PATHOLOGY
OF THE
NERVOUS SYSTEM

A STUDENT'S INTRODUCTION

BY

J. HENRY BIGGART, C.B.E., M.D., D.Sc.

Professor of Pathology, Queen's University, Belfast; Pathologist to the Royal Victoria Hospital, Belfast Hospital for Sick Children, Claremont Street Hospital for Nervous Diseases, Mater Infirmorum Hospital; sometime Examiner in the Universities of Bristol, Dublin, Edinburgh and Liverpool; formerly Pathologist to the Scottish Asylums Board; Neuropathologist to the Royal Infirmary, Edinburgh.

FOREWORD

BY

PROFESSOR A. MURRAY DRENNAN
M.D., F.R.C.P.E., F.R.S.E.

With 232 *Illustrations*
and 10 *Coloured Plates*

SECOND EDITION

EDINBURGH
E. & S. LIVINGSTONE LTD.
16 AND 17 TEVIOT PLACE
1949

PATHOLOGY OF THE NERVOUS SYSTEM

PREFACE TO THE SECOND EDITION

THE general plan of the book has been preserved and it still remains a student's introduction. Some chapters have been largely rewritten and additional sections in others included. New facts have been incorporated in all chapters. Thirty half-tone illustrations and ten figures in colour have been added and some of the figures of the first edition replaced. Additional references for further reading have been provided, but these are still confined to papers in English.

In spite of some requests no attempt has been made to develop the text into a reference book, but the dates of publication of the various references scattered throughout have been inserted and should assist the post-graduate student to a wider knowledge of the problems involved.

I am indebted to Mr David Mehaffey, A.R.P.S., of my department, for the new half-tone illustrations, and to him and Mr T. Dodds, F.R.P.S., F.I.B.P., of the Pathology Department, Edinburgh University, for the coloured plates. The new histological preparations are the work of my senior technician, Mr Robert Russell, A.I.M.L.T. Once again I owe my best thanks to my publishers for their courtesy and unfailing patience.

J. HENRY BIGGART.

January 1949.

PREFACE TO THE FIRST EDITION

THIS introduction to the pathology of the central nervous system has grown out of the lectures given to the medical undergraduates and to those preparing for the examination for the Diploma of Psychiatry. It has been written in the hope that it will help the student to apply the general principles of pathology, which he has already learnt in his study of the disease process in other organs, to the lesions of the nervous system.

The student of neurology is all too frequently disposed to be content with an anatomical diagnosis, which, taken in conjunction with certain changes in the eye or cerebrospinal fluid, fits in with some textbook syndrome. The author hopes that through familiarity with the pathology of the various lesions the student will be tempted to envisage what is actually happening in the nervous tissues, and to take a more active interest in the elucidation of possible etiological factors. For this and other reasons no attempt has been made to cover deficiencies in our knowledge by the extensive quotation of the many hypotheses which have been put forward.

Whilst it is felt that the only true classification of disease is on an etiological basis, the rarity and chronicity of many of the lesions of the central nervous system have rendered this treatment sometimes impossible. In such cases, *e.g.*, the disseminated demyelinisations, diseases showing a similar anatomical process are grouped together, though eventually they may be found to include several different disease entities.

No attempt has been made to furnish an extensive bibliography, but references are given to a few papers as far as possible of a monographic nature. It is realised that students generally do not consult the papers given in extensive bibliographies, and so by curtailing the number of references, and by limiting these entirely to papers in English, it is hoped that some students will read a little more widely on the subject.

The great majority of the illustrations are from cases studied in the Laboratory of the Scottish Asylums Board, and to the

affiliated asylums I am greatly indebted for a continuous supply of material as well as for a grant towards the expenses. I wish also to acknowledge my indebtedness to the following for generously allowing me to make use of material in their possession : Professor A. Murray Drennan, Mr N. M. Dott, F.R.C.S., Colonel Harvey, Director of the Laboratory of the Royal College of Physicians, Edinburgh, and Professor J. S. Young, of Queen's University, Belfast. The illustrations, except where otherwise indicated, are the work of Mr T. Dodds of the Pathology Department. His photographic ability was suitably acknowledged by the award of the Rodman Medal for a selection of these photographs. The histological preparations are evidence of the patience and skill of my technicians under the capable direction of Mr J. Sommerville. To my wife I am indebted for much help in the preparation of the manuscript and for the index. Finally, I would thank my publishers for their unfailing courtesy and help.

J. HENRY BIGGART.

April 1936.

FOREWORD

As a subject grows the tendency always is to subdivide it to facilitate study in greater detail of its several parts. With such subdivision comes, inevitably, specialisation and specialists. While intensive study may advance knowledge in the section studied, it may lead to a loss of balance or to a forgetfulness of the general principles of the whole subject.

