochemical studies (Grisham 1952), histological studies (Gricouroff 1953) and electron-microscopic studies (Oota and Takahashi 1958, Mylius 1960) have revealed the myo-epithelial cells lying in intercalated and intralobular ducts between the basal membrane and the luminal epithelium; they are regarded as the possible origin of mesenchyma-like components in the so-called mixed tumours.

The intercalated ducts have a simple low cuboidal epithelium, while the larger ducts are lined with columnar cells. These ducts may be regarded as proliferation centres (Shaper and Cohen 1905, Bauer and Byrne 1950 and Glucksman and Cherry 1962). In the larger ducts the epithelium is columnar and pseudo-stratified and contains occasional goblet cells. Near the opening of the duct its mucous membrane becomes stratified for a short stretch and is then followed by stratified squamous epithelium.

There are often large islands of lymphoid tissue in the normal large salivary glands, e.g. the parotid, and inclusions of salivary gland tissue are occasionally found in pre-aurical lymph nodes of children and adults. Salivary gland tumours originate from normally localized salivary gland tissue within the major and minor salivary glands or from heterotopic salivary gland tissue within lymph nodes.

A purely histological classification of salivary gland tumours is clinically impracticable.

The study of salivary gland tumours by various groups has resulted in a variety of classifications, each with its good points. Complete classifications have been presented by Stein and Geschikter (1934), Marshall and Miles (1947), Rawson et al. (1950), Kirklin et al. (1951), Bauer (1953), Foote and Frazell (1954), Azzopardi and Smith 1959) and Rauch (1959).

In spite of all these classifications there is still uncertainty in the distinction between benign and malignant tumours and in the grading of malignancies.

Several factors contribute to this. In the past, some pathologists and clinicians have tended to draw conclusions from the morphological appearance alone; however, the assumption that the microscopic structure of a small fragment of tissue is representative of the whole lesion is an important source of error. The most formidable difficulty lies in the limitations of the microscope and the inability to predict the biological behaviour of a cell from its microscopic structure, although in many cases one can make a clear distinction between a benign and a malignant tumour on the basis of the morphological aspects and wellknown previous clinical and statistical arguments.

It should be emphasized that the microscopic findings, important as they are, must be interpreted in the light of the clinical picture; their importance should be neither minimized nor exaggerated. Usually the microscopic findings are all-important and they alone establish diagnosis, prognosis and treatment. Just what part each plays, and the exact condition which determines the relative values of different findings, microscopic and clinical, is a matter of delicate decision and astute clinical judgement.

The most satisfactory classification of these salivary gland tumours would be a histological one in which some correlation could be established between the histological aspects and the clinical course, based on a long-term follow-up. An attempt at this is made in this presentation.

Case material

All cases of salivary gland lesions, tumours included, registered during the period 1940—1964 at the Central Pathological Laboratory of Rotterdam (Dr. H. E. Schornagel) were labelled. The lesions, involving 1002 patients, were classified under different headings. The diagnoses in these 1002 patients with salivary gland lesions are illustrated in table I.

To evaluate which clinical conclusions could be drawn from the histological structures of the various types of salivary gland tumour, a follow-up study of the tumours concerned was made.

The histological re-examination of these tumours was carried out with the co-operation of Dr. H. E. Schornagel-pathologist and head of the above-mentioned laboratory. From the files of the various Rotterdam hospitals, case histories were available, and symptoms and signs of the tumours, surgical intervention, etc., were recorded. Much help was received from the Rotterdams Radiotherapeutisch Instituut (former head Prof. Dr. K. Breur, now Mrs. Den Hoed-Sijtsema) in tracing the clinical and radiotherapeutic records of the patients treated at this institute.

Due to administrative difficulties in tracing the clinical data on most patients between the years 1940 and 1947, the period starting January 1947

and ending December 1958 was chosen for the investigation, which thus included 452 patients with various types of salivary gland tumour.

The case material is presented in table 3.

Table 1. Histological classification of salivary gland lesions during the period 1940—1964, Central Pathological Laboratory of Rotterdam.

Diagnosis	Number of patients	
Lesions inflammatory and obstructive:		240
Inflammations	218	
Stones	22	
Haemangioma		8
Lymphangioma		1
Lipoma		3
Neurinoma		3
Neurofibroma:		8
benign	5	
malignant	3	
Cysts		35
Lymph node hyperplasia		5
Benign lympho-epithelial lesion		11
Mixed tumours:		455
so-called benign	410	
malignant	45	
Cystadenoma lymphomatosum		35
Oncocytoma		3
Muco-epidermoid tumours		11
Squamous cell carcinoma		33
Cylindroma		15
Acinic cell adenocarcinoma		11
Mucus-producing adenocarcinoma		1
Adenocarcinomas (miscellaneous forms)		56
Malignant melanoma		3
Hodgkin's disease		2
Sarcomas:		9
fibrosarcoma	5	
reticulum cell sarcoma	3	
lymphosarcoma	1	
Miscellaneous (salivary gland tissue without pathological findings)		54
Total		1002

Of these patients, 38 (8,4 per cent) gave no co-operation in tracing personal or clinical data. The remaining 414 patients (see table 3, determinate group) were followed up for 5 to 16 years.

In some cases the patient did not report for follow-up examination, and information as to whether or not the patient was still alive could only be obtained from the registrar's office.

The aim of this study was to establish the tumour group and especially the malignant types. In table 2 the tumour group is illustrated and compared with other large series from the literature.

Table 2. Comparison between the tumour material of the Central Pathological Laboratory of Rotterdam and other large series from the literature.

Author	Kirklin	Foote & Frazell	Eneroth	Our series
Year	1951	1953	1964	1940-1964
Total number of cases	717	877	802	708
Composition of material	parotid tumours	major salivary glands	parotid tumours	all types of salivary glands
	%	%	%	%
Vascular tumours	—	—	0,2	1,2
Lipoma	0,7	—	0,1	0,4
Neuro-tumours	—	—	0,9	1,5
Cysts	1,0	—	2,5	5,0
Lymph node hyperplasia	—	—	0,9	0,7
Cystadenoma lymphomatosum	2,0	6,0	5,1	5,0
Adenomas	1,0	0,2	0,5	0,4
Mixed tumours (all types)	79,0	66,0	71	64,5
Cylindromas	4,7	4,0	2,4	2,1
Muco-epidermoid tumours	—	11,7	4,2	1,5
Squamous cell carcinoma	1,8	4,7	0,1	4,7
Acinic cell adenocarcinoma	—	2,5	4,5	1,5
Mucus-producing adenocarcinoma	—	0,1	1,5	0,1
Adenocarcinomas (miscellaneous types)	7,5	4,6	3,2	8,0
Hodgkin's disease	—	—	0,1	0,2
Boeck's disease	—	—	0,5	—
Melanomas	—	—	0,2	0,4
Sarcomas (different types)	0,4	—	0,4	1,3
Mikulicz's disease	0,4	—	—	—

Table 3. Histopathological diagnosis in the 452 patients with salivary gland lesions during the period 1947—1959.

Diagnosis	Number of patients	Determinate group
Haemangioma	6	6
Lymphangioma	1	1
Lipoma	3	3
Neurinoma	2	2
Neurofibroma	5	5
Cysts	27	27
Benign lympho-epithlial lesion	8	8
Mixed tumours (all types)	293	264
Papillary cystadenoma lymphomatosum	18	18
Oncocytoma	3	3
Muco-epidermoid tumours	7	6
Squamous cell carcinoma	18	17
Cylindroma	13	12
Acinic cell adenocarcinoma	6	5
Adenocarcinomas (miscellaneous types)	31	26
Melanoma	2	2
Hodgkin's disease	1	1
Sarcomas (various types)	8	8
Total	452	414

For this investigation we initially used a simple histological classification covering the majority of these salivary gland tumours. This was achieved by subdividing these tumours into:

I. Tumours primarily in the salivary gland:

A. Epithelial tumours; this group includes all tumours derived from the salivary gland parenchyma.

1. Mixed tumours
2. Adenomas
3. Papilliferous cystadenoma
4. Papillary cystadenoma lymphomatosum
5. Muco-epidermoid tumours
6. Squamous cell carcinoma
7. Cylindroma
8. Adenocarcinomas:
   Acinic cell adenocarcinoma
   Mucus-producing adenocarcinoma
   Miscellaneous types of adenocarcinoma
9. Cysts

B. Mesenchymal tumours.

1. Haemangioma
2. Lymphangioma
3. Lipoma
4. Neurinoma
5. Neurofibroma
6. Fibrosarcoma

C. Miscellaneous tumours.

1. Benign lympho-epithelial lesion
2. Mikulicz's disease
3. Boeck's disease
4. Hodgkin's disease
5. Lymphosarcoma
6. Reticulum cell sarcoma

II. Metastatic tumours.

These usually originate from primary cancers in tissues which normally drain into the lymph nodes adjacent to the salivary glands (especially in the parotid and submandibular areas), e.g. intra-oral carcinomas (mouth, tongue, etc.) or melanomas.
In rare cases the source of the metastases may be in remote organs, e.g. kidney and testicle.

HISTOLOGICAL AND CLINICAL ASPECTS OF SALIVARY GLAND TUMOURS

A. Epithelial tumours.

1. *Mixed tumours*

Synonyms:
Epithelial mixed tumour (Therkelsen 1934)
Complex adenoma (Foote and Fazell 1954, Johnson & Childers 1954)
Pleomorphous adenoma (Willis 1960)
Pleomorphous sialadenoma (Rauch 1959)
Epithélioma à stroma remanié (Redon 1960)

These tumours form the most common group of salivary gland tumours.

Histological features

A mixed tumour is characterized by epithelial and connective tissue-like components. The outstanding histological feature is the extremely variable structural pattern. In almost every mixed tumour there is a broad range of histological patterns and hardly any tumour shows a homogeneous make-up.

The epithelial cells proliferate in masses and strands. If this component dominates, the tumour appears to be highly cellular (see fig. 1.).
Well-defined tubular structures are common in mixed tumours, but they do not dominate the microscopic picture. Such a tumour is often diagnosed as an adenoma, but in the opinion of Rawson et al. (1950), Kirklin et al. (1951), Willis (1953) and Mathis (1954), pure adenomas do not occur and such a neoplasm is actually a mixed tumour with predominance of the epithelial component.

In some mixed tumours, there may be areas formerly described as 'cylindromatous' simulating the cylindroma.

Squamous epithelium can also be found in mixed tumours. One can trace all degrees of metaplasia; the development of intercellular bridges, keratohyaline granules and finally keratinized epithelial pearls (see fig. 2.). Well-differentiated squamous epithelium can be found in a good many cases.

A mixed tumour may exhibit markedly pleomorphous epithelial structures. These growth alterations may proceed along the lines of adenocarcinoma or squamous cell carcinoma (fig. 3.).

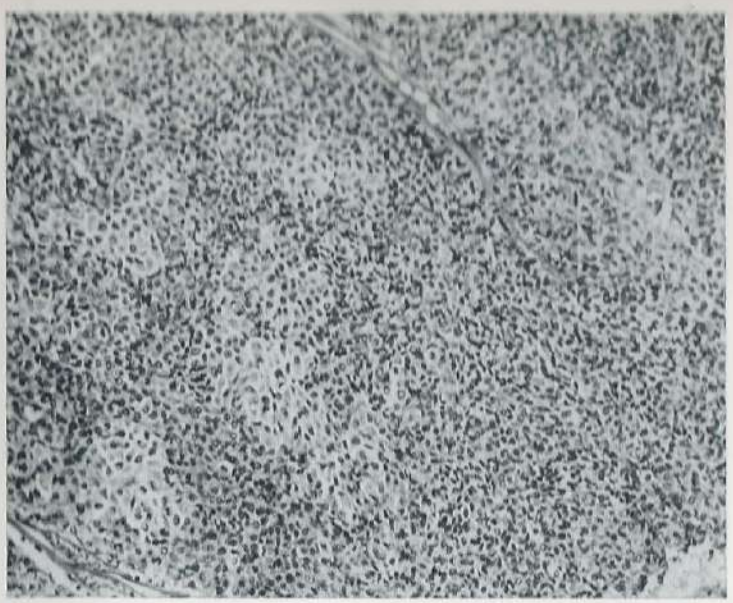


Fig. 1. Cellular part of a mixed tumour with predominance of the epithelial component.
Photomicrograph × 140.

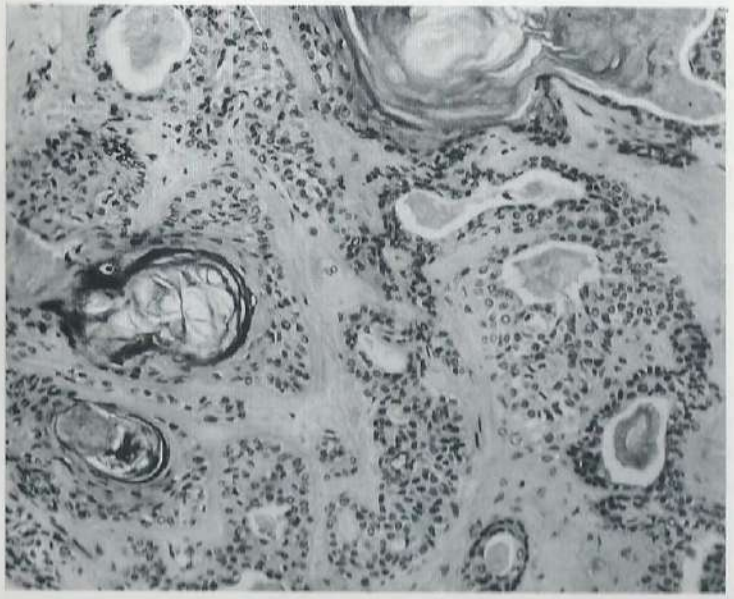


Fig. 2. Area of mixed tumour showing squamous metaplasia with pearl formation.
Photomicrograph × 140.

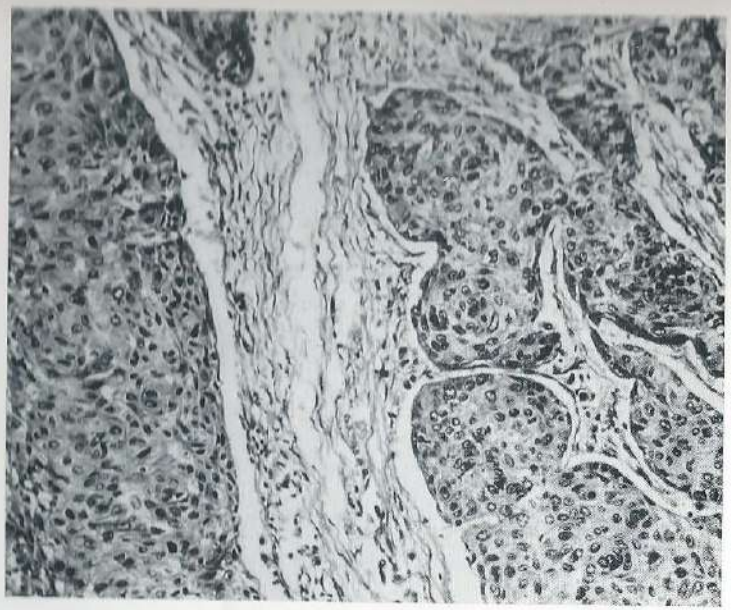


Fig. 3. Mixed tumour area with structural traits of epidermoid carcinoma. Photomicrograph × 140.

The connective tissue-like components usually consist of hyaline, myxoid and chondroid structures. In some cases the connective tissue-like components may predominate, the tumour then having a lower epithelial cellular content (see fig. 4 and fig. 5.).

In rare cases this predominance can go so far that the tumour is characterized by a great abundance of cells, in the form of palisade-like formations of spindle cells. These tumour cells resemble those in tumours of the smooth muscle, and Sheldon (1943) believes that in those cases they are derived from the myo-epithelial cells of the ducts. One should make a careful attempt to differentiate these cells from dedifferentiated forms of squamous epithelial cells.

Behaviour

The decision as to what should be considered infiltrative growth presents difficulties in the case of these particular tumours.

From the developmental embryological point of view, one can regard the salivary gland tissue as infiltrative, lying in a mesenchymal matrix. Grobstein's (1955) animal experiments have clearly demonstrated the influence of the mesenchyma on the epithelial part of the organ during embryonic life.

A true capsule does not exist; expansion of the growing tumour results in compression of the surrounding tissue to form a pseudo-capsule.

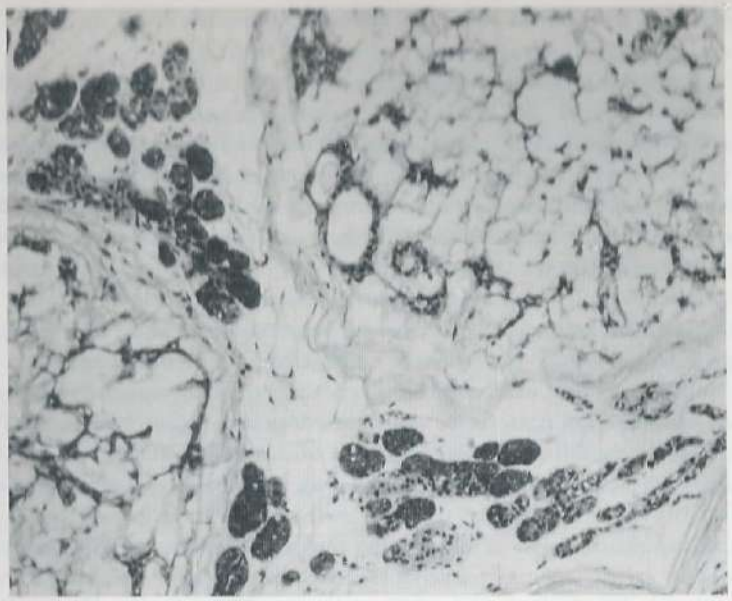


Fig. 4. Myxoid mixed tumour; a region of direct transformation of the stroma of the acini into myxoid tissue. Photomicrograph × 140.

Fig. 5. Mixed tumour with predominance of the connective tissue-like components, tending toward infiltrative growth at the periphery. Photomicrograph × 140.

In mixed tumours the relation between tumour tissue and adjacent normal tissue varies greatly.

In some instances the tumour is completely surrounded by a fibrous 'capsule' of varying thickness. Incomplete 'encapsulation' to a varying extent is also found. The pseudo-capsule may be lacking, still leaving the tumour relatively circumscribed. A combination of encapsulated nodules and nodules partially encapsulated and more or less clearly delimited from the surrounding tissue can be found especially in recurrent tumours. In some instances tumour tissue can be seen growing into the 'capsule' or through the 'capsule' into the surrounding tissue.

Although the infiltrative growth of tumours has been the subject of extensive clinical and experimental investigations, we still have a poor understanding of the local conditions prevailing when tumour cells invade normal tissue. The pattern of infiltrative growth also varies. One can certainly discover differences in the extent of the infiltrative growth. In some instances one can find diffuse invasion, in others local invasion without reaction of the surrounding tissue. Localized invasion of salivary gland tissue, localized invasion of blood and lymph vessels or a more tentacular invasion of salivary gland tissue or surrounding tissue can also be found.

What are the pathologist's difficulties in determining whether these tumours are benign or malignant?

The existing uncertainty is due to the difficulty of objective evaluation of various histological features. Of importance are:

1. The histological appearance (cellularity, pleomorphism etc.).
2. The relative importance of various tumour components (predominance of either epithelial or mesenchymal components).
3. The invasive growth (Only one or a few blocks of tissue are studied, so one is never absolutely certain about conditions elsewhere in the tumour. This is especially of importance because many tumours were extirpated, not 'in toto' but in several fragments).

The literature contains several careful descriptions of various histological structures of mixed tumours, but we found no clinical follow-up on mixed tumours associated with the problem of infiltrative growth.

Great prognostic importance has been attached to the fact that infiltrative growth is actually a sign of malignancy of these tumours, but no report deals with conclusive evidence that inclination towards infiltrative growth also has prognostic implications.

In this presentation an attempt is made to study the correlation between the histological features of mixed tumours and the clinical course. The histological features were studied on the basis of various tumour components, morphological signs suggesting malignancy and the relation between tumour tissue and adjacent normal tissue.

It was extremely difficult to study 'capsular' structure in the totality of the external aspect of the tumour. In doubtful cases, new sections were cut.

Nevertheless there were frequent difficulties due to artefacts in preparing the slides, or lack of radicality in surgical excison (the tumour was often received in fragments; in many cases, moreover, only needle biopsies were available).

The histological features of the mixed tumour material during the period 1947—1959 are presented in table 4.

In table 5, an attempt is made to study the correlation between the clinical course and histological features regardless of invasiveness. In table 6, an attempt is made to study the influence of invasiveness on the clinical course. The results of the investigation shown in table 5 are:

The group with predominance of epithelial components includes 88 patients with complete follow-up; 2 of these patients died of the tumour disease, and one died of intercurrent disease.

Fifty-six patients were treated surgically only, and 32 patients received combined treatment (surgery and postoperative radiotherapy). After treatment the tumour recurred in 13 patients; in one case, metastases subsequently developed.

The group with predominance of connective tissue-like components includes 113 follow-ups; one patient died of the tumour disease, and 4 died of intercurrent disease. Ninety-seven patients were treated surgically, and 16 patients received combined therapy. After treatment the tumour recurred in 4 patients; in 1 case metastases subsequently developed.

The group without predominance of any component includes 38 follow-ups. No death occurred in this group; 15 patients were treated surgically and 23 patients received combined therapy. The tumour recurred in 5 patients.

The group of mixed tumours with morphological signs of malignancy includes 25 patients with complete follow-up; 12 patients died of the tumour disease and 4 other deaths were possibly due to the tumour disease; 2 other patients died of intercurrent disease. One patient was treated surgically, 5 patients received radiotherapy only and 19 patients received combined therapy. The tumour recurred in 8 patients.

At the first examination 2 patients had regional metastases; in 10 patients, metastases subsequently developed.

In table 6, invasiveness is expressed as the relation between tumour tissue and adjacent normal tissue. The result in table 6 shows:

Infiltrative growth into the surrounding tissue was demonstrated in 9 out of 264 mixed tumours without morphological signs of malignancy of the individual cells. Five follow-ups included 2 patients who died of the tumour growth. A local recurrence occurred in 2 patients. One patient subsequently developed metastases.

Penetration into the 'capsule' could be demonstrated in 6 out of 264 mixed tumours without morphological signs of malignancy. Follow-up over 5—16 years disclosed no death in these cases.

Infiltrative growth into the surrounding tissue was demonstrated in 15 out

Table 4 Histological features of mixed tumour material 1947—1959.

Histological features	Number of patients	Completely encapsulated	Incompletely encapsulated	Absence of capsule clearly delimited	Penetration into the capsule	Infiltration into surrounding tissue
Predominance of epithelial components	99	16	53	20	3	7
Predominance of connective tissue components	123	24	80	15	2	2
No definite predominance of any component	42	8	26	7	1	—
Pleomorphous epithelial structural traits of adenocarcinoma epidermoid carcinoma or sarcomatoid structures	29	—	5	5	4	15
Total	293	48	164	47	10	24

Table 5 Mixed tumours: correlation between histological and clinical features (5—16 years' follow up).

Histological features	Number of patients								THERAPY			Died of disease		5-year survival
	Total	Sex F	Sex M	Followed up	No follow up	Local recur.	Metastasis developed Prim.	Metastasis developed subsequently	Surgery	Radiotherapy	Combined	Intercurrent	Tumour disease	Total
Predominance of epithelial components	99	64	35	88	11	13	—	1	56	—	32	1	2	85/88
Predominance of connective tissue components	123	77	46	113	10	4	—	1	97	—	16	4	1	108/113
No definite predominance of any component	42	23	19	38	4	5	—	—	15	—	23	—	—	38/38
Pleomorphous epithelial structural traits of adenocarcinoma, epidermoid carcinoma or sarcomatoid structures	29	12	17	25	4	8	2	10	1	5	19	2	12 + 4?	7/25
Total	293	176	117	264	29	30	2	12	169	5	90	7	15 + 4?	238/264

Table 6 Mixed tumours: correlation between invasiveness and clinical features (5—16 years' follow up).

	Relation between tumour tissue and adjacent normal tissue	Number of patients: Total	Sex: F	Sex: M	Followed up	No follow up	Local recur.	Metastasis developed: Prim.	Metastasis developed: subsequently	THERAPY: Surgery	THERAPY: Radiotherapy	THERAPY: Combined	Died of disease: Intercurrent	Died of disease: Tumour disease	5-year survival: Total
No morphological signs of malignancy	Completely encapsulated	48	31	17	45	3	—	—	—	39	—	6	—	—	45/45
	Incompletely encapsulated	159	92	67	143	16	18	—	—	112	—	31	5	—	138/143
	Absence of a capsule still clearly delimited	42	32	10	40	2	2	—	1	13	—	27	—	1	39/40
	Penetration into the capsule	6	4	2	6	—	—	—	—	2	—	4	—	—	6/6
	Infiltration into surrounding tissue	9	5	4	5	4	2	—	1	2	—	3	—	2	3/5
Morphological signs of malignancy	Incompletely encapsulated	5	3	2	4	1	3	—	3	—	—	4	1	3	0/4
	Absence of a capsule still clearly delimited	5	2	3	4	1	1	1	2	—	1	3	—	1 + 2?	1/4
	Penetration into the capsule	4	2	2	4	—	—	—	1	—	—	4	—	1	3/4
	Infiltration into surrounding tissue	15	5	10	13	2	4	1	4	1	4	8	1	7 + 2?	3/13
	Total	293	176	117	264	29	30	2	12	169	5	90	7	15 + 4?	238/264

of 29 mixed tumours with morphological signs of malignancy. Follow-up over 5—16 years of 13 cases disclosed 7 deaths due to the disease and 2 deaths possibly due to the disease; only one patient died of intercurrent disease. One patient had local metastases at the first examination; in 4 cases, metastases subsequently developed. In 4 patients the tumour recurred after treatment.

Penetration into the 'capsule' was demonstrated in 4 out of 29 mixed tumours with morphological signs of malignancy. Follow-up revealed one death due to the tumour disease; in one case metastases developed subsequently.

Before discussing the prognostic value of the various morphological characteristics of these tumours, the clinical course in the patients who died due to the tumour disease will be analysed.

Summaries of these case histories are presented in the appendix.

Discussion and conclusion

It is generally accepted that infiltrative growth of a tumour into the surrounding tissue is a criterion of malignancy. In recent years it has been frequently demonstrated that all criteria of malignancy (nuclear changes, anaplasia, loss of polarity, infiltration, progressive growth and metastases) are not always found together. There are tumours which possess some of these characteristics and lack others, e.g. basal carcinomas of the skin, which have a wellknown definitely infiltrative growth, but a very low metastatic potency. The carcinoma in situ shows no infiltrative growth and by definition does not metastasize.

On the other hand, such tumours as haemangiomas and dermatofibromas, which are considered benign, may show a certain degree of infiltrative growth; the tendency toward infiltrative growth, therefore, is no absolute index of malignancy, although it can be demonstrated in practically all malignant tumours.

The complex process of tumour invasion — subject of many clinical and experimental studies — is analysed with difficulty.

In mixed tumours of the salivary glands with an apparently benign appearance but showing infiltrative growth into the surrounding tissue, the latter is menacing but not necessarily catastrophic in all cases (table 6.), while in mixed tumours with morphological signs of malignancy (e.g. cellularity, pleomorphism, mitosis etc.) there is a much stronger indication of tumour aggressiveness.

The study of tumour tissue within normal boundaries, and of invading cells in the cases of mixed tumours with an apparently benign morphological appearance, has shown that no distinction can be made between the epithelial cells within normal boundaries and the invading epithelial cells, regardless of whether they penetrate the 'capsule', or infiltrate the 'capsule' or the surrounding tissue.

In this series the highest frequency of infiltrative growth into the surrounding tissue was demonstrated in mixed tumours with morphological signs suggestive of malignancy; these were followed by the group of mixed tumours with predominance of the epithelial component (Table 4).

Foote and Frazell (1954) studied the influence of cellularity on the clinical course in 250 mixed tumours, but could not reach any conclusions. The series with predominance of the epithelial component (see table 5 — 99 cases) showed two cases associated with malignancy demonstrated in mortality due to the disease out of 88 followed up cases. In only one case was infiltrative growth into the surrounding tissue demonstrated (case 47/25435 see appendix). Further analysis of cases which subsequently developed metastases has shown that a stage of histological malignancy can be found, before the tumour becomes fatal.

A complete study of mixed tumours and their clinical picture in this series has revealed the following groups:

1. Epithelial neoplasia with a morphologically benign appearance and a benign course.
2. Epithelial neoplasia with a morphologically benign appearance, but with slight local infiltration of the 'capsule', leading to recurrences in most cases.
3. Epithelial neoplasia with a morphologically benign appearance and a protracted clinical course, which has given rise to carcinoma in the long run.
4. Epithelial neoplasia of malignant character, with a slow clinical course.
5. Epithelial neoplasia of malignant character, with a rapid clinical course.

Some observers might label groups 2 and 3 potentially malignant or potentially carcinomatous, while others regard them as early stages of carcinoma.

This investigation of mixed tumours, based on a follow-up study over 5 to 16 years, has shown that classification of mixed tumours into malignant and benign types is merely an easy way out of a complicated situation. The present limitations of our knowledge make this problem infinitely more difficult.

Interpretation of the benign type of mixed tumour is beset by difficulties due to the diversity in morphogenesis of these tumours. The tumour usually starts in the epithelium cells of the intercalated ducts (zones of proliferation, Cohen and Schaper 1905). The abnormal state of these epithelium cells probably begins before the mitotic process is evident. The earliest state of a tumour therefore is not one that can be discovered by palpation or microscopic examination. In this stage the epithelial neoplasia is still confined within normal boundaries. How long this confinement may continue is another question. For some unknown reason the division gives

rise to cells that possess the potential plasticity to differentiate into serous, oxyphilic granular, clear cell, sebaceous and squamous types of epithelium capable of individual existence, multiplication, autonomous growth and metastasis. Close scrutiny also revealed special epithelial elements participating in the process, namely: the myo-epithelial elements.

It is unfortunate that at the present state of our knowledge we cannot establish beyond all question that a state of malignancy is present until the disease has reached a rather advanced stage.

Because of their slow growth, their supposed 'encapsulation' and the rarity of metastases, some types of mixed tumour have often been considered benign. In this study of the correlation between the histological and clinical features, it has been shown that some forms of so-called benign mixed tumour based on their morphological appearance may become malignant.

On the basis of the data obtained in this survey, mixed tumours of the salivary glands should be treated as a malignant tumour; different mixed tumours may show different degrees of malignancy.

If the prognosis in patients with mixed tumours must depend upon the morphological diagnosis, two histological types can be distinguished, namely: one type of mixed tumour without morphological signs of malignancy which are clinically benign or at the most show a low degree of clinical malignancy and a second type of mixed tumour with definite morphological signs of malignancy with a high degree of clinical malignancy.

A2. Adenomas

In literature, many purely epithelial tumours containing serous cells of salivary gland acini and cuboidal cells of the ducts are described as adenomas (Stohr and Risak 1926, MacFarland 1927, Lang 1929, Skorpil 1940, Mettler 1956).

Various types were described by von Albertini (1959) as alveolar, tubular tubulo-alveolar, trabecular, etc. MacFarland (1927) regarded most of the so-called adenomas as varieties of mixed tumours showing a preponderance of glandular tissue.

A critical study of these adenomas often reveals that, apart from the exclusively homogeneous areas, small areas like those commonly seen in mixed tumours can be found. In the opinion of Rawson et al. (1950), Kirklin et al. (1951), Willis (1953) and Mathis (1954), pure adenomas do not occur. Such a neoplasm must be regarded as actually a mixed tumour with predominance of the epithelial component.

Such cases necessarily broaden rather than narrow one's structural concepts of mixed tumours of the salivary glands. Measured by this standard, only a few adenomas or adenoma-like conditions with distinct histological characteristics, commonly mentioned in literature as possible separate types, will be considered.

Sebaceous cell adenoma

Sebaceous cells can be found in the buccal mucosa (Margolies and Weidman 1921, Weatherford 1944) and in rare instances in the major salivary glands as solitary cells (Zimmerman 1927) or as a group of cells (Meza Chavez 1949, Rawson et al. 1950, Foote and Fazell 1954, Bain et al. 1956).

Genuine tumours seldom develop from these cells (Rauch and Maszhoff 1959). Hartz (1946) has shown in serial sections that in his case sebaceous glands arose as branching outgrowths of the parotid ducts. Meza-Chavez (1949) observed sebaceous glands associated with ducts in two parotid glands resected for adenomas.

Two cases of sebaceous cell adenoma were described by Rawson et al. (1950) and one possible case was mentioned by Foote and Frazell (1954). Not a single case of sebaceous cell adenoma could be found in our series. These tumours are generally considered to be benign.

Oncocytoma

Synonyms:
Oxyphilic granular cell adenoma (Meza-Chavez 1949)
Oxyphil cell adenoma (Foote and Frazell 1954)
Azidophiles adenoma (Rauch 1959)
Definition:
According to Hamperl (1962), the term oncocytoma must be used only to denote that the tumour completely or mainly consists of oncocytes.

The studies of Hamperl (1931) focused attention upon the existence of these cells as oncocytes. They occurred in a variety of organs such as salivary glands, trachea, pharynx, oesophagus, buccal musoca, pancreas, hypophysis, breast, fallopian tube, etc. The origin of the oncocytes lies in the multipotential cells of the intercalated ducts, as demonstrated by the transition of small cuboidal lining cells into swollen oxyphilic granular cells (Bauer and Bauer 1953). According to Batsakis and Martz (1960), oncocytes never occur before age 20, and seldom before age 50, but they are usually found after age 70 (Hamperl 1962). Skorpil (1940) suggested that oncocytes comprise an irreversible type of transformed glandular epithelium. Foot and Frazell (1954) were of the opinion that the oncocytes in oncocytomas retain their ability to differentiate into other types of tumour.

Histological features

The cells of the oncocytoma are homogeneous, relatively large and polygonal, with distinct contours. They are eosinophile and finely granular, with comparatively small, dark, well-defined nuclei (see fig. 6).

They are most characteristically arranged in columns or cords, only a few cells thick, and these units are separated only by the faintest, sparsely vascularized stroma.

