



UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

PATHOLOGY OF THE HEAD AND NECK: A RETROSPECTIVE APPRAISAL

WILLEM F.P. VAN HEERDEN MChD, FC Path(SA), PhD

Published work submitted to the University of Pretoria for the degree of
Doctor of Science in Odontology (Oral Pathology)

Promoter: Professor Dr A.J. Ligthelm
Dean
School of Dentistry
Faculty of Health Sciences
University of Pretoria

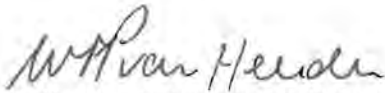
June 2003

Examiners: Professor Dr W.H. Binnie
Dallas, Texas, USA

Professor Dr T. Solheim
Oslo, Norway

DECLARATION

I, the undersigned, declare that the work contained in this presentation of publications is my own original work, as set forth in the statements which precede the published articles, and has not previously in its entirety or in part been submitted at any University for a degree.



WFP VAN HEERDEN

I certify that on the 16 day of July 2003, Willem Francois Petrus van Heerden signed this declaration in my presence.



COMMISSIONER OF OATH

COMMISSIONER OF OATHS DIST. PTA,
Ref. 9/1/B/2 (AE) 21/05/28
PROF JH MEIRING, School of Medicine
U.P. Box 2034, PRETORIA 0001
TEL. (012) 319-2233 / 082 655 6010

DEDICATION

To Marlene, Cherese and Bernice

INTRODUCTION

The author graduated as a dentist (BChD) from the University of Pretoria in 1981 where after he completed his two-year compulsory national military service as a dental officer with the rank of lieutenant. He was stationed at the Maphuta-L-Malatji hospital, a rural hospital in the vicinity of Phalaborwa in the Limpopo province. It was during this period that his interest in Oral Pathology was stimulated. He was exposed to a wide spectrum of tumours and conditions of the head and neck and was fortunate to assist in many surgical procedures. After an eighteen-month period in general private practice in London, UK, he was appointed as registrar in Oral Pathology at the University of Pretoria. This four-year specialization course had laid the foundation for his future academic career. His training in Anatomical Pathology was under the expert guidance of Profs Ian Simson and Leonora Dreyer who were responsible for installing a foundation and passion for histopathology. The author completed his Oral Pathology training under the auspices of Prof At Ligthelm, the then head of Department of Oral Pathology and Oral Biology. He was also fortunate to be exposed to the Oral Pathology training programme at the University of the Witwatersrand under the supervision of Prof Mario Altini. The author completed his MChD degree (*cum laude*) in 1988 and was appointed as specialist/senior lecturer in the Department of Oral Pathology at the Medical University of Southern Africa (Medunsa). He worked at Medunsa with Prof Erich Raubenheimer for 8 years where after he was appointed as head of the Department of Oral Pathology and Oral

Biology, at his Alma Mater, The University of Pretoria. He obtained his PhD degree in 1998.

Oral pathology is the speciality of dentistry and pathology that deals with the nature, identification, and management of diseases affecting the oral and maxillofacial regions. It is a science that investigates the causes, processes and effects of these diseases. The practice of oral pathology includes research, diagnosis of diseases using clinical, radiographic, microscopic, biochemical or other examinations, and management of patients. Oral pathology is one the six specialities officially recognised by the Health Professions Council of South Africa.

Diagnostic histopathology is based on morphological features of the tissues examined. These entail the categorization of cells in the tissue, their morphology as well as their growth pattern. Apart from the standard haematoxylin and eosin staining, the use of histochemical and immunohistochemical techniques are widely used and are still the cornerstones of the diagnostic histopathological process. The rapid advancement in science and technology, especially in the field of molecular techniques, has contributed significantly to our understanding of the disease processes. The use of non-isotopic *in situ* hybridisation (NISH) to detect the presence of possible infective agents, the availability of high resolution DNA flow cytometry for ploidy analyses as well as the numerous applications of the polymerase chain reaction (PCR) are all accessible

techniques that have been used. These developments are reflected in the research profile of the author.