Neuropathology is an example of such a subdivision. Its more intensive study may be said to date from 1922 when Hortega introduced his special methods. These have been extensively used, and much knowledge has been gained of the finer structure of the nervous system, both normal and abnormal. It is of interest to recall, that as far back as 1899, the late Dr Ford Robertson, of Edinburgh, introduced—and described them in his "Pathology of Mental Diseases"—certain special methods for the demonstration of glial tissue. These seem to have been rather overlooked, though the results compared favourably with some of the more recent procedures.

It will be unfortunate, however, if neuropathology is to lose contact with its parent, general pathology, for the same problems concern both.

In this book Dr Biggart has kept the relationship, and throughout there will be found analogies between the disease processes seen in the nervous tissue and in other tissues of the body. The apparent differences are shown to be due to the different anatomical factors—glial tissue in place of fibrous tissue, Virchow-Robin space for perivascular lymphatics, and so on. The predilection of certain virus infections for the nervous tissue may have a parallel, for example, in the affinity of the rheumatic infective agent for joints or heart tissue.

Fortunately, Dr Biggart is well qualified to draw such parallels, for he has had a wide experience of general pathological processes while working in the pathological departments of Queen's University, Belfast, and afterwards—as a Commonwealth Fellow—with Professor W. G. MacCallum at Johns Hopkins Hospital Medical School, Baltimore. While for the last three years he has been research pathologist to

the Scottish Asylums Board, he has kept close touch with general pathology in the University and Royal Infirmary departments. Such experience is reflected in Dr Biggart's treatment of neuropathology.

The book makes no pretence to be a complete compendium of knowledge of the pathological processes in the nervous system, but it sets out to lead the way to a more detailed knowledge of disease in the nervous system than that given in general textbooks on pathology. Not the least of its merits is the very fine series of completely new illustrations which it offers.

A. M. D.

"THE STUDY OF THINGS CAUSED MUST PRECEDE THE STUDY OF THE CAUSES OF THINGS!"

First Edition 1936
Reprinted 1940
Second Edition 1949

Made and Printed in Great Britain

TABLE OF CONTENTS

PATHOLOGY OF THE NERVOUS SYSTEM

CHAPTER I

THE NEURONE AND ITS REACTIONS TO DISEASE

WHILST the parenchymatous cells of the liver all appear more or less alike, the manifold functions of the central nervous system have resulted in the differentiation of a large variety of nerve-cell forms, ranging from the large pyramidal cells to the small round cells composing the molecular layer of the cerebellum. All these diverse forms are alike, in that part of the cell body is continued as a long process, the axis cylinder, which subserves the function of conduction of the nervous impulse, and in possessing a rather large vesicular nucleus and a well-defined nucleolus. When stained by basic dyes the cytoplasm of most of the larger cells is found to contain a number of deeply staining bodies which were first described by Nissl, and hence are known as *Nissl substance*. In the cells of the anterior horn and the Betz cells of the motor cortex this substance is found as rhomboidal and linear masses arranged in a more or less definite pattern throughout the cytoplasm. It is present in the dendritic processes of the cell, but is absent from the axis cylinder and from the point at which this process arises from the cell body.

Nissl substance represents masses of an iron-containing protein, which is in no way specific for the cells of the nervous system. It can also be demonstrated in the cells of the liver, adrenal, and pancreas. Whether or not it is present in similar form in the living cell is of little importance. The fact remains that it appears in a constant form in histological preparations of normal nerve cells, and that changes in its appearance and distribution can be correlated with alterations in cellular function. What function it serves is by no means clear, but it

tends to disappear in cells which have been fatigued by constant stimulation, and to reappear after an interval of functional inactivity. It is not seen when living cells are examined by ordinary methods of illumination, but photographs of living cells examined in ultra-violet light show very similar masses in the cytoplasm (Weimann, 1925).

One of the difficulties in the histological examination of the nervous system is that no general description of the

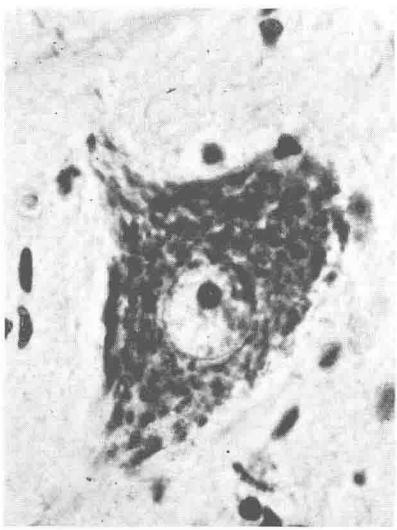

FIG. 1

Ganglion cell from the anterior horn of the spinal cord, stained with cresyl violet to show Nissl substance. × 650.