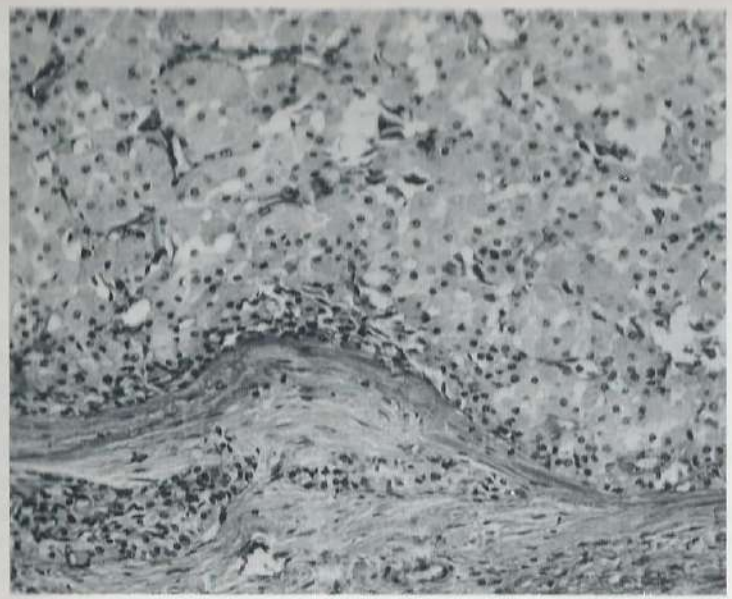


Fig. 6. Oncocytoma showing infiltrative growth into surrounding tissue. Photomicrograph × 140.

In our series from 1947 to 1959, only 3 of these tumours were found. The first case, 52/2900, was in a woman aged 55.

Clinical history: In 1949, a clinically benign tumour below the left ear was incompletely removed.

Microscopic diagnosis: Oncocytoma

After this operation the tumour recurred again and again (in 1950, 1951 and 1955), and each recurrence was extirpated. Comparison of the microscopic findings (1949, 1950, 1951, and 1955) revealed the same appearance except infiltrative growth into the surrounding tissue in the last preparations. After operative treatment in 1955, the patient received X-ray therapy (3000 R air dose in 11 days). During the lastmentioned operation, local tumour destruction of the zygomatic bone was noticed.

Further follow-up revealed a new recurrence in March 1956, the tumour now invading the left cheek. This time the patient was treated by radium punctures, with reasonable success. In January 1957 a swelling above the first left molar was noticed; this was again extirpated, with subsequent X-ray therapy. Another swelling above the left ear was manifest in May 1958; this too was extirpated. In January 1959 another local recurrence developed underneath the old surgical scar.

A needle biopsy revealed microscopically: adeno-carcinomatoid structures

suggestive of carcinoma (Z. 28671). The patient received Telecobalt treatment. In April 1959 a rapidly growing tumour was again found in front of the left ear, for which X-ray therapy was given. In March 1960 the patient complained of disturbed vision; a fluctuating tumour was found on the left lateral side of the orbit.

In August 1961 definite tumour invasion of the fronto-temporal part of the skull called for a decompression operation, but the patient's general condition contraindicated radical surgery. A gradual deterioration in the general condition led to death on 5th November 1961.

The second case, 58/15644, in a woman aged 40.

Clinical history: Since a few years there had been a painless swelling in the right parotid area, without symptoms. A clinically benign tumour was found in this area at examination.

Operation on 5th March 1958.

Microscopic diagnosis: (P. 15644) Oncocytoma, with local infiltrative growth.

At subsequent follow-ups this patient showed no local signs of recurrence; she was still free of symphoms when seen in December 1964.

The third case, 48/300330, was in a man aged 64.

Clinical history: A palpable mass had existed in front of the left ear for the past year. No further complaints. The lesion was first treated by the general practitioner by local applications of unguents. In April 1949 the growth increased and the patient was referred to the surgeon. At examination a clinically benign tumour was found in the left parotid region.

A biopsy was taken on 12th July 1949.

Microscopic diagnosis: (T. 17939) Oncocytoma.

In August 1949 the patient was admitted for surgery.

Microscopic diagnosis of the resected specimen (T. 18188): Malignant oncocytoma.

The patient received postoperative X-ray therapy (3400 r in 12 days).

Follow-up revealed no peculiarities locally. In 1963 the patient was hospitalized for treatment of a carcinoma of the bladder. In January 1964 he was still alive.

Discussion and conclusion

The finding of oncocytic structures in mixed tumours has been reported by various authors (Christopherson 1949, Rawson et al. 1950, Foote and Frazell 1954). This has led to a discussion as to whether oncocytomas should be separated from other types of salivary gland tumour. To many authors

(e.g. Ackerman 1943, Foote and Frazell 1954, Schafer et al. 1956) oncocytomas are a separate type of tumour with histologically characteristic features.

Hamperl (1962) traced 44 cases of oncocytoma in the literature. No definite conclusions could be drawn. Oncocytomas are extremely rare, and are generally described as benign. Bauer and Bauer (1953) were the first to report a malignant oncocytoma with metastases in the lungs, liver, dura and pituitary gland. They described the microscopic features of the metastases as identical to those of the original tumour, but in fact gave a description of oxyphilic granular cells in the metastases. In my opinion, these cells differed from the cells in the primary tumour. Identical malignant neoplastic cells were seen in the needle biopsies in case 52/2900, with adeno-structures.

Other cases of malignant oncocytoma were reported by Buxton et al. (1953 — 9 cases); Hamperl (1962) saw one case, with origin in the nasal mucous membrane.

In view of the cases of Bauer and Bauer, Buxton et al. and Hamperl, and the cases in our series, oncocytomas should be regarded as malignant, with probably a very low degree of malignancy.

A3 *Papilliferous cystadenoma*

Synonym: intraductal papilloma (Castigliano and Gold 1954)

Histologically, this type of tumour is characterized by the presence of intracystic papillary projections, the papillae being lined by columnar basophile epithelial cells. The nuclei are hyperchromatic.

The cystic spaces may be empty or filled with an oxyphilic substance. This condition resembles that seen in intraductal papillomas of the breast. These tumours are exceedingly rare.

Clinical data pointing out definite malignancy have not been found in the literature.

A3 *Papillary cystadenoma lymphomatosum*

Synonyms:
Papilläres Zystadenoma in Lymphdrüsen (Albrecht & Artzt 1910)
Papillary cystadenoma lymphomatosum (Whartin 1929)
Adenolymphoma (Gaston & Tedeschi 1946)
Papillary cystadenolymphoma (Thompson & Bryant 1950)

This tumour is considered a separate type of salivary gland tumour. It has a characteristic histological pattern, dominated by papillary epithelial structures, lining spaces embedded in a lymphoid stroma.

The epithelial cells lining cystic spaces are arranged in 2 layers. The cells near the lumen are arranged in a palisade pattern. These are tall oxyphilic columnar cells, the cytoplasm of which contains numerous

minute oxyphilic granules. The cells have large oval nuclei arranged in an even row toward the luminal ends of the cells. The basal layer consists of irregularly arranged, small polyhedral cells with smaller nuclei and less oxyphilic cytoplasm. These cells rest on a thin basal membrane.

The general morphology is variable; some tumours are mainly cystic, while others are alveolar; still others are tubular, and most often all these different features are present in a single tumour.

The cysts may contain material which is finely granular and slightly oxyphilic, sometimes homogeneously and deeply stained. Desquamated cells, fatty globules and cholesterol crystals may be found in this substance. The stroma is dense, composed of a delicate reticulum containing many lymphocytes, and often showing numerous follicles.

The tumour is usually surrounded by a thin capsule of fibrous tissue.

Our series included 18 cases of this type of tumour. Follow-ups over 5—16 years revealed no case of death due to the tumour, nor any sign of malignancy. Only 1 case with a recurrence was found in this series. The clinical course was usually slow, the tumour remaining stationary for many years; the tumour occurred predominantly in males, with an age distribution from 33 to 70 years.

These tumours are generally considered benign, but some authors dispute this (Szobolew 1912, Stohr and Risak 1926, Hanford 1931, Gödel quoted by Skorpil 1939, Lederman 1943). Orloff (1956), evaluating 5 cases of supposedly malignant transformation in the literature (abovementioned authors), found no acceptable instances of malignancy of papillary cystadenoma lymphomatosum; we must conclude that these neoplasms are to be regarded as benign.

A5 *Muco-epidermoid tumours*

Separation of this type of tumour was due to the work of Stewart et al. (1945) and Linell (1948). In many classifications, however, this tumour is still not considered a separate type (e.g. Mathis 1954, Redon 1960, Willis 1960).

Synonyms:
Schleimbildendes Epitheliom (Schilling 1921)
Epithélioma à double métaplasie (Masson et Berger 1924)
Mixed epidermoid mucus-secreting carcinoma (De and Tribedi 1939)

Histological features

The term muco-epidermoid refers to the content of two main types of cells, mucin-secreting cells and epidermoid cells. The microscopic picture is characterized by a mixture of cell types; the mucin-secreting cells, large

cylindrical epithelial cells, the epidermoid cells and the cells referred to as intermediate cells.

The frequency of occurrence of these different types of cells varies in different tumours and in different areas of the same specimen (see fig. 7a and 7b). According to Stewart et al., the intermediate cells are capable of differentiation into mucous or into epidermoid and then into squamous cells. Cyst formations are a common finding in these tumours; small cysts may coalesce to form larger cysts filled with mucoid material.

On the basis of the degree of differentiation, this type of tumour has been subdivided into various groups. Stewart et al. divided them into a highly differentiated and a poorly differentiated group. As highly differentiated tumours are considered the tumours presenting all cell types, and as a rule pronounced epidermoid cell differentiation and numerous mucus-containing cysts. In the poorly differentiated tumours, epidermoid cells predominate while mucin-secreting cells are less numerous. The highly differentiated tumours can usually be diagnosed easily, but the poorly differentiated tumours are a subject of much confusion, because in some cases it is difficult to differentiate this condition from poorly differentiated adenocarcinomas or poorly differentiated squamous cell carcinomas.

Foote and Frazell and Sharp & Helsper (1960) described an intermediate group of borderline cases. This made the subdivision into groups infinitely more difficult, as the criteria for deciding which tumour was to be included into which group became very uncertain. No one can state exactly how much differentiation is required for a case to exceed the 'borderline' margin.

In an attempt to clarify the problem, Marcial-Rojas & Sommers (1954) in their study of muco-epidermoid tumours expressed the opinion that only the highly differentiated tumours should be considered muco-epidermoid tumours, while the poorly differentiated tumours should be regarded as undifferentiated or poorly differentiated carcinomas. On one hand, the difficulty of separating the different groups histologically in a uniform way leads to a varying distribution of these tumours in different series; on the other hand, different authors use different criteria of diagnosis. If any comparison is to be made, the only solution is to assemble muco-epidermoid tumours in one single group, including only well-defined tumours. To reach such a standard definition we should include only tumours with well developed epidermoid cell and mucin-secreting cell components, readily demonstrable by haematoxylin and eosin staining (Woolner et al. 1954, Gray et al. 1963).

Applying this standard to our series, we could find only 7 tumours with well-developed epidermoid cell and mucin-secreting cell components.

Clinical data were lacking in only 1 of these 7 cases. Follow-up examination in the other 6 cases revealed no evidence of metastasis or death due to the tumour. In 3 patients the tumour recurred. The clinical findings and follow-up information are summarized in table 7. This series is too small to warrant definite conclusions.

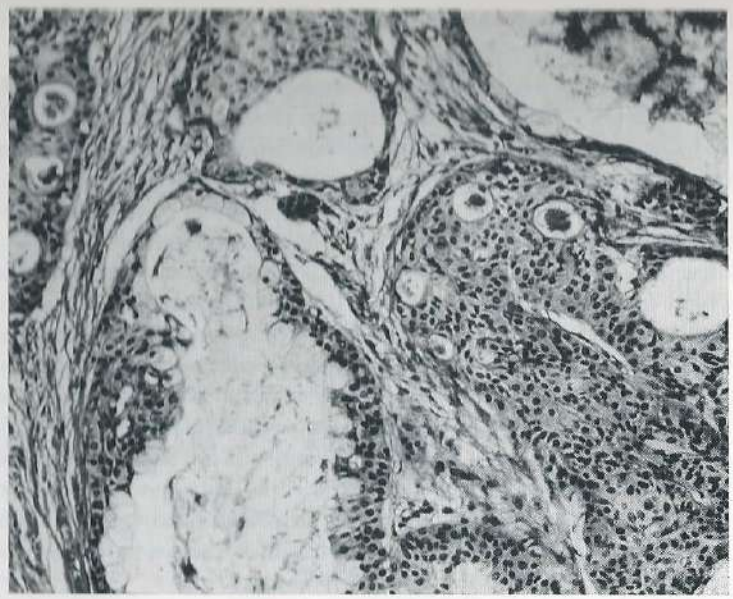


Fig. 7a. Muco-epidermoid carcinoma.
Photomicrograph × 140.

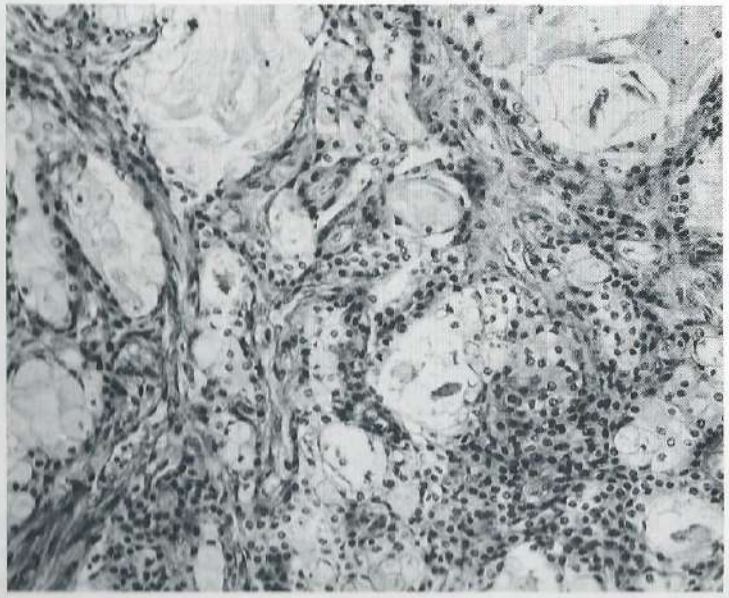


Fig. 7b. Muco-epidermoid carcinoma Mucus secreting cells in microcyst formation.
Photomicrograph × 140.

Table 7 Muco-epidermoid carcinoma: correlation histological and clinical features (5—16 years' follow up)

Case No.	Site	Age	Sex	Degree of differentiation	Clinical signs before treatment	Initial Treatment	Subsequent course
48/32906	parotid	47	F	highly differentiated	16 years	Excision	Recurr. tumour excised 1950-X-ray ther. still alive.
56/3599	parotid	35	F	highly differentiated	1 year	Wide Excision X-ray ther.	Still alive-local asymptomatic.
53/1381	submax.	44	F	highly differentiated	7 months	Excision X-ray ther.	Died of metastasis from cancer of the breast 1954.
55/2788	mandible	45	F	poorly differentiated	2 years	Excochl. X-ray ther.	Gradual disappearance of cystic bone cavity of the R. mandibula. Still alive without complaints.
58/33929	parotid	5	F	highly differentiated	unknown	Exicision	Recurr. tumour excised May 1959-X-ray ther. Recurr. tumour excised Jan. '60-X-cay treat. 1964 still alive without evidence of local recurr.
54/164	parotid	14	M	highly differentiated	5 years	Excision	Recurr. tumour excised Dec. '55; X-ray ther. total parotidectomy for recurr. tumour April '55-X-ray ther. May '57: excision and combined radical neck dissection for recurr. tumour with reg. lymph node involvement-X-ray ther. Recurr. tumour excised from left external meatus Jul. '61. 1964 still alive, locally asymptomatic.

In the case numbers, the first two digits represent the year of admission.

Discussions and conclusion:

Woolner et al. (1954), in a report on 36 tumours, divided them into two groups: 1. muco-epidermoid tumours not giving rise to metastases nor leading to death, and 2. muco-epidermoid carcinomas (subdivided into three subgroups with different histological patterns). All 3 types demonstrated the ability to metastasize. They concluded, like Foote and Frazell, that benign tumours or those with a low grade of malignancy follow a clinical course closely parallel to that of apparently benign mixed tumours, characterized by slow growth but fairly frequent recurrences.

Gray et al. (1963), in a clinico-pathological study of 35 muco-epidermoid tumours, concluded that the tumours which recur rapidly and metastasize, cannot always be recognized morphologically and separated from those that

do not. A similar opinion had been previously expressed by Beahrs et al. (1960). They believed that most muco-epidermoid tumours have a low grade of malignancy and tend to infiltrate locally; but there are conditions of an obviously anaplastic character which show a more pronounced tendency towards infiltrative growth and metastases.

The controversy about the grade of malignancy in the literature is due to several factors: 1. The comparative rarity of these tumours.

2. Different criteria of diagnosis in different authors' series. The current general opinion is that these tumours must be considered malignant. Although no definite prognostic conclusions can be drawn from the morphological appearance alone, the separation of these tumours into two groups on the basis of their degree of differentiation is of importance on clinical grounds. It is clear that most authors refer to a morphological distinction between the highly differentiated type with a low grade of clinical malignancy and the poorly differentiated type with a high grade of clinical malignancy.

A6 *Squamous cell carcinoma*

Synonym: epidermoid carcinoma

Histological features

The wellknown ability of epithelium of salivary gland ducts to undergo squamous metaplasia is also found in salivary gland tumours. In cases of this type of tumour the salivary gland is often almost completely or completely replaced by tumour, and in some instances it is difficult to ascertain that a particular tumour is of salivary gland origin. In some cases, however, these tumours may represent metastatic carcinoma. In other cases mixed tumours may show an overgrowth of squamous cell carcinoma. The squamous cell carcinomas are usually well differentiated and do not differ from squamous cell carcinomas arising at other sites; the differentiation of these tumours is based on more or less pronounced keratinization.

Most classifications use the designation well differentiated and partially or poorly differentiated, and the criteria are not strict; they partly depend on the thoroughness of the histological examination, which in different parts of the tumour may disclose different aspects.

These tumours are highly infiltrative. Most carcinomas are well differentiated. The poorly differentiated tumours may be confused with the poorly differentiated muco-epidermoid carcinomas or anaplastic or undifferentiated carcinomas (see fig. 8).

In 18 cases of our series a salivary gland tumour was microscopically

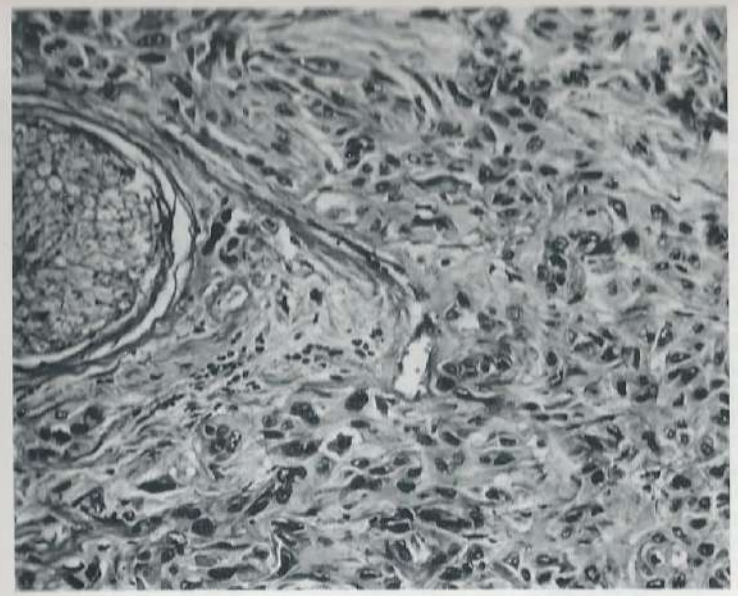


Fig. 8. Undifferentiated squamous cell carcinoma. Photomicrograph × 140.

diagnosed as squamous cell carcinoma. But when the clinical findings became available for study and more material from the primary tumour or recurrent tumour was obtained, the final diagnosis had to be changed in 2 cases. In these two cases the diagnosis was changed to metastatic carcinoma. In one case the primary source was a carcinoma of the lip. In the other case no definite primary site could be clinically detected and, because the primary lesion was probably located in the neck, this condition was referred to as metastatic branchiogenous carcinoma.

In 16 cases squamous cell carcinoma of salivary gland origin was definitely diagnosed: 1 lost for follow-up. In table 8, the clinical findings are presented. A history of the presence of a quiescent tumour is seldom encountered in these cases. The disease is found predominantly in males. The age distribution in this series ranged from 59 to 91 years.

In table 9 the clinical course and survival rate is given. The clinical course is generally one of rapid evolution, with rapid regional metastatic growth. Survival is poor. The vast majority of these tumours are obviously clinically malignant from the onset. The vast majority of the patients die as a result of intractable local disease and regional lymph node involvement. Distant metastases are found in a minority of cases. The local disease often causes intractable pain and is often complicated by ulceration of the overlying skin or mucous membrane, and hemorrhage. It may be concluded that these tumours must be considered very aggressive and highly malignant.

Table 8 Clinical findings of squamous cell carcinoma: 15 cases.

Case No.	Site	Age	Sex	Clinical signs before treatment	Clinically malignant
49/31793	submax.	74	M	6 weeks	—
49/31161	parotid	60	F	6 months	+
50/35433	parotid	80	M	4 months	—
50/32582	parotid	63	M	2 months	+
51/39724	subling.	72	M	5 months	±
51/39356	parotid	74	M	4 months	+
52/55008	parotid	64	M	3 weeks	+
54/287	parotid	76	F	4 months	+
54/554	submax.	69	M	6 months	+
55/2594	parotid	79	M	6 weeks	+
56/731	parotid	59	F	3 months	+
56/4096	submax.	59	M	2 years	+
57/1637	parotid	84	M	4 months	+
57/10309	parotid	81	F	7 weeks	—
58/546	parotid	91	M	2 months	+

In the case numbers, the first two digits represent the year of admission.

A 7 *Cylindroma*

Synonyms:

Zylindrom (von Ribbert 1907, Rawson et al. 1950, Kirklin et al. 1951, Rauch 1959, Gläser 1962)
Basal cell carcinoma (Krompecher 1908)
Adenoid cystic carcinoma (Spies 1930, Foote and Frazell 1954)
Adenomyoepithelioma (Bauer and Fox 1945)
Adenocarcinoma of cylindroma type (Quattlebaum et al. 1946)
Adenocarcinoma (Willis 1953)

For many years it has been recognized that salivary gland tumours of cylindromatous type are found in the major salivary glands (parotid and submandibular), in the minor salivary glands within the oral cavity (palate, floor of the mouth, tongue, lips) and in the mucous glands elsewhere (nose, nasopharynx, sinuses, respiratory tract). Most authors dealing with the problem of the origin of these tumours agree that cylindromas arise directly from these glands. However, cylindroma of the salivary glands has only recently been recognized as a distinct entity (Quattlebaum et al. 1946), and it is now generally agreed that a clear distinction should be made between cylindromas of the salivary glands and those occasional tumours which appear to show the same characteristics as bronchial cylindromas (von Albertini 1955), breast tumours showing cylindromatous patterns and some skin tumours derived from the sweat glands.

Table 9 Squamous cell carcinoma: clinical course and survival rate.

	Number of patients								THERAPY			Died of disease		5-year survival
	Total	Sex F	Sex M	Followed up	No follow up	Local recur.	Metastasis Prim.	Metastasis developed subsequently	Surgery	Radiotherapy	Combined	Intercurrent	Tumour disease	Total
Squamous cell carcinoma	16	5	11	15	1	4	6	8	—	6	9	2	12	1/15

Table 11 Cylindroma: clinical course and survival rate.

	Number of patients						THERAPY				Died of disease		5-year survival
	Total	Followed up	No follow up	Local recur.	Metastasis Prim.	Metastasis developed subsequently	Surgery	Radiotherapy	Combined	Asymptomatic	Intercurrent	Tumour disease	Total
Cylindroma	13	12	1	7	1	4+1?	—	2	10	5	1	4	7/12

Histological features:

This type of tumour is characterized by the formation of cystic spaces, solid epithelial areas and stromal changes. The characteristic picture is the formation of epithelial islands, composed of rather small, dark staining cells with relatively little cytoplasm, in combination with myxoid, hyalinized areas, giving the appearance of a cribriform structure (see fig. 9).

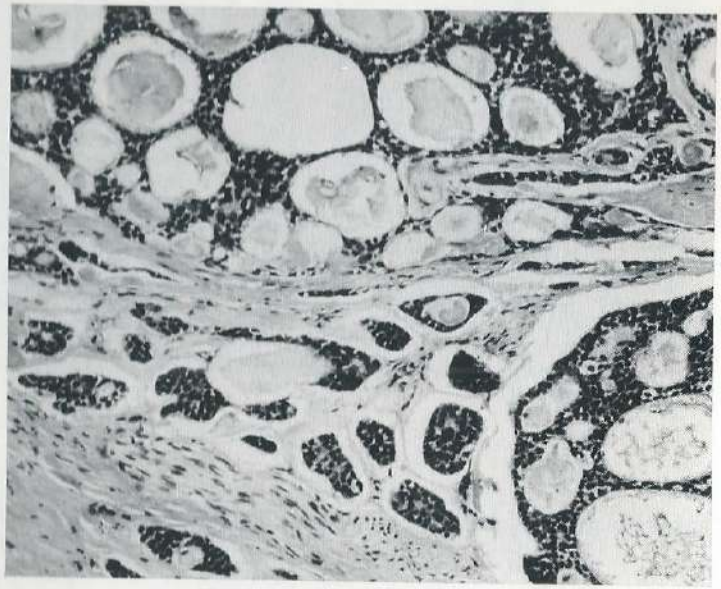


Fig. 9. Cylindroma; typical cribriform pattern. Photomicrograph × 140.

Alternating cystic areas as well as solid cellular areas are common. Ringertz (1938) on this basis divided cylindromas into solid basaliomas and adenocystic epitheliomas.

A rather scanty fibrous stroma is commonly found, but the stroma may be abundant and frequently hyalinized. The hyalin is either changed stromal connective tissue or it represents a product of the tumour cells being laid down in the stroma. Hyalinization often breaks up the cribriform pattern into smaller cell groups (see fig. 10).

The deposition of mucinous material in the stroma or 'replacement' of the stroma by myxoid material is not uncommon; however, the tumour cell masses remain sharply defined and do not merge with the mucoid material. The myxoid areas can be distinguished from the myxoid components of mixed tumours (Thackray and Lucas 1960).

In our series, 13 cases of cylindroma were found. The results of the study are listed in tables 10 and 11 (page 33, 35). In one case no clinical data were available. The results of the study of the remaining 12 cases showed no special

Table 10. 12 cases of cylindroma and their subsequent clinical course.

Case No.	Site	Age	Sex	Clinical signs before treatment	Initial Treatment	Subsequent course
47/1730	parotid	47	F	1½ years	Excision	Recurrent tumour excised May 1952 followed by X-ray therapy 3900 r in 22 days. Still alive, locally asymptomatic.
54/4478	submand.	53	F	2 months	Excision and postoperative X-ray therapy	May 1956 infiltration of the floor of the mouth; treated by Radium puncture. Gradual increase of pulmonary metastases from Jan. 1959 to Dec. 1959. Death in May 1962.
58/55731	submand.	65	F	5 months	Excision	Still alive; locally asymptomatic.
51/23066	submand.	46	M	2 years	Excision	Recurrent tumour excised Sept. 1958; still alive without complaints- locally asymptomatic.
55/3687	parotid	38	F	1½ years	Excision and postoperative X-ray therapy	Still alive; locally asymptomatic.
50/741	pharynx	36	F	1 year	Excision	Regional lymph node involvement Oct. 1953. June 1954 tumour invasion of tonsil and palate. Nov. 1954 neck dissection; Febr. 1955 multiple recurrences in the neck scar; pulmonary metastases. May 1955 metastases to the bones (spine and right scapula). Uncontrollable local invasion and further metastases leading to death in July 1955.
56/1932	hard palate	70	M	1½ years	Biopsy and X-ray therapy	Recurrent tumour May 1960; Aug. 1961 hemorrhagic discharge from the nose due to tumour invasion into the left nasal cavity- X-ray therapy. May 1962 enlarged lymph nodes inguinal and right axillary regions- deterioration of the general condition leading to death in June 1962.
57/2150	right alveolar process	67	M	3 months	Biopsy partial resection of the maxilla postoperative X-ray therapy	Death followed a week after operation. At autopsy no definite cause of death could be found; microscopically, pulmonary metastases could be demonstrated.
55/2604	nasal cavity	28	M	1 year	Excision	Recurrent tumour excised June 1957 combined with radium puncture. June 1960 tumour invasion into the palate and left inferior concha. Metastases into the lungs. Nov. 1960 neuro-surgical intervention for tremendous facial pains. Aug. 1961 removal of sequesters of the palate. Dec. 1961 death due to uncontrollable tumour disease.
58/928	rhinopharynx	80	M	1 year	Biopsy Telecobalt	Jan. 1964 still alive with rest of tumour invading into the palate. No evidence of metastasis.
52/1116	soft palate	60	M	5 weeks	Excision and postoperative X-ray therapy	Recurrent tumour excised Sept. 1962 followed by Telecobalt therapy. Jan. 1964 still alive with tumour rests in the left choane.
57/3906	parotid	37	F	2 years	Excision and postoperative X-ray therapy	Recurrent tumour excised Oct. 1960. Still alive, locally asymptomatic.

In the case numbers, the first two digits represent the year of admission.

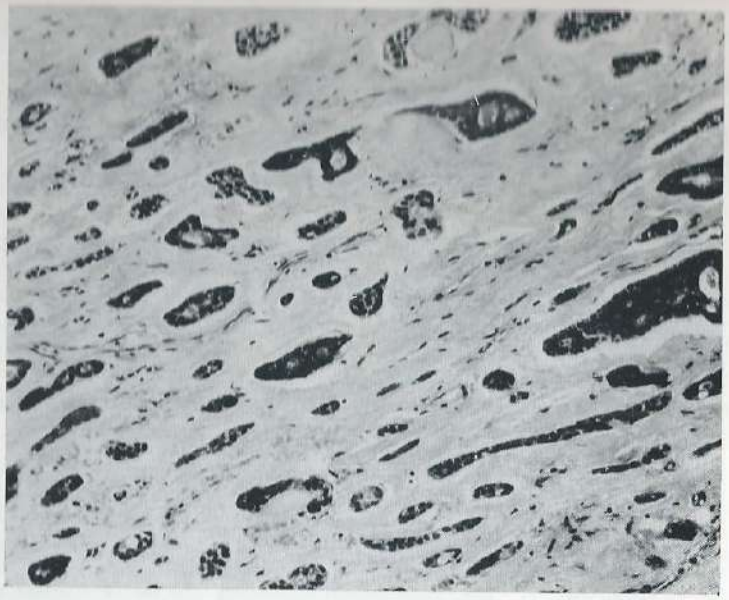


Fig. 10. Cylindroma with a more solid and diffuse growth pattern. Photomicrograph × 140.

preference for any sex. As judged by the history prior to treatment, there was moderately rapid growth, generally, and the estimated duration of the symptoms and signs varied between five weeks and a few years.

Three cases showed localization in the parotid gland, three cases in the submandibular gland, 1 case in the alveolar process, 2 cases in the palate, 2 cases in the pharynx and 1 case in the mucosa of the nasal cavity. Follow-up information over 5 to 16 years revealed that 4 patients died of the tumour; one patient died postoperatively without definite cause of death. Local recurrences occurred in 7 out of 12 patients. Metastases in regional lymph nodes were rare — only one case — while distant metastases, especially in the lungs, were more frequent. Five patients out of 12 survived and were found asymptomatic at the last follow-up in January 1964.

The response to irradiation therapy was generally unsatisfactory.

Conclusion:

The results of this investigation show that cylindromas are malignant, associated with malignant infiltrative growth with distant metastases, and death is usually due to pulmonary metastases. Metastases in regional lymph nodes are quite rare. The incidence of metastases in the literature is reported as 25—50 per cent (Quattlebaum et al. 1946, Kirklin et al. 1951, Frazell 1954).

There is usually a history of multiple recurrences in the subsequent course. The incidence of local recurrence is between 50 and 75 per cent (Quattlebaum et al. 1946 and Frazell 1954).

A 8 *Adenocarcinomas*

Acinic cell adenocarcinoma.

Histological features:

This tumour is composed of acinic-like cells, usually closely packed in a small amount of vascular stroma in acinar groups. The cells are round or polygonal, with a small dark excentric nucleus, and have a distinct cell membrane (see fig. 11a) page 38. The cytoplasm is usually finely granular, and at times water clear (see fig. 11b, page 38).

Numerous intercellular vacuoles containing products of secretion may be present. Duct formation is lacking. Cystic transformation may be found in some cases. In rare cases, papillary and cystic qualities may also be highly developed, so that differentation from papillary adenocarcinoma may be difficult.

In our series, 6 cases of acinic adenocarcinoma were found. The results of the study of five cases are listed in table 12. In one case no clinical data could be obtained. This type of tumour was in the past considered an adenoma — Masson (1921) epithelioma glandulaire, Corridan (1956) clear cell adenoma — and described as benign. Metastases of these tumours have been described (Foote and Frazell 1954, Godwin et al. 1954, Grage et al. 1961). According to Rauch (1959), metastases are extremely rare.

In view of the limited number of cases in our material, no definite conclusion can be drawn from the results of the present correlation study. It can be noted that this type of tumour is a slow growing tumour, which occurs predominantly in females. The general concept concerning acinic cell adenocarcinoma, however, is that this type of tumour is malignant, probably with a low grade of malignancy.

Mucous cell adenocarcinoma

Synonyms:
Mucus-producing adenocarcinoma
Mucus-producing adenopapillary carcinoma (Eneroth 1964)

Histological features:

The characteristic structures of this type of tumour are the papillary excrescences and glandular mucous containing lumina, lined by pleomorphous cylindrical mucus-producing epithelial cells with a pale cytoplasm, one or several layers thick. Alternating cystic and solid areas may be found as well as

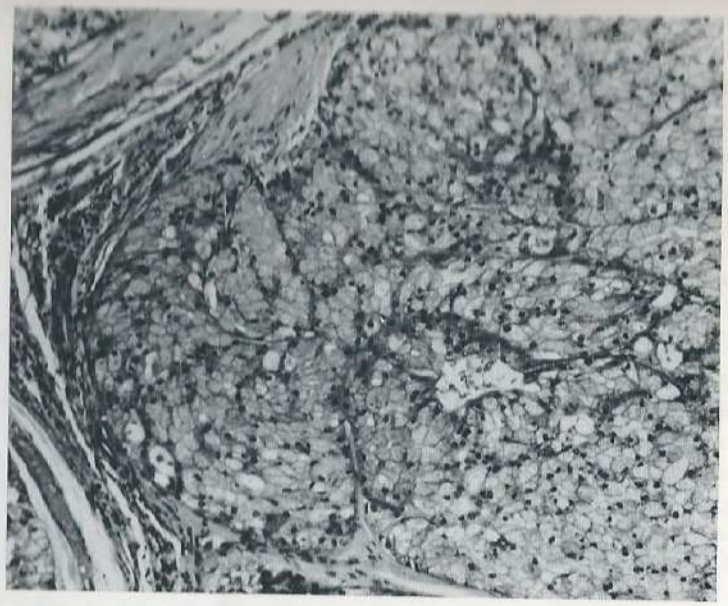


Fig. 11a. Acinic cell adenocarcinoma.
Photomicrograph × 140.

