

A text-book of pathology in relation to mental diseases.

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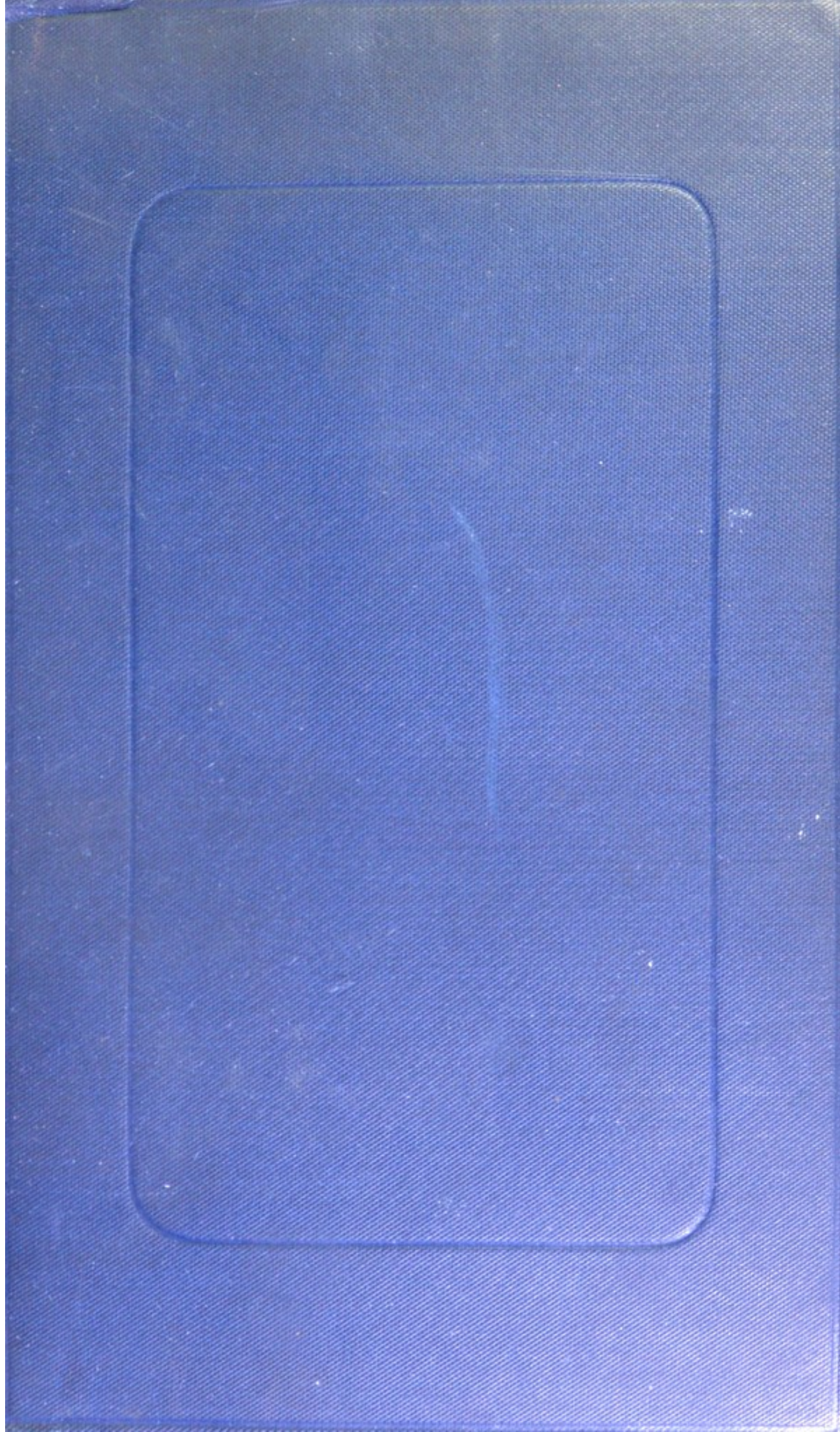
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A TEXT-BOOK OF PATHOLOGY

IN RELATION TO

MENTAL DISEASES



63.0216

A
TEXT-BOOK
OF
PATHOLOGY
IN RELATION TO
MENTAL DISEASES

BY
W. FORD ROBERTSON, M.D.