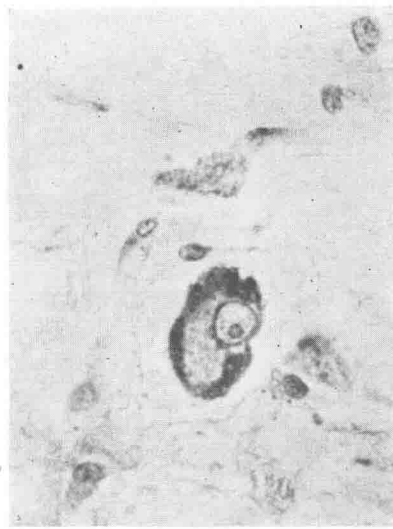

FIG. 2

Cell from the nucleus supra-opticus, showing the peripheral arrangement of the Nissl substance. In certain nuclei this is quite normal. Cresyl violet. × 600.

distribution and amount of the Nissl substance can be given. Thus, whilst it is found in the anterior horn cells as large rhomboidal masses arranged more or less regularly throughout the cytoplasm, in other cells, which have been subjected to the same fixative and staining method, it can only be demonstrated around the periphery of the cell body, *e.g.*, nucleus supra-opticus, cells of Clarke's column. In others, *e.g.*, the molecular layer of the cerebellum, in which there is only a narrow rim of cytoplasm, no such substance can be found.

Hence in the estimation of changes in the Nissl substance in disease it is of importance to compare the cells affected with cells from the same area in the normal brain.

A very different picture of the structure of the nerve cell is obtained by impregnating sections by Bielschowsky's silver method. The Nissl substance is no longer seen. Instead, the cytoplasm is found to contain a large number of fine silver-staining fibrils, the *neurofibrils*, which are continued into the axis cylinder and the dendrites. Like the Nissl substance, these cannot be demonstrated in the normal living cell, but appear rapidly if it is subjected to even minor degrees of injury. This pattern also differs in the various cell types.

Other structures normally found in the nerve cell are the mitochondria and the Golgi apparatus, but, as we shall see, these are of little help in the estimation of the amount of cellular damage present in disease. Pigment of the nature of melanin is found in the cells of the substantia nigra and in some of the cells of the vagus nucleus. It is not to be confused with the lipoid pigmentation of the nerve cell, which is a constant accompaniment of age.

Our interpretation of nerve-cell damage depends upon changes in these intracellular structures. To be of much value such structures must be easily demonstrated in human post-mortem material, and be relatively resistant to autolysis. The Golgi apparatus, for example, undergoes rapid autolysis, and as this begins in man within two hours after death it is generally impossible to utilise changes in this structure for the estimation of the degree of cellular damage. Similarly, it is not always possible to demonstrate the oxidising enzymes of the nerve cell in post-mortem material, whilst the demonstration of other substances may be rendered useless by their rapid diffusion into the surrounding tissues. The pathologist is therefore limited to an examination of the site of the lesion, to changes in the size of the cell, the nucleus and nucleolus, the Nissl substance, the neurofibrils, the axis cylinder and myelin sheath, and to variations in the amount of intracellular fat. The presence of unusual substances in the cytoplasm may also be of importance. In seeking for such changes we are merely trying to find histological pictures equivalent to those of cloudy swelling, fatty change, pigmentary atrophy, etc., in

the parenchymatous tissues of other organs. Many of the changes in function of the nerve cell, however, in their earlier stages represent merely some alteration in cell metabolism, and cannot be demonstrated by histological methods.

The commonest pathological change seen in the parenchymatous cells of the nervous system is *cloudy swelling*. This is exactly analogous to the process seen in the parenchymatous cells of other organs. Study of fresh material shows that, just as in other cells, the mitochondria increase in size and in number (Choja, 1936), but as the damage increases they disappear. In the nerve cell, however, the change is most apparent in sections stained to show the Nissl substance. The cell body is swollen. The Nissl bodies are found fragmented and undergoing a process of dissolution. Chemical analyses suggest that masked iron, normally present in the Nissl granules, disappears as they fragment and dissolve. This change may be most apparent at the periphery of the cell, or in the zone around the nucleus, but no deductions as to the nature of the toxin or infectious process can be drawn from its distribution. It is entirely non-specific. The nucleus is also swollen, and the neurofibrils appear thickened or even fragmented. As the most striking feature of the histological picture is the change in the Nissl substance, cloudy swelling in nerve cells is usually termed *chromatolysis* or *tigrolysis*. The great diversity of nerve-cell forms renders it necessary to compare the sections of the diseased nervous tissue with sections from the same area of a normal brain. For example, the normal distribution of the Nissl substance in the cells of Clarke's column in the spinal cord, and in some of the hypothalamic nuclei, has frequently been interpreted as the result of a perinuclear chromatolysis.