Participation in multi-disciplinary research programmes involving national or international collaboration is an important evaluation criterion in the allocation of research grants. This and the complexity of advanced techniques are reflected in the well-established fact that most research papers nowadays have multiple authors. Joint authorship from one department is also commonplace when such a department has more than one research interest.

The author was fortunate to be associated with outstanding researchers throughout his career. The enthusiasm and guidance received from Prof Erich Raubenheimer have played a valuable role in developing and stimulating his research interest. Their close collaboration is reflected in the number of co-authored publications. Similar collaborations with world authorities in specific fields have also lead to the successful completion of multidisciplinary research projects. The roles of Prof Joerg Hemmer, head of the division of Tumour Biology at the University of Ulm, Germany, with regard to high-resolution flow cytometry and Prof Estrelita van Rensburg, head of the Department of Medical Virology, University of Stellenbosch, with regard to molecular and viral associated research, need to be mentioned.

The papers are grouped into three sections. The first section deals with several studies on squamous cell carcinoma of the head and neck. It includes studies on the clinical presentation of oral cancer, the role of viruses in the development of oral squamous cell carcinoma, the potential of DNA flow cytometry in the management of this disease and the role of certain tumour suppressor genes in the oral carcinogenesis process. Section 2 includes several studies on tooth composition as well as the presentation of selected tumours and cysts of the jaws. Section 3 consists of studies on saliva and salivary gland neoplasms.

ACKNOWLEDGEMENTS

- My parents for their love, encouragement and support.
- My wife, Marlene for her love, support and for the sacrifices she has made towards her career to allow me the opportunity to develop mine.
- My daughter, Bernice for being the motivation to do my best.
- Professors Ian Simson and Leonora Dreyer for being role models in my formative years as an Oral Pathologist.
- Professor Erich Raubenheimer, a colleague and friend, who introduced me to all the aspects of research and with whom I had the privilege of working and co-authored numerous scientific papers.
- Professors Joerg Hemmer and Estrelita van Rensburg for their friendship and valuable contribution towards the development of my academic career.
- My promoter Professor At Ligthelm under whom I qualified as an Oral Pathologist, for his advice and guidance throughout my academic career as well as in the preparation of this presentation.
- All my colleagues throughout my academic career, especially the very competent laboratory staff that I worked with.

SUMMARY

This presentation consists of 52 selected publications that have appeared in national and international peer reviewed journals over the last 14 years (1989 – 2003). The presentation consists of the following headings: Studies on squamous cell carcinoma of the head and neck; dental hard tissues, tumours and cysts of the jaws and saliva and salivary gland neoplasms.

Squamous cell carcinoma of the head and neck

Twenty-three publications are presented in this section. The clinical and histological diagnostic criteria of oral cancer and premalignant lesions, especially aimed at the general practitioner, are discussed. Studies on the role of the Epstein-Barr and human papillomavirus in the pathogenesis of various squamous cell carcinomas of the head and neck region and different patient groups are included. The importance of DNA ploidy in oral carcinoma obtained with high-resolution flow cytometry is described. Valuable information can be obtained with this technique even when using archival paraffin-embedded tissues. Molecular studies, including gene sequencing and protein expression of the p53 suppressor gene as well as the *FHIT* gene, a candidate suppressor gene, were reported. This includes the evaluation of novel antibodies used for Fhit protein expression in oral squamous cell carcinomas.

Dental hard tissues and tumours and cysts of the jaws

In this section, 19 publications are presented. Two publications described the inorganic composition of dentine. The suitability of the sealing ability of a tri-cure glass ionomer material as a retrograde root filling material is illustrated. A unique case of permanent tooth germ injury is reported. A unusual case of amelogenesis imperfecta with multiple impactions associated with tumourous fibrous proliferations is described while a case of papillomavirus infection in an ameloblastoma is documented. The remaining publications include newly described entities as well as exceptional presentations of jaw tumours and cysts. The majority of these publications documented tumours and cysts in a Black African population and described the features seen in neglected and late presentation of these tumours.