Fig. 11b. Coarse granulations in the cytoplasm of an acinic cell adenocarcinoma.
Photomicrograph × 385.

Table 12 5 cases of acinic adenocarcinoma and their subsequent clinical course.

Case No.	Site tumour	Age	Sex	Clinical signs before treatment	Treatment	Subsequent course
47/31334	parotid	68	M	7 years	Excision	Recurr. tumour excised June 1953 total parotidectomy 1960 for new loc. recurr. Still alive, locally asymptomatic.
47/924	parotid	50	F	10 years	Excision	Recurr. tumour excised July '49 Radical operation for recurr. 1952; X-ray ther. Still alive, locally asymptomatic.
50/33372	alveolar ridge	74	F	30 years	Biopsy X-ray ther. 2000 r tot.	March '55 fistula of the cheek Jan. 56 uncontrollable tumour growth locally and to regional lymph nodes of the neck. Died May '56.
50/772	parotid	31	F	7 years	Excision X-ray ther.	Still alive, locally asymptomatic.
52/2686	parotid	76	F	14 years	Excision	7 months later new loc. recurr. X-ray ther. Aug. '53 Enlarged lymph nodes submandibular region X-ray ther. Aug. '54 the pat. died of pneumonia in a psychiatric clinic.

In the case numbers, the first two digits represent the year of admission.

adeno-papillary structures. Infiltrative growth into the surrounding tissue is common.

No such case is found in our series from 1947 to 1959. It is generally accepted that this type of tumour is malignant, with a relatively high grade of clinical malignancy (Eneroth 1964).

Miscellaneous types of adenocarcinoma

Although no entirely apt diagnostic terms can be found to separate these types into specific histological categories, some types of adenocarcinomas will be discussed on the basis of their architecture, growth pattern and degree of differentiation. Grossly these tumours are of the diffusely infiltrating type.

Trabecular or solid adenocarcinoma

Histological features:

This tumour usually grows in solid trabeculae without the formation of open glandular spaces. There is little connective tissue between the strands of solidly growing cells. The tumour is made up of pleomorphous cells, with hyperchromatic nuclei of varying sizes, and mitoses are usually numerous, with definite evidence of infiltration. These tumours are generally

poorly differentiated and in some instances it is difficult to differentiate them from the solid anaplastic adenocarcinomas.

The failure to carry our complete studies of some tumours explains the divergent incidences of these tumours, reported in the literature.

Anaplastic or undifferentiated adenocarcinoma

Histological features:
This type of tumour, occasionally possessing adenocarcinomatoid structures, consists of quite small pleomorphous undifferentiated epithelial cells, very compactly put together, usually lying in broad bands or rounded clumps; it misses the typical trabeculae seen in trabecular adenocarcinomas. The cell masses are separated by fairly abundant connective tissue stroma, rich in collagen and often hyalinized. The tumour shows diffuse infiltration into the surrounding tissue.

Papillary adenocarcinoma

Histological features:
In the papillary varieties of adenocarcinoma, the walls of the dilated ducts are lined with single or multiple layers of tall columnar or cuboidal cells (see fig. 12), occasionally interspersed with mucus-producing cells. The papillary processes usually project into the dilated lumina. Cystic transformation may be found in some cases.

Discussion:

In our series, 22 cases of trabecular or solid adenocarcinoma were found. When the clinical findings became available and more material from the primary tumour was obtained, the final diagnosis had to be changed in 4 cases to mixed tumour with an overgrowth of the adenocarcinoma pattern, and in 2 cases to metastatic carcinoma (in 1 case of metastatic adenocarcinoma, the lungs were the primary site of origin, and 1 case of metastatic adenocarcinoma originated from a sweat gland).

The remaining 16 cases included 3 in which no clinical data were available. Seven cases of anaplastic or undifferentiated adenocarcinoma were found, including 2 in which no clinical data were available.

Two cases of papillary adenocarcinoma were encountered.

Table 13 gives the correlation between these three types of adenocarcinoma and their clinical features.

Results:

As can be seen in table 13, 8 out 13 patients died of the tumour; only one patient died of intercurrent disease. Metastases were found in 3 cases at

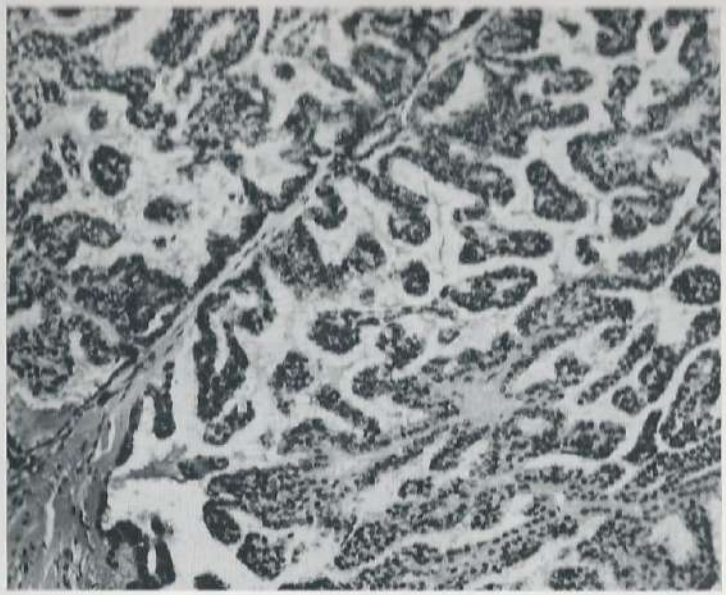


Fig. 12. Papillary adenocarcinoma.
Photomicrograph × 140.

the first examination and in 3 other cases metastases developed subsequently, after the first treatment. In addition, a local recurrence was seen in 4 cases.

Two out of five patients with anaplastic adenocarcinomas died of the tumour. Metastases were demonstrated in 1 case at the first examination, and in 1 case developed subsequently, after treatment. No local recurrence occurred in 2 cases. The 2 cases of papillary adenocarcinoma (the less frequent form, included one death from an intercurrent disease. The tumour recurred locally in both patients.

In view of the limited material of papillary adenocarcinoma, no definite conclusions can be drawn from the results of the present investigation. The histological appearance and infiltrative growth give the impression that this form of adenocarcinoma does not differ in its clinical behaviour from the abovementioned forms.

Conclusion:

The results of the present investigation show that such histological forms as trabecular, anaplastic and papillary adenocarcinomas must be considered highly malignant tumours. There was no convincing evidence that these three tumour types differ in their clinical course.

Table 13 Adenocarcinomas: Miscellaneous forms-correlation between histological and clinical features (5—16 years' follow up).

Histological features	Number of patients								THERAPY			Died of disease		5-year survival
	Total	Sex F	Sex M	Followed up	No follow up	Local recur.	Metastasis Prim.	Metastasis developed subsequently	Surgery	Radiotherapy	Combined	Intercurrent	Tumour disease	Total
Solid adenocarcinoma	16	5	11	13	3	4	2	3	4	5	4	1	8	4/13
Anaplastic adenocarcinoma	7	2	5	5	2	2	1	1	—	—	5	1	2	2/5
Papillary adenocarcinoma	2	1	1	2	—	2	—	1	—	—	2	—	1	1/2
Total	25	8	17	20	5	8	3	5	4	5	11	2	11	7/20

A 9 Cysts

This group comprises cysts without evidence of malignant neoplastic tissue. Microscopically, the cyst walls are lined by one or several layers of columnar or cuboidal epithelium. Inflammatory changes may be found. The most common cyst is the retention cyst. The obstruction may be due to a stone or inflammation or trauma (direct or operative). Congenital cysts due to developmental anomalies are extremely rare. The ranula is the most common form. Cysts of the salivary glands are regarded as benign tumours. Cases of branchial cysts of the parotid are described in the literature (Stark 1959, Hoffman 1960).

The microscopic appearance of a branchial cyst is as follows:

a. An inner layer of stratified squamous or low columnar epithelium.

b. A subdermal layer of focal lymphocytic infiltration.

These conditions are rare.

Mesenchymal tumours

This group consists of non-glandular tumours arising from the interstitial tissues. Only a brief account will be given of these tumours, as their histological characteristics and clinical course are well known from occurrence at other sites of the body.

B 1 *Haemangioma*

Ninety per cent of these tumours are recorded in infants in the first year and located especially in the parotid gland and, in exceptional cases, in the submandibular gland (MacFarland 1931).

The lesion is more common in females than in males.

There are two histological types, the papillary haemangiomas and the cavernous haemangiomas. Both types are considered to be slightly different manifestations of the same congenital vascular dysplasia. These findings suggest that this group of vascular tumours is similar to the haemangiomas of the skin. The haemangiomas of the salivary gland exhibit a progressive growth, infiltrating adjacent tissues. This infiltrative growth alone cannot be considered sufficient evidence of malignancy.

Reports of malignant varieties in infants are not found noted in the literature. In our series, 6 cases of haemangioma were encountered. The site of the tumour was the parotid in 5 cases, and only 1 case involved the submandibular gland. The age distribution ranged from 4 weeks to 6 months.

B 2 *Lymphangioma*

The very few cases described in the literature occurred in the parotid gland in children. They are usually slow growing tumours, and congenital.

Microscopically the picture is the same as in haemangiomas, but the endothelial spaces are filled with clear lymph and a few lymphocytes instead of blood. The lesion is usually localized, but may be diffuse. Distinction between lymphangioma and lymphangiectasis may be very difficult in some cases.

Only 1 case of lymphangioma was found in our series.

B 3 *Lipoma*

These usually occur in the parotid gland (Gilman et al. 1956, Godwin et al. 1958) and occasionally in the submandibular gland (Calhoun 1963). This tumour is benign and one of the most frequently encountered.

Microscopically it consists of fat, usually arranged in lobules separated by fibrous septa. These lipomas never seem to develop into liposarcomas.

In our series three cases of lipoma were found, all occurring in the parotid region.

B 4 *Neurinoma* (Neurilemmoma)

Of importance are the neurilemmomas of the facial nerve, simulating parotid tumours. These tumours are more common than might be assumed from the cases reported in the literature (Roos et al. 1956). The clinical course is usually slow and never painful.

Microscopically they are characteristic. Two distinct types may by found — one with very prominent palisading of cells and the second type with loose oedematous myxomatous and cystic areas.

These tumours are regarded as invariably benign. Our series included 2 cases of neurilimmoma of the facial nerve, clinically simulating parotid gland tumours.

B 5 *Neurofibroma*

This tumour is usually benign and microscopically characterized by the presence of all elements which compose the nerve trunk, namely sheath cells, axons and connective tissue. For reasons not yet known, this tumour sometimes becomes malignant in the course of time, and develops into a malignant neurofibroma.

The malignant type may be highly cellular and markedly fasciculated with extensive invasion and/or may contain few pleomorphous cells with a fibrous stroma.

Neurofibromas in the parotid region may be part of the disseminated process of von Recklinghausens's disease.

Discussion:

It is important to the clinician to realize that in some cases it may be difficult if not impossible to differentiate between the benign and malignant forms of neurofibroma on the basis of the histological appearance. In our series 5 instances of neurofibromas were found; 3 cases were identified as benign neurofibromas and 2 as probably malignant neurofibromas. In these 5 cases the affected parotid region was part of an area of generalized neurofibromatosis. The neurofibromatous conditions in these parotid regions probably originate from the subcutaneous nerves, and secondarily infiltrate the parotid gland. A definite neurofibroma of the facial nerve could not be found. Perineural fibroma of the salivary glands is rare. MacFarland (1927) reported 2 cases with recurrence, developing in childhood and growing slowly, producing signs of tumour only. Occasionally there may be twinges of pain. Some may undergo malignant change. Wheeloch and Madden (1949) also reported one case in their series of uncommon tumours of the salivary glands.

B 6 *Sarcoma*

Cases of genuine sarcoma of the salivary glands are not numerous in the literature. Upon critical analysis the number of sarcomas becomes even smaller.

Two kinds of sarcoma are described in the literature, viz:

1. Those that start as sarcomas — fibrosarcomas occurring chiefly in childhood.
2. Those that start as 'mixed tumours' and eventually become sarcomas; these reported cases actually represent highly malignant epithelial tumours.

Microscopically, 2 patterns of fibrosarcoma can be found, namely:

a. The well-differentiated form with well-differentiated fibroblasts, mitosis being uncommon.

b. The less differentiated form with a bizarre structure. In some cases of fibrosarcomas it may be difficult to differentiate from neurofibrosarcoma and amelanotic malignant melanoma.

The outstanding feature of fibrosarcoma is infiltrative growth and metastases leading to death.

Another important type of fibrosarcoma is 'irradiation fibrosarcoma'. Although it is extremely difficult to prove the definite causal relation between irradiation and the development of fibrosarcoma, the recent literature occasionally features articles dealing with fibrosarcomas following irradiation therapy (Warren and Sommer 1936, Carroll 1947, Stout 1948, Jones 1949, Stewart et al. 1951, Aub. et al. 1952, Pettit et al. 1954, Tonkes 1961). It is rare for fibrous tissue altered by irradiation to proliferate to the extent

that tumour-like masses are formed, and it is even more unusual that such growths become malignant. Most articles on irradiation fibrosarcoma emphasize the necessity of prolonged exposure to heavy doses of roentgen rays to produce the lesion (e.g. Pettit et al. 1954). Furthermore, cases of cancer are mentioned in which the tumour treated by X-ray or radium 'disappeared' for a long time, until later a sarcoma developed in the irradiated area (e.g. Kolar et al. 1959). Chassman et al. (1957) described two patients exposed to moderate irradiation over a short period. Postoperatively applied roentgen irradiation for salivary gland tumours may possibly be an aetiological factor in rare cases of fibrosarcoma, erroneously diagnosed as primary fibrosarcomas of the salivary glands.

Sometimes a carcinoma may present a sarcomatoid appearance.

In our material, a fibrosarcoma was diagnosed in 5 cases. When the clinical data became available, a primary fibrosarcoma was definite in only 1 case; in 2 instances the diagnosis had to be changed to mixed tumour with predominantly sarcomatoid structures; in 2 cases 'irradiation fibrosarcoma' was thought possible. These two cases will be briefly mentioned.

Case 48/24649:

A man aged 48. Clinical history: in 1931 a mixed tumour of the palate without evidence of malignancy was diagnosed by biopsy and the patient was treated with X-rays. A second course of X-ray treatment followed in 1932, after which the tumour disappeared completely. Ten years later the tumour recurred and was again treated with X-rays. In March 1948 the patient complained of difficulties in speech and swallowing. Examination revealed a large tumour (10 × 5 × 5 cm.), originating on the left side of the soft palate and invading the epipharynx and hypopharynx.

Operation was contraindicated, and the patient was again treated with X-rays. From May 1949 until February 1952, after a slight decrease in tumour size, speech and swallowing slightly improved. In August 1952 the patient had severe pains: there was an intractable tumour with perforation and ulceration in the region of the left mandibular angle. Diathermal excision was carried out.

Microscopic diagnosis:

Fibrosarcoma without any suggestion of a possible epithelial tumour. The patient died in February 1954.

The following scheme is an attempt to analyse the dosimetry (see page 47).

In this case the irradiations in 1931, 1932, 1944 and 1948 may have been an aetiological factor in the development of the fibrosarcoma.

Another difficulty was encountered in the following case 51/38944. A man aged 63. Clinical history: in 1948, a left parotid tumour was removed. *Microscopic diagnosis:* mixed tumour with predominance of the epithelial component.

Year	Irradiated area	Tumour area
	Left mandibular area	Hypopharynx and uvula
1931	total dose unknown	tumour dose unknown
1932	total dose unknown	tumour dose unknown
1944	10/5—3/6 3000 R (air) Approx. skin dose 5000 R	tumour dose 4500 R
1948	17/3—16/ 2000 R (air) Approx. skin dose 3400 R	tumour dose 3100 R

In 1951 a recurrent tumour was excised. *Microscopic diagnosis:* papillary adenocarcinoma .After this operation the patient received X-ray therapy. Dosimetry:

10th—14th September 1951: left parotid area total dose 2000 R (air); estimated skin dose — total 2500 R; approximate tumour dose:

depth — 1 cm. 2400 R total.

depth — 2 cm. 2300 R total.

depth — 3 cm. 2100 R total.

In February 1954 a recurrent tumour was excised. *Microscopic diagnosis:* Fibrosarcoma in all microscopic sections.
This patient died in September 1954.

From the casual cases of fibrosarcoma published in the literature it is difficult to evaluate exact criteria concerning average dose and average latent period necessary for the development. Supposedly, the dosage should be high — the latent period is variable but not too short. Some authors (e.g. Aub et al. 1952) give an average of 21.4 years (12—31 years). However, in cases of fibrosarcoma arising in bone tissue after irradiation 'Sabanas et al. 1956 found a latent period of 2¾—30 years (average 9¾ years) and a total tumour dose of 1400—10.000 R with an average of 4800 R.

The total number of mesenchymal tumours 1947—1959 are assembled in table 14.

Table 14 Different mesenchymal tumours: clinical course and survival rate.

Diagnosis	Number of patients			Died of disease		5-year survival
	Total	Followed up	Local recur.	Inter-current	Tumour disease	Total
Haemangioma	6	6	—	—	—	6/6
Lymphangioma	1	1	—	—	—	1/1
Lipoma	2	2	—	—	—	2/2
Neurinoma	2	2	—	—	—	2/2
Benign neurofibroma	3	3	2	—	—	3/3
Malignant neurofibroma	2	2	1	—	1	1/2
Fibrosarcoma	1	1	—	—	1	0/1

Miscellaneous

C 1. *Benign lympho-epithelial lesion:*

This tumour was defined by Godwin et al. 1952.

Histological features:

The histological features are characterized by a lymphoid component containing solid epithelial islands. The epithelial cells are rather poorly differentiated.

Whether this lesion must be regarded as neoplastic (Kirklin et al. 1951, Bauer and Bauer 1954, Seifert and Geiler 1956) or inflammatory (Daly 1959) is still disputed. Azzopardi and Smith (1959) have maintained that this lesion is a manifestation of Mikulicz's disease.

The benign lympho-epithelial lesion is generally considered benign, as the name implies. Hilderman et al. (1962) reported a case of dubious malignancy. This tumour is rare and data concerning its definite clinical course are unreliable.

In our series, 8 cases of benign lympho-epithelial lesion were found. The glandular enlargements were painless and in most instances the tumours were growing slowly, with a clinical history of several years.

C 2 *Mikulicz's disease.*

In 1892 Mikulicz described a lesion characterized by bilateral chronic painless enlargements of the lacrimal and salivary glands (usually parotid and submandibular gland). Mikulicz's disease is still a poorly understood entity. The disease progresses slowly. The vast majority of patients are women, although men were in the majority in Bhaskar and Bernier's (1960) series.

Histologically, Mikulicz's disease is characterized by replacement of the acinar parenchyma by lymphoid tissue and intraductal proliferation of two cell elements, epithelial and myo-epithelial, with the formation of epi- and myo-epithelial islands. The diffuse cellular infiltration of lymphosarcoma and lymphatic leukaemia resembles the picture seen in Mikulicz's disease. The most reliable distinction is the presence of the typical epithelial islands in Mikulicz's disease.

According to Morgan and Castleman (1953) it seems likely that Mikulicz's disease is not a distinct entity but merely a manifestation of a more generalized symptom complex such as Sjögren's syndrome. In Sjögren's syndrome there is enlargement of salivary glands and conjunctivitis associated with rheumatoid arthritis.

Mikulicz's disease is benign and chronic in character. The condition has been successfully treated by resection of the affected gland and radiotherapy. Bhasker and Bernier (1960) suggest no active treatment other than removal of the affected area.

C 3 *Boeck's disease.*

When in Boeck's disease the mediastinum, the lungs and other organs are affected, simultaneous involvement of the salivary glands, especially the parotid, can be found in 1 to 4 per cent of cases (Pfeiffer 1963). The involvement is usually bilateral.

The wellknown microscopic findings are characterized by tubercle-like lesions composed of epithelioid and giant cells, with no caseous necrosis. The disease takes a benign though sometimes prolonged course; many cases clear up spontaneously and death due to sarcoidosis per sé is rare.

C 4 *Hodgkin's disease.*

This disease is a progressive, fatal condition involving principally the lymph nodes and other lymphoid tissue of the body. It may have its first clinical manifestation in unilateral swellings of the neck simulating a tumour of salivary gland origin in the parotid and submandibular regions. Rare cases of Hodgkin's disease in oral tissues are described in the literature, e.g. one case of atypical Hodgkin's disease (Wheelock and co-workers 1949) and Eisenbud and Kotch's (1954) case localized in the cheek, in the region of the opening of Stenson's duct.

Histologically, the morphological changes may be different in various cases and in some cases difficulties may be encountered in establishing the correct diagnosis.

Only one case of Hodgkin's disease was found in our series, its first clinical manifestation being unilateral enlargement of the parotid gland.

C 5 *Lymphosarcoma.*

Sometimes the primary clinical manifestation of lymphosarcoma may be found in a salivary gland, although other localizations (for instance in the mediastinum) may be much more extensive. Primary clinical manifestations of lymphosarcoma arising in the salivary glands were described by Thayssen (1911), Efremow (1925), Sidahara (1937), Botsztejn (1949), Wheelock and Madden (1949), Mannino (1950) and Hamilton and Leopold (1959).

Microscopically the typical neoplastic lymphocytes can be found in some stage of development.

One case of lymphosarcoma with primary manifestation in the parotid region was found in our series.

C 6 *Reticulum cell sarcoma.*

Apart from the typical clinical manifestations, reticulum cell sarcoma resembles lymphosarcoma in that it is not unusual for the primary site to be extranodal, in the tonsils, nasopharynx or parotid.

Microscopically, the cells are usually larger than lymphocytes, with cytoplasmic processes suggesting reticulum cells as their origin. In some cases the histological picture may simulate that of anaplastic carcinoma or amelanotic melanoma, from which these tumours must be distinguished. Clinical considerations are an aid in establishing the diagnosis.

In our series, two cases of reticulum cell sarcoma are diagnosed. In both cases, enlargement of the parotid was the first clinical manifestation of the disease.

Reticulum cell sarcoma is malignant, with a moderate grade of clinical malignancy.

All miscellaneous tumours from the series 1947—1959 are assembled in table 15.

II *Metastatic tumours.*

Metastatic malignant lesions first appearing in the lymph nodes in the parotid region and submandibular region may occasionally be found, this condition being extremely rare in the submental area.

Parotid nodes. There are groups of lymph nodes localized on and within the parotid salivary gland. The most important of this group are the lymph nodes situated in front of the tragus of the ear, draining the skin of the temporal and frontal parts of the scalp, the eyelid and the mucosa of the upper lip. The second group of lymph nodes is situated in the region of the lower pole of the parotid gland, draining lymph from the middle ear, soft palate, upper and posterior parts of the nasopharynx, parotid gland and some of the channels of the upper lip. The efferent lymph vessels of these nodes drain into the superficial and deep cervical chain.

In the submandibular area, three groups of lymph nodes can be found

Table 15 Miscellaneous benign and malignant tumours: clinical course and survival rate.

Diagnosis	Number of patients				THERAPY			Died of disease		5-year survival	
	Total	Followed up	Metastasis developed Prim.	subsequently	Surgery	Radiotherapy	Combined	Intercurrent	Tumour disease		Total
Benign lympho-epithelial lesion	8	8	—	—	6	—	2	—	—		8/8
Hodgkin's disease	1	1	—	1	—	1	—	—	1		0/1
Lymphosarcoma	1	1	1	—	—	1	—	—	1		0/1
Reticulum cell sarcoma	2	2	—	1	—	1	—	—	1		1/2

STELLINGEN

1

De nog steeds toegepaste enucleatie methode van de z.g. mengtumor van de glandula parotis moet als obsoleet worden beschouwd.

2

Bij speekselkliertumoren met een hoge graad van maligniteit, verdient het aanbeveling de primaire operatie uit te breiden met een regionaal lymphkliertoilet.

3

Bij de vele maatregelen ter voorkoming van postoperatieve wondinfecties heeft de prophylactische toepassing van antibiotica een omstreden plaats.

4

De meting van de Achillespees reflex is waarschijnlijk het eenvoudigste en betrouwbaarste hulpmiddel bij de controle van schildklierfunctie stoornissen.

Sherman, L. Lancet 1, 243, 1963.

5

Het staat niet vast, dat de veneuze 'by pass' in het femoro-poplitea traject, op den duur veel betere resultaten geeft dan de 'by pass' met alloplastisch materiaal.

6

De prognose van de facialis paralyse van Bell is slechts vast te stellen aan de hand van dagelijks herhaald onderzoek van de elektrische prikkelbaarheid van de zenuw.

Laumans, E. P. J. Arch. Otolaryng. 81, 478, 1965.

7

De in de meeste handboeken beschreven relatie tussen de rechter N. phrenicus en het diaphragma moet als onjuist beschouwd worden. De zenuw vertakt zich nl. niet onder maar boven het diaphragma.

Scott, R. Thorax 20, 357, 1965.

8

Bij het verlenen van hulp aan de West-Indische Rijksdelen moet hetzelfde beginsel gelden als t.a.v. andere ontwikkelde landen.

9

De rechtsverhouding zoals neergelegd in het Statuut voor het Koninkrijk der Nederlanden is aan herziening toe.

10

Linkshandigheid vormt geen belemmering voor het uitvoeren van operatieve ingrepen.

Behoort bij proefschrift: E. A. MARTIS

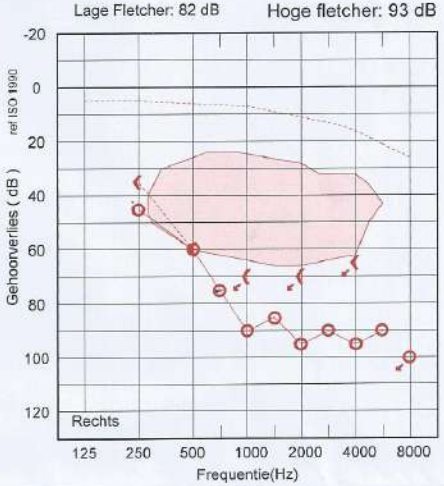
Patient Nr.	: 12345678910
Patient naam	: N. Kaplan-Ozcan
Geboortedatum	: 15/04/1962
Geslacht	: Vrouw
Verzekering	:
Onderzoeker	: M. de Vreeze
Datum	: 08/09/2021

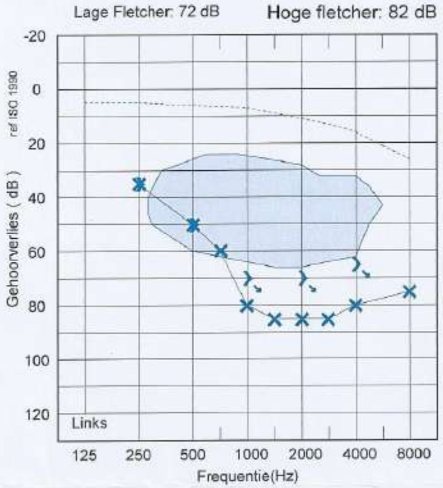
BovenIJ ziekenhuis

zorg goed voor elkaar

Weber

Toonaudiogram



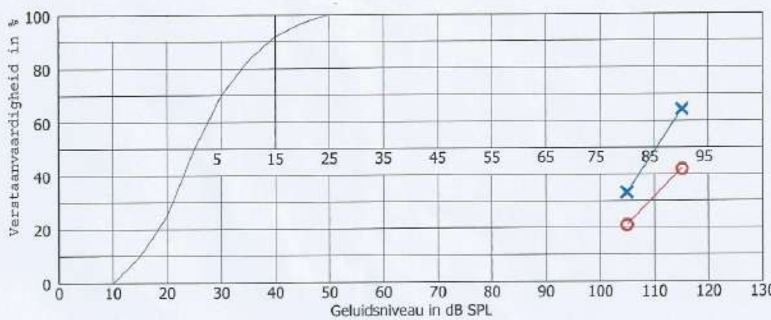


Maskering (dBHL)	Lucht
	Been

Maskering volgens Hood

Opmerkingen

Spraakaudiogram



Opmerkingen

mevrouw ervaart de tin. bij ongeveer 6000 Hz

C 5 *Lymphosarcoma.*

Sometimes the primary clinical manifestation of lymphosarcoma may be found in a salivary gland, although other localizations (for instance in the mediastinum) may be much more extensive. Primary clinical manifestations of lymphosarcoma arising in the salivary glands were described by Thayssen (1911), Efremow (1925), Sidahara (1937), Botsztejn (1949), Wheelock and Madden (1949), Mannino (1950) and Hamilton and Leopold (1959).

Microscopically the typical neoplastic lymphocytes can be found in some stage of development.

One case of lymphosarcoma with primary manifestation in the parotid region was found in our series.

C 6 *Reticulum cell sarcoma.*

Apart from the typical clinical manifestations, reticulum cell sarcoma resembles lymphosarcoma in that it is not unusual for the primary site to be extranodal, in the tonsils, nasopharynx or parotid.

Microscopically, the cells are usually larger than lymphocytes, with cytoplasmic processes suggesting reticulum cells as their origin. In some cases the histological picture may simulate that of anaplastic carcinoma or amelanotic melanoma, from which these tumours must be distinguished. Clinical considerations are an aid in establishing the diagnosis.

In our series, two cases of reticulum cell sarcoma are diagnosed. In both cases, enlargement of the parotid was the first clinical manifestation of the disease.

Reticulum cell sarcoma is malignant, with a moderate grade of clinical malignancy.

All miscellaneous tumours from the series 1947—1959 are assembled in table 15.

II *Metastatic tumours.*

Metastatic malignant lesions first appearing in the lymph nodes in the parotid region and submandibular region may occasionally be found, this condition being extremely rare in the submental area.

Parotid nodes. There are groups of lymph nodes localized on and within the parotid salivary gland. The most important of this group are the lymph nodes situated in front of the tragus of the ear, draining the skin of the temporal and frontal parts of the scalp, the eyelid and the mucosa of the upper lip. The second group of lymph nodes is situated in the region of the lower pole of the parotid gland, draining lymph from the middle ear, soft palate, upper and posterior parts of the nasopharynx, parotid gland and some of the channels of the upper lip. The efferent lymph vessels of these nodes drain into the superficial and deep cervical chain.

In the submandibular area, three groups of lymph nodes can be found

Table 15 Miscellaneous benign and malignant tumours: clinical course and survival rate.

Diagnosis	Number of patients				THERAPY			Died of disease		5-year survival	
	Total	Followed up	Metastasis developed Prim.	subsequently	Surgery	Radiotherapy	Combined	Intercurrent	Tumour disease		Total
Benign lympho-epithelial lesion	8	8	—	—	6	—	2	—	—		8/8
Hodgkin's disease	1	1	—	1	—	1	—	—	1		0/1
Lymphosarcoma	1	1	1	—	—	1	—	—	1		0/1
Reticulum cell sarcoma	2	2	—	1	—	1	—	—	1		1/2

preglandular, intraglandular and the pre- and retrovascular nodes, which in general drain the mucosa of the cheeks, the gums, the floor of the mouth, the anterior portions of the tongue and then empty into the deep cervical chain.

Submental lymph nodes: these lymph nodes drain the superficial tissues and skin of the chin, lower lip, tip of the tongue and floor of the mouth. Metastases seldom first appear in these nodes.

The parotid gland as a focus of metastasis:

In the region of the parotid, skin carcinomas and melanomas may metastasize to the pre-aurical or intraglandular lymph nodes. Conley et al. (1963), analysing 81 patients with involvement of the parotid gland by extension of malignant tumours, found in 45.7 per cent the gland involved with metastatic melanoma, in 37 per cent with squamous cancer and in 17.3 per cent with other types of malignant lesions. The paraglandular lymph nodes were the site of metastases in 40.7 per cent of the cases; the intraglandular nodes in 35.8 per cent and the parenchyma of the gland in 23.5 per cent. The primary tumour was often located in the temple and scalp and somewhat less frequently in the ear, auditory canal or postaurical area. The skin of the face and neck were the source when the spread to the parotid gland was by direct extension. In most instances metastasis to the parotid gland was associated with extension to the neck or with general dissemination.

The submandibular gland may be the focus of metastases, the primary tumour usually being located in skin, oral cavity (lip, floor of the mouth, buccal mucosa), nasal fossa, nasopharynx and oropharynx.

Our series included 6 instances in which the diagnosis metastatic tumour was made after evaluating clinical data in the different cases. In 2 cases of metastatic tumour the diagnosis of malignant melanoma of the parotid was changed to metastatic malignant melanoma. Malignant melanoma occurs very rarely in the parotid gland. In the cases described in the literature, great difficulty is encountered in deciding between primary or secondary tumour. Greene and Bernier (1961) suggested the presence of DOPA-positive cells in the acini and ducts of normal human parotid glands as a theoretical basis indicating a primary salivary origin.

In the other 4 cases of metastatic carcinoma, the primary lesion was traced to the lungs in 1 case of metastatic adenocarcinoma of the parotid gland; to the skin in 1 case of metastatic parotid adenocarcinoma originating in a sweat gland; to the skin in 1 case of parotid metastatic squamous cell carcinoma; to the lips in 1 case of submandibular metastatic carcinoma. All 6 cases of metastatic tumour led to a fatal issue within a few years.

General discussion and conclusion.

It is customary to divide tumours into two groups, the benign and the malignant group. In general, benign tumours develop slowly and painlessly,

occasionally causing local mechanical pressure with disturbance of function, and they present signs of a well-defined, mobile, more or less firm tumour. Benign tumours of the salivary glands may arise in the following ways: A. as a primary salivary gland tumour and B. as a pseudo-tumour; this heading, which is clinical rather than pathological, includes conditions such as inflammation, obstructive and inflammatory lesions, and lesions associated with collagen disease (e.g. Heerfordt syndrome, Sjögren's syndrome).

They may present the cardinal symptoms of a tumour but the clinical course and the histology disprove the tentative diagnosis.

Malignant tumours usually grow rapidly; there may be functional disturbance due to invasion of local structures or regional lymph nodes, and in that case they no longer show the physical signs of a well defined tumour. Malignant tumours of the salivary glands may arise in the following ways: A. as a primary epithelial malignant tumour in a previously normal gland; B. in a pre-existent clinically benign tumour which develops symptoms or signs of malignancy; C. as a mesenchymal tumour; D. as a malignant lymphoma; E. as a metastatic tumour.