Following division of the axis cylinder process, some degree of change is usually seen in the Nissl substance of the affected cell. This is found fragmented and dust-like in the zone of cytoplasm around the nucleus. A similar change is found in many toxic conditions, so that there is nothing specific about this reaction. If repair of the axis cylinder is successful, the Nissl substance is reformed and the histological appearance of the affected cell becomes normal.

The nerve cell, provided the injurious agent ceases to act, may recover from the stage of cloudy swelling, and resume

not only its normal appearance but also its normal function. When, however, the injury is more severe, or continued over a longer period of time, other histological changes, indicative of more severe cellular damage, are found. Large vacuoles may appear in the cytoplasm as the result of hydropic degeneration.

Damage to the function of the nerve cell may also be manifested by its shrinkage. The nucleus is elongated, often

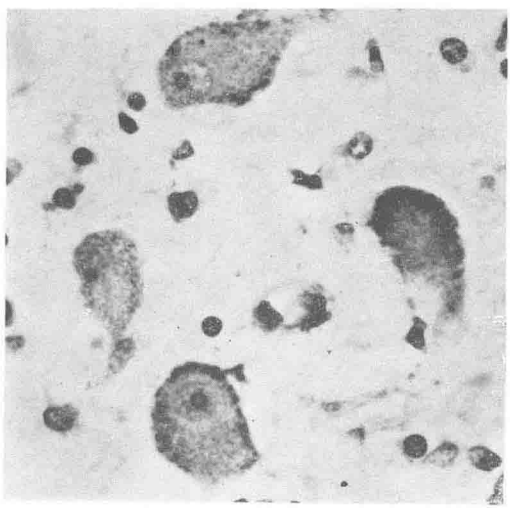

FIG. 3

Chromatolysis. Note the disappearance of the Nissl substance, the eccentric nuclei and swollen nucleoli. Encephalitis lethargica. Cresyl violet. ×525.

triangular, and stains darkly. The Nissl substance appears more compact, and seems to fill the whole body of the cell. The cellular processes become tortuous. This change, often described as *chronic cell change*, may be found not only in chronic disease of the nervous system but also in acute toxic and anoxæmic states. Indeed, it appears to be produced occasionally as an artifact, for the outer layers of ganglion cells in the cortex of quite normal laboratory animals may show a similar shrinkage and staining after formalin fixation. Occasionally the shrunken cell body and its processes are found encrusted with small granules which stain deeply with

basic dyes. In spite of the appearance of the cell it is probable that functional recovery is possible.

Some injured cells show a complete disappearance of the Nissl substance. Their cytoplasm appears homogeneous, whilst the nucleus is elongated and hyperchromatic and often displaced towards the periphery of the cell. This change, which bears some resemblance to the early stages of coagulation necrosis in other tissues, is non-specific, but is perhaps most commonly seen in conditions of anoxæmia, especially in the neighbourhood of anæmic infarcts. Hence it is frequently referred to as *ischæmic cell change*.

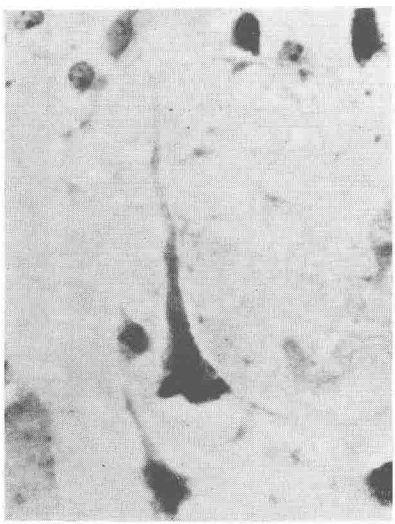

FIG. 4

Chronic cell change. Note the dense staining of the cytoplasm in which the individual Nissl bodies cannot be distinguished, and the tortuosity of the dendrite. Cortical nerve cell from case of vascular dementia. Cresyl violet. ×700.

The toxic or inflammatory process may, however, progress so that the nerve cells die. When death is sudden, as in infarcts, the nerve cells are found somewhat swollen. There is a complete disappearance of the neurofibrils and Nissl substance, and whilst the nuclear outline may still be recognised the nucleus and cytoplasm both appear homogeneous. Somewhat less rapid but fatal damage is usually best indicated by changes in the nucleus. Staining of the linin network, fragmentation of the chromatin, swelling and extrusion of the nucleolus are findings which suggest that cell recovery is impossible. The dead cells may undergo liquefaction, or may be phagocytosed and removed by the cerebral histiocytes.

Fatty Change.—Many normal nerve cells are found to contain a certain quantity of lipoid. This is present in the form of granules of lipofuscin, which are insoluble in alcohol and xylol, and so appear in paraffin or celloidin sections of