Saliva and salivary gland neoplasms

Ten publications are presented in this section that include a study of immunoglobulin concentrations in saliva of multiple myeloma patients as well as the role of salivary glands in vertebrates. The remaining publications describe several aspects of salivary gland neoplasms. These include epidemiological data, diagnostic criteria, the role of DNA flow cytometry and unusual case presentations.

CONTENTS

DECLARATION	i
DEDICATION	ii
INTRODUCTION	iii - vi
ACKNOWLEDGEMENTS	vii
SUMMARY	viii – ix
CONTENTS	x
LIST OF PUBLISHED SUBMISSIONS	xi – xviii
1. Studies on squamous cell carcinoma of the head and neck	
Declaration	1 – 2
Abstract	2 – 12
2. Studies on dental hard tissues and tumours and cysts of the jaws	
Declaration	13 – 14
Abstract	14 – 19
3. Studies on saliva and salivary gland neoplasms	
Declaration	20
Abstract	21 - 25

LIST OF PUBLISHED SUBMISSIONS

SECTION 1: STUDIES ON SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

1. **LIGTHELM AJ, WEBER A, VAN NIEKERK PJ, VAN HEERDEN WFP.** Diagnosis of oral precancer and cancer. *Journal of the Dental Association of South Africa* 1989; suppl: 2-5. **26 - 29**
2. **VAN HEERDEN WFP, SWART TJP.** Oral Cancer. *MIMS Disease Review* 1999; 3: 448-451. **30 - 33**
3. **VAN HEERDEN WFP, BÜTOW K-W.** The role of the dentist in the prevention and early diagnosis of oral cancer. *Journal of the Dental Association of South Africa* 2002; 57: 22-24. ... **34 - 36**
4. **VAN RENSBURG EJ, VAN HEERDEN WFP, RAUBENHEIMER EJ.** Langerhans cells and Human papillomaviruses in oesophageal and laryngeal carcinomas. *IN VIVO* 1993; 7: 229-232. **37 - 40**
5. **VAN RENSBURG EJ, VAN HEERDEN WFP, VENTER EH, RAUBENHEIMER EJ.** Detection of human papillomavirus DNA using in situ hybridisation in oral squamous carcinoma in a rural black population. *South African Medical Journal* 1995; 85: 894-896. **41 - 43**
6. **VAN RENSBURG EJ, ENGELBRECHT S, VAN HEERDEN WFP, RAUBENHEIMER EJ, SCHOUB BD.** Human papillomavirus DNA in oral squamous cell carcinomas in an African population sample. *Anticancer Research* 1996; 16: 969-974. **44 - 48**

7. **POSTMA TC, VAN HEERDEN WFP.** Is the human papillomavirus a mutual aetiological agent in oral and cervical squamous cell carcinoma? *Anticancer Research* 2003; In Press. **49 - 60**

8. **VAN RENSBURG EJ, ENGELBRECHT S, VAN HEERDEN WFP, RAUBENHEIMER EJ, SCHOUB BD.** Detection of EBV DNA in oral squamous cell carcinomas in a black African population sample. *IN VIVO* 1995; 9: 199-202. **61 - 64**

9. **VAN HEERDEN WFP, VAN RENSBURG EJ, ENGELBRECHT S, RAUBENHEIMER EJ.** Prevalence of EBV in oral squamous cell carcinoma in young patients. *Anticancer Research* 1995; 15: 2335-2340. **65 - 69**

10. **VAN DER HOVEN AE, VAN RENSBURG EJ, ENGELBRECHT S, VAN HEERDEN WFP, SWART TJP.** Prevalence of Epstein-Barr virus in nasopharyngeal carcinoma in a South African population sample. *Southern African Journal of Epidemiology and Infection* 2000; 15: 36-39. **70 - 73**