The clinical differentiation between benign and malignant salivary gland tumours is usually not difficult. It is only when the salivary gland tumour has an unusual onset that the diagnosis is difficult. A true diagnosis is made only upon pathological examination of the tissue submitted.

Full assessment of the patient and his disease depends on the integration of all available clinical and histological information. There must be close co-operation between the clinician and the pathologist The pathologist should know the name, age and sex of the patient, duration of the disease, exact location of the lesion in relation to other organs, all details of previous treatment, and information on the results of other laboratory examinations.

The clinician, however, wants to draw conclusion concerning therapy and prognosis. If a classification of salivary gland tumours is to be of practical clinical value, therefore, it must allow clinical conclusions to be drawn from the histological features of the various types of tumour.

The various types of tumour described in this chapter are well defined histologically. A study of the correlation between the histological features and the clinical course permitted of a division into benign and malignant tumours, while the different malignant tumours showed different degrees of malignacy. The structure of the tumour parenchyma, invasiveness, metastasis, clinical evolution and mortality due to the disease were used as criteria in grading the malignancies. The results of the study of the correlation between the histological and clinical features allowed these salivary gland tumours to be divided into:

A. Benign tumours:

Epithelial: Mixed tumour type without morphological signs of malignancy, encapsulated (often incompletely encapsulated) without penetration into or through the capsule.

Papilliferous cystadenoma
Papillary cystadenoma lymphomatosum
Cysts

Mesenchymal: Haemangioma
Lymphangioma
Lipoma
Neurinoma

Miscellaneous: Benign lympho-epithelial lesion
Mikulicz's disease
Boeck's disease

Symptoms and signs:

Patients with these benign tumours rarely show any symptom other than the presence of a swelling. Most tumours grow at an extremely slow rate, and they are usually present for many months or years. The tumour is circumscribed. The overlying skin or mucous membrane is always intact and there is no evidence of attachment of the tumour to surrounding structures.

Characteristics of histological features: These tumours have a morphologically benign appearance.

Clinical course:

All tumours of this group remain circumscribed throughout their clinical course. They never metastasize. The patient never dies of the tumour disease.

B. Malignant tumours with a low grade of clinical malignancy.

Epithelial: Mixed tumour without (evident) morphological signs of malignancy, which is behaving pathologically.
Oncocytoma
The highly differentiated type of muco-epidermoid carcinoma
The acinic cell adenocarcinoma

Symptoms and signs:

The clinical findings in this group are essentially the same as those of the benign tumours, i.e. slow growth and the presence of a swelling.

Characteristics of histological features:

Dependent on the stage of the disease in this group, one can find circumscribed and infiltrative types. Invasion, however, is limited to the pseudo-

capsule or locally to tissues in the immediate vicinity. It is this tendency towards infiltrative growth rather than the development of metastases that characterizes these neoplasms.

Clinical course:

Metastases are uncommon; nevertheless the primary tumour is in some instances responsible for metastases and death. There is a high incidence of local recurrences, but the prognosis after adequate primary therapy is good.

C. Malignant tumours with a moderate grade of clinical malignancy.

Epithelial: cylindroma
Miscellaneous: reticulum cell sarcoma.

Symptoms and signs:

These tumours may grow slowly, but usually exhibit a moderately rapid growth. Although they may remain localized for a long time, they infiltrate and destroy adjacent structures. There may be ulceration of the overlying skin or mucous membrane. Regional metastases may also occur but these are rare.

Characteristics of histological features:

These tumours are characterized mainly by diffuse growth and in some instances by destruction of adjacent structures.

Clinical course.

In their infiltrative stage, distant metastases may be demonstrable in a significant number of cases, while regional metastases are extremely rare. Distant metastases are of slow evolution and patients with extensive secondary disease may live for years in relative comfort.

D. Malignant tumours with a high grade of clinical malignancy.

Epithelial: mixed tumour with definite histological signs of malignancy,
the poorly differentiated type of muco-epidermoid carcinoma,
squamous cell carcinoma,
miscellaneous types of adenocarcinoma: trabecular, anaplastic, papillary,
mucus cell adenocarcinoma

Mesenchymal: fibrosarcoma

Miscellaneous: lymphosarcoma
Hodgkin's disease
metastatic tumours.

Symptoms and signs:

Early in the course of the disease the patient may complain of a swelling. There is a history of rapid growth and symptoms and signs resulting from invasion of the surrounding structures, e.g. pain or neurological symptoms, ulceration of the overlying skin or mucous membrane.

Characteristics of histological features:

These truly malignant tumours are characterized by pronouncedly aggressive, infiltrative growth and the early development of local regional metastases, with occasional distant dissemination.

Clinical course:

The course of these tumours is characterized by rapid growth and early development of local metastases.

It can be emphasized that, very early in their course, these malignant tumours may give rise to the erroneous impression of a circumscribed tumour, while at operation the whole gland is involved by tumour, so that the surgeon is unable to determine the contours of the neoplasm; as the dissection proceeds, involvement of adjacent structures may be demonstrated.

Lymph node involvement may not be evident at clinical examinaition but is frequently found at exploratory surgery. In the majority of cases there is local invasion, and regional metastases occur in the absence of distant metastases. Even though death due to uncontrolled disease occurs only in a minority of cases, distant dissemination is found at the postmortem. These highly malignant tumours carry a hopeless prognosis.

This classification enables the pathologist to classify correctly the several members of the group and predict their behaviour accurately. The surgeon must be prepared to interpret the histopathological diagnosis in terms of prognostic implications and must then recognize the indications for the various surgical procedures and for irradiation therapy. His thoroughness in performing these, largely determines the chance of cure of the lesion under discussion.

OVERALL RESULTS AND FACTORS INFLUENCING THE PROGNOSIS OF CANCER OF THE SALIVARY GLANDS

A great deal can be learned about these specific and rare malignant salivary gland tumours and the methods of treatment by calculating survival rates in minority groups designated on the basis of individual factors relating to the patient or to the methods of treatment.

Analysis of the data obtained by follow-up in the investigation of the series from 1947—1959 of the determinate group discloses as overall results that 55 (16.4 per cent) of the 336 patients died of the neoplastic disease for which they received treatment (see table 16). If only the epithelial tumours of salivary gland origin are considered the overall results are not appreciably changed. Thus, if one excludes the 6 patients with metastatic tumours as well as the 5 with tumours classified as Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma, 45 (13.8 per cent) of the remaining 325 patients died of the disease.

An attempt to calculate corrected survival rates statistically has proved of no clinical value for the tumours with a low grade or moderate grade of malignancy, as seen from the point of view of their natural history. Meinsma (1965), in a calculation of corrected survival rates of 109 patients (50 males and 59 females) registered at the Centrale Kanker Registratie of the Netherlands during the period 1956—1958, reports as gross survival rate for all types of malignant salivary gland tumours 42 per cent for males and females, and as corrected survival rate 50 per cent for men and 48 per cent for women.

For the group of tumours classified as high grade malignant in this series, corrected survival rates have been calculated by the methods of Berkson (1942) and of the World Health Organization (1950). The calculating method is based on the available life expectancy tables for the Netherlands during the years 1951—1960 and on the age and sex scale of the group of the patients under consideration. With the aid of this method we established a correction factor for the group on the basis of the supposition that all patients who died would have died of cancer alone.

The results of the corrected survival rates of these high grade malignant tumours are given in table 17.

Before discussing the figures in this table, a survey will be presented of the age and sex distribution of the patients for whom the corrected 5-year survival was calculated, with their respective correction factors.

The group of mixed tumours with morphological signs of malignancy

le 16 Overall results in determinate group of salivary gland tumours.

		Total number of cases	No follow up	Determinate group	Postoperative death	Dead, other cause without disease	Dead, other cause, cancer present	Dead as result of cancer	Gross 5-year survival
xed tumour without rphological sings of malignancy	Group A	264	25	239	—	5	—	3	236/239
cocytoma	Group A	3	—	3	—	—	—	1	3/3
ghly differentiated co-epidermoid carcinoma	Group A	5	—	5	—	1	—	—	4/5
nic cell adenocarcinoma	Group A	5	—	5	—	1	—	—	4/5
indroma	Group B	13	1	12	1	1	—	4	7/13
iculum cell sarcoma	Group B	2	—	2	—	—	—	1	1/1
xed tumour with rphological sings of malignancy	Group C	29	4	25	—	2	4	12	9/25
uamous cell carcinoma	Group C	16	1	15	—	1	1	13	1/15
orly differentiated co-epidermoid carcinoma	Group C	1	—	1	—	—	—	—	—
rosarcoma	Group C	1	—	1	—	—	—	1	—
dgkin's disease	Group C	1	—	1	—	—	—	1	—
mphosarcoma	Group C	1	—	1	—	—	—	1	—
scellaneous forms of enocarcinoma	Group C	25	5	20	—	1	1	12	7/20
tastatic tumours	Group C	6	—	6	—	—	—	6	—
tal all tumours		372	36	336	1	12	6	55	
tal epithelial tumours salivary gland origin		361	36	325	1	12	6	45	

consisted of 25 patients (15 males and 10 females). Their sex and age distribution is given in table 18. The correction factor for this group is 0.8186 for men (Pmen = 0.8186) and 0.9302 for women (Pwomen = 0.9302).

The group of miscellaneous forms of adenocarcinoma includes 20 patients (13 males and 7 females) with the sex and age distribution illustrated in table 18. For this group the correction factor for men is 0.7631 (Pmen = 0.7631) and that for women is 0.8663 (Pwomen = 0.8663).

The group of squamous cell carcinomas, includes 15 patients (11 males

Table 17 Corrected survival rates (5-year period) of the different highly malignant tumours.

Diagnosis		No. of patients	Known alive after 5-years	Gross surv. rate	Corrected surv. rate
Mixed tumour with morphological signs of malignancy	M	15	5	33	40
	F	10	4	40	43
Squamous cell carcinoma	M	11	1	10	15
	F	4	—	—	—
Poorly differentiated muco-epidermoid carc.	M				
	F	1	1	—	—
Miscellaneous forms of adenocarcinomas	M	13	6	46	60
	F	7	1	14	16
(Hodghin's disease)	M				
	F	1	—	—	—
Lymphosarcoma	M				
	F	1	—	—	—
Metastatic tumours	M	5	—	—	—
	F	1	—	—	—

and 4 females). For this group the correction factor for men is 0.6685 (Pmen = 0.6685) and that for women is 0.7455 (Pwomen = 0.7455).

The results of the corrected 5-year survival illustrated in table 17 show no appreciable sex difference in the patients with mixed tumours with morphological signs of malignancy (40 per cent for males and 43 per cent for females). For the squamous cell carcinomas the prognosis is grave; no survivals in the female group and 15 per cent in males. In the group of miscellaneous forms of adenocarcinoma the corrected 5-year survival for men is 60 per cent, that for females is only 16 per cent.

The ultimate prognosis of these salivary gland tumours is dependent on numerous characteristics, often related to the histological type of the tumour. Certain factors of prognostic importance may be tabulated, but others cannot be detected either clinically or by microscopic examination of the tumour. Apart from the pathology, other factors of prognostic importance influence the results of treatment of cancer of these salivary glands. The most important factors will be discussed under the following headings.

Table 18 Age and sex distribution of the highly malignant tumors with the calculated correction factors for men and women, respectively.

Age-group	Mixed tumours with morphological signs of malignancy		Squamous cell carcinoma		Miscellaneous forms of adenocarcinoma	
	Male	Female	Male	Female	Male	Female
0—4						
5—9						
10—14						
15—19		1				
20—24		1				
25—29		1			1	
30—34	1					
35—39		1				
40—44	1	1				1
45—49	2	2				1
50—54	1		1		2	
55—59	1	1		1	2	2
60—64	1		2	1		1
65—69	4		1		1	
70—74		1	3		2	
75—79	3	1	1	1	4	2
80—84	1		2	1	1	
85—89			1			
total	15	10	11	4	13	7

P (men) = 0,8186 P (women) = 0,9302 | P (men) = 0,6685 P (women) = 0,7455 | P (men) = 0,7631 P (women) = 0,8663

1. The location of the primary lesion.

By location we can classify the salivary glands as:

A. Glands which open into the vestibule of the mouth.

1. parotid
2. labial glands
3. buccal glands

B. Glands which open on the bottom of the oral cavity between the tongue and mandibula.

1. submandibular
2. sublingual glands, situated beneath the mucous membrane at the side of the frenulum of the tongue

C. Glands of the tongue.

1. anterior lingual glands (glands of Blandin or Nuhn)
2. posterior lingual glands (glands of Ebner) and the mucous glands of the root of the tongue.

D. Glands of the palate.

E. Salivary gland tissue occurring in scattered locations in the oropharynx (pharynx and paranasal sinuses).

The parotid, submandibular and sublingual glands are also referred to as major salivary glands, in contrast to the other glands, designated as accessory, ectopic or intra-oral minor salivary glands.

The great majority of salivary gland tumours occur in the parotid gland, a few in the submandibular and palate glands. Tumour formation in the palate is frequent because the submucosa contains more glands than any other area (350—375 independent glands). Involvement of the sublingual gland is quite rare. As to the ectopic area or rather minor salivary gland tumours: Larson and Schmidt (1958) in a survey of the literature found a total of 181 tumours of the minor salivary glands, distributed as follows: 51 per cent in the palate, 29 per cent in the lip, 6 per cent in the tongue and 6 per cent in the cheek, the remainder scattered in the mucous glands of the alveolar ridge, tonsil, nasal cavity, epiglottis and nasopharynx.

The frequency of location in our series from 1947 to 1959 revealed 312 tumours of the major salivary glands; parotid 87.5 per cent, submandibular 12.2 per cent and sublingual 0.3 per cent; 24 tumours were located in the accessory salivary glands: 37.5 per cent in the palate, 25 per cent in the buccal mucosa, 8.3 per cent in the labial glands, the remainder being scattered in the mucous glands of the nasopharynx and posterior tongue, and 1 ectopic case with location in the mandibula (table 19).

All tumour types found in the major salivary glands were also found in the minor salivary glands, except papillary cystadenoma lymphomatosum. Irrespective of the site of origin, one should expect these tumours to take the same clinical course.

Malignant tumours are equally common in the minor and major salivary glands (Chaudhry et al. 1961).

In table 19, the overall results are presented according to the glands involved. The prognosis of tumours of the parotid, buccal mucosa, lip and palate is much better than that of tumours in other anatomical locations.

The overall 5-year survival for parotid tumours in this table is favourable (84 per cent); that for submandibular tumours is less favourable. Tumours in the nasopharynx have the poorest prognosis.

ble 19 Overall results according to glands involved.

ation	Number of patients	Group A	Group B	Group C	5-year survival Total.
otid	273 (87.5 per cent)	219	5	49	230/273 (84 per cent)
mandibular	38 (12.2 per cent)	20	3	15	24/38
lingual	1 (0.3 per cent)	—	—	1	1/1
eal mucosa	6 (25 per cent)	5	—	1	6/6
	2 (8.3 per cent)	2	—	—	2/2
ate	9 (37.5 per cent)	6	2	1	8/9
rynx	4 (11 per cent)	—	3	1	1/4
eolar ridge	1	—	1	—	—
terior tongue	1	—	—	1	—
ndibula	1	—	—	1	1/1
al	336	252	14	70	273/336

2. Sex.

In table 20, the overall results are given according to sex. According to this table the prognosis of tumours of the salivary glands in general is much better in females than in males.

The tumours assembled in group A were far more frequent (154 = 61 per cent) in females, while highly malignant tumours (group C) were frequent (44 = 63 per cent) in males.

3. Age at operation.

In table 21, the overall results are given according to age at operation. The overall prognosis following treatment appears to be fair for the first, second, third, fourth and fifth decades of life (average 89 per cent), dropping from 55 per cent survival in the sixth and seventh decades to 10 per cent in the eighth and ninth decades of life. The less favourable prognosis is explained by the high frequency of high-grade malignant tumours in the older age groups: 7 cases (2 per cent) under 40 and 63 (19 per cent) over 40 years of age.

4. Chronology of metastases.

In table 22, the overall results are presented according to the chronology of metastases. If metastases were present when the patient first reported, the 5-year survival proved to be low (1/20), whereas if metastases developed subsequently the 5-year survival was higher (7/17).

This difference is ascribed to the fact that, when metastases were present at first examination, the case was usually considered 'inoperable'. When metastases developed subsequently (i.e. after eradication of the primary lesion), metastatic nodes in the neck usually received further treatment.

Table 20 Overall results according to sex involved.

Sex	Number of patients	Group A	Group B	Group C	5-year survival Total
Males	148	98	6	44	112/148
Females	188	154	8	26	161/188
Total	336	252	14	70	273/336

Groups A, B and C were specified in table 16.

Table 21 Overall results according to age at operation.

Age at operation	Number of patients	Group A	Groep B	Groep C	5-year survival Total	%
0—20	12	10	—	2	10/12	
20—40	102	93	4	5	100/102	99
40—60	127	99	4	24	105/127	83
60—80	85	50	5	30	57/85	55
80—100	10	—	1	9	1/10	10
Total	336	252	14	70	273/336	10

Groups A, B and C were specified in table 16.

Table 22 Overall results according to the chronology of metastases.

Chronology of metastases	Number of patients	Group A	Group B	Group C	5-year survival Total
None recorded or present	289	245	9	35	265/289
Proved metastases at first attendance of the patient	20	—	2	18	1/20
Metastases subsequently developed	27	7	3	17	7/27
Total	336	252	14	70	273/336

Groups A, B and C were specified in table 16.

Table 23 Overall results according to treatment.

Choice of initial treatment	Number of patients	Group A	Group B	Group C	5-year survival Total
Surgery only	184	168	1	15	173/184
Surgery + irradiation	116	83	9	24	92/116
Irradiation only	35	1	4	30	8/35
No treatment	1	—	—	1	—
Total	336	252	14	70	273/336

Groups A, B and C were specified in table 16.

5. Choice of initial treatment.

In table 23, the overall results are given according to the choice of initial treatment. This table shows that the prognosis following early surgical treatment is by far the better one, followed by that after combined treatment (surgery and postoperative irradiation), while sole irradiation has the less favourable prognosis. The good prognosis for surgery only is attributed to the high frequency of the tumours assembled in group A: 168 (92 per cent) of the 184 patients were treated by surgery only. The poor prognosis in the patients treated by irradiation only is ascribed to the high frequency of highly malignant tumours considered inoperable. Furthermore, it may be presumed that surgical therapy combined with postoperative irradiation carries a better prognosis than irradiation alone.

Details concerning the methods of treatment and their efficacy will be discussed in the next chapter. The factors influencing the prognosis after treatment of these salivary gland tumours are summarized in table 24.

The failure to find one special form of treatment with the best overall results in this series made it necessary to evaluate the therapeutic methods in order to develop a methodology and systematology for the treatment of these malignant salivary gland tumours.

Before discussing the evaluation of therapeutic methods, the position of treatment in this series will be tested by comparing the results in 71 patients with malignant epithelial tumours of the major salivary glands with the results in a group of 201 patients with comparable histopathological lesions from Frazell's series (1954).

The 5-year results and the factors influencing the prognosis after treatment are compared in table 25.

No appreciable difference is found in the overall 5-year survival of the whole group (81/201 or 40 per cent in Frazell's series and 27/71 or 38 per cent in our series). The slight difference must be ascribed to the outstanding results obtained in Frazell's series by surgery combined with radium therapy (radon seeds).

Table 24 Factors influencing the prognosis of treatment in 336 determinate cases of tumours of the salivary glands.

	Number of patients	Total 5-year survival
Pathology of the primary lesion		
Mixed tumour without morphological signs of malignancy	239	236/239
Oncocytoma	3	3/3
Highly differentiated muco-epidermoid carcinoma	5	4/5
Acinic cell adenocarcinoma	5	4/5
Cylindroma	12	7/12
Reticulum cell sarcoma	2	1/2
Mixed tumour with morphological signs of malignancy	25	9/25
Squamous cell carcinoma	15	1/15
Poorly differentiated muco-epidermoid carcinoma	1	1/1
Fibrosarcoma	1	—
Hodgkin's disease	1	—
Lymphosarcoma	1	—
Miscellaneous forms of adenocarcinoma:		
solid adenocarcinoma	13	4/13
undifferentiated adenocarcinoma	5	2/5
papillary adenocarcinoma	2	1/2
Metastatic tumours	6	—
Location		
Parotid	273	230/273
Submandibular	38	24/38
Sublingual	1	1/1
Buccal mucosa	6	6/6
Lip	2	2/2
Palate	9	8/9
Pharynx	4	1/4
Alveolar ridge	1	—
Posterior tongue	1	—
Mandible	1	1/1
Sex		
Males	148	112/148
Females	188	161/188
Age at operation		
0—20	12	10/12
20—40	102	100/102
40—60	127	105/127
60—80	85	57/85
80—100	10	1/10
Chronology of metastases		
None recorded or present	289	265/289
Proved metastases on admission	20	1/20
Metastases developed subsequently	27	7/27
Treatment		
Irradiation only	35	8/35
Surgery only	184	173/184
Surgery + irradiation	116	92/116
No treatment	1	—

Table 25 Comparison of the results between our series and Frazell's series (1954).

	Frazell 1954		This series	
	Number of cases	5-year survival Total	Number of cases	5-year survival Total
40	41	24/41	12	11/12
40—50	41	17/41	12	6/12
50—60 age	43	18/43	11	3/11
60 plus	71	21/71	36	7/36
Unknown	5	1/5	—	—
Males	105	33/105	40	12/40
Females	96	48/96	31	15/31
Parotid	155	71/155	56	20/56
Submandibular	42	8/42	14	6/14
Sublingual	4	2/4	1	1/1
Unclassified malignancies	26	4/26	—	—
Mixed tumour with morphological signs of malignancy	38	16/38	23	8/23
Muco-epidermoid tumours:				
Low grade	29	27/29	5	4/5
High grade	23	7/23	—	—
Squamous cell carcinoma	26	5/26	15	1/15
Cylindroma	25	6/25	6	6/6
Acinic cell adenocarcinoma	12	10/12	4	3/4
Adenocarcinoma miscellaneous forms	22	6/22	18	6/18
Metastatic nodes:				
none recorded	138	71/138	33	22/33
nodes on admission	35	5/35	20	1/20
after admission	28	5/28	18	4/18
Treatment:				
irradiation only	75	12/75	21	1/21
surgery only	89	45/89	22	14/22
surgery plus irradiation	29	24/29	27	12/27
untreated failures	8	—	1	—
Total	201	81/201	71	27/71

METHODS OF TREATMENT AND THEIR EFFICACY

Introduction.

There is a great responsibility in managing patients suffering from salivary gland tumours. The responsibility factor is especially heavy due to the fact that no single individual can boast of wide experience in this respect, partly because of the relative infrequency of these tumours, especially the malignant ones, and partly because these cases call for a variety of skills at present considered the provinces of different surgical specialties. The treatment of these lesions consequently lies in a medical no man's land.

The angle of the mandible especially is a point in question. The general surgeon, the radiotherapist, the plastic surgeon and the dental surgeon meet warily at this anatomical point, and none of them has so far staked a valid claim. Recent radical surgical advances in the treatment of these tumours at different sites have made it necessary for the general surgeon to study and employ many of the basic principles of reconstructive surgery. Reconstruction involves replacement of the structures most needed, maintenance of function in remaining structures (by minimizing cicatrix and displacement), and in some instances substitution of function. Many attempts at repair have left the patient a crippled, drooling, depressed 'survivor', on the other hand, excellent function is no consolation if residual cancer is left behind. Both types of failures are a grave reflection on the surgical profession, and as long as these failures occur in unnecessary numbers it is understandable that many physicians turn to X-ray or radium therapy, even though these treatments seem to offer a poor prognosis, and distressing post-therapeutic complications.

It is time for all surgeons who conscientiously treat salivary gland tumours to marshal any and all methods that ensure fewer recurrences, less deformity and better function in the increasing number of patients who not only give the encouragement to continue to use the scalpel against cancer but also suggest what aspects must be considered to be most in need of alleviation.

Knowledge of the anatomy of head and neck and the location and distribution of the lymphatic channels; knowledge of the pathology and natural course of the various types of salivary gland tumours; some endoscopic skill; familiarity with the indications and contraindications of radiotherapy and a good basic general surgical training are all required to meet the demands of the therapy of these tumours.

One of the disadvantages of specialization has been that some of the lines

between specialties are too rigidly drawn; absolute insistence that a member of a certain specialty be responsible for the treatment of any form of disease should yield to the more practical contention that the individual responsible for the actual therapy should be one who by education, interest and inclination has best prepared himself for the job.

I feel that one who has had the benefit of a good surgical education may hope to answer this description approximately.

Usual therapeutic procedures.

The usual three methods of treatment to choose from are surgery, radiosurgery and radiotherapy.

The principles of treatment are based on the following considerations:

1. The location of the disease.
2. The nature of the disease.
3. The extent of the local disease in relation to its environment, and its invasive character.
4. The presence of metastases in regional lymph nodes and elsewhere.
5. The clinical course of the disease in the individual case, the patient's age and any other factors bearing on prognosis and expectation of life.

In the past, many operative procedures devised for the treatment of these salivary tumours were either ill-conceived or ill-performed. The older surgical method consisted of intracapsular enucleation, but 'extra-capsular' excision with or without additional radiotherapy was later advocated.

For the majority of clinically benign tumours of the salivary glands, surgical excision was generally the treatment of choice.

For the intra-oral minor salivary gland tumours, local excision with the removal of normal surrounding tissue and overlying mucosa was considered adequate.

For clinically benign submandibular and sublingual tumours, total removal of the gland with the tumour was a usual procedure despite the dangers of lesion of the lingual and hypoglossal nerves and the submandibular duct in the sublingual region.

The surgery of parotid tumours has long been influenced by the presence of the facial nerve, which is intimately associated with the gland.

Bailey (1940) believed that the parotid can be divided into a superficial and a deep lobe, separated by the facial nerve. Because of this division, many authors (State 1949, Eddey 1951, Sinclair 1951, Byars 1952, Slaughter 1953, Patey 1953, Tabah 1954, Conley 1954, Ross 1954, Ariel et al. 1954, Lyle 1954, Beahr et al. 1957 etc.) believe that some benign tumours and

especially the so-called benign mixed tumours call for a superficial lobectomy.

Various other authors (Redon 1941, Trueblood 1949, Perruchio 1950, McCune 1952, Clark 1952, Riesnner 1952, Lathrop 1953, Winston and Ward 1957, Wieberdink and van Slooten 1958, Stijn 1958, etc.) have proposed total parotidectomy with preservation of the facial nerve as treatment of the so-called benign mixed tumours.

They feel this treatment is indicated to decrease the rate of recrudescence. Surgery in the treatment of the malignant (clinically malignant) tumours is more complicated.

A prerequisite of operability is the absence of distant metastases, no invasion of vital structures such as the carotid artery or the base of the skull, and no involvement of large areas by massive tumours whose removal produces a surgical cripple without a reasonable chance of cure.

The usual surgical therapy for clinically malignant lesions in the absence of clinically demonstrable involvement of the regional lymph nodes is a more radical extirpation of the whole gland or region involved, followed by some form of irradiation when the histological diagnosis has been established.

Radical removal of the submandibular gland for cancer entails no important mutilation, and is usually carried out without difficulty. Radical removal of the parotid gland for cancer usually entails sacrificing the facial nerve, and sometimes other adjacent structures. These may include the external auditory canal, the ascending ramus of the mandible, sometimes the mastoid bone and frequently a wide strip of skin.

A radical neck dissection may be carried out if clinical evidence of cervical metastases is present. The usual indications for a radical neck dissection are:

1. There should be definite clinical evidence that cancer is present in the cervical nodes.
2. The primary lesion giving rise to the metastases should be controllable.
3. There should be a reasonable chance of complete removal of the cervical metastatic cancer.
4. Surgery should offer a more reliable chance of cure than irradiation.
5. The patient's general condition must permit of a major operation.

The essential requirement in treatment of malignant tumours of the intra-oral minor salivary glands is adequate local excision of the primary tumour (if possible).

When the tumour adjoins or overlies bone, an adequate amount of bone must be resected. Any lesion attached to bone or ulcerating into bone must be considered as a lesion invading bone, and not amenable to local excision only.

Radiotherapy.

The usual forms of radiotherapy used for the treatment of these salivary gland tumours are:

1. external irradiation by X-rays; high voltage or supervoltage X-rays. or gamma rays; e.g. telecobalt.
2. interstitial radium application.

The decision whether the treatment is to be by external irradiation or gamma rays is determined by the type of tumour, its site and accessibility. This decision is closely linked to problems of technique and fractionation of the suitable dose.

Radiotherapy can be used either as palliative, as curative or as a support to surgical treatment.

Palliative.

It is often apparent at the first assessment of malignant disease that a fatal issue is irrevocable. Attempting a cure in such cases may not only shorten the patient's life, but also impair the quality of such life as remains. The desire to prolong life should not be allowed to overrule the clinician's better judgement, and he should always be satisfied that the intervention chosen makes life more tolerable; the benefit should be weighed against the discomforts of irradiation and complications, all adding to the patient's burden of suffering.

In practice, the large majority of patients with malignant salivary gland tumours seen by the radiotherapist have inoperable lesions.

Radiotherapy is therefore often of considerable value as a palliative.

Curative.

Radical therapy by irradiation depends not only upon the radiosentitivity of the tumour cells, but also upon the reaction of the tumour bed, and the host response. In the literature, various concepts concerning the radiocurability of these salivary gland tumours can be encountered.
According to Baclesse (1940, 1946) the adenocarcinomas, variously classified as cylindroma, acinic cell adenocarcinomas, etc., are not only radiosensitive but also radiocurable (the malignant varieties of mixed tumours also being radiosensitive).

According to Smith (1949) once surgery has established the histological diagnosis of malignant tumour and a recurrence follows, radiotherapy is more advantageous than a secondary operation.

Smiddy (1956) is also of the opinion that radiotherapy is capable of controlling recurrent malignant tumours.

Radiotherapy has further been capable of controlling small metastases (2—3 cm. in diameter) in the cervical lymph nodes (Moss 1959), and it has surprising temporary beneficial effects in the treatment of pulmonary metastases (Baclesse 1946, Vellios 1955).

At present an appraisal of the true value of irradiation as curative therapy is still impossible due to lack of correlation with the pathological data. Sizable series of cases treated by irradiation with histological studies assessing the biological efficacy and with sufficient follow-up are yet to be produced.

Radio-surgical treatment.

Irradiation as support to surgery has been applied and advocated by various authors (e.g. Quick and Johnson 1922, Hintze 1934, Ahlbom 1935, Stewart 1935, Baclesse 1940/1946, Smith 1949, Edvall 1954, Frazell 1954). Most case reports contain statements in regard to irradiation given after operation. Routine pre-operative irradiation for salivary gland tumours has been abandoned.

At present pre-operative irradiation (gamma rays or X-rays) is occasionally applied in the treatment of vascular salivary gland tumours arising from the tongue, palate and nasal sinuses or pharynx. In these cases the object of irradiation is to facilitate a complete excision by shrinking and reducing the vascularity of the tumour.

It is obvious that the complementary role of irradiation in radiosurgical treatment lies in the attempt at radiological sterilization by destruction of malignant cells inadvertently left in the operative field; particularly the skin flaps. For this reason many authors (e.g. Ahlbom 1935, Edvall 1954) employ and advocate routine postoperative treatment by some form of irradiation in all malignant types of salivary gland tumours.

The following main trends can be distinguished in the indications for radiotherapy.

1. Tumours initially best treated by radiation, e.g. lymphosarcoma, Hodgkin's disease, reticulum cell sarcoma.
2. Cancer too far advanced for surgery.
3. Cancer when surgery is refused.
4. Cancer when surgery cannot be performed because of the patient's physical condition.
5. Empirically, as a postoperative adjunct to surgical treatment of (highly) malignant tumours.
6. Secondary tumours occurring in the salivary glands.

Apart from the usual methods of treatment, the facilities available in some clinics have come to provide us with other methods of treatment worthy of mention.

The chemosurgical method of Mohs.

Mohs (1949) developed a special technique which, after the application of Mohs' paste and by virtue of its microscopic control of excisions, enables eradication of the neoplasm.

The therapeutic results are very favourable; 60 per cent survivals after 5 years or more.

The advantages of this method are:

1. Its reliability, ensured by systematic microscopic control of excisions.
2. Its conservatism.
3. Its low operative mortality.

The disadvantages:

1. The multiple-stage procedure required for chemosurgical excision of advanced neoplasms is time-consuming for the surgeon and painful for the patient. However, the disadvantages seem insignificant since advanced neoplasms would probably be fatal otherwise.
2. Mohs' avoidance of the treatment and follow-up reports on clinical and occult metastases.
3. Another disadvantage is that special skill and constant practice of the technique are essential for optimal results, and that a special clinic is required with provisions for the preparation of frozen sections of an unusual kind.

The results with the chemosurgical method of Mohs suggest that there is a definite place for this form of therapy in the palliative and possibly curative approach to malignant disease of these salivary glands.

Chemotherapy by arterial infusion.

In recent years the concept of introducing a drug which adversely affects tumour cells through the arterial system providing the major supply of blood to the tumour area, for the purpose of tumour regression, has been gaining ground (Aust et al. 1959, Creech et al. 1959, Vink and Zwaveling 1961, Ryan 1964, Westbroek and Zwaveling 1964).

Most of the drugs and the techniques of their administration are still of unproven value. Chemotherapy of cancer by regional perfusion is still in the investigative stage. During the past two years, regional perfusion chemotherapy has been combined with surgery for head and neck cancer and especially for oral cancers (Des Prez et al. 1964). Although the results are considered promising, no increased survival rates have been observed.

Efficacy of the methods of treatment in our series.

An evaluation of the operation records discloses the difficulty of controlling the primary lesion due to the lack of a pattern in handling these salivary gland tumours.

In order to evaluate the efficacy of the surgical procedures and irradiation therapy, either alone or in combination, in the management of cancer of the salivary glands, and to find principles of methodology and systematology suitable for determination of the type and extent of the initial therapy best suited to a particular type or group of tumours, an analysis of the applied therapy was made in correlation with the pathology of the lesions.

In accordance with the usual standards used in reporting the results of cancer therapy, the 5-year period of freedom of disease (from the first treatment) was taken as evidence of 'cure'.

Although it is wellknown that cancer may recur even after a five-year period of freedom of disease, the 5-year survival result is nevertheless generally accepted as a practical and reasonable standard.

The tumours classified as Group A (see Chapter IV) will be considered in table 26.

Local excison to varying extents was applied in 149 (59 per cent) patients, local excision with postoperative X-ray therapy in 78 (31 per cent), complete removal of the gland with the tumour (total conservative parotidectomy and total removal of the submandibular gland) in 24 patients; irradiation therapy only, after biopsy, in a single case of acinic cell adenocarcinoma considered 'inoperable'. Of the total group of 252 patients, 231 patients (91 per cent) are alive at 5 years and present no evidence of residual or recurrent disease.

