

Copyright is owned by the Author of the thesis. Permission is given for a copy to be downloaded by an individual for the purpose of research and private study only. The thesis may not be reproduced elsewhere without the permission of the Author.

THE RETINAL PATHOLOGY OF OVINE CEROID-LIPOFUSCINOSIS

A thesis presented in fulfilment
of the requirement for the degree of
Master of Veterinary Science
at Massey University

Russell John Graydon

1984

ABSTRACT

Ovine ceroid-lipofuscinosis is an animal model of a rare genetic disease of man and some domestic animals. The disease is characterized by blindness idiocy and premature death.

In order to investigate the development of pathological changes in this model it was important to be able to accurately diagnose those sheep affected at an early age before clinical disease was apparent. In this thesis a number of methods such as skin biopsy, bone marrow examination and brain biopsy were investigated and it was concluded that brain biopsy was the most suitable and reliable method for establishing the preclinical diagnosis of ceroid-lipofuscinosis.

On clinical grounds the ovine disease most closely resembled the juvenile form of human disease and blindness was the important clinical finding in both diseases. A time course study of the development of retinal pathology was carried out.

Electroretinography was used as a clinical tool to ascertain the functional status of the retina. Pathological changes to the retina were investigated using light and electron microscopy.

Electroretinography revealed a decline in rod and cone 'b' wave amplitudes over a relatively short time span. Changes to the rod responses preceded, and were generally more dramatic than those of the cones. These changes paralleled a loss of rod and cone photoreceptor cells. Although there was some variation between animals and between readings it was suggested that

electroretinography was a useful method of monitoring changes to the retina and may be useful in assessing therapeutic strategies.

In affected retinas photoreceptor cell outer segments appeared to be shorter than those of controls. By 84 weeks of age the outer nuclear layer was reduced to a single row of nuclei with only remnants of outer segments present. Electron microscopy confirmed these findings and showed that the formation of abnormal dystrophic outer segments of photoreceptor cells was a significant early pathological change. Most cell types in the retina contained autofluorescent lipopigment bodies in their cytoplasm with the ganglion cells usually containing the largest amount. Ultrastructural studies showed that the storage bodies were made up of electron dense granular material and a variety of membranous and tubular structures giving them a similar appearance to those which were reported in the central nervous system. Very small electron dense 'smudges' were seen in the cytoplasm of some cells and these may have been early storage body precursors.

This study showed that electroretinography could be used to monitor the development of blindness in ovine ceroid-lipofuscinosis. It also revealed early severe pathological changes to the photoreceptor outer segments which may be of pathogenic significance in ovine and juvenile human ceroid-lipofuscinosis and therefore worthy of further investigation.

ACKNOWLEDGEMENTS

This thesis reflects a substantial part of the research carried out by me whilst I was employed as a Research Officer in the Department of Veterinary Pathology and Public Health at Massey University.

I would like to thank Dr. R. D. Jolly for allowing me to be a part of his research team and for his helpful advice and encouragement during my employment and during the long gestation of this thesis. Thanks are also due to Professor B. W. Manktelow for allowing departmental facilities to be used during these experiments.

I would like to thank the following people for their assistance. Mrs P. Slack and Miss S. Malloch for their assistance in preparing sections for light and electronmicroscopy. Helpful advice on the preparation of samples for electronmicroscopy was given by Mr. D. Hopcroft and the electronmicrographs were printed by Mr R. Bennett, both of the Department of Scientific and Industrial Research. Mr. T. Law printed the other figures and micrographs. Special thanks are due to the farm and hospital staff, especially Mr. W. Morris, for their care and attention to the experimental flock. I am indebted to my wife Joy and to Mrs. E. Bristol for typing the manuscript. My sincere thanks to Joy for her encouragement during our stay in New Zealand and during the preparation of this thesis.

Thanks are due to the Director and staff, especially Dr. B. Gorman, of the Queensland Institute of Medical Research for allowing

me to use the Institute's word processing facilities in the preparation of this thesis.

The research in this thesis was supported by a grant from the United States National Institute of Neurological and Communicative Disorders and Stroke, Grant Number NS 11238.

TABLE OF CONTENTS

	Page
LIST OF TABLES	vii
LIST OF FIGURES	viii
INTRODUCTION	1
CHAPTER 1	2
Review of the retinal pathology of ceroid-lipofuscinosis.	
CHAPTER 2	23
Early diagnosis.	
CHAPTER 3	33
Electroretinography and Ophthalmoscopy.	
CHAPTER 4	46
Retinal Pathology.	
CHAPTER 5	67
General Discussion	
REFERENCES	72

LIST OF TABLES

Table		Page
2.1	Subjective classification of autofluorescent material in the apocrine sweat glands of South Hampshire and control sheep.	29

LIST OF FIGURES

Figures	Page
2.1	27
3.1	41
3.2	41
3.3	42
3.4	42
3.5	43
4.1	50
4.2	52
4.3	52
4.4	54
4.5	55
4.6	56
4.7	57
4.8	59
4.9	60
4.10	60
4.11	60
4.12	62
4.13	62
4.14	63
4.15	63