11. **JANSE VAN RENSBURG E, VAN HEERDEN WFP, ROBSON BA, SWART TJP, ENGELBRECHT S.** Epstein-Barr virus strain characterisation in South African patients with nasopharyngeal carcinomas. *Anticancer Research* 2000; 1953-1958. **74 - 78**

12. **VAN HEERDEN WFP, RAUBENHEIMER EJ, LE ROUX R, VAN RENSBURG EJ.** DNA content and histologic grading of oral squamous cell carcinoma. *European Journal of Laboratory Medicine* 1995; 3: 117-120. **79 - 82**

13. **VAN HEERDEN WFP, RAUBENHEIMER EJ, VAN RENSBURG EJ, LE ROUX R.** Lack of correlation of DNA ploidy, Langerhans cell population and grading in oral

- squamous cell carcinoma. *Journal of Oral Pathology and Medicine* 1995; 24: 61-65. 83 - 87
14. **HEMMER J, KREIDLER J, VAN HEERDEN WFP, RAUBENHEIMER EJ, SCHÖN E.** Flow cytometric cellular DNA content and lymph node metastasis in squamous cell carcinoma of the oral cavity. *International Journal of Oncology* 1995; 6: 1237-1242. 88 - 93
15. **HEMMER J, VAN HEERDEN WFP, RAUBENHEIMER EJ, KREIDLER J, SCHÖN E.** Flow cytometric DNA ploidy and recurrence development in squamous cell carcinoma of the oral cavity. *International Journal of Oncology* 1996; 8: 113-116. 94 - 97
16. **HEMMER J, THEIN T, VAN HEERDEN WFP.** The value of DNA flow cytometry in predicting the development of lymph node metastasis and survival in patients with locally recurrent oral squamous cell carcinoma. *Cancer* 1997; 79: 2309-2313. 98 - 102
17. **VAN HEERDEN WFP, DREYER L, SWART TJP, VAN HEERDEN MB, BOY SC.** The suitability of paraffin-embedded material to predict metastatic potential of oral squamous cell carcinoma. *Anticancer Research* 2002; 22: 4147-4150. 103 - 106
18. **VAN RENSBURG EJ, ENGELBRECHT S, VAN HEERDEN WFP, KOTZE MJ, RAUBENHEIMER EJ.** Detection of p53 gene mutations in oral squamous cell carcinomas of a black African population sample. *Human Mutation* 1998; 11: 39-44. 107 - 112
19. **VAN HEERDEN WFP, VAN RENSBURG EJ, HEMMER J, RAUBENHEIMER EJ, ENGELBRECHT S.** Correlation between p53 gene mutation, p53 protein labeling and PCNA expression in oral squamous cell carcinomas. *Anticancer Research* 1998; 18: 237-240. 113 - 116

20. **VAN HEERDEN MB, SWART TJP, VAN HEERDEN WFP.**
Rapid acetone tissue processing: an economical alternative.
Medical Technology South Africa 2000; 14: 320-322. 117 - 119
21. **VAN HEERDEN WFP, SWART TJP, VAN HEERDEN MB,
VAN RENSBURG EJ, ENGELBRECHT S, DREYER L,
HUEBNER K.** Immunohistochemical evaluation of Fhit
protein expression in oral squamous cell carcinomas. *Journal
of Oral Pathology and Medicine* 1999; 28: 433-437. 120 - 124
22. **VAN HEERDEN WFP, SWART TJP, ROBSON B, SMITH T-
L, ENGELBRECHT S, VAN HEERDEN MB, VAN
RENSBURG EJ, HUEBNER K.** *FHIT* RNA and protein
expression in oral squamous cell carcinomas. *Anticancer
Research* 2001; 21: 2425-2428. 125 - 128
23. **VAN HEERDEN WFP, SWART TJP, VAN HEERDEN MB,
PEKARSKY Y, SUTHERLAND R, HUEBNER K.** Fhit protein
expression in oral epithelium: Immunohistochemical
evaluation of three antisera. *Anticancer Research* 2001; 21:
2419-2424. 129 - 133