The tumour recurred in 17 patients (approximately 7 per cent). These recurrences were ascribed mainly to inadequate local excisions. The more radical the excision, the fewer the recurrences.

No recurrences were found in 24 patients in whom the total gland with the tumour was removed. It is difficult to evaluate the efficacy of radiation therapy (external X-rays) in this group of tumours. No difference was found between the results obtained by adequate surgical excision alone and those obtained by excision in combination with irradiation. No significant decrease of the recurrence rate in the group of patients treated by local excision and combined postoperative irradiation could be demonstrated.

It may be concluded from this table that local excision to varying extents was the principal treatment in this group of low-grade tumours, followed by local excision combined with irradiation. No further efficacy of radiation therapy could be noted. To improve results, nothing short of total conservative removal of the gland with the tumour is advisable in the case of mixed tumours without histological signs of malignancy, in the early stages of oncocytoma, in the highly differentiated muco-epidermoid carcinoma and in the acinic cell adenocarcinoma.

ble 26 Group A; results of initial treatment procedures.

gnosis	Number of cases	Biopsy and irradiation	Excision tumour	Excision and irradiation	Removal gland with tumour	Total removal gland and irradiation	Comb. operat.
xed tumour without morphological igns of malignancy	239	—	144	71	24	—	—
cocytoma	3	—	2	1	—	—	—
ghly differentiated muco-epidermoid arcinoma	5	—	1	4	—	—	—
nic cell adenocarcinoma	5	1	2	2	—	—	—
tal	252	1	149	78	24	—	—
currences	17	—	12	5	—	—	—
vical nodes on admission	—	—	—	—	—	—	—
vical nodes developed subsequently	4	1	3	—	—	—	—
mary distant metastases	—	—	—	—	—	—	—
sequent distant metastases	—	—	1	—	—	—	—
ing free of disease at 5 years: total	231/252	—	136/149	71/78	24/24	—	—

ble 27 Group B; results of initial treatment procedures.

gnosis	Number of cases	Biopsy and irradiation	Excision tumour	Excision and irradiation	Removal gland with tumour	Total removal gland and irradiation	Comb. operat.
indroma	12	2	2	6	1	1	—
iculum cell sarcoma	2	2	—	—	—	—	—
al	14	4	2	6	1	1	—
currences	4	—	1	3	—	—	—
vical nodes on admission	—	—	—	—	—	—	—
vical nodes developed subsequently	—	—	—	—	—	—	—
mary distant metastases	—	—	—	—	—	—	—
sequent distant metastases	—	—	—	4	—	—	—
ing free of disease at 5 years: total	3/14	—	1/2	1/6	—	1/1	—

Group B (the moderately malignant tumours) is considered in table 27. Since the treatment of reticulum cell sarcomas is wellknown from other locations no account of them will be given. Irradiation is considered adequate for these lesions. Cylindromas; these neoplasms are characterized by rather slow growth, frequent recurrence, and delayed and slow evolution of distant metastases.

Of 12 patients with these tumours, only 3 are alive and free of disease after therapy.

Experience with these tumours has revealed that, when growth is uncontrollable, death from metastases, especially pulmonary metastases, results. Furthermore, the cylindromas in our series were radioresistant.

When one is faced with a large cylindroma arising from minor salivary glands of the palate, cheek or base of the tongue, it is usually necessary to take a less aggressive approach because the limits and planes are not apparent and disability and morbidity from anatomical defects are greater. It is especially in these locations that, when growth is uncontrollable, death from local extension and/or pulmonary metastases results.

Further analysis of locations in this series reveals a good prognosis for cylindromas located in the parotid and submandibular glands. The patients concerned (3 parotid and 3 submandibular) are all alive and free of disease at 5 years.

In conclusion I believe that the abovementioned characteristics make cylindroma an ideal lesion for radical surgery.

Radical removal of the lesion, if necessary combined with homolateral radical neck dissection in the presence of enlarged involved cervical nodes, satisfies requisites of adequate surgery.

Palliative irradiation may have a transient beneficial effect in some cases of pulmonary metastases.

The next group to be considered is the group classified as group C (highly malignant tumours).

The initial treatments of 70 patients are listed in table 28.

In 28 patients only radiotherapy (external X-rays, interstitial radium or telecobalt) was given as palliation. Palliation was decided upon without surgical exploration.

In my opinion the term 'inoperable' has been somewhat loosely used in the majority of cases.

Contraindications to surgery must be considered, bearing in mind that untreated cancer is inevitably fatal and that little can be expected of other methods.

In so far as the primary lesion is concerned, irradiation affords an alternative in some instances, but, as pointed out by Huffman et al. (1953), general opinion holds that regardless of whether irradiation or surgery is the method of choice for the primary lesion or metastases in the neck, acceptance of contraindications sentences the patient to death.

Only two absolute preoperative contraindications appear to be acceptable,

able 28 Group C; highly malignant tumours- results of initial treatment procedures.

iagnosis	Number of cases	Biopsy and irradia- tion	Excision tumour	Excision and irradia- tion	Removal gland with tumour	Total removal gland and irradia- tion	Comb. operat.
ixed tumour with morphological signs of malignancy	25	6	6	8	2	3	—
quamous cell carcinoma	15	8	1	5	—	—	—
oorly differentiated muco-epidermoid carcinoma	1	—	—	1	—	—	—
brosarcoma	1	—	—	1	—	—	—
mphosarcoma	1	1	—	—	—	—	—
odgkin's disease	1	1	—	—	—	—	—
iscellaneous forms of adenocarcinoma	20	9	6	4	—	1	—
etastatic tumours	6	3	—	2	—	—	1
otal	70	28	13	21	2	4	1
currences	6	—	3	1	1	1	—
rvical nodes on admission	20	13	1	4	—	2	—
rvical nodes developed subsequently	10	3	2	5	—	—	—
imary distant metastases	—	—	—	—	—	—	—
bsequent distant metastases	24	10	2	5	—	2	—
ing free of disease at 5 years: total	10/70	—	6/13	3/21	—	1/4	—

the first being evidence of distant metastases and the second an uncontrollable primary lesion.

Arguments presented as contraindications (e.g. fixation to surrounding tissues and involvement of vital structures) are valid only if the surgeon has explored the primary lesion and/or has opened the neck, and found that he cannot remove the primary lesion and/or the metastatic tumour. To assume that this is so preoperatively, considering that life is at stake, is an error; one is often fooled, and seemingly impossible dissections often prove to offer no actual difficulty.

Nor should one accept as contraindication the presumable biological character of the tumour, which is often incorrectly assumed to be associated with a poor prognosis.

Of particular interest is the high incidence (13) of cervical node involvement among these 28 patients, with absence of clinical evidence of distant metastases at first examination.

Follow-up of the 15 patients without cervical node involvement at first examination revealed subsequent development of cervical node involvement in 3 cases, and remote metastases in 10 cases.

The radiotherapy used in this group of 28 patients was mainly deep X-ray therapy for the local disease; a few cases were treated with telecobalt.

Despite radiotherapy, respiratory complications due to local spread of

the disease accounted for immediate death in most cases, followed by distant metastases in a minority of cases. No definite local response to irradiation was noted; in some instances a temporary regression of the tumour or small involved cervical nodes was demonstrated. No evidence of a definite cure of cervical node involvement was obtained.

In 13 patients, only local excision of the primary lesion was performed; a survey of the operation records shows that the lesions in these cases were well-defined (circumscribed).

In 1 case, a node removed at operation showed metastatic tumour although no cervical nodes had been clinically demonstrable. Follow-up of the patients in this group revealed 3 recurrences; regional cervical nodes developed subsequently in 2 patients; 6 patients were alive and free of disease at five years.

It may therefore be said that local excision is dangerous in patients whose cancer is well-defined (circumscribed).

Local excision combined with radiotherapy was used in 21 patients. In 4 patients, nodes removed during the operation proved to contain metastases.

Only 3 patients in this group were found alive and free of tumour at 5 years. The results of this therapy in this group of patients are less than encouraging.

Clinically radical removal of the lesion was performed in 2 instances; in 1 case the tumour recurred. No survivals were seen at 5 years.

Radical removal of the lesion followed by postoperative X-ray therapy was used in 4 cases; distant metastases developed later in 2 cases.

Only 1 patient was alive and well at 5 years.

Excision combined with radical neck dissection was the initial therapy in only 1 patient; a case of metastatic tumour.

Therapeutic neck dissections were performed in only 3 patients out of 70 with these highly malignant tumours.

The smallness of this group warrants no conclusions concerning the efficacy of radical neck dissections in this series. The credit for the development of neck dissection as a curative operation for cervical node metastases goes mainly to Crile (1906). A great deal of work has since been done, and today the dissection has become a standard procedure.

It is generally agreed that proper radical neck dissection should remove the lymphathics from the mandible as far as the clavicle and from the anterior edge of the trapezius as far as the midline of the neck (Ward et al. 1950, Martin et al. 1951, Garcia 1952, Speir 1952, Huffman et al. 1952, James 1953). In 1955, Pressman proposed that the range of the standard radical neck dissection should be extended so as to include the lymphatics in the area adjacent to the midline of the neck, both above and below the hyoid bone — a region which, he maintained, has not been given the surgical attention it deserves.

It is difficult to establish whether this extended retrohyoid radical neck dissection contributes greatly to the radicality of the standard operation.

Clinical experience has shown that the common carotid artery, vagus nerve and scalenus muscles are more often invaded by the metastatic cancer than the ribbon muscles and the hyoid bone. I completely agree with Martin (1957) that a proper perspective based on clinical experience favours the standard neck dissection as a basic routine, and that the indication for resection of any additional tissues must be based on special factors in the individual case. Radical neck dissections performed alone, as a discontinuous procedure, can of course be properly performed only in cases in which the primary lesion has been adequately controlled. The efficacy of therapeutic neck dissection is as follows. Martin (1951) reports a 5-year cure of 34 per cent, Tailhefer (1952) 20 per cent and recently Blady and Harwick (1964) 28,4 per cent.

Is cancer of the salivary glands a localized disease? How frequently do these tumours spread to regional lymph nodes? The answer to these questions have direct bearing upon the problem of therapy, for in the absence of metastases, local excision of circumscribed tumours has proved to be successful.

Each cancer of the salivary gland has its own individual characteristics, its particular mode of local evolution and lymphatic and/or haematogenic spread.

One of the fundamental rules of cancerology is that, in any cancer susceptible to lymphatic metastases, therapy must be aimed, not only at the primary tumour, but also at the corresponding lymphatic area.

Should this idea be revised in cases of cancer of the salivary glands? The incidence of involvement of cervical lymph nodes in these cancers varies in the literature. The frequency of regional metastases was approximately 29 per cent in our cases of highly malignant tumours.

Of 28 patients with malignant salivary gland tumours described by Ahlbom (1935) 20 per cent had metastases at admission, but the proportion of metastases later rose from an initial 20 per cent to 33 per cent.

Of 44 patients followed from initial symptoms to postmortem, 24 (50 per cent) had lymph node metastases.

Stout (1954) found that 25 per cent of his patients with malignant tumours presented metastases.

The surgical procedure selected for a given case, therefore, should obviously be that most likely to ensure extirpation, in a single effort, of the whole tumour and its adjacent regional metastases.

It need not be said that, if a conservative and a radical operation for cancer are equally likely to ensure a cure, then the conservative operation with its lesser operative risk, lesser morbidity and better cosmetic and functional results, is to be preferred. An unsuccessful operation for cancer indicates in the majority of cases that the first surgical attempt was inadequate, not because an unjustifiable radical operation was performed, but rather because the first procedure was of too limited scope.

In such cases it must be conceded that the patients' chances for cure were

lost, or at least markedly reduced because the first surgeon was unwilling to propose and undertake a more radical procedure.

Examples of this may be found in situations where a too restricted excision for cancer is done, or where excision of a cervical node is preferred to a radical neck dissection.

It is the responsibility of the therapist to select and apply as initial therapy that particular method and technique that gives the greatest chance for cure, rather than try a conservative method in the hope of attempting the more radical procedure if the first operation fails.

If in the opinion of the surgeon a radical operation is necessary for a cure, he must firmly hold to the proposition that such a radical measure is in the patient's interest.

While a radical approach, where indicated, results in a cure, on the other hand in judiciously selected cases a local excision often serves as well as the more radical operation.

Our series includes many examples of small — or moderate — size lesions locally excised with reasonably safe margins, providing as good a chance of cure as would more radical excisions, but without the latter's greater functional and/or cosmetic damage.

It is difficult to draw a clear line of differentiation between lesions suitable for local excision and those requiring radical excision. The lesions with a tendency toward or with definite infiltration of surrounding tissues are the most definite contraindications to conservative local excision. The greatest incidence of parotid tumours, for instance, is in the superfical lobe and for this reason extirpation of the superficial lobe along with the tumour may be adequate in a great majority of cases with circumscribed tumours of this lobe.

In view of the incidence of involved cervical nodes in malignant salivary gland tumours, the procedure theoretically required for a cure is radical extirpation with a radical neck resection in continuity on the homolateral side, as determined by the tumour location.

Martin et al. (1951) state 'The policy of routine prophylactic neck dissections is considered illogical and unacceptable'.

Frazell (1954) questions whether neck dissection is necessarily indicated in patients in whom cervical lymph nodes do not seem clinically to be involved.

Perzik et al. (1958), Lane et al. (1954) and Monaco et al. (1962) suggest the superiority of prophylactic neck dissections in their series of melanomas of the skin, carcinomas of the oral cavity and carcinomas of the tongue.

If such conflicting opinions exist in large medical centres, then how is the individual surgeon to prescribe the proper therapeutic course for the occasional patient?

The factors determining whether or not nodal dissection should be performed in a special case of cancer, and when, are supposed to be as follows:

1. The rate of failure to control the primary disease.

The likelihood of controlling the primary lesion must be considered, for if this is not accomplished the patient cannot benefit appreciably from neck dissection even if the removed nodes contain occult metastases.

Local persistence rates vary, depending on the site and type of the primary tumour. Almost without exception a low persistence rate might be expected for the low-grade tumours of salivary gland origin, e.g. mixed tumours without histological signs of malignancy, the oncocytomas, the early stages of highly differentiated muco-epidermoid carcinomas and acinic cell adenocarcinomas, because total resection, if adequately performed, may be carried out without difficulties in these cases.

For cylindromas associated with a malignant infiltrative growth with frequent distant metastases, a higher rate of local recurrence or local persistence may be expected.

For the highly malignant tumours characterized by rapid, aggressive and extensive growth, the highest rate of failure to control the primary lesion may be expected.

Since the patient who is to suffer local recurrence cannot be detected with certainty in advance, all must be treated as though it could occur.

The incidence of persistence of the tumour must not be overlooked in cases of cancers of the oral cavity, for it is as great as or probably greater than the incidence of occult regional metastases; according to Del Regato (1948), Judd and Beahrs (1949) and Martin et al. (1941), cancers of the lip are not locally controlled in 5 to 10 per cent of cases.

This frequency is doubled in patients with lymph node metastases (Cross et al. 1948, Klippel et al. 1958), and trebbled in patients who have unsuccessful therapy (Gladstone and Kerr 1958).

Cancers of the tongue are locally controlled in approximately 50 per cent (Ash and Miller 1955), Richards 1942 and Budd 1950) and the data for cancers arising elsewhere in the oral cavity can be expected to be similar.

Local recurrence, difficult as it is to measure it in advance in a given clinical situation, can therefore not be ignored, for it weighs heavily in terms of the ultimate benefit derived from prophylactic dissections.

2. The rate of nodal metastases.

The rate of nodal metastases varies from tumour to tumour.

This rate may be expected to be low for the low-grade tumours of salivary gland origin. Mixed tumours without histological signs of malignancy rarely metastasize.

In a very small percentage of cases of low-grade muco-epidermoid carcinomas, oncocytomas and acinic cell adenocarcinomas, late regional metastases may be found.

Regional lymph node involvement in cylindromas is rare.

The highest frequency of nodal involvement is found in the group of highly malignant tumours.

In assessing accurate percentages of regional involvement of lymph nodes, the fallibility of palpation in the diagnosis of these nodes plays an important role.

Palpability of a node depends upon its location and consistency. In the neck the average size and the lower limit of palpability is approximately 0,5 centimetre in a superficial area; for submental or submaxillary nodes and in a deeper area it is 1 centimetre.

In a report by Sako et al. (1963) on 235 patients, 112 or 47.7 per cent had clinically palpable nodes. The cleared surgical specimens showed that the clinical evaluation was accurate in 72.3 per cent of the palpable and 72.4 per cent of the non-palpable nodes. The error was thus 27.6 per cent for non-palpable nodes. This error was higher, 35.3 per cent, when lesions of the anterior portions of the tongue and the floor of the mouth were considered. Even small primary lesions in these areas showed a rather high incidence (25 per cent) of non-palpable metastatic nodes.

The number of occult positive non-palpable nodes is therefore too large to be ignored in cases of primary cancers giving metastatic spread to the cervical lymphatics. It may be assumed that prophylactic dissections are more profitable for these highly malignant tumours than for those with more favourable clinical characteristics.

3. The operative mortality from nodal metastases.

The operative mortality from dissection of nodal metastases is of primary importance in justifying the surgical indication.

For neck dissections, the operative mortality varies according to the experience of the surgeon. The operative mortality per sé in present day surgical practice should not exceed 3 per cent.

The rates found in the literature: Barclay et al. (1951) 3.1 per cent, Martin et al. (1952), Beahrs et al. (1959), Ward et al. (1959) 1 to 2 per cen, Cade (1952) 1 to 3 per cent and finally the highest encountered: Blady and Harwick (1964) 5.2 per cent, (these authors considered post-operative all deaths which occurred until the 38th day).

4. The death rate after prophylactic dissection has disclosed nodal metastases.

One of the principal objections to prophylactic nodal dissection has been that it is performed with or soon after treatment of the primary cancer, before sufficient time has passed to allow one to ascertain the efficacy of treatment of the primary cancer or to detect the presence of distant metastases.

Before dissection, however, we cannot establish the actual extent of a malignant tumour, nor judge its spread.

Even with a negative report it is impossible to be certain that none of the sections not examined contains evidence of malignancy.

To gain an impression of the survival rate after 'prohylactic' neck dissection disclosing cervical metastases, the literature was searched for series including such cases.

Tailhefer (1952), performing prophylactic neck dissections for cancer of the tongue, noted a survival of 26 per cent.

In a retrospective study of a series of 441 cases of head and neck tumours, Blady and Harwick (1964) found a survival rate of 56 per cent.

5. The death rate after therapeutic nodal dissection removing nodal metastases after treatment of the primary cancer.

The results of treatment of cervical metastatic cancer in large series of head and neck tumours are found to be 34.3 per cent (Martin 1951), 36 per cent (Tailhefer 1952) and recently 28.4 (Blady and Harwick 1964).

6. The death rate from nodal metastases without operative treatment.

Experience in our series of salivary gland tumours has shown that surgically untreated cervical metastases are invariably fatal, especially in the highly malignant tumours. Radiotherapy alone is of little avail.

Spread of the tumour beyond the cervical lymphatics is relatively infrequent so that death in these cases ordinarily occurs with the lesion still confined to supraclavicular site, the patient succumbing to inanition, haemorrhage, respiratory obstruction and infection.

Estimates as high as 80 per cent (Barclay et al. 1951, Watson et al. 1951) are given for the incidence of lesions remaining confined to the limits of the head and neck, and therefore surgically accessible in most cases. The fact that reported cures resulting from present standard operative procedures are encouraging, indicates that more patients can be cured. Since we can circumvent the local spread, we can in most cases cure the patient. For practical purposes one may conclude that prophylactic neck dissection is justified when the survival rate after nodal dissection for metastases appearing after surgical treatment of the primary cancer is significantly less than the survical rates in patients with metastases found in their operative specimens after 'prophylactic' dissection for the same cancer. A method of evaluating the merits of elective versus therapeutic nodal dissection in the treatment of cancer as used by Del Regato and Ackerman 1962), is presented in table 29.

In this respect, we can ignore the low-grade malignancy cases in our series, and the cylindromas; their natural course is so slow as to obviate the necessity of prophylactic neck dissections.

Table 29 Method of evaluating the merits of prophylactic versus therapeutic nodal disection in the treatment of cancer.

head and neck highly malignant tumour series	Failure to control primary cancer %	Occult nodal metases at time of treatment %	Operative mortality %	Survival among patients with metastases found in elective nodal dissection specimen %	Survival after therapeutic dissection for nodal metastases appearing after primary treatment %	Net improvement in survival expected from nodal dissection %
Tailhefer	?	43	1	26	20	+ 2,5
Blady and Harwick 1964	—	8	5,2	56	28,4	+ 12
Hypothetically in our series	24	17	3	50	30	+ 8

For the tumours classified as highly malignant in our series, a hypothetical calculation of the net improvement in survival was attempted and we compared them with a group of histologically more or less similar tumours of the head and neck from Blady and Harwick's (1964) series. For the calculation, approximate data from the literature were used. Table 29 shows that, in Tailhefer's series (1952) prophylactic neck dissection for tongue cancers caused no significant net improvement of the survival rate.

Blady and Harwick's series (1964) showed a significant net improvement (+12) when prophylactic dissections were performed.

In our series of highly malignant tumours, too, a significant improvement (+8) might hypothetically have been obtained if adequate standard procedures had been used.

In spite of various objections, therefore, the possibility of prophylactic radical neck dissection in continuity with the primary operation must be given serious consideration for resectable highly malignant primary salivary gland tumours.

CHAPTER VI

DIAGNOSTIC PROCEDURES AND PROBLEMS ASSOCIATED WITH THE SURGICAL APPROACH TO SALIVARY GLAND TUMOURS

Examination of the head and neck.

A correct clinical diagnosis may be made in many lesions, as in most other regions of the body. The history and clinical examination, plus a biopsy if indicated, often present the diagnosis and clarify decisions concerning therapy.

Careful clinical history taking is very important in evaluating diseases of the salivary glands. The mode of onset, sudden increase in size and duration of symptoms must be determined as accurately as possible. A mass of short duration in the parotid region, or one recurring at intervals, may be inflammatory. A lesion existing for a long period may be congenital, or a benign tumour. Rapidly enlarging masses are often malignant.

The history of previous operations or previous other treatment is important. The patient presenting a submandibular mass, for example, may give a history of a previous operation for a tumour localized somewhere in the oral cavity. The history of dental treatment is often important in arriving at a correct diagnosis of inflammatory lesions of the upper neck.

Specific inquiry should be made regarding difficulties in talking, chewing or swallowing. Pain must be noted. For example, parotid tumours are seldom painful, while parotid carcinomas often cause pain. Pain in the ear often indicates a lesion of the pharynx or larynx.

Examination of the head and neck should be orderly and follow a definite pattern. Inspection is frequently the most important part of the examination. It should include appraisal of the skin and contours of the region as well as careful inspection of the oral and nasal cavities, the external auditory canal, the pharynx and larynx and in many instances the nasopharynx.

The presence of ulceration, abnormal swelling, oedema or exudate must be noted. Abnormal function resulting from injury to the cranial nerves must be detected.

Tumour invasion of the facial nerve results in inability to wrinkle the forehead, close the eyes or purse the lips.

Loss of hypoglossal nerve function causes deviation of the tip of the tongue to the side of the lesion.

Horner's syndrome may result from involvement of the cervical sympathetic trunk.

Palpation greatly aids in the evaluation of these salivary gland tumours. The consistency must be noted.

Palpation may disclose a cervical mass which was overlooked at inspection. Masses in the upper cervical region are far more often related to primary cancers of the head and neck region.

Insertion of the finger into the oral cavity allows of a more accurate estimation of the size of a visible lesion as well as determination of its consistency, tenderness and fixation to adjacent structures.

The submandibular region of the neck can be most adequately examined by bimanual palpation with one finger on the floor of the mouth and the other hand beneath the mandible. The submandibular salivary gland is then readily outlined and enlarged lymph nodes within or about it can be easily palpated. The same is true for sublingual glands.

The palpating finger can quickly be swept across the base of the tongue and up behind the soft palate so as to detect a hidden tumour mass missed at the usual routine inspection of the oral cavity with a tongue depressor. Each side of the neck should be palpated methodically so that no cervical masses are overlooked. The patient's head is tilted gently from one side to the other so that the sternocleidomastoid muscle can relax, allowing the thumb and fingers of the examining hand to encircle it and palpate the jugular chain of lymph nodes. The posterior triangle of each side of the neck is palpated by moving the fingers horizontally over this region so as to detect small and often deep-seated nodes.

The surgeon treating diseases located in the head and neck area must be able to visualize the nasopharynx, hypopharynx and larynx. Direct examination requires premedication and spraying of the region with a local anaesthetic.

Radiological diagnosis

Sialography may be useful as a radiological procedure to demonstrate the presence or absence of distortion or involvement of the parotid and submandibular glands. We have not found sialography helpful in the diagnosis of tumours. In the study of tumours of soft parts, X-rays may be an aid in detecting bone invasion and may contribute valuable information concerning the size and extent of the tumour by demonstrating distortion of adjacent tissues in some cases. Because of the complexity of the cranial bone structure, stereoscopic X-rays are in some cases necessary for evaluation. A routine chest X-ray should be taken in all salivary gland tumours. Pulmonary mestastases usually develop slowly and remain symptomless for many years.

Carotid arteriograms may aid in the localization and study of intracranial pathology as well as certain occlusive lesions of the carotid vessels themselves.

Routine blood counts should be made in all cases.

Diagnostic procedures during operations.

In most lesions, biopsy taking for diagnostic purposes is a relatively common procedure; as a rule, a portion of every lesion suspected of malignancy should be removed for immediate microscopic examination before definite therapy is attempted. Exceptions to this rule are lesions in accessible localizations which may be easily removed in toto with an adequate margin of normal tissue; these should always be entirely excised.

Masses in the major salivary glands should be removed in toto, if possible, preferably with the involved lobe or with the whole gland.

The specimen should be labelled.

The pathologist has the advantage of having a block of tissue for gross examination and for multiple sections. He can study, not only the individual cells but also the architecture and behaviour of the neoplasms, and evaluate the margins of excision.

If resection of the whole lesion is not possible before finishing the operation, it is necessary to take biopsies from different parts of adjacent tissues in order to obtain information on radicality.

Frozen sections.

The possibility of microscopic examination of tissue during operation is a valuable aid to the clinician in making therapeutic decisions, provided he knows the limitations of the frozen section technique and of the pathologist he is working with.

Approach.

The primary object in performing operations on the head and neck area is to achieve good exposure of the operative field so as to eradicate the disease completely.

A matter of secondary but none the less real importance is the appearance of the patient's face after completion of the operation.

In the earliest times, operative incisions were made where they would be most effective to expose or excise the pathological lesion concerned, with little regard to the resulting scar.

The elation which follows liberation from the disease may be somewhat dampened when the patient is left with embarrassing deformities and scars, which make him reluctant to appear in public. It can be said that no price is too high for the cure of cancer, but the cost in terms of deformity and disability should not be greater than necessary.

For over a hundred years, surgeons operating in the head and neck area have referred to Langer's lines as the most appropriate guides for incisions which would heal with minimum cicatrization.

Langer's (1861) observations were based on postmortem studies, ignoring the physiological elasticity of various surface regions, which in the living subject differ from the lines of skin tension in cadavers.

Even today, many eminent surgeons recommend their use in theory, and yet make their elective incisions in the normal wrinkle lines of the skin, often erroneously referring to them as Langer's lines. Charts of Langer's lines continue to appear in textbooks and articles on general and plastic surgery written by authors who advocate their use.

In 1935, Webster reviewed the various factors which produce deforming scars. He stated: 'The simplest rule for making incisions in the most favourable direction is to follow the natural wrinkle lines'.

In 1941, Cox wrote a thesis on the cleavage lines of the skin, indicating a difference in pattern between these cleavage lines and Langer's lines.

He emphasized the importance of following cleavage lines in surgery, and demonstrated the persistence of cleavage lines in excised skin.

Ragnell (1954) corroborated Langer's statement by demonstrating that the tensility of human skin is approximately one-third greater at right angles to the lines of Langer than it is along them.

Looking at the face of an individual we immediately realize that a scar would be least conspicuous if it fell in one of these wrinkle lines. Langer's lines of tension and the folds of expression are parallel in many areas; in others they diverge, e.g. in the lateral aspects of the cheek and at the side of the head.

One would hardly make an elective incision following the lines of Langer in the latter regions.

Since the face is such an expressive part of our anatomy, the constant use of facial expression deepens the wrinkle lines as age advances. The skin adapts itself to shortening of the muscle without corresponding shortening of the skin, by forming folds at right angles to the line of contraction of the underlying muscle (Kraisl and Conway 1949). See fig. 13.

The relation of wrinkle lines to muscular contraction is emphasized in facial paralysis, where these lines are conspicuous for their absence. The circular lines in the area of the neck are caused by flexion of the head on the neck.

Many younger subjects do not have evident wrinkle lines, but careful inspection of the skin reveals lines of cutaneous relaxation. In order to exaggerate these, one needs only to ask the patient to contract the muscles in the region concerned, and the lines become apparent.

Not all subjects are precisely the same. Variations due to differences in contour and muscular development exist. No chart of facial and neck lines, therefore, serves for all cases. Consideration of the formation of wrinkle lines about the face and neck, in combination with the principles of wound healing, makes it possible to develop a fairly definite pattern for planning incisions on the face and neck.

In making incisions we should consider the dynamic effects of the muscular contractions acting on the undersurface of the skin through the resulting scar.

In surgery, it is wellknown that a scar across a fold of expression is

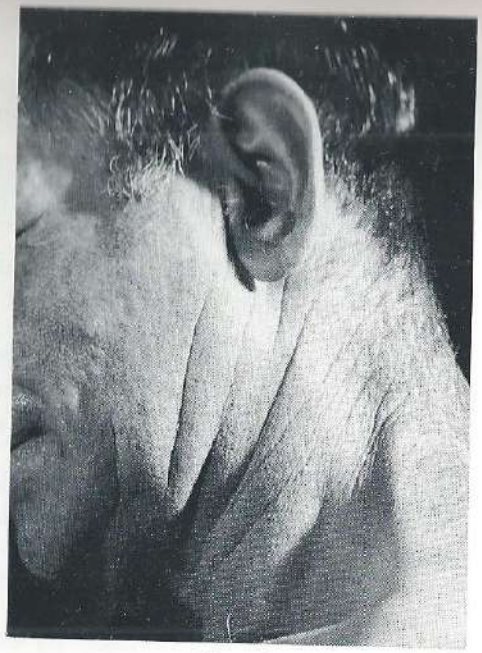


Fig. 13

constantly subject to stress during muscular activity, causing trauma which leads to fibrosis and thickening of the scar. Changing the direction of such a scar by Z-flaps prevents recurrence of thickening; this can also be achieved by changing the direction of the scar tissue so that the flaps are spared the pull of muscles.

For practical considerations, therefore, skin incisions for exploration or excision of a lesion should be planned to have the resulting scar in the wrinkle lines.

Although many incisions for the external approach to lesions localized in the lateral parts of the face and neck can be found in literature, no specific incision has received universal acceptance.

Most of the skin incisions for the approach to lesions in the parotid area are illustrated in fig. 14.
Of these incisions, Redon's bayonet incisions and Bailey's Y-shaped incision are the most commonly used.

The conventional simple incision for the approach to submandibular lesions is illustrated in fig. 15.
This incision is usually 4 centimetres long and made below and parallel to the body of the mandible, forward to the submental area. It is deepened through the skin and platysma.

The general standard approach to accessible intra-oral lesions is through the open mouth. For the less accessible lesions in the oral cavity, incisions for the reflection of an upper cheek flap (e.g. Weber-Ferguson) or flap

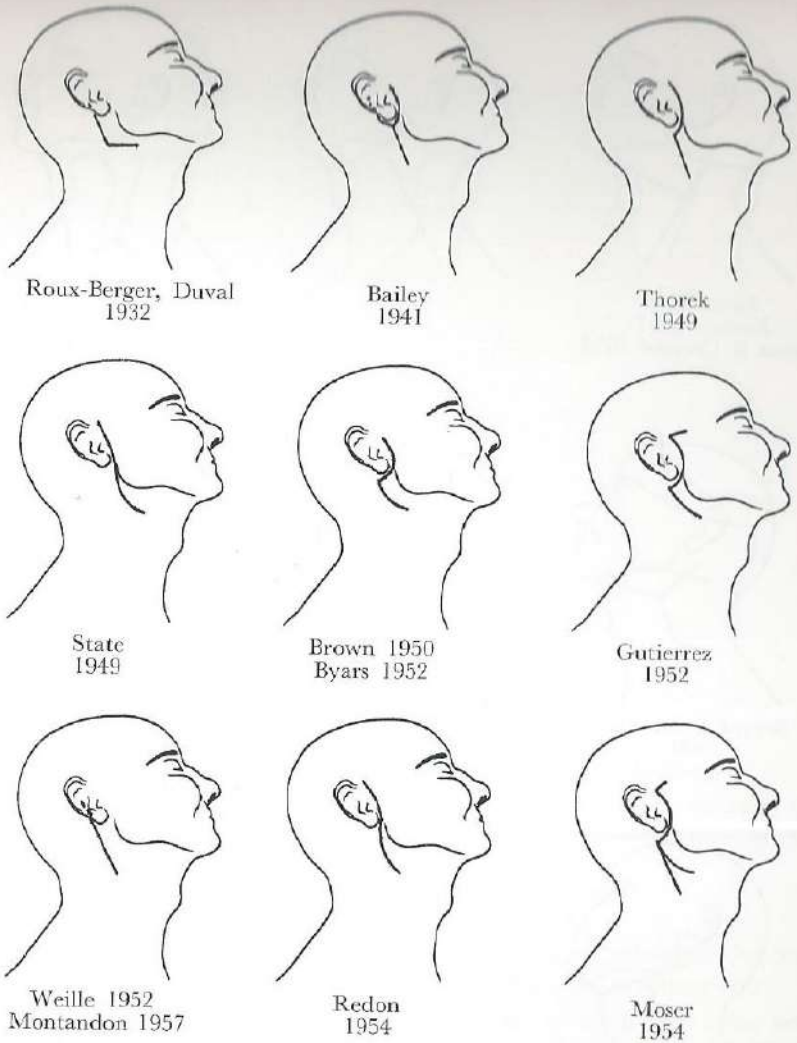


Fig. 14. Incisions for the approach to parotid lesions

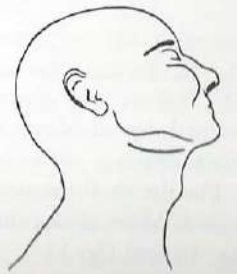


Fig. 15. Conventional submandibular incision

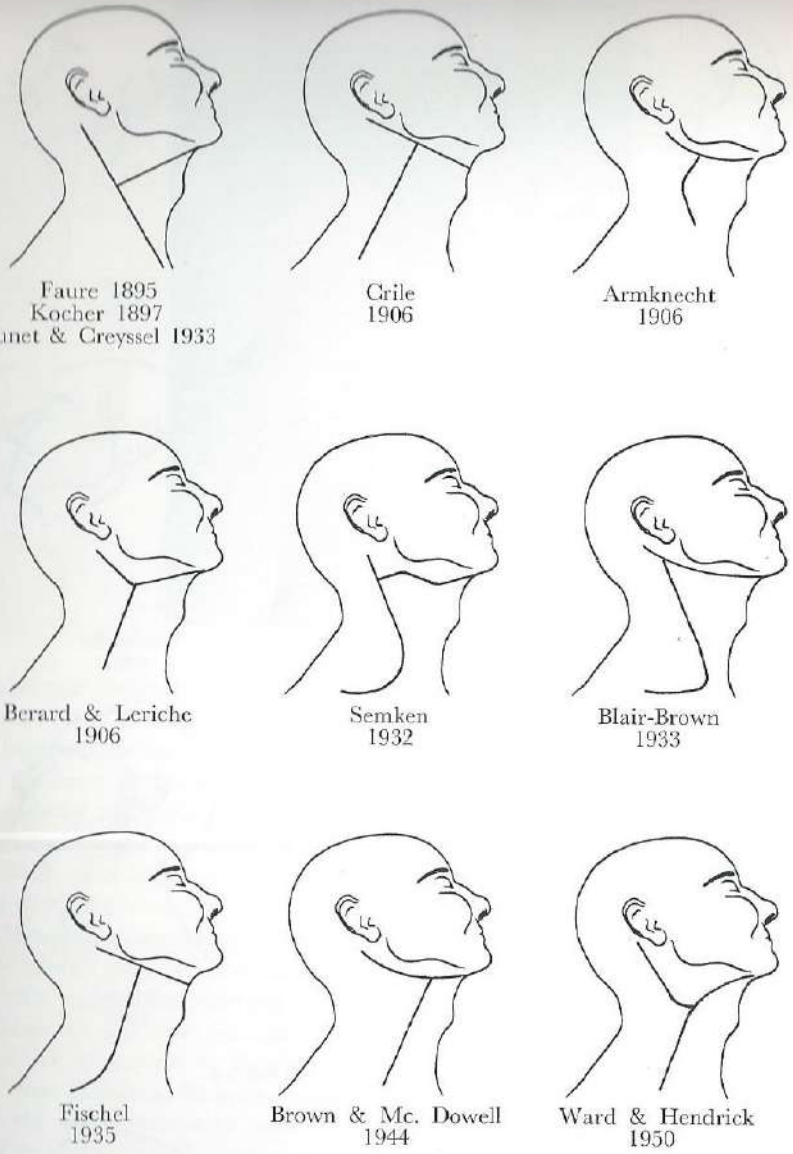


Fig. 16. Incisions for radical neck dissections.

formed by dividing the lower lip and skin of the chin and neck are advocated.