PATHOLOGIST TO THE SCOTTISH ASYLUMS; FORMERLY PATHOLOGIST
TO THE ROYAL EDINBURGH ASYLUM

ILLUSTRATED WITH SIXTEEN LITHOGRAPHIC PLATES
IN BLACK AND IN COLOURS AND
THIRTEEN ENGRAVINGS



EDINBURGH
WILLIAM F. CLAY, 18 TEVIOT PLACE
1900

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Dedicated to

T. S. CLOUSTON, M.D., F.R.C.P.E.,

PHYSICIAN-SUPERINTENDENT OF THE ROYAL EDINBURGH ASYLUM
AND LECTURER ON MENTAL DISEASES IN THE UNIVERSITY OF EDINBURGH,
FIRST CHAIRMAN AND NOW SECRETARY AND TREASURER OF THE
EXECUTIVE COMMITTEE OF THE LABORATORY
OF THE SCOTTISH ASYLUMS,

IN GRATEFUL ACKNOWLEDGMENT OF
HIS KINDLY INTEREST AND WARM APPRECIATION
WHICH HAVE BEEN THE AUTHOR'S CHIEF ENCOURAGEMENT
IN HIS WORK THROUGHOUT THE
LAST SEVEN YEARS,
AND IN RECOGNITION OF
THE EARNEST EFFORTS HE HAS LONG
MADE TO PROMOTE THE STUDY OF THE PATHOLOGY
OF INSANITY IN SCOTLAND, BUT FOR WHICH THE ORIGINAL
RESEARCHES UPON WHICH THIS BOOK IS FOUNDED
WOULD NOT HAVE BEEN UNDERTAKEN.



PREFACE

THE publication of this book marks the completion of an enterprise which was commenced by Dr James Middlemass and myself in 1894, while we were both upon the staff of the Royal Edinburgh Asylum. We outlined a series of articles upon "The Pathology of the Nervous System in relation to Mental Diseases," which, with the kind consent of Dr Joseph Bell, who was then editor, we intended to publish in the *Edinburgh Medical Journal*, and afterwards to issue in book-form. Articles duly appeared upon morbid conditions of the scalp and hæmatoma auris, morbid conditions of the skull and dura mater (the coverings of the brain being included in our scheme), changes in the weight, etc., of the brain, and morbid conditions of the pia-arachnoid. This carried the work up to the fifth article, the second half of which was published in the issue of the *Edinburgh Medical Journal* for May 1895. In the early part of this year an entirely unexpected contingency arose. Dr Middlemass, who when we commenced our series of articles was third assistant medical officer (having previously been pathologist), was suddenly called upon, owing to the appointment of his senior colleagues to superintendentships of asylums, to undertake the relatively very arduous duties and heavy responsibilities of first assistant medical officer, stationed at Craig House. It naturally became impossible for him to continue the laboratory work necessary for the preparation of those of the remaining articles that had been especially allotted to him. I was therefore obliged to continue the enterprise alone. I published two papers upon the intracranial vessels in 1896. At the end of this year circumstances arose through which the arrangement with regard to the series of articles naturally lapsed. Nevertheless I continued to work out the scheme that Dr Middlemass and I had started, taking up successively the subjects of the neuroglia and the nerve-cells. My appointment to the post of Pathologist to the Scottish Asylums, in 1897, for a time interrupted the progress of this particular work, but in the following year my committee took a step which I sincerely trust they will feel has been justified by the event. They agreed to recognise the issue of a Text-Book of Pathology in relation to Mental Diseases as a part of my official work. Accordingly I directed my

chief labours to this object, hoping that by its successful completion I might do something to encourage the study of the pathology of insanity in this country.

The long time that has elapsed since the publication of the articles in the *Edinburgh Medical Journal*, the great advances that have lately been made in our knowledge of the Pathology of Insanity through the researches of many workers, more especially on the Continent, and the fact that I have myself made more recent investigations upon several of the subjects dealt