SECTION 2: STUDIES ON DENTAL HARD TISSUES AND TUMOURS AND CYSTS OF THE JAWS

24. **WEBER A, VAN HEERDEN WFP, VAN DER MEULEN
PM.** Injury to the permanent tooth germ following trauma to
the deciduous predecessor. *Journal of the Dental
Association of South Africa* 1988; 43: 411-413. 134 - 136
25. **VAN HEERDEN WFP, RAUBENHEIMER EJ, DREYER
AF, BENN AML.** Amelogenesis imperfecta: multiple
impactions associated with odontogenic fibroma (WHO)
type. *Journal of the Dental Association of South Africa*

1990; 45: 467-471.	137 - 141
26. VAN HEERDEN WFP, RAUBENHEIMER EJ, DREYER AF. Regional odontodysplasia associated with soft tissue swelling. <i>Hands-On</i> 1991; 3: 23-24.	142 - 143
27. PRETORIUS S, VAN HEERDEN WFP. The use of tricure glass ionomer cement as an apical sealant after apicoectomy. <i>Journal of the Dental Association of South Africa</i> 1995; 50: 367-370.	144 - 147
28. NKHUMELENI FS, RAUBENHEIMER EJ, DAUTH J, VAN HEERDEN WFP, SMITH PD, PITOUT MJ. Amino acid composition of dentine in permanent human teeth. <i>Archives of Oral Biology</i> 1992; 37: 157-158.	148 - 149
29. NKHUMELENI FS, RAUBENHEIMER EJ, VAN HEERDEN WFP, TURNER ML, DREYER MJ. Inorganic contents of opaque and translucent dentine. <i>Journal of Dental Research</i> 1993; 72: 822.	150
30. VAN HEERDEN WFP, RAUBENHEIMER EJ, WEIR RG, KREIDLER J. Giant ossifying fibroma: a clinico-pathologic study of 8 tumors. <i>Journal of Oral Pathology and Medicine</i> 1989; 18: 506-509.	151 - 154
31. RAUBENHEIMER EJ, SEELIGER JE, VAN HEERDEN WFP, DREYER AF. Adenomatoid odontogenic tumour: a report of two large lesions. <i>Dentomaxillofacial Radiology</i> 1991; 20: 43-45.	155 - 157
32. WEBER A, VAN HEERDEN WFP, LIGTHELM AJ, RAUBENHEIMER EJ. Diffuse peripheral odontogenic fibroma - report of 3 cases. <i>Journal of Oral Pathology and Medicine</i> 1992; 21: 82-84.	158 - 160

33. **RAUBENHEIMER EJ, VAN HEERDEN WFP, SITZMANN F, HEYMER B.** Peripheral dentinogenic ghost cell tumor. *Journal of Oral Pathology and Medicine* 1992; 21: 93-95. **161 - 163**
34. **RAUBENHEIMER EJ, VAN HEERDEN WFP, NOFFKE CEE.** Infrequent clinicopathological findings in 108 ameloblastomas. *Journal of Oral Pathology and Medicine* 1995; 24: 227-232. **164 - 169**
35. **VAN HEERDEN WFP, VAN RENSBURG EJ, RAUBENHEIMER EJ, VENTER EH.** Detection of human papilloma virus DNA in an ameloblastoma using the in situ hybridization technique. *Journal of Oral Pathology and Medicine* 1993; 22: 109-112. **170 - 173**
36. **ROOS RE, RAUBENHEIMER EJ, VAN HEERDEN WFP.** Clinico-pathological study of 30 unicystic ameloblastomas. *Journal of the Dental Association of South Africa* 1994; 49: 559-562. **174 - 177**
37. **KREIDLER J, RAUBENHEIMER EJ, VAN HEERDEN WFP.** A retrospective analysis of 367 cystic lesions of the jaw - the Ulm experience. *Journal of Cranio-Maxillofacial Surgery* 1993; 21: 339-341. **178 - 180**
38. **RAUBENHEIMER EJ, KREIDLER J, VAN HEERDEN WFP.** Classification of odontogenic cysts of the jaws. *Dental Update* 1994; 2: 3-6. **181 - 184**
39. **HAUK KS, RAUBENHEIMER EJ, VAN HEERDEN WFP, BUCH B, DREYER AF.** Differential diagnosis of dentigerous like cysts: Clinico-pathologic features of 63 cases. *Journal of the Dental Association of South Africa* 1993; 48: 557-559. **185 - 187**
40. **VAN HEERDEN WFP, RAUBENHEIMER EJ, TURNER**