For the performance of radical neck dissections numerous incisions can be found. Most of the incisions encountered in the literature are illustrated in fig. 16 and fig. 17.

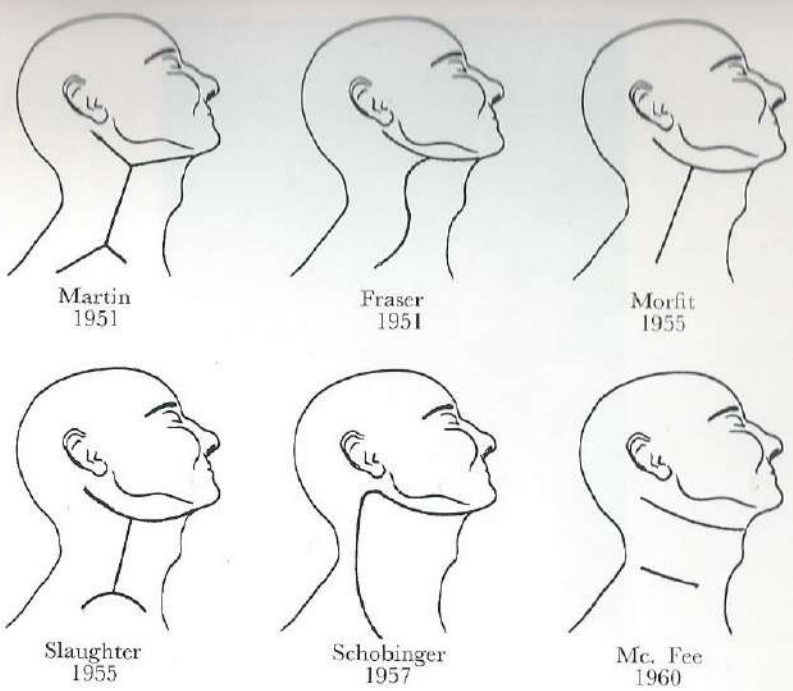


Fig. 17. Incisions for radical neck dissections.

Of these incisions, Martin's incision is the most commonly used.

Apart from adequate exposure, it can be noted that, if we take the preceding principles into consideration, the main disadvantages of the incisions illustrated are:

1. Lack of appreciation of individuality.
2. Lack of appreciation of the dynamic effects of muscular function acting on the undersurface of the skin through the resulting scar.

A few examples of resulting scars due to wrong incisional directions, with plastic correction of some, will be demonstrated. See figs. 18, 19, 20, 21 and 22.

In fig. 19 an irradiated scar from a conventional incision along the anterior border of the sterno-cleido-mastoid muscle is illustrated.

Fig. 20 represents the correction of this scar according to the principles discussed.

Fig. 21 shows a scar formation after total parotidectomy and radical neck dissection on the same side, using Martin's incisions.

In fig. 22 the freshly healed wound after correction of the scar and facial deformity is illustrated.

The basis for selection of appropriate lines of elective incisions in head and neck surgery.

Fig. 18. Deforming scar after exploratory Y-shaped neck incision.

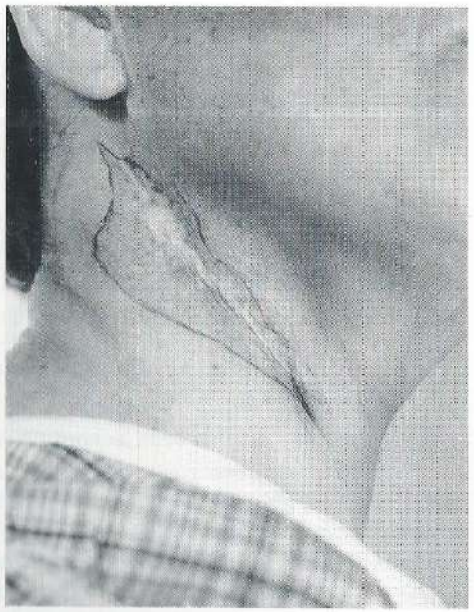


Fig. 19. Scar from longitudinal incision along anterior border of sterno-cleido-mastoid.

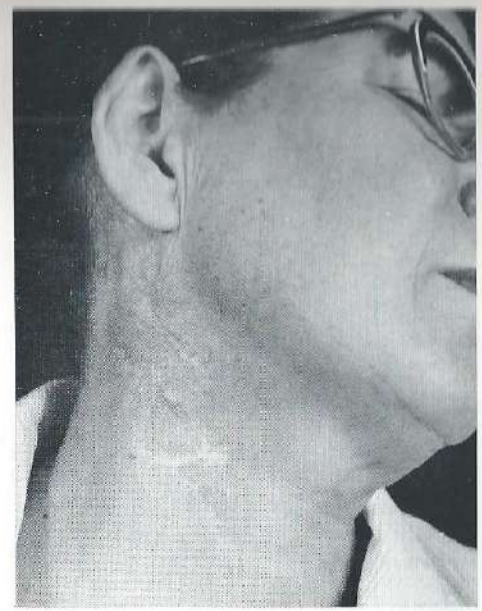


Fig. 20. Corrected scar from fig. 19.

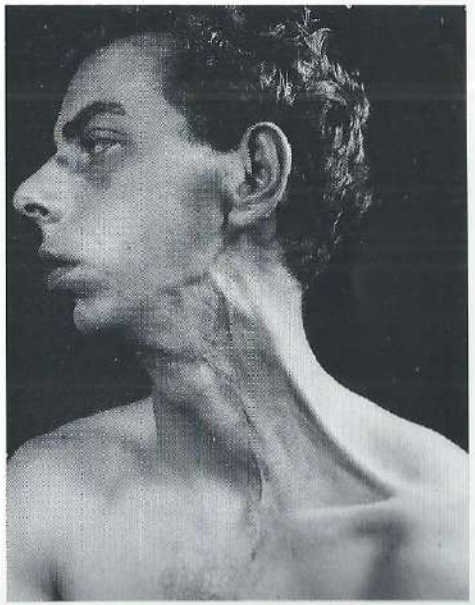


Fig. 21. Scar formation after total parotidectomy and radical neck dissection.

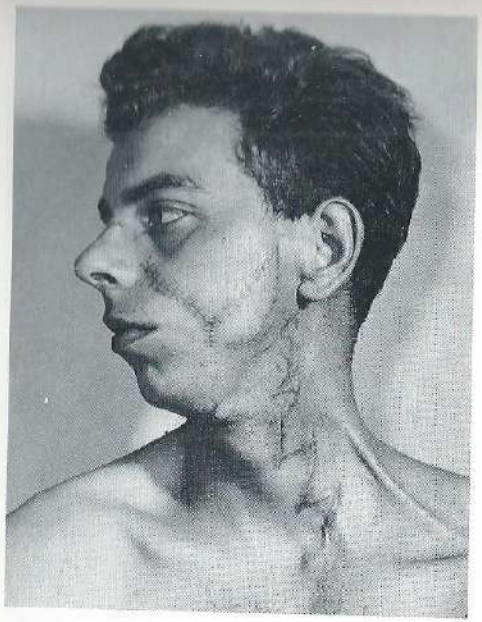


Fig. 22. Scars from fig. 21 after correction.

Recognition of the above principles leads to application of 'accordion' incisions for the external approach to facial and neck lesions. By 'accordion' incisions we mean incisions coinciding with the folds which occur in the skin of the neck area when the head is inclined in various directions; these folds are reminiscent of the folds in the bellows of an accordion.

The skin flaps, once elevated, ensure adequate exposure of the entire operative field, and the scar does not interfere with motion.

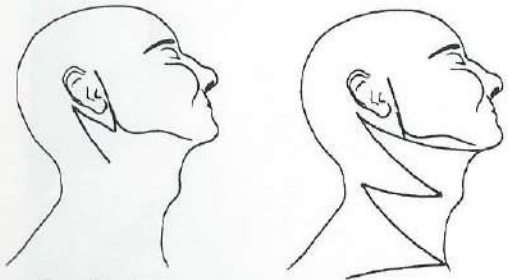


Fig. 23 A

Fig. 23 B

Figs. 23 A and B give an example of the primary incision and extension of this incision according to the same principles when a radical neck dissection has to be performed in continuity.

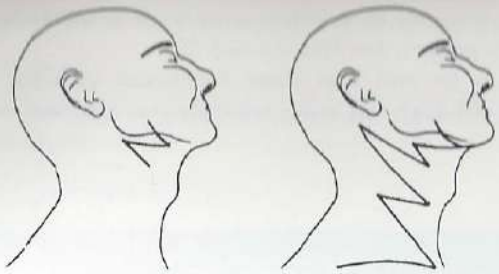


Fig. 24 A

Fig. 24 B

Fig. 24 A illustrates the approach to submandibular lesions, and fig. 24 B illustrates the extension of this incision when a radical neck dissection must be performed in continuity.

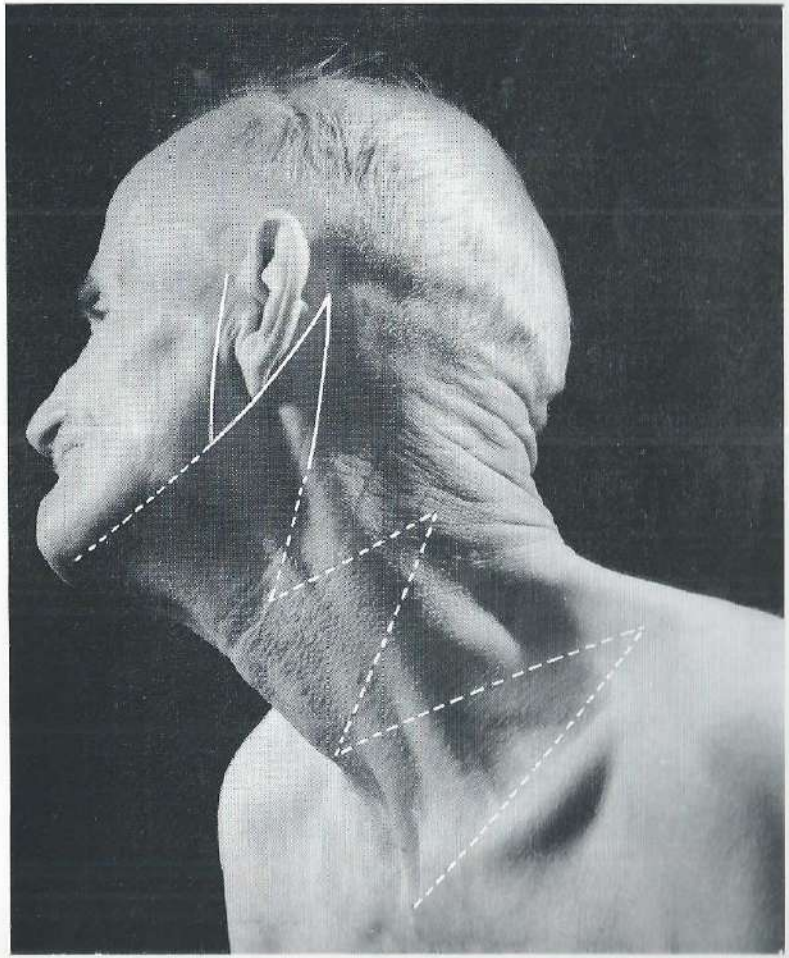


Fig. 25

The proposed incisions are schematically illustrated by beans of 2 photographs of a patient. See figs. 25 and 26.

It need not to be said that these functional incisions vary for each individual case, although the same principles are retained.

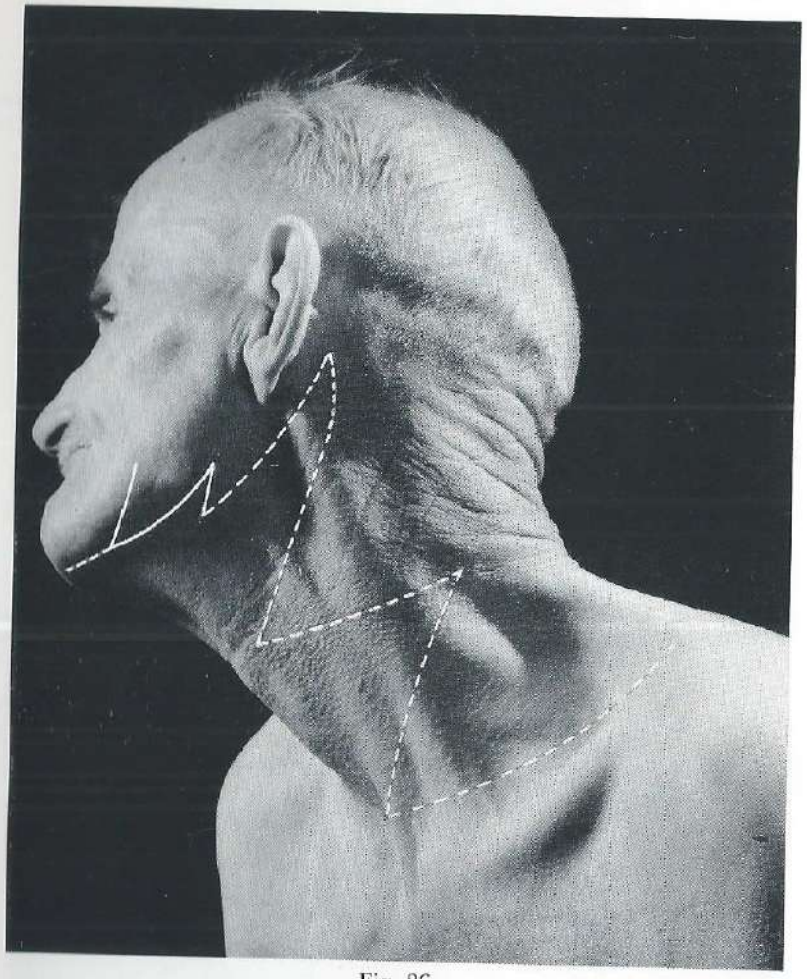


Fig. 26

Further care must be taken in designing the skin flaps. These should be neither too narrow nor too long. Fig. 27 illustrates the author's modification of Weber-Ferguson's incision.

What are the prospects of improvement of the proposed incisions?

1. Adequate exposure.
2. The incisions can be extended in every required direction, retaining the same principles.
3. Prevention of restriction of motion.
4. Good cosmetic results.

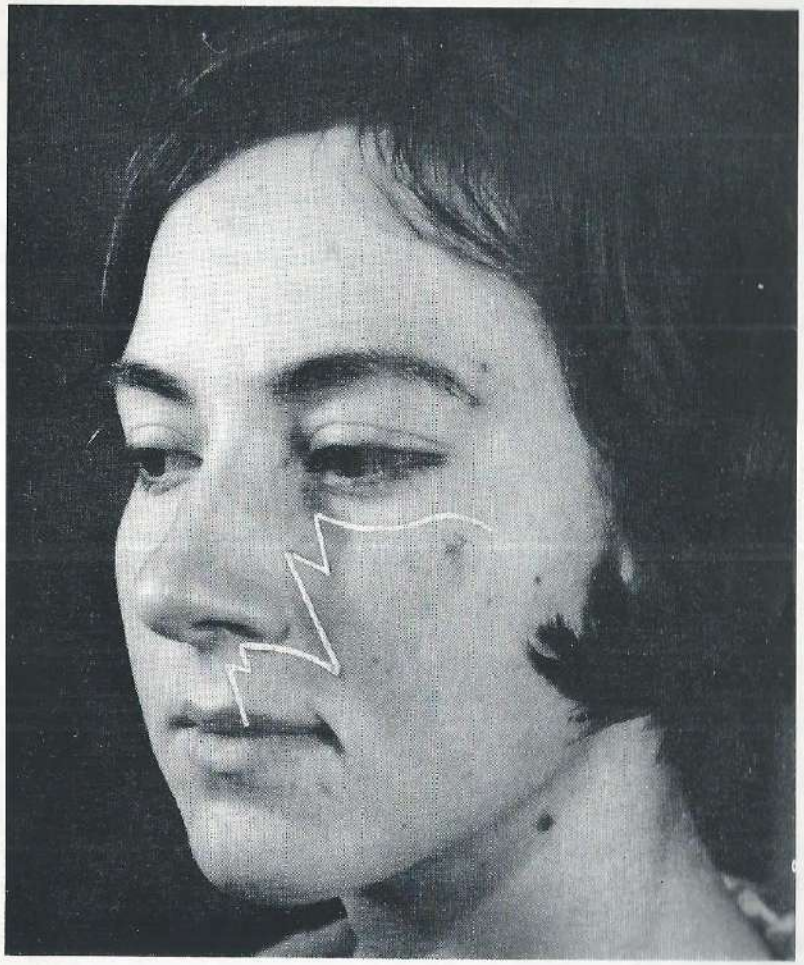


Fig. 27

DISCUSSION AND CONCLUSIONS REGARDING THERAPEUTIC IMPLICATIONS

The types of salivary gland tumour described in chapter III are well defined histologically. If a classification of salivary gland tumours is to be of practical value, it should make it possible to draw clinical conclusions from the histological features.

In a follow-up study over 5 to 16 years on a series of 414 patients with primary salivary gland tumours during the period 1947—1959, the clinical course of the various types of tumour was analysed.

A study of the correlation between the histological features and the clinical course permitted of a division into benign and malignant tumours. Clinical evolution, morphological characteristics, invasiveness, metastases and mortality due to the disease were used as criteria in grading the malignant tumours into three groups: malignant tumours with a low grade of clinical malignancy, malignant tumours with a moderate grade of clinical malignancy and malignant tumours with a high grade of clinical malignancy.

The study of the histological features made it possible to divide the group of mixed tumours into two morphological subgroups, namely: mixed tumours without morphological signs of malignancy and mixed tumours with definite morphological signs of malignancy.

Because of their slow growth, supposed encapsulation and rarity of metastases, mixed tumours without evident signs of malignancy have been designated 'benign' by various authors (e.g. McCune 1951, Kirklin et al. 1951, Foote and Frazell 1954, Eneroth 1964) or 'semi-malignant' (e.g. Edvall 1954, Agner and Nielsen 1956, Rauch 1959, Mylius 1960, Hellner 1962, Morehead 1962).

The biological potencies of the epithelial cells of these tumours are not sufficiently described by the terms benign or semi-malignant.

It is impossible by present methods to decide at what point apparently normal epithelial cells begin to manifest their propensities for malignant change.

In this study it was particularly difficult to evaluate the benignancy of the type of mixed tumour designated 'benign', because their morphology parallels the early stages of the definitely malignant type of mixed tumour. Reliable differentiation between these two entities must wait until our knowledge of the biological state of the epithelial cells comes to depend less on morphological appearances alone than it does at present.

The correlation of the histological and clinical features of mixed tumours

in this investigation made it possible to divide the group of mixed tumours into two groups, namely: mixed tumours without morphological sgns of malignancy, exhibiting a benign or at the most a low grade of clinical malignancy, and mixed tumours with morphological signs of malignancy with a high grade of clinical malignancy.

Oncocytomas, generally regarded as benign (e.g. Foote and Frazell 1954, Schäfer et al. 1956, Beahrs et al. 1960, Batsakis and Martz 1960), were in this investigation found to be malignant, with a low grade of clinical malignancy.

It has been demonstrated that the highly differentiated type of muco-epidermoid carcinoma was of low grade malignancy instead of benign (e.g. Stewart et al. 1945, Marcial-Rojas and Sommers 1954) or semi-milignant (e.g. Rauch 1959, Gläser 1962, Hellner 1962, Morehead 1962).

Acinic cell adenocarcinomas also proved to be malignant with a low grade of clinical malignancy.

Cylindromas, still considered semi-malignant (e.g. Rauch 1959, Hellner 1962, Gläser 1962, Morehead 1962), in this investigation proved to be definitely malignant, with a moderate grade of clinical malignancy.

Miscellaneous types of adenocarcinoma (trabecular, anaplastic, papillary), mucus-producing adenocarcinoma, the mixed tumour with morphological signs of malignancy, the poorly differentiated types of muco-epidermoid carcinoma and squamous cell carcinomas must be regarded as highly malignant tumours.

It has been demonstrated that a workable concept based on histological and clinical features makes it possible to classify the several members of the group of tumours correctly and to predict clinical behaviour accurately. The pathologist carries a heavy responsibility in the management of patients with these salivary gland tumours. The use of fresh frozen sections during operations is essential to establish the histopathological nature and guide definite therapy.

The surgeon must be prepared to interpret the histopathological diagnosis in the terms of its prognostic implications, and he must then recognize the indications for the various surgical procedures. His thoroughness in performing these operations then largely determines the chances of a cure of the lesion in question.

Therapeutic implications.

The initial treatment of these salivary gland tumours must be planned on the basis of clinical rather than pathological findings. On the basis of clinical manifestations, patients with symptoms and signs relating to these salivary gland tumours can be divided into three groups.

Group I.

Patients exhibiting symptoms and signs of a circumscribed tumour or area of origin.

In these cases the circumscribed nature of the lesion must be confirmed at operation. After adequate exposure the initial surgical effort should be directed at conservative removal of the entire lesion, along with as wide a margin of clinically normal tissue as is consistent with sound surgical judgement.

An incisional biopsy should never be attempted in these circumscribed tumours. If at operation the pathological findings indicate that removal has been complete and that the tumour is either benign or of a low or moderate grade of malignancy, then the surgeon may generally be confident that no further therapy is required.

If, however, the pathological findings indicate that the excision has been incomplete or that the tumour is infiltrative rather than circumscribed, then additional surgery is required.

Infiltrative low-grade and moderate-grade tumours are best treated by radical local excision.

Postoperative irradiation for low-grade tumours is of very doubtful value.

If complete resection of the lesion is impossible, it is necessary to take biopsies from different distant parts of the surrounding tissues in order to obtain information on the radicality. In these cases some form of radiotherapy may be of benefit in controlling the rapidity of further local spread. The objections to biopsy for circumscribed tumours are based on the fact that any diagnostic or therapeutic procedure which disrupts the continuity is hazardous. Especially the low-grade and moderate malignant tumours of epithelial origin are the most transplantable of all salivary gland neoplasms, and in the past it has been clearly demonstrated that both biopsy and incomplete removal are followed by increased rates of recurrence.

Group II.

Patients exhibiting symptoms and signs indicating:

a. an infiltrative tumour, which has largely replaced either the gland or the area of origin,

b. induced ulceration of the overlying skin or mucous membrane,

c. invasion of adjacent structures,

d. regional metastases,

e. distant metastases

or combinations of these.

In these cases biopsy should be the first step in routine procedure. If clinical examination shows that the regional lymph nodes are involved,

then these rather than the primary tumour are the elective site for biopsy. In the presence of distant metastases, treatment is usually non-surgical and consists of some type of irradiation.

In some cases a palliative surgical intervention combined with radiotherapy may be beneficial.

Exploration must be done; in the absence of operative contraindications during this operation an attempt must be made to identify the tumour and confirm its infiltrative nature.

Surgical treatment depends upon the type and extent of the disease. If lymph node involvement has been demonstrated pathologically, and if the primary disease is controllable, treatment should include radical regional therapy as well. If the disease is surgically uncontrollable, radiotherapy should be instituted.

Elective dissection of the regional lymphatics in the treatment of controllable highly malignant tumours of salivary gland origin without clinical evidence of cervical lymph node involvement, is still a highly controversial subject. I think that the incidence of nodal involvement in the absence of distant metastases in surgically controllable cases of these highly malignant tumours appears to give us more hope to control this stage of the disease than do therapeutic procedures when the disease has reached this dangerous stage.

In rare instances the surgeon is confronted with a metastatic tumour simulating a parotid or submandibular gland tumour, while the primary tumour remains undetected. The histology in these cases is of value both to the surgeon and to the radiotherapist. If the pathological findings indicate a radiosensitive tumour, radiotherapy will probably result in prolonged survival. In all other instances, although the prognosis for metastatic cancers in general is poor regardless of therapy, a combination of surgery and radiotherapy would appear to result in slightly better palliation than is effected by irradiation alone.

Group III.

Finally, the surgeon dealing with these salivary gland tumours is faced with recurrent tumours.

The pathologist encounters great difficulties with these recurrent salivary gland tumours, especially after various previous surgical interventions. In general, the microscopic appearance remains the same as that of the original growth, but in many instances there is a definite increase in invasive character and dedifferentiation.

In practically all instances recurrent tumours can be ascribed to the fact that, owing to insufficient radicality of the first operation, tumour fragments are left behind in the salivary gland tissue as well as in surrounding tissues.

Recurrences are seen after excision of all types of malignant tumours

and reach their peak one year after operation (Rawson et al. 1950). Overall recurrence rates after first treatment vary in the literature from 10 to 20 per cent, e.g. Pricolo et al. (1954) 10 per cent, Welti (1955) 15 per cent. Moyse (1955) 13 per cent, Lyle (1956) 18 per cent, Utendorfer (1956) 15 per cent.

Initial treatment of recurrent tumours must be planned on the basis of the pathological examination of the original tumour, and the treatment must be completed according to the findings at operation.

In general, more procedures are needed for these recurrent tumours. In recurrent tumours of low-grade and moderate-grade types, an attempt should be made to remove all tumour tissue completely, preserving if possible all structures necessary for the normal functioning of the part.

If secondary tumours have been demonstrated in the regional lymph nodes prior to operation, radical regional as well as radical local excision is carried out.

If in recurrent highly malignant tumours the disease is uncontrollable at exploration, treatment should be non-surgical, and consist of some type of radiotherapy. If the recurrent highly malignant tumour is still controllable, radical local as well as radical regional therapy should be carried out, followed by postoperative radiotherapy. Throughout this discussion, surgery has been emphasized as the treatment of choice for these salivary gland tumours.

Although radiotherapy has been used in the treatment of the malignant salivary gland tumours, a definite appraisal of its true curative value has not been possible.

A combination of surgical excision and postoperative radiotherapy has given notable results in some institutions (e.g. Ahlbom 1935, Smith and Stenström 1949, Kidd 1950, Kirklin et al. 1951, Kepp 1952, Clarke 1952, Hunter 1954, Pricolo et al. 1954, Smidd- 1956).

The value of exclusive curative radiotherapy for malignant salivary gland tumours is still uncertain.

Effects of irradiation on salivary glands have been studied mainly in animal experiments, e.g. English 1955/1960, English et al. 1955, Shafer 1952/1953, Shafer and Muhler 1953, Cherry and Glucksmann 1959/1962.

The effects of irradiation vary with the cell, organ and type of animal exposed.

Cherry and Glucksmann (1959), in their experiments in male rats, studied the relation between radiosensitivity of the various glandular components and their mitotic and functional activities. These experiments have shown that the excretory ducts are the least sensitive and the acini the most sensitive elements of the three major salivary glands (parotid, submandibular and sublingual), and that the acini disappear after various cycles of cellular degeneration and incomplete recovery. They also noted differences in the type of secretory activity.

Little is known about radiation injuries and their repair in normal human

salivary glands. Taking the results of these animal experiments into consideration, we may expect human salivary gland tissue to react in a more or less similar way.

It appears desirable to relate radiation effects on salivary glands to general considerations concerning the histogenesis of the malignant salivary gland tumours of epithelial origin.

It may be assumed that malignant tumours of ductal origin (e.g. mixed tumours, cylindromas, muco-epidermoid carcinomas, adenocarcinomas, squamous cell carcinoma) are radioresistant or relatively radioresistant, whereas malignant tumours histogenetically originating in the acini (e.g. acinic cell adenocarcinoma) are radiosensitive.

Because studies concerning the biological efficacy of radiotherapy, considering the various histological types of these malignant salivary gland tumours, are non-existent, it must be pointed out that the proper place of irradiation in the treatment of salivary gland tumours awaits further study.

SUMMARY

The uncertainty in the classification of salivary gland tumours is illustrated by the fact that, since it has been difficult to define these tumours histologically, it has also been difficult to evaluate them in terms of malignancy on the basis of their natural course.

This implies that, in many classifications, the various types of salivary gland tumours are denoted as benign, semi-malignant or potentially malignant and malignant. A division into benign and malignant is to be preferred for clinical purposes. Discussing the literature of salivary gland tumours, the main object of this investigation was to test and ascertain which histologically well-defined types of tumour can be classified as definitely benign or malignant, with special reference to the malignant types.

An analysis was made of 1002 patients with salivary gland lesions (primary and recurrent) during the period 1940—1964, whose microscopic findings were registered at the Central Pathological Laboratory of Rotterdam. A histological re-examination was made of the tumour material, which was classified according to such principles that the various types of tumour were morphologically defined.

Follow-up data and clinical findings on 414 patients with different types of tumour seen during the period from January 1947 through December 1959, were used for this study and analysed.

The malignancy of the tumours was evaluated in a study of the correlation between the histological and clinical features of the different types of tumour. The correlation study made it possible to divide these tumours into benign and malignant tumours, with the different malignant tumours exhibiting different grades of malignancy.

Clinical evolution, morphological characteristics, invasiveness, metastases and mortality due to the tumour disease, were used as criteria for the grading of the malignancies.

These criteria afforded a workable clinical concept for the classification of these salivary gland tumours into: Benign tumours, malignant tumours with a low grade of clinical malignancy, malignant tumours with a moderate grade of clinical malignancy and malignant tumours with a high grade of clinical malignancy.

Mixed tumours, designated 'benign' by several authors because of their slow growth, supposed encapsulation and rarity of metastases, could not be called benign in this investigation. If the prognosis in patients with mixed tumours has to depend upon the morphological diagnosis, two histological types can be distinguished, namely: one type of mixed tumour without morphological signs of malignancy which is clinically benign or at the most show a low degree of clinical malignancy and a second type of mixed tumour with definite morphological signs of malignancy and a high degree of clinical malignancy.

Oncocytomas, highly differentiated types of muco-epidermoid carcinoma and the acinic cell adenocarcinoma have a low grade of clinical malignancy.

Cylindromas and reticulum cell sarcomas were found to show a moderate grade of clinical malignancy.

Poorly differentiated types of muco-epidermoid carcinoma, miscellaneous types of adenocarcinoma (trabecular, anaplastic and papillary) and mucus cell adenocarcinomas, squamous cell carcinomas, fibrosarcomas, lymphosarcomas, Hodgkin's disease and metastatic tumours in the salivary glands were found to show a high grade of clinical malignancy.

The treatment of neoplasms of salivary glands is essentially a surgical problem. Irradiation treatment of these tumours is of little value. The surgeon who undertakes treatment of these salivary gland tumours must subscribe to the modern concept of adequate surgical removal.

The therapeutic implications of the proposed classification indicate that a more definite surgical approach should be used for the eradication of both benign and malignant types of salivary gland tumour. Adequate surgery for the patient with any type of salivary gland tumour calls for close cooperation between the clinician and the pathologist, and a successful outcome depends on the skilful and unified efforts of this team in evaluating and managing the numerous problems which may arise in an often difficult situation.

Each cancer of the salivary glands has its individual characteristics and its particular mode of local evolution and lymphatic extension. One of the fundamental rules of cancerology is that, in any cancer capable of producing lymphatic metastases, therapy must be directed not only at the primary tumour but also at the corresponding lymphatic area.

An evident propensity to form lymphatic metastases is found especially in the group of truly malignant tumours of epithelial origin with a high grade of clinical malignancy. For these tumours, neck dissection in continuity with radical local surgery is the method of choice, regardless of whether there are palpable cervical metastases or not.

It is true that, in some fortunate cases, a highly malignant tumour which is still well localized, can be cured by conservative operation; in view of such results, it is only natural that, in apparently similar cases, one resorts to more drastic measures only with regret.

Before the dissection, however, we cannot definitely establish the actual extent of these highly malignant tumours, nor judge their histological spread. Even with a negative report, the surgeon cannot rule out the possibility of malignancy in one of the sections not examined.

The mode of therapy outlined in this review affords the possibility of

treating most salivary gland tumours radically at first detection. Since long periods of observation are required to evaluate any method of therapy, a solution of this question will of necessity be postponed until some future time.

Full exposure is required in the regions of the parotid and submandibular glands. It has been shown in the past that these salivary gland tumours reappear frequently after surgical intervention undertaken through an inadequate and usually short skin incision. It is only when the whole operative field is exposed that the true location and extent of the disease can be assessed with the degree of accuracy necessary to formulate a considered opinion on the indications for the various surgical procedures.

In an attempt to improve functional and cosmetic results, it has been demonstrated that practical consideration of the formation of wrinkle lines about the face and neck, in combination with the principles of wound healing, makes it possible to develop a fairly definite pattern for planning incisions on the face and neck.

SAMENVATTING

De onzekerheid over de indeling van speekselkliergezwellen in bepaalde groepen wordt verklaard door het feit dat zowel de histologische typering als de bepaling van de graad van maligniteit op grond van hun natuurlijk verloop moeilijk is. Dit brengt met zich mee, dat men bij het maken van een classificatie veelal de termen goedaardig, semi-maligne, potentieel-kwaadaardig en kwaadaardig gebruikt voor het aanduiden van de verschillende typen gezwellen.

Voor klinische doeleinden verdient de indeling in goedaardig en kwaadaardig de voorkeur.

Het voornaamste doel van dit onderzoek was te bepalen welke histologisch duidelijk getypeerde tumoren gezien konden worden als beslist kwaadaardig of beslist goedaardig, vooral met betrekking tot de kwaadaardige typen.

Bij de analyse waren 1002 patienten met speekselkleirgezwellen (primair en recidief) betrokken in de periode 1940—1964; de resultaten van het microscopisch onderzoek berusten bij het Centraal Pathologisch Laboratorium te Rotterdam. Nadat het tumor materiaal opnieuw histologisch was onderzocht, werd een indeling gemaakt naar de morphologische structuur van de verschillende typen gezwellen.

Het onderzoek omvatte tevens de analyse van de gegevens verkregen bij controle en klinisch na-onderzoek van 414 patienten met verschillende typen gezwellen in de periode januari 1947 tot december 1959.

De maligniteit van de gezwellen werd bepaald door de bestudering van de correlatie tussen de histologische en klinische aspecten van de verschillende typen gezwellen. Hierdoor werd het mogelijk de benigne gezwellen van de maligne te onderscheiden waarbij de diverse maligne gezwellen een verschillende graad van maligniteit vertoonden.

De criteria voor het bepalen van de graad van maligniteit waren: het klinisch beloop, de morfologische kenmerken, de infiltratieve groei, de metastasering en de mortaliteit als gevolg van deze tumoren.

Door het hanteren van deze criteria werd een praktische klinische indeling verkregen door de speekselkliergezwellen te verdelen in benigne tumoren, maligne tumoren met een lage graad van maligniteit, maligne tumoren met een matige graad van maligniteit en maligne tumoren met een hoge graad van maligniteit.

Mengtumoren, door verscheidene auteurs 'goedaardig' genoemd, omdat zij langzaam groeien, afgekapseld zouden zijn en zelden metastaseren, konden

in dit onderzoek niet als geheel goedaardig worden beschouwd. Alleen de mengtumoren zonder morfologische tekenen van maligniteit met 'kapsel' (vaak partieel), zonder penetratie in of door de 'kapsel' zijn in dit onderzoek benigne gebleken. (Zie tabel 6) De morfologische benigne mengtumor echter, die zich pathologisch gedraagt, moet als maligne met een geringe graad van maligniteit beschouwd worden.

Oncocytomen, hoog gedifferentieerde typen muco-epidermoid carcinoom en het sereuse cel adenocarcinoom bleken maligne met een lage graad van maligniteit.

Cylindromen en reticulum cel sarcomen bleken een matige graad van maligniteit te hebben.

Mengtumoren met histologische bevindingen van carcinoom, weinig gedifferentieerde typen muco-epidermoid carcinomen, verscheidene typen (adeno-)carcinomen (trabeculair, anaplastisch en papillair) en slijmcel adenocarcinomen, plaveiselcel carcinomen, fibrosarcomen, lymfosarcoom, de ziekte van Hodgkin en metastatische tumoren in de speekselklieren bleken een hoge graad van maligniteit te bezitten.

De behandeling van speekselkliertumoren is hoofdzakelijk een chirurgisch probleem. Bestraling van deze tumoren heeft weinig zin.

Voor adequate chirurgische behandeling van de patient met een speekselkliertumor, dienen de clinicus en de patholoog-anatoom nauw samen te werken; een goed resultaat hangt af van de kunde en het gezamelijk pogen van dit team om de oplossing te vinden voor de talrijke problemen die zich in een vaak zeer moeilijke situatie kunnen voordoen.

Elke kanker van de speekselklier heeft zijn eigen karakteristieke kenmerken en zijn eigen wijze van ontwikkeling en lymfatische en/of haematogene verspreiding.

Een van de grondregels van de carcinoomchirurgie is, dat bij elke kanker waarbij lymphogene metastasering kan optreden, de therapie niet alleen gericht moet zijn op de primaire tumor maar ook op de bijbehorende regionale lymphklieren. Een duidelijke neiging tot het vormen van lymfatische metastase, werd vooral gevonden in de groep van maligne tumoren van epitheliale oorsprong met een hoge graad van maligniteit. Voor deze tumoren is het wenselijk, indien het primair gezwel curatief behandeld kan worden, tevens onmiddellijk een homolaterale nek dissectie te verrichten, ook al zijn er geen voelbare metastasen in de hals. In enkele gevallen heeft men het geluk dat een goed gelocaliseerde tumor met een hoge graad van maligniteit genezen kan worden door de kleinste ingreep. Er zijn zulke gevallen bekend en daarom spreekt het vanzelf dat men met spijt tot drastische maatregelen overgaat in gevallen die daarop schijnen te lijken. Niettemin kan men vóór de exploratie toch niet met zekerheid vaststellen hoe uitgebreid een tumor met hoge graad van maligniteit is en in hoeverre verdere verspreiding heeft plaatsgevonden. Zelfs bij een negatief resultaat kan de chirurg de mogelijkheid van maligniteit in één van de niet-onderzochte gedeelten niet uitsluiten.

De wijze van behandeling, hier gegeven, geeft de mogelijkheid tot radicale behandeling van speekselkliertumoren.

Voor exploratie van een tumor in de streek van de oorspeekselklier en de submandibulaire klier is ruim blootleggen van het operatie-gebied van essentieel belang. Het operatieterrein dient geheel open te liggen voordat men de juiste plaats en de omvang van de tumor met de nodige nauwkeurigheid kan bepalen om dan een weloverwogen oordeel te kunnen vormen omtrent de uitgebreidheid van de verschillende chirurgische procedures. In het verleden werd reeds aangetoond dat speekselkliertumoren dikwijls opnieuw optreden na een chirurgische ingreep waarbij de huidincisie inadequaat en gewoonlijk te kort was.

Bij een poging de functionele- en esthetische resultaten te verbeteren, werd aangetoond dat het mogelijk is een plan te maken voor de incisies in gezicht en hals door de principes van wondgenezing te combineren met de rimpelvorming.

RÉSUMÉ

Classer les tumuers des glandes salivaires présente deux difficultés: définir ces tumuers histologiquement et évaluer leur degré de malignité sur base de leur évolution naturelle. Il en résulte que, dans de nombreuses classifications, l'on caractérise les différents types de tumeurs des glandes salivaires de bénins, semi-malins ou potentiellement malins et malins.

Pour l'usage clinique, il serait préférable de les subdiviser en bénins et malins.

Le but de cette étude est de déterminer et d'analyser quels sont les types de tumeurs bien définis histologiquement et pouvant être définitivement classifiés en bénins ou malins, en tenant principalement compte des types malins.

Au cours de la période 1940—1964, l'on a examiné 1002 patients ayant des lésions (primaires et récidivantes) des glandes salivaires, dont les caractères microscopiques ont été enregistrés au Laboratoire Central de Pathologie de Rotterdam. L'on a procédé à un nouvel examen histologique du matériel tumoral qui fut classifié suivant des principes permettant de définir morphologiquement les différents types de tumeur. Cette étude a nécessité l'utilisation et l'analyse des contrôles et des conclusions cliniques sur 414 patients atteints de divers types de tumeur et examinés au cours de la période s'étendant de janvier 1947 à décembre 1959.

Une étude sur la corrélation extistant entre les caractéristiques histologiques et cliniques des différents types de tumeur a permis d'évaleur la malignité de ceux-ci. D'après cette corrélation, il a été possible de diviser ces tumeurs en bénignes et malignes, ces dernières pouvant présenter divers degrés de malignité.

Les critères utilisés pour définir ce degré de malignité sont: l'évolution clinique, les caractéristiques morphologiques, l'envahissement, les métastases et la mortalité due aux tumeurs.

Ces critères permettent d'établir une conception clinique de la classification de ces glandes salivaires en: tumeurs bénignes, tumeurs malignes avec faible degré ou degré modéré ou degré élevé de malignité clinique.

On a découvert que les tumeurs mixtes sans signes histologiques évidents de malignité, les oncocytomes, les types hautement différenciés de carcinomes muco-épidermoides et les adénocarcinomes à cellules aciniques ont un faible degré de malignité clinique.

Tandis que les cylindromes et sarcomes à cellules réticulées présentent un degré moyen de malignité clinique.

Les tumeurs mixtes avec signes histologiques de malignité, les types peu différenciés de carcinomes muco-épidermoïdes, les divers types d'adénocarcinomes (trabéculaire, anaplastique et papillaire) et les adénocarcinomes à cellules à mucus, les carcinomes à cellules squameuses, les fibrosarcomes, les lymphosarcomes, les maladies d'Hodgkin et les tumeurs métastatiques des glandes salivaires présentent un degré élevé de malignité clinique.

Les tumeurs mixtes, que plusieurs auteurs qualifient de 'bénignes' à cause de leur croissance lente et de leurs métastases rares et bien encapsulées, ne pourraient conserver cette appellation dans cette étude (planche 6).

Le traitement des néoplasmes des glandes salivaires est essentiellement chirurgical.

Le traitement de ces tumeurs par irradiation est peu efficace.

Le chirurgien qui entreprend le traitement de ces tumeurs devra s'adapter à la conception moderne exigeant une exérèse chirurgicale adéquate.

Sur le plan thérapeutique, il résulte de la classification proposée qu'il faudrait faire une intervention chirurgicale élargie pour l'excision de ces divers types de tumeurs, bénins et malins.

Le traitement adéquat pour le patient atteint de n'importe quel type de tumeur des glandes salivaires exige une collaboration étroite entre le clinicien et le pathologiste; un résultat satisfaisant dépendra des efforts habiles et conjugués de cette équipe à évaluer et maïtriser les nombreux problèmes pouvant se présenter dans une situation souvent difficile.

Le type de traitement exposé dans ce travail offre la possibilité de traiter la plupart de ces tumeurs radicalement au premier examen positif.

Comme de longues périodes d'observation seront nécessaires pour établir tout mode de traitement, la solution à ce problème devra nécessairement être reportée à plus tard. Dans les régions des glandes parotides et sous-maxillaires, l'irradiation complète sera nécessaire.

Il a été démontré dans le passé que ces tumeurs réapparaissent fréquemment après une intervention chirurgicale effectuée par une incision inadéquate et limitée de la peau.

Ce n'est que lorsque la totalité du champ opératoire est exposé que l'on peut évaluer la situation et l'étendue du mal avec le degré de précision nécessaire pour se faire une opinion sur les diverses indications chirurgicales. Dans le but d'améliorer les résultates fonctionnels et esthétiques, il a été démontré que l'utilisation des plis ainsi qu'une bonne cicatrisation rendaient possible l'élaboration d'un plan à peu près définitif des incisions du visage et du cou.

Tout cancer des glandes salivaires présente ses caractéristiques propres et son mode d'évolution locale et d'extension lymphatique.

L'une des règles fondamentales en cancérologie est que, dans tout cancer capable de produire des métastases lymphatiques, la thérapeutique doit non seulement porter sur la tumeur mère mais également sur la zone lymphatique correspondante.

L'on note une propension manifeste à la formation de métastases lym-

phatiques dans le groupe de tumeurs malignes d'origine épithéliale avec degré élevé de malignité clinique. Pour ces tumeurs, la méthode de choix sera la dissection du cou accompagnée d'une exérèse locale radicale, qu'il y ait ou non des métastases cervicales palpables.

Il est vrai que dans certains cas heureux, une tumeur fortement maligne mais bien localisée peut être traitée par une intervention 'conservative'; à la vue de tels résultats, il est normal que l'on recoure avec regret à des mesures plus drastiques dans des cas apparemment similaires.

Cependant, il ne nous est pas possible, avant la dissection, d'évaluer la véritable extension de ces tumeurs à degré élevé de malignité ni de juger leur envahissement histologique.

Même en présence d'un résultat négatif, le chirurgien ne peut écarter la possibilité de malignité dans l'une des coupes non examinées.

APPENDIX

Predominance of epithelial components

Case 47/25435 *

Woman aged 47. Clinical history: At age 9 a tumour (1.8 × 1.8 centimetres) was noticed in the right parotid area, growing slowly without symptoms. The last 2 years showed a more rapid growth still without further symptoms. Examination disclosed a clinically benign tumour in the right parotid area. Operation on 18th October 1947.

Microscopic diagnosis:
Mixed tumour with predominance of the epithelial component and with local invasive growth.

The patient was given radiotherapy postoperatively (2600 R tumour dose in 19 days). When seen on 3rd June 1948, she complained of severe pain in the maxilla and mandibula on the operated side. X-ray examination of the skull showed bone destruction of the right maxilla and coronoid process of the mandibula. In July 1948 the symptoms were less severe. In October 1948 there was a deterioration of the patient's general condition, with severe pain and vomiting, and disturbed vision. Another cranial X-ray revealed further tumour invasion into the base of the skull. The patient died in December 1948.

Case 55/125

Man aged 44. Clinical history: At age 18 a swelling was noticed in the right parotid area, growing slowly without symptoms. Clinical examination revealed a clinically benign tumour (1.5 × 1.5 cm.) in the right parotid area. A subtotal parotidectomy was done in October 1955.

Microscopic diagnosis:
Mixed tumour with predominance of the epithelial component, incompletely encapsulated.

* In the case numbers, the first two digits represent the year of admission.

After the operation the tumour recurred 5 times. The last removal of a recurrence was on 11th November 1958.

Microscopic diagnosis:
Mixed tumour with predominance of the epithelial component; no capsule.

The patient was again seen on 14th January 1959; the tumour had recurred. At clinical examination a tumour (1.5 × 1.5 cm.) was found, together with an enlarged palpable lymph node behind the insertion of the sternocleidomastoid muscle. This time the patient was given radiotherapy (4050 R tumour dose in 14 days). No success was achieved by this therapy, and the patient was hospitalized for treatment by radium puncture.

Microscopic diagnosis of the tumour removed before applying radium:
Adenocarcinoma of the salivary glands.

In the period from February until April 1960 there was a gradual expansion of the tumour with an increase in the palpable lymph nodes along the sternocleidomastoid muscle. Telecobalt therapy (5900 R tumour dose in 24 days) followed in April 1960.

Routine chest X-rays during this period showed metastases in the lungs. The patient died on 10th August 1960.

Further study of the cases in this group revealed two more cases which merit special mention. These two patients are still alive.

Case 47/20597
Man aged 30. Clinical history: Underneath the left earlobe there was a tumour of three years' standing, growing slowly without giving rise to symptoms. Examination disclosed a clinically benign tumour.

Microscopic diagnosis:
Mixed tumour with predominance of the epithelial component; no capsule.

The patient received radiotherapy (2400 R air dase in 6 days) postoperatively.

In October 1961 the patient returned to the out-patient clinic complaining of facial paralysis on the left side, with a solid local recurrence. A radical operation was attempted on 26th October 1961.

Microscopic diagnosis:
Trabecular adenocarcinoma of the salivary gland.

Apart from Frey's syndrome after this operation, no pecularities until August 1962; when another local recurrence was found. In September 1962 this tumour was extirpated, with subsequent radium puncture.

Microscopic diagnosis: Adenocarcinoma
This patient was still alive and free of symptoms when seen in December 1963.

Case 17:537-1949

Man aged 47. Clinical history: In 1917, he underwent an operation for lymphomas on the left side of the neck, followed by radiotherapy. In 1949 a small tumour was removed from the left parotid area.

Microscopic diagnosis:
Mixed tumour with predominance of the epithelial component; incompletely encapsulated.

In 1958 the tumour recurred and was again extirpated.

Microscopic diagnosis:
Mixed tumour with predominance of the epithelial component (highly cellular); no capsule.

Postoperative radiotherapy (1400 R airdose in 4 days) was given. The tumour recurred again in February 1962 and was again extirpated.

Microscopic diagnosis:
Mixed tumour with markedly pleomorphous epithelial cellular structures, incompletely encapsulated.

This patient was still alive and showed no signs of recurrence when seen in December 1963.

Predominance of connective tissue components
Case 47/24733

Woman aged 47. Clinical history: In the right parotid area a tumour of 12 years' standing. Examination revealed a clinically benign tumour (10 × 9 cm.) which was extirpated on 5 th May 1948.

Microscopic diagnosis:
Mixed tumour with predominance of the connective tissue component (especially myxoid pattern), infiltrating the surrounding tissue.

Postoperatively the patient received radiotherapy (2000 R air dose in 10 days).

After 6 months a recurrent tumour was extirpated, followed by radium treatment (800 mg.hrs.).

Microscopic diagnosis:
Mixed tumour with predominance of the connective tissue component and with necrotic areas; no capsule.

When seen in January 1950 the patient complained of pain in the operated area. Examination disclosed no sign of a local recurrence. Chest X-rays showed metastases in the lungs. The patient died on 16th February 1950. No autopsy was done. Because the paraffin block of the first microscopic examination was lost, no serial sections could be made in this exceptional case.

Mixed tumours with definite morphological signs of malignancy

Case 49/32057

Man aged 60. Clinical history: Tumour in the left submandibular region since 6 to 8 weeks. This tumour was extirpated on 29th December 1949, together with a lymph node near the tumour.

Microscopic diagnosis:
Mixed tumour with chondroid substance, hyaline matrix and adenocarcinoma infiltrating normal salivary gland tissue and perineural areas.

In the removed lymp node too, groups of carcinoma cells were found. The patient received radiotherapy postoperatively (2000 R air dose in 5 days).
In June 1950, enlarged lymph nodes were palpable along the border of the sternocleidomastoid muscle and behind the left clavicle. In September 1950, induration of the operated area was noticed.

Needle biopsy microscopically revealed adenocarcinoma.

Further treatment consisted of radiotherapy alone (June 1950: 1500 R air dose in 5 days; August 1950: left supraclavicular region 2400 R air dose in 17 days; right supraclavicular region 3300 R air dose in 17 days; September 1950: left parotid region 3000 R air dose in 22 days; left neck area: 3000 R air dose in 14 days; October 1950: left supraclavicular region 3000 R air dose in 10 days; November 1950: chin area 1500 R air dose in 5 days; December 1950: left axilla 1200 R in 5 days; right supraclavicular region 1200 R air dose in 4 days).

In January 1951, poor general condition; diffusely enlarged lymph nodes in the right supraclavicular region, infiltration of the left sternocleidomastoid muscle and skin metastases. The patient died on 19th February 1951.

Case 49/28231

Woman aged 48. Clinical history: Since 1942, nasal obstruction. In 1949, a tumour in the left nasopharynx was found and removed.

Microscopic diagnosis:
Mixed with predominance of epithelial structures and marked pleomorphism, infiltrating the surrounding tissue.

Postoperative radiotherapy by irradiation and radium application (2000 R air dose in 16 days; 1219 mg.hrs. respectively).

In 1951: symptoms of paralysis of the abducens nerve, severe headache, diplopia and deafness of the left ear. Rhinoscopy: thin fibrinous layer on the left nasopharyngeal wall. Cranial X-rays revealed: lesser density and disappearance, of the structure of the pars basilaris ossis occipitalis and the foramen magnum occipitale, respectively.

X-ray follow up in 1952: no changes in the above mentioned findings.

At physical examination, no signs of brain metastases or increased intracranial pressure. In 1953, radionecrosis of the palate with defects; the patient was treated by means of a palatal prosthesis.

Early in 1954 the patient complained of haemorrhage in the throat and a foetid discharge from the nose.

In August 1954, admitted to the neurosurgical department with symptoms of dizziness and epistaxis, and with cranial X-rays showing increased bone destruction by the tumour process.

Operation on 17th September 1954: subtemporal decompression operation with drainage according to Thorkildsen.

The patient died on 17th January 1955.

Case 49/31112

Man aged 44. Clinical history: Since three years a slow growing tumour in the right parotid region; the last four months increasingly rapid growth without pain.

At examination a clinically malignant tumour was found in the right parotid region, without evidence of regional lymph node involvement. In September 1949 a biospsy was done.

Microscopic diagnosis:
Mixed tumour with adenocarcinoma-like structures, infiltrating the surrounding tissue.

This patient received X-ray treatment (2400 R air dose in 6 days). Follow-up in July 1950: the tumour measured 4 × 3 cm. The patient then received another series of X-ray irradiations (3000 R air dose in 12 days).

In April 1951 the tumour measured 2 × 2 cm. The patient complained of pain and facial paralysis. In October 1951, radium treatment (1440 mg.hrs.) was applied; this lead to practically complete disappearance of the tumour in January 1952.

In March 1954 the patient showed increased tumour activity with induration of the right mandibula. X-rays of the mandible revealed no evidence of bone destruction.

In May 1954 aggravation of symptoms: hemianopsia, mental disorders and brain metastases. Operation for brain metastases in January 1955.

Microscopic diagnosis:
Partly solid adenocarcinoma with local myxoid areas as seen in mixed tumours.
This patient died in April 1955.

Case 50/183

Man aged 25. Clinical history: In March 1950, operation for a tumour of the right parotid of 2 years' standing.

Microscopic diagnosis:

Mixed tumour with pleomorphous cellular components, incompletely encapsulated.
A recurrent tumour was excised in October 1956.

Microscopic diagnosis:
Mixed tumour with predominantly adenocarcinoma-like pattern.

The patient received X-ray therapy (2000 R air dose in 10 days) postoperatively. December 1957: radical neck dissection for acquired regional involvement of the lymph nodes of the right side of the neck.

Microscopic diagnosis:
Metastatic adenocarcinoma with partially solid and partially papillary structures.

X-ray treatment (3000 R air dose in 10 days) followed this operation. In January 1958, tumour invasion was noted in the right external auditory canal and excised. Chest X-rays revealed metastases in the lungs. The patient was treated with Telecobalt (3000 R in 14 days). In August 1958: further tumour infiltration under the old surgical scar with ulcerations and new infiltrations in the external auditory canal. Gradual deterioration of the general condition. Death in September 1958.

Case 51/39826

Man aged 76. Clinical history: 3 month ago a poorly healing wound in the right submandibular region, followed by a slow growing tumour in this region. The tumour was extirpated on 3rd October 1951.

Microscopic diagnosis:
Mixed tumour with carcinoma-like structures, infiltrating the surrounding tissue.

Postoperatively the patient received X-ray therapy (3000 R air dose in 14 days). Lymphatic leukaemia was diagnosed when the blood was re-examined in November 1951.

When seen in January 1952, the patient showed signs of facial paralysis on the right side, induration underneath the scar, with palpable lymph nodes on the right side of the neck. X-ray irradiation (3000 R air dose in 24 days) of the lymph nodes resulted in subtotal regression of these nodes. August 1952: complaints of low back pain. X-rays of the lumbar spine showed questionable metastases in the first lumbar vertebra.
The patient died on 8th May 1953.

Case 53/3289

Woman aged 53. Clinical history: At age 6 a slow growing tumour was seen underneath the left earlobe. The tumour was removed elsewhere when the patient was 26 years old. Probably no microscopic examination was made. In August 1953, when the patient was seen, she had a recurrent tumour of 6 months' standing and was complaining of hypersalivation. Operation on the 3rd September 1953.

Microscopic diagnosis:
Mixed tumour with markedly pleomorphous cellular components infiltrating the capsule.

The patient received postoperative X-ray therapy (2000 R air dose in 11 days).

In March 1957 she complained of severe headache and symptoms of a cervical syndrome; in March 1958 she showed symptoms of focal epilepsy and increasing paralysis which, according to the attending neurologist, could be ascribed to brain metastases. Chest X-rays during the period showed pulmonary metastases also.
Death followed in June 1958.

Case 53/3791

Female aged 16. Clinical history: Since 2 months, nodular enlargements in the right submandibular region and on the right side of the neck. Tuberculosis was suspected and the patient was treated by UV irradiation. This treatment was ineffective, and later the patient complained of oppressed breathing when swallowing. A biopsy was done in May 1957.

Microscopic diagnosis:
Mixed tumour with structures of adenocarcinoma.

The tumour was extirpated in October 1953. X-ray therapy (2000 R air dose in 12 days) was given postoperatively. Until 1954 no pecularities were noted except marriage in the meantime. When seen in September 1954, the patient was pregnant, and there was a local recurrence measuring 3 × 3 cm. Further treatment was postponed until after the delivery.

December 1954: the local recurrence increassed with palpable enlarged lymph nodes on the right side of the neck. April 1955: diffuse swelling of the right nasopharynx was also noted. Radical neck dissection on the right side was carried out in May 1955.

Microscopic diagnosis: Adenocarcinoma.

November 1955: palpable enlarged lymph nodes on the left side of the neck. X-ray therapy (2000 R air dose in 10 days). During this treatment an acute enlargement in the left submandibular region was noticed, which disappeared completely in January 1956. February 1956: again palpable nodes on the right side of the neck, tumour infiltration of the right tonsilar area, soft palate and probably also the pharynx. December 1956: pulmonary metastases, together with swelling of the epiglottis and hypopharynx. There was dyspnoea and stridor.
Death followed in March 1957.

Case 54/2423

Man aged 65. Clinical history: In 5 weeks the right cheek had swollen rapidly, with symptoms of facial paralysis on the right side. At examination a clinically malignant tumour was found in the right parotid area, with enlarged lymph nodes along the border of the sternocleidomastoid muscle. A needle biopsy was done on 16th July 1954.

Microscopic diagnosis:
Mixed tumour with a pattern of adenocarcinoma; no capsule.

The patient was treated by X-ray therapy (4500 R air dose in 24 days). In March 1955, metastases were found in the lungs, bone and brain.
The patient died on 9th May 1955.

Case 54/4294

Man aged 50. Clinical history: Since 14 years a slow growing tumour in the left submandibular region, with more rapid growth during the last 2 years.

No complaints of pain. The tumour was extirpated in December 1954; X-ray therapy (1600 R air dose in 9 days) followed.

Microscopic diagnosis:
Mixed tumour with markedly pleomorphous epithelial components; no capsule.

The tumour recurred in January 1957, and enlarged lymph nodes were palpable in the left supraclavicular area.
A radical operation with combined left neck dissection was performed.

Microscopic diagnosis:
Mixed tumour with predominance of structures of squamous cell carcinoma.
The removed lymph nodes contained carcinoma; only structures of squamous cell carcinoma were found.

Postoperative X-ray therapy totalled 1600 R air dose in 9 days.
Severe pain persisted; there was a gradually increasing cachexia, and the patient died in October 1957.

Case 54/728

Man aged 46. Clinical history: In August 1953 a painless swelling was noticed behind the left ear. Signs of facial paralysis developed in November 1953. Operation in February 1954.

Microscopic diagnosis:
Mixed tumour with a pattern suggestive of adenocarcinoma and in part indicating squamous cell carcinoma; local infiltrative growth into the surrounding tissue.

The patient received postoperative X-ray treatment (2000 R air dose in 11 days). In March 1955 he was re-admitted because of increasing neurological disturbances.
The patient died on 25 March 1955.

Postmortem findings:
Squamous cell carcinoma originating from the left parotid gland, growing subperiostally into the sulcus transversus ossis occipitalis and into the left hemisphere of the cerebellum; tentorial herniation, haemorrhagic bronchopneumonia and primary tuberculosis of the upper lobe of the left lung.

Case 55/...

Woman aged 71. Clinical history: In November 1955: operation for a tumour on the left side of the face.

Microscopic diagnosis:
Mixed tumour with predominance of markedly pleomorphous epithelial structures, incompletely encapsulated.

A recurrent tumour was excised in September 1956. Another recurrence was excised in February 1957.

Microscopic diagnosis: Identical findings as before.
When seen in June 1957, the patient complained of severe pain in the thoracic spine. X-rays revealed metastases in the thoracic vertebrae. A neurosurgical operation was done in June 1957. In August 1957 the patient had a manifest Brown-Sequard syndrome, localized at the level of Th. 6. Myelographic examinations showed a block at this level, due to an extradural tumour. The metastatic tumour was then removed. After this operation the patient's general condition gradually deterioated, and death occurred on 18th October 1957.

Case 55/3203

Man aged 75. Clinical history: Complaints of hypersalivation in July 1955, with signs of facial paralysis on the right side. Further complaints of neuralgia in the right side of the face. Examination disclosed a small tumour measuring 35 × 10 mm. in the right submandibular region. No enlarged lymp nodes were palpated. The tumour was removed on 9th September 1955.

Microscopic diagnosis:
Mixed tumour with predominance of markedly pleomorphous epithelial structures, mitosis, infiltrative growth into the capsule and surrounding tissue: carcinoma.

The patient was treated by X-ray irradiation (3900 R air dose in 15 days) postoperatively.

In March 1956: palpable lymph nodes on the right side of the neck; X-ray irradiation (3000 R air dose in 11 days). In September 1956: increase in the number of palpable lymph nodes on the right side and also palpable lymph nodes on the left side of the neck.

In January 1957: progression. No treatment was given.

The patient died on 20th January 1957.

Case 57/5716

Man aged 57. Clinical history: A right parotid tumour was extirpated in May 1957.

Microscopic diagnosis:

Mixed tumour with predominance of structures of squamous cell carcinoma. In October 1957 a recurrent tumour was excised, followed by X-ray therapy (dose unknown).

This patient refused further treatment and died from an unknown cause in December 1957.

Case 58/985

Woman aged 76. Clinical history: Since December 1957 there had been a swelling in the right parotid area, without symptoms. Examination disclosed a clinically malignant tumour measuring 6 × 7 cm. In the neck, one enlarged lymph node was palpated, and there was also a subcutaneous swelling which looked like a skin metastasis. A biopsy was taken on 18th March 1958.

Microscopic diagnosis:
Mixed tumour with a pattern of squamous cell carcinoma; no capsule.

The patient was treated by radiotherapy (4000 R air dose in 20 days).

Definite regression was demonstrable. The patient died in August 1958; no conclusive definite evidence of the cause of death was obtained.

Case 58/3189

Woman aged 55. Clinical history: The last 6 weeks a painless swelling behind the right ear. Examination revealed a clinically benign tumour (3 × 3 cm.) behind the right ascending ramus of the mandible; no enlarged lymph nodes were palpated. The tumour was removed.

Microscopic diagnosis:
Extremely pleomorphous cellular mixed tumour with sarcomatoid structures; infiltrative growth into the surrounding tissue.

Postoperatively, the patient received X-ray therapy (3600 R air dose in 20 days).
Physical examination in December 1959 disclosed a recurrence.

X-rays of the mandible showed sequestration. In July 1960: severe pains, vomiting, hepatomegaly and deterioration of the general condition.

The patient died on 9th August 1960.

Postmortem findings:
Lymphogenous metastases in the paratracheal, parabronchial and bronchopulmonary lymph nodes; pericanalicular spread to the right lower lobe

of the lung with carcinomatous pleurisy. Metastases in the lymph nodes along the portal vein and haemogenous metastases in the liver and adrenal glands.

Microscopic diagnosis of the metastases: Very cellular mixed tumour with areas of undifferentiated adenocarcinoma.

Case 58/2625

Man aged 52. Clinical history: Since 8 weeks a swelling behind the mandibular angle; three months previously a similar swelling had been noticed, which disappeared spontaneously. Examination disclosed a tumour of questionable malignancy underneath the right earlobe; no enlarged lymph nodes were palpated. Operation on 5th November 1958.

Microscopic diagnosis:
Mixed tumour with structures of squamous cell carcinoma.

Postoperative X-ray therapy totalled 4000 R (air dose) in 26 days.

A recurrent tumour was excised in April 1959, with subsequent Telecobalt therapy (5500 R tumour dose in 25 days).

In July 1959 the patient was hospitalized because of vomiting and abdominal pain. A mass was palpated in the upper abdomen. There was also protrusion of the right eye, probably due to retrobulbar tumour invasion.

The patient died on 7th October 1959.

Ackerman, L. V. (1943): Oncocytoma of the parotid gland. Arch. Path. 36, 508.
Ackerman, L. V. and del Regato, J. A. (1962): Cancer. 3rd. ed. The C. V. Mosby Co. St. Louis.
Agner, O. and Nielsen, K. (1956): Spytkirtelblandningstumores. Ugeskr. Leag. 118,121.
Ahlbom, H. E. (1935): Mucous- and salivary gland tumours. Acta Radiol. Suppl. 23.
Albertini, A. v. (1955): Histologische Geschwulstdiagnostik. Georg Thieme, Stuttgart.
Albrecht, H. and Arzt, L. (1910): Papilläre Cystadenome in Lymphdrüsen. Frankfurt Z. Path. 4,47.
Ariel, I. M., Jerome, A. P. and Pack, G. T. (1954): Treatment of tumours of the parotid salivary gland. Surgery 35,124.
Armknecht, W. (1906): Heilungsergebnisse beim lippenkrebs. Ein Beitrag zur Technik der Radicalen Lymphdrüsenextirpation. Dtsch. Z. Chir. 85,641.
Ash, C. L. and Millar, O. B. (1955): Radiotherapy of cancer of the tongue and floor of the mouth. Amer. J. Roentgenol. 73,611.
Aub, J. C., Evans, R. D., Hempelmann, L. H. (1952): Late effects of internally deposited radioactive materials in man. Medicine 31,221.
Aust, J. B., Griffen, W. A. and Ausman, R. K. (1959): Isolated perfusion of head and neck tumours. Society of Head and Neck Surgeons, Washington D. C.
Azzopardi, J. G. and Smith, O. D. (1959): Salivary gland tumours and their mucins. J. Path. Bact. 77,131.

Baclesse, F. (1940): Radiosensibilité et metastases observées au cours de l'evolution des cylindromes. Bull. Ass. franc. Cancer 41,260.
Baclesse, F. (1946): Les metastases et la radiosensibilité des cylindromes et des tumeurs des glandes salivaires. Rev. Stomat. (Paris) 47,469.
Bailey, H. (1941): The treatment of tumours of the parotid gland with special reference to total parotidectomy. Brit. J. Surg. 28,337.
Bain, G. O., Kowalewski, K. P. and Mac Gregor, J. W. (1956): Mixed tumours of the salivary glands. Acta gastro-ent. Belg. 19,70.
Barclay, T. H. C., Peltier, L. F. and Kramer, A. J. (1951): Neck dissections in the treatment of cancer of the head and neck; an analysis of 221 patients. Ann. Surg. 143,328.
Batsakis, J. G. and Martz, D. G. (1960): Oxyphil cell tumour of submaxillary gland. U.S. armed Forces med. J. 11,1383.
Baud, J. (1950): End results of radiotherapy of cancer of the tongue. Amer. J. Roentgenol. 63,701.
Bauer, W. H. and Bauer, J. O. (1953): Classification of glandular tumours of salivary glands. Arch. Path. 55,328.
Bauer, W. H. and Byrne, J. J. (1950): Induced tumours of the parotid gland. Cancer Res. 10,755.
Bauer, W. H. and Fox, R. A. (1945): Adenomyoepithelioma (cylindroma) of palatal mucous glands. Arch. Path. 39,96.

Beahrs, O. H., Devine, K. D. and Henson, S. W. (1959): Treatment of carcinoma of the tongue. End results in 168 cases. Arch. Surg. 79,399.
Beahrs, O. H. and L'Esperance, B. F. (1956): The facial nerve in parotid surgery. J. Amer. med. Ass. 162,261.
Beahrs, H. O., Woolner, L. B., Carveth, S. W. and Devine, K. D. (1960): Surgical management of parotid lesions. Review of 760 cases. Arch. Surg. 80,899.
Benedict, E. G. and Meigs, J. V. (1930): Tumours of the parotid gland. Surg. Gynec. Obstet. 51,626.
Bérard, A. (1841): Des operations que reclament les tumeurs developpées dans la regin parotidienne. Thesis Paris.
Berdal, P. and Mylius, E. (1954): Cylindromas of respiratory tract, uper part of digestive tract and adjoining organs. Acta oto-laryng. (Stockh.) Suppl. 118,32.
Berkson, J. (1942): The calculation of survival rates. W. B. Saunders & Co., Chapter XXII.
Bhaskar, G. N. and Bernier, J. L. (1960): Mikulicz's disease; clinical features, histology and histogenesis; report of 73 cases. Oral Surg. 13,1387.
Billroth, T. (1859): Beobachtungen über Geschwülste der Speicheldrüsen. Virchows Arch. path. Anat. 17,357.
Blady, J. V. and Harwick, R. D. (1964): Analysis of radical neck dissections in the treatment of cervical metastases. Amer. J. Surg. 108,465.
Botsztejn, Ch. (1949): Geschwülste der Parotisregion. Zürcher Erfahrungen bei 64 Fällen. Oncologia (Basel) 2,133.
Braambergh, H. S. (1829): De extirpatione glandulae parotidis et submaxillaris. Thesis Groningen.
Broca, P. P. (1875): Sarcome parotidien. Propagation par une veine et un nerf, repullulation rapide dans les poumons et dans le foie. Bull. Ass. franç. Anat. p. 814.
Brown, J. B. and Blair, V. P. (1933): The treatment of cancerous or potentially cancerous cervical lymph nodes. Ann. Surg. 98,650.
Brown, J. B. and McDowell, F. (1944): Neck dissections for metastatic carcinoma. Surg. Gynec. Obstet. 79,115.
Bruzelius, S., Cederquist, E., Linell, F. and Bergman, F. (1957): Tumours of the parotid gland. A histological study and results of combined surgical and radiological treatment. Acta chir. scand. 114,1.
Buxton, R. W., Maxwell, J. H. and French, A. J. (1953): Surgical treatment of epithelial tumours of the parotid. Surg. Gynec. Obstet. 97,401.
Byars, L. T. (1952): Preservation of the facial nerve in operations for benign conditions of the parotid area. Ann. Surg. 136,412.

Cade, S. (1952): Discussion of the treatment of cervical metastatic cancer. Proc. roy. Soc. Med. 45,757.
Calhoun, N. R. (1963): Lipoma of buccal space. Oral Surg. 16,246.
Carroll, W. W. (1947): Principles involved in surgical therapy of encapsulated fibrosarcoma of soft tissues. Surg. Gynec. Obstet. 84,703.
Castigliano, S. G. and Gold, L. B. (1954): Intraductal papilloma of hard palate. Oral Surg. 7,232.
Chassman, L. R. Robertson, D. C. and Fanner, A. W. (1957): Irradiation sarcoma. Plast. reconstr. Surg. 20,55.
Chaudhry, A. P., Vickers, R. A. and Gorlin, R. J. (1961): Intra-oral minor salivary glands. Oral Surg. 14,1194.
Clarke, T. H. (1952): Parotid gland tumours. Surg. Clin. N. Amer. 32,175.
Conerly, D. B. and McSwain, (1954): Mixed tumours of the salivary glands. Amer. Surg. 20,844.
Conley, J. and Sebastian, A. (1963): Parotid gland as a focus of metastasis. Arch. Surg. 87,757.

Conley, J. J. (1957): Surgical management of tumours of the parotid gland. Trans. Amer. Acad. Ophthal. Otolaryng. 61,499.
Corridan, M. (1956): Glycogen rich clear cell adenoma of the parotid gland. J. Path. Bact. 72,623.
Cox, H. T. (1941): The cleavage lines of the skin. Brit. J. Surg. 29,234.
Cramer, H. and Gummel, H. (1951): Richtlinien für die Früherkennung, Behandlung und Vorbeugung von bösartigen Geschwülsten in tabellarischen Form. Strahlentherapie 85,401.
Creech, O., Krementz, E. T., Ryan, R. T., Reemtsma, K., Winblad, J. N. and Ellioth, R. T. (1959): Treatment of cancer by perfusion. Arch. Surg. 79,963.
Crile, G. (1906): Excision of cancer of the head and neck with special reference to the plan of dissection based on 132 operations. J. Amer. Med. Ass. 47,1780.
Cross, J. E., Guralnick, E. and Daland, E. M. (1948): Carcinoma of the lip. Surg. Gynec. Obstet. 87,153.

Daly, J. F. (1959): Papillary cystadenoma lymphomatosum of the parotid gland. Laryngoscope (St. Louis) 69,1040.
Dancot, H. (1954): Les cylindromas des glandes salivaires et leur traitement. Acta oto-rhino-laryng. belg. 7,591.
Dargent, M. (1952): Definitions et principes du traitement des tumeurs primitives malignes des glandes salivaires. Acta Un. int. Cancr. 8,359.
De, M. N. and Tribedi, B. P. (1939): A mixed epidermoid and mucus-secreting carcinoma of the parotid gland. J. Path. Bact. 49,432.
Del Regato, J. A. (1958): Discussion of paper of roentgentherapy of carcinoma of the lip. Radiology 51,717.
DesPrez, J. D., Kiehn, C. L., Benson, J. W. (1964): Combination of surgery and chemotherapy in the treatment of oral cancer. Amer. J. Surg. 108,583.
Dockerty, M. B. and Mayo, C. W. (1942): Primary tumours of the submaxillary gland with special reference to mixed tumours. Surg. Gynec. Obstet. 74,1033.
Dolbeau, H. (1858): Des tumeurs cartilagineuses de la parotide et de la region parotidienne. Gax. Hebd. Med. et d. Chir. Paris.
Duguied, P. H. (1829): De l'extirpation de la squirrheuse. Thesis Paris.
Dunet, Ch. and Creyssel, J. (1933): Cancers des glandes salivaires. G. Doin et Cie. Paris.
Duplessis, D. J. (1951): Mixed salivary gland tumours. Thesis University of Johannesburg.
Durrani, K. M. (1964): Malignant mixed tumours of the submaxillary salivary gland. Plast. reconstr. Surg. 33,237.

Eddey, H. H. (1951): Subtotal parotidectomy for mixed salivary tumour. Aust. N. Z. J. Surg. 21,13.
Edvall, C. A. (1954): Mucous- and salivary gland tumours. Acta chir. scand. 107,313.
Efremow, W. (1925): Primäres Lymphosarkom der Parotis. Beitr. path. Anat. 73,486.
Eisenbud, L. and Kotch, R. (1954): Hodgkin's 'sarcoma' of the cheek. Report of a case. Oral Surg. 7,213.
Eneroth, C. M. (1964): Histological and clinical aspects of parotid tumours. Acta oto-laryng. (Stockh.) suppl. 191.

Fischel, E. (1935): Unilateral Block Resection of Lymph nodes of the neck for carcinoma. Amer. J. Surg. N. S. 30,27.
Foote, F. W. and Frazell, E. L. (1954): Tumours of the major salivary glands. Atlas of Humour Pathology, Sect. IV, Fasc. 11. Armed Forces Institute of Pathology, Washington, D.C.

Fox, N. M., Remine, W. H. and Woolner, L. B. (1963): Acinic cell carcinoma of the major salivary glands. Amer. J. Surg. 106,860.
Fraser, C. G. (1951): A more plastic incision for radical neck dissection. Plast. reconstr. Surg. 8, 465.
Frazell, E. L. (1954): Clinical aspects of tumours of the major salivary glands. Cancer (Philad.) 7, 637.

Garcia, T. F. (1952): Essential points in the diagnosis and management of malignant lumps in the neck. Acta med. philipp. 9,41.
Gaston, E. A. and Tedeschi, C. G. (1946): Adenolymphoma of the parotid and submaxillary gland. Ann. Surg. 123,1075.
Gilman, R. A., Schwartz, M. and Gilman, J. S. (1956): Fatty infiltration of the parotid gland. Report of a case simulating a tumour. J. Amer. med. Ass. 160,48.
Gladstone, W. S. and Kerr, H. D. (1958): Epidermoid carcinoma of the lower lip. Amer. J. Roentgenol. 79,101.
Gläser, A. (1962): Die Geschwülste der Kopfspeicheldrüsen. VEB Verlag Volk und Gesundheit, Berlin.
Glucksman, A. and Cherry, C. P. (1962): The induction of adenomas by irradiation of salivary glands of rats. Radiat. Res. 17,186.
Godwin, J. T. and Dew, J. H. (1958): Fatty infiltration of parotid glands. Report of a case. Arch. Surg. 76,525.
Godwin, J. T., Foote, F. W. and Frazell, E. (1954): Acinic cell adenocarcinoma of the parotid gland. Amer. J. Path. 30,465.
Grage, Th. B., Lober, P. H. and Shahon, B. B. (1961): Benign tumours of the major salivary glands. Surgery 50,625.
Gray, J. M., Hendrix, R. C. and French, A. J. (1963): Mucoepidermoid tumours of salivary glands. Cancer (Philad.) 16, 183.
Greene, G. W. and Bernier, J. L. (1961): Primary malignant melanomas of the parotid gland. Oral Surg. 14,108.
Gricouroff, G. (1953): Interpretation et classifaction des tumeurs des glandes salivaires. Acta Un. int. Cancr. 9,840.
Grisham, E. (1952): Histochemical analysis of mucopolysaccharides occuring in mucous producing tumours. Cancer (Philad.) 5,700.
Grobstein, C. (1955): Tissue interactions in the morphogenesis of mouse embryonic rudiments in vitro. Aspects of synthesis and order in growth. Princeton Univ. Press, Princeton.
Guttierez, V. (1952): Tumour maligno de la parótidea extirpado conservando el nervio facial. Rev. Cir., B. Aires 15,288.

Hamilton, R. S., Leopold, J. H. (1959): Lymphosarcoma of lacrimal and salivary glands. Amer. J. Ophthal. 47,859.
Hamperl, H. (1962): Benign and malignant oncocytoma. Cancer (Philad.) 15,1019.
Hanford, J. M. (1931): Branchiogenic adenoma of the neck. Ann. Surg. 94,461.
Harrison, K. (1956): Study of ectopic mixed salivary tumours. Hunterian lecture. Ann. roy. Coll. Surg. England 18,99.
Hartz, P. H. (1946): Development of sebaceous glands from intralobular ducts of the parotid gland. Arch. Path. 41,651.
Hatziotis, J. and Asprides, Ch. (1964): Primary lymphosarcoma of the submaxillary salivary gland. Oral Surg. 17,503.
Hellner, H. (1962): Die Behandlung der Parotis geschwülste. Chirurg 33,152.
Henke, F. and Lubarsch, O. (1924—1939): Handbuch der speziellen pathologischen Anatomie und Histologie. Springer, Berlin.
Hilderman, W. C., Gordon, J. S., Large, H. L. and Carrol, C. F. (1962): Malignant lymphoepithelial lesion with carcinomatous component apparently arising in parotid gland. A malignant counterpart of benign lymphoepithelial lesion? Cancer (Philad.) 15,606.

Hintze, A. (1934): Gutartige und bösartige Parotisgeschwülste und ihre Heilungsmöglichkeiten. Langenbecks Arch. klin. Chir. 180,606.
Hoffman, E. (1960): Branchial cysts within the parotid gland. Ann. Surg. 152,290.
Huffman, W. C. and Lierle, D. M. (1953): Neck dissections. Plast. reconstr. Surg. 11,115.
Hunter, R. (1954): Conservative surgical treatment of mixed tumours of parotid. Brit. J. Surg. 41,435.

James, A. G. and Piatt, B. J. (1953): Radical neck surgery; clinical considerations and nursing care. Amer. J. Nursing 53,930.
Janes, R. M. (1940): Treatment of tumours of salivary glands by radical excision. Canad. med. Ass. J. 43,554.
Johnson, J. K. and Childers, J. H. (1954): Tumours of the salivary glands. Tex. Rep. Biol. Med. 12,979.
Jones, A. (1953): Irradiation sarcoma. Brit. J. Radiol. 26,273.
Judd, E. S. and Beahrs, O. H. (1949): Epithelioma of the lower lip. Evaluation of dissection of cervical lymph nodes. Arch. Surg. 59,422.
Jüngling, H. (1949): Allg. Strahlentherapie. Stuttgart.

Kepp, R. (1952): Grundlagen der Strahlentherapie. Stuttgart.
Kidd, H. A. (1950): Complete excision of parotid gland with preservation of the facial nerve. Brit. Med. J. 1,989.
Kirklin, J. W., McDonald, J. R., Harrington, S. W. and New, G. B. (1951): Parotid tumours. Histopathology, clinical behaviour and end results. Surg. Gynec. Obstet. 92,721.
Klippel, A. and Eckert, C. (1958): Suprahyoid neck dissection for epidermoid carcinoma of the lower lip. Amer. Surg. 24,197.
Kolar, J., Vrabec, R. and Kral, Z. (1959): Ueber Sarkombildung in der Strahlenbeschädigten Haut. Fortschr. Röntgenstr. 91,312.
Kraissl, C. J. and Conway, H. (1949): Excision of small tumours of the skin of the face with special reference to the wrinkle lines. Surgery 25,592.
Krompecher, E. (1908): Ueber die Beziehungen zwischen Epithel und Bindgewebe bei den Mischgeschwülsten der Haut und der Speicheldrüsen und über das Eustehen der Karzinosarkoma. Beitr. path. Anat. 44,88.
Kyll, J. B. (1822): De induratione et extirpatione glandula parotidis. Thesis Bonn.

Lang, F. J. (1929): Pathologische Anatomie der groszen Kopfspeicheldrüsen. Handbuch der spez. pathol. Anatomie und Histologie V/2, ed. Henke, F. and Lubarsch, O. Berlin, Springler-Verlag, Vol. 5, PT. 2, p. 1.
Langer, K. (1861): Ueber die spaltbarkeit der cutis. Sitzungsb. d.k. Akad. D. Wissensch. Math.-Naturw. Kl. 43,233.
Lathrop, F. D. (1953): The facial nerve; technique of exposure and repair. Surg. Clin. N. Amer. 33,909.
Lebert (1845): quoted by Dunet and Creyssel.
Lederman, M. (1943): Mucous- and salivary gland tumours. Brit. J. Radiol. 16,383.
Linell, F. (1948): Mucus-secreting and cystic epidermoid carcinomas of the mucous- and salivary glands. Acta path. microbiol. scand. 25,801.
Lyle, F. M. (1956): Surgical consideration of parotid tumours. Amer. J. Surg. 91,332.

Mac Cune, W. S. (1951): Total parotidectomy in tumours of the parotid gland. Arch. Surg. 62, 715.
Mac Farland, J. (1926): Ninety tumours of the parotid region. Amer. J. med. Sci. 172,804.
Mac Farland, J. (1927): Adenoma of the salivary gland. With report of a possible case. Amer. J. med. Sci. 174,362.

Mac Farland, J. (1930): Congenital capillary angioma of the parotid gland. Arch. Path. 9,820.
Mac Fee, W. F. (1960): Transverse incisions for neck dissections. Ann. Surg. 151,279.
Mannino, R. (1950): Sopra un caso di linfosarcoma della parotide. Oncologia (Basel) 3,45.
Marcial-Rojas, R. A. and Sommers, S. C. (1954): Differentiated mucoepidermoid tumours of salivary glands. Arch. Otolaryng. 59,135.
Margolies, A. and Weidman, F. (1921): Statistical and histologic studies of Fordyce 's disease. Arch. Derm. Syph. (Chic.) 3,723.
Marshall, S. F., Miles, G. O. (1947): Tumours of maxillary and parotid gland areas. Surg. Clin. N. Amer. 27,501.
Martin, H. (1941): The treatment of cervical metastatic cancer. Ann. Surg. 114,972.
Martin, H. (1948): Cancer of the head and neck. J. Amer. med. Ass. 137,1306.
Martin, H. (1957): Surgery of head and neck tumours. Paul B. Hoeber Inc., New York.
Martin, H. E., Del Valle, B., Ehrlich, H. and Cahan, W. G. (1951): Neck dissection. Cancer (Philad.) 4,441.
Martin, H., Mac Comb, W. S. and Blady, J. V. (1941): Cancer of the lip. Ann. Surg. 114,226.
Masson, P. (1922): Polarité cellulaire et structure des tumeurs paradoxales. Bull. Ass. franç. Cancer 11,345.
Masson, P. (1924): Tumeurs des glandes annexes des muqueuses de la face et du cou. Atlas du Cancer III et IV. Ed. d. l'Ass. Fr. d. Cancer.
Masson, P. and Berger, L. (1924): Epitheliomas á double métaplasie de la parotide. Bull. Ass. franç. Cancer 13,366.
Mathis, H. (1954): Die Erkrankungen der Speicheldrüsen. Carl Hanser, München.
Meinsma, L. (1965): Resultaten behandeling kankerpatienten 1956-1958. Uitgave Stichting 'Landelijke Organisatie voor de Kankerbestrijding'.
Mettler, H. (1956): Das sezernierende Epitheliom der groszen Speicheldrüsen und der bukkalen und parabukkalen Schleimdrüren. Pract. oto-rhino-laryng. (Basel) 18,99.
Meza-Chávez, L. (1949): Oxyphilic granular cell adenoma of the parotid. Report of 5 cases and study of oxyphilic granular cells (oncocytes) in normal parotid glands. Amer. J. Path. 25,523.
Mikulicz, J. (1892): Ueber eine einartige symmetrische Erkrankung der Thränen- und Mundspeicheldrüsen. Beitr. z. Chir. Festschr. f. Theodor Billroth, p. 610.
Mohs, F. E. (1949): Chemosurgical treatment of tumours of the parotid gland. Ann. Surg. 129,381.
Montant, R. and Sarasin, R. (1947): Réflexions sur les tumeurs de la parotide. Schweiz med. Wschr. 77,1223.
Morehead, R. P. (1962): The pathological basis for the treatment of epithelial tumours of salivary glands. Laryngoscope (St. Louis) 72,1007.
Morfit, H. M. (1952): Simultaneous Bilateral Radical Neck Dissection. Surgery 31,216.
Morfit, H. M. (1955): Retromandibular parotid tumours. Arch. Surg. 70,906.
Morgan, W. S. and Castleman, B. (1953): A clinico-pathologic study of Mikulicz's disease. Amer. J. Path. 29,471.
Moser, F. (1954): Zur operativen Behandlung der Parotis geschwülste. Z. Laryng. Rhinol. 33,195.
Moss, W. T. (1959): Therapeutical radiology. St. Louis. The C. V. Mosby Co.
Moyse, M. P. (1955): A propos de 200 tumeurs parotidiennes opérées. Mém. Acad. chir. (Paris) 81,999.
Mylius, E. A. (1960): The identification and the role of the myoepithelial cell in salivary gland tumours. Oslo University Press, Oslo.

Naumann, H. (1958): Ueber Zylindrome. Z. Laryng. Rhinol. 37,92.

Oota, K. and Takahashi, N. (1958): Electron microscopic studies on the so-called benign mixed tumour of the salivary gland. Gann. 49,234.
Orloff, M. J. (1956): Benign epitheliolymphoid lesions of the parotid gland, papillary cystadenoma lymphomatosum and Mikulicz's disease. Surg. Gynec. Obstet. 103,521.

Patey, D. H. (1954): The present position of parotidectomy in the surgery of the parotid gland. Arch. Middx. Hosp. 4,91.
Perruchio, P. (1950): Parotidectomie totale avec conservation du facial pour tumeur mixte. Bordeaux chir. 2,64.
Perzik, S. L. (1958): Diagnosis and management of parotid tumours. Arch. Otolaryng. 67,319.
Pettit, V. D., Charmers, J. T. and Ackerman, L. V. (1954): Fibromatosis and fibrosarcoma following irradiation therapy. Cancer (Philad.) 7,149.
Pfeiffer, K. (1963): Ueber die Boecksche Erkrankung der Kopfspeicheldrüsen, zugleich ein Beitrag zur Analyse des Mikulicz-syndroms. Der Radiologe, 3,165.
Pressman, J. J. (1955): Extended retrohyoid radical neck dissection for malignant tumours of the oral cavity and neck. Trans. Amer. Acad. Ophthal. Otolaryng. 59,366.
Pricolo, V., Di Pietro, S. and Catania, C. V. (1954): I tumori della parotide e la loro terapia. Tumori 40,333.

Quattlebaum, F. W. Dockerty, M. B. and Mayo, C. W. (1946): Adenocarcinoma cylindroma type of the parotid gland. Surg. Gynec. Obstet. 82,342.
Quick, D. A. and Johnson, F. M. (1922): Radium treatment of parotid tumours. N. Y. St. J. Med. 22,297.

Ragnell, A. (1954): The tensibility of the skin; an experimental investigation. Plast. reconstr. Surg. 14,317.
Rauch, S. (1959): Die Speicheldrüsen des Menschen. Georg Thieme, Stuttgart.
Rauch, S. and Maszhoff, W. (1958): Sialomata with a sebaceous gland-like structure. Frankfurt Z. Path. 69,513.
Rawson, A. J. and Horn, R. C. (1950): Sebaceous gland containing tumours of the parotid gland. Surgery 27,93.
Rawson, A. J., Howard, J. M., Royster, H. P. and Horn, R. C. (1950): Tumours of the salivary glands. A clinicopathologic study of 160 cases. Cancer (Philad.) 3,445.
Redon, H. (1942): Remarques sur le traitement des tumeurs mixtes. Mém. Acad. Chir. 68,338.
Redon, H. (1960): Traitement des cancers de la parotide. Fortschr. Kiefer-u. Gesichtschir. 6,222.
Ribbert, M. W. H. (1907): Ueber des Zylindrom. Dtsch. med. Wschr. 33,126.
Richard (1856): quoted by Dunet and Creyssel.
Richards, G. E. (1942): Treatment of cancer of the tongue. Amer. J. Roentgenol. 47,191.
Riessner, D. (1952): Surgical procedure in tumours of the parotid gland. Preservation of facial nerve and preservation of postoperative fistulas. Arch. Surg. 65,831.
Ringertz, N. (1938): Pathology of malignant tumours arising in the nasal and paranasal cavities and maxilla. Acta oto-laryng. (Stockh.) suppl. 27.
Rodriquez, A. (1942): Complimentary extirpation of lymph glands. Critical study. Indications and technique. Arch. Path. 14,71.
Roos, D. B., Byars, L. T. and Ackerman, L. V. (1956): Neurilemomas of the facial nerve presenting as parotid gland tumours. Ann. Surg. 144,258.
Ross, D. E. (1955): Salivary gland tumours. Thomas, Springfield.
Ross, D. E. (1954): Parotid tumours. West. J. Surg. 62,462.
Russell, H. (1955): Adenomatous tumours of anterior foregut region showing cylindroma pattern. Brit. J. Surg. 43, 248.

Sabanas, A. O., Dahlin, D. C., Childs, D. S. and Irvins, J. C. (1956): Postradiation sarcoma of bone. Cancer (Philad.) 9,528.
Sako, K., Marchetta, F. C. and Pichrer, J. W. (1963): Fallability of palpation in the diagnosis of metastases to cervical nodes. Amer. J. Surg. 106,797.
Schafer, E. L., Gruet, M. and Jackson, A. S. (1956): Oncocytic cell adenoma of the parotid gland. Amer. J. Surg. 91,272.
Schaper, A. and Cohen, C. (1905): Beiträge zur Analyse des thierischen Wachstums. Ueber zell proliferatonische Wachstumzentren und deren Beziehungen zur Regeneration und Geschwulstbildung. Wilhelm Roux' Arch. Entwickl.-Mech. Org. 19,348.
Schilling, F. (1921): Beitrag zur Kenntnis der Parotisgeschwülste. Beitr. path. Anat. 68,139.
Schobinger, R. (1957): The use of a long anterior skin flap in radical neck dissections. Ann. Surg. 146,221.
Seifert, G. and Geiler, G. (1956): Zur Pathologie der Kindlichen Kopfspeicheldrüsen. Beitr. path. Anat. 116,1.
Semken, G. H. (1932): Surgery of the neck. Nelson New Loose-Leaf Surgery, Vol. 2, Ch. 14, p. 763.
Sharp, G. S. and Helsper, J. T. (1960): Salivary gland tumours. Calif. Med. 93,187.
Sheldon, W. H. (1943): So-called mixed tumours of the salivary glands. Arch. Path. 35,1.
Sidahara, G. (1937): Ein operativ geheilter Fall von Lymphosarkom der Parotis. Gann 31,41.
Siebold, Ch. G. (1793): Dissertatio de squirrho parotidis, Marburg.
Siebold, J. B. (1797): Historia systematis salivalis physiologica et pathologica considerata accessoria ex eadem doctrina corrolaris chirurgica. Jena.
Sinclair, W. J. (1951): Pleomorphic adenoma and adenocarcinoma of parotid gland. Northw. Med. (Seattle) 50,852.
Skorpil, F. (1939): Ueber die Lymphoepithelioma der Speicheldrüsen. Frankfurt Z. Path. 53,450.
Skorpil, F. (1940): Ueber das Speicheldrüsenadenom. Virchows Arch. path. Anat. 306,714.
Slaughter, D. P. (1955): Neck dissection: Complications and safeguards. Surg. Clin. N. Amer. 35,31.
Slaughter, D. P., Southwick, H. W. and Walter, L. (1953): Parotid gland tumours. A report of 212 cases. Surg. Gynec. Obstet. 96,535.
Smiddy, F. G. (1956): Treatment of mixed parotid tumours. Brit. Med. J. 1,322.
Smith, M. J. Stenström, K. W. (1949): Parotid tumours. Radiology 52,655.
Speir, E. B. (1952): Indications for radical neck dissection. West. J. Surg. 60,74.
Spies, J. W. (1930): Adenoid cystic carcinoma. Generalized metastases in three cases of basal cell type. Arch. Surg. 21,365.
Stark, D. B. (1959): Congenital tract of neck and ear. Plast. reconstr. Surg. 23,621.
State, D. (1949): Superficial lobectomy and total parotidectomy with preservation of the facial nerve in the treatment of parotid tumours. Surg. Gynec. Obstet. 89,237.
Stein, I. and Geschikter, C. F. (1934): Tumours of the parotid gland. Arch. Surg. 28,492.
Stewart, C. B. and Pendugrast, W. J. (1951): Fibrosarcoma developing in heavily irradiated skin. J. med. Ass. Ga. 40,24.
Stewart, F. W. (1933): Radiosensitivity of tumours. Arch. Surg. 27,979.
Stewart, F. W., Foote, F. W. and Becker, W. F. (1945): Muco-epidermoid tumours of salivary glands. Ann. Surg. 122,820.
Stöhr, F. and Risak, E. (1926): Zur Klinik und Anatomie der Parotis Geschwülste. Langenbecks Arch. klin. Chir. 143,609.
Stout, A. P. (1948): Fibrosarcoma; the malignant tumour of the fibroblast. Cancer (Philad.) 1,30.

Stijn, R. W. (1958): Chirurgische behandeling van parotis tumoren. Thesis Amsterdam.
Szobolew, L. W. (1912): Zur Kasuistik der Branchinome. Frankfurt Z. Path. 11,462.

Tabah, E. J. (1954): The surgical management of parotid tumours. Canad. med. Ass. J. 71,456.
Tailhefer, A. (1952): Discussion of the treatment of cervical metastatic cancer. Prov. roy. Soc. Med. 45,757.
Thackray, A. C. and Lucas, R. B. (1960): The histology of cylindroma of mucous gland origin. Brit. J. Cancer 14,612.
Thaysen, Th. E. H. (1911): Ueber die Lymphomatosen der Tränen- und speicheldrüsen. Beitr. path. Anat. 50,487.
Therkelsen, F. (1934): Ueber den histologischen Bau der primären Mischgeschwülste in den Speicheldrüsen des Menschen. Acta path. microbiol. scand. 11,275.
Thompson, A. S., Bryant, H. C. (1950): Histogenesis of papillary cystadenoma lymphomatosum (Whartin's tumour) of the parotid salivary gland. Amer. J. Path. 26,241.
Thorek, M. (1949): Modern surgical technic. New York Ed. Lippincott p. 268.
Tonkes, E. (1961): Kanker na bestraling. J. belge Radiol. 44,57.
Trueblood, D. V. (1949): Additional experience with parotid gland tumours. West. J. Surg. 57,463.

Utendorfer, R. W. (1956): Total parotidectomy for mixed tumour. Amer. J. Surg. 91,159.

Vellios, F. and Davidson, D. (1955): The natural history of tumours peculiar to the salivary glands. Amer. J. clin. Path. 25,147.
Vink, M. en Zwaveling, A. (1961): Enkele facetten der hedendaagse kankerchirurgie. Ned. T. v. Geneesk. 106,204.
Virchow, R. (1863): Die krankhaften Geschwülste. Berlin, A. Hirschwald, vol. 1. p. 502.
Ward, G. E., Edgerton, M. T., Chambers, R. G. and McKee, D. M. (1959): Cancer of the oral cavity and pharnynx and results of treatment by means of the composite operation. Ann. Surg. 150,202.
Ward, G. E. and Hendrick, J. W. (1950): The diagnosis and treatment of tumours of the head and neck. Baltimore, Williams & Wilkins Co., p. 730.
Warren, S. and Sommer, G. N. J. (1936): Fibrosarcoma of the soft parts; with special reference to recurrence and metastasis. Arch. Surg. 33,425.
Watson, W. L. (1951): Radical surgery for head and neck cancer. N. Y. St. J. Med. 51,2631.
Weatherford, H. L. (1944): A textbook of histology. The Blakiston Company, p. 319.
Webster, J. P. (1935): Deforming scars, their cause, prevention and treatment. Penn. med. J. 38,929.
Weille, F. L. (1952): Aural approach to parotid gland. Ann. Otol. (St. Louis) 61,90.
Welti, H. (1955): A propos de 35 tumeurs parotidiennes opérées. Mém. Acad. chir. 81,1007.
Westbroek, D. L. en Zwaveling, A. (1964): Continue intra-arteriële toediening van kankerchemotherapeutica. Ned. T. v. Geneesk. 108,401.
Whartin, A. S. (1929): Papillary cystadenoma lymphomatosum. J. Cancer Res. 13,116.
Wheelock, M. C. and Madden, T. J. (1949): Uncommon tumours of the salivary glands. Surg. Gynec. Obstet. 88,776.
Wieberdink, J. en van Slooten, E. A. (1957): Totale parotidectomie wegens menggezwellen van de oorspeekselklier. Ned. T. v. Geneesk. 101,663.

Willis, R. A. (1953): Pathology of tumours. 2nd. ed. C. V. Mosby Co., St. Louis.
Willis, R. A. (1960): Pathology of tumours, 3rd. ed. C. V. Mosby Co., St. Louis.
Winsten, J. and Ward, G. E. (1957): Mixed tumours of the parotid. Surgery 42,1029.
Woolner, L. B., Pettet, J. R. and Kirklin, J. W. (1954): Muco-epidermoid tumours of major salivary glands. Amer. J. clin. Path. 24,1350.
World Health Organization (1950): Registration of cases of cancer. Expert Committee on Health statistics, 1950 (Technical report series No. 25).

Zimmerman, K. W. (1927). Die Speicheldrüsen der Mundhöhle und die Bauch speicheldrüse; in Möllendorf, W. Handbuch der mikroskopischen Anatomie des Menschen. Springer, Berlin, V. 5., p. 128.

STELLINGEN

1

De nog steeds toegepaste enucleatie methode van de z.g. mengtumor van de glandula parotis moet als obsoleet worden beschouwd.

2

Bij speekselkliertumoren met een hoge graad van maligniteit, verdient het aanbeveling de primaire operatie uit te breiden met een regionaal lymphkliertoilet.

3

Bij de vele maatregelen ter voorkoming van postoperatieve wondinfecties heeft de prophylactische toepassing van antibiotica een omstreden plaats.

4

De meting van de Achillespees reflex is waarschijnlijk het eenvoudigste en betrouwbaarste hulpmiddel bij de controle van schildklierfunctie stoornissen.

Sherman, L. Lancet 1, 243, 1963.

5

Het staat niet vast, dat de veneuze 'by pass' in het femoro-poplitea traject, op den duur veel betere resultaten geeft dan de 'by pass' met alloplastisch materiaal.

6

De prognose van de facialis paralyse van Bell is slechts vast te stellen aan de hand van dagelijks herhaald onderzoek van de elektrische prikkelbaarheid van de zenuw.

Laumans, E. P. J. Arch. Otolaryng. 81, 478, 1965.

7

De in de meeste handboeken beschreven relatie tussen de rechter N. phrenicus en het diaphragma moet als onjuist beschouwd worden. De zenuw vertakt zich nl. niet onder maar boven het diaphragma.

Scott, R. Thorax 20, 357, 1965.

8

Bij het verlenen van hulp aan de West-Indische Rijksdelen moet hetzelfde beginsel gelden als t.a.v. andere ontwikkelde landen.

9

De rechtsverhouding zoals neergelegd in het Statuut voor het Koninkrijk der Nederlanden is aan herziening toe.

10

Linkshandigheid vormt geen belemmering voor het uitvoeren van operatieve ingrepen.

Behoort bij proefschrift: E. A. MARTIS