- ML.** The glandular odontogenic cyst. *Head and Neck* 1992; 14: 316-320. **188 - 192**
41. **VAN HEERDEN WFP, RAUBENHEIMER EJ.** Pigmented neuroectodermal tumour of infancy. *Hands-On* 1992; 4: 9-11. **193 - 195**
42. **BOY SC, DINKEL JE, SWART TJP, VAN HEERDEN WFP.** Epstein-Barr virus prevalence in Burkitt's lymphoma in a South African population sample. *Southern African Journal of Epidemiology and Infection* 2003, In Press. **196 - 209**

SECTION 3: STUDIES ON SALIVA AND SALIVARY GLAND NEOPLASMS

43. **RAUBENHEIMER EJ, VAN HEERDEN WFP, DAUTH J, DREYER MJ.** The role of salivary glands in vertebrates. *Hands-On* 1992; 1: 6. **210**
44. **RAUBENHEIMER E, VAN HEERDEN W, DAUTH J, VAN DER WALT T.** Salivary immunoglobulin related proteins in 24 patients with multiple myeloma. *Oral Oncology, European Journal of Cancer* 1993; 29B: 295-297. **211 - 213**
45. **VAN HEERDEN WFP, RAUBENHEIMER EJ.** Intraoral salivary gland neoplasms: a retrospective study of 70 cases in an African population. *Oral Surgery Oral Medicine Oral Pathology* 1991; 71: 579-582. **214 - 217**
46. **VAN HEERDEN WFP, RAUBENHEIMER EJ.** Evaluation of the nucleolar organizer region associated proteins in salivary gland tumors. *Journal of Oral Pathology and Medicine* 1991; 20: 291-295. **218 - 222**
47. **VAN HEERDEN WFP, RAUBENHEIMER EJ, LE ROUX**

- R. The relationship between nucleolar organizer regions and DNA content in salivary gland neoplasms. *Medical Technology South Africa* 1993; 6: 85-87. 223 - 225
48. **RAUBENHEIMER EJ, VAN HEERDEN WFP.** A review of recent developments in the diagnosis of epithelial neoplasms of salivary gland origin. *European Journal of Laboratory Medicine* 1995; 3: 107-112. 226 - 231
49. **HEMMER J, VAN HEERDEN WFP, POLACKOVA J, KRAFT K.** High-resolution flow cytometry in papillary cystadenoma lymphomatosum (Warthin's tumor). *Journal of Oral Pathology and Medicine* 1998; 27: 405-406. 232 - 233
50. **VAN HEERDEN WFP, KRAFT K, HEMMER J, SWART TJP, VAN HEERDEN MB, VAN RENSBURG EJ.** Warthin's tumour is not an Epstein-Barr virus related disease. *Anticancer Research* 1999; 4: 2881-2884. 234 - 236
51. **VAN HEERDEN WFP, RAUBENHEIMER EJ, SWART TJP, BOY SC.** Intraoral salivary duct carcinoma: A report of 5 cases. *Journal of Oral and Maxillofacial Surgery* 2003; 61: 126-131. 237 - 242
52. **RAUBENHEIMER EJ, VAN HEERDEN WFP, THEIN T.** Tyrosine-rich crystalloids in a polymorphous low-grade adenocarcinoma. *Oral Surgery Oral Medicine Oral Pathology* 1990; 70: 480-482. 243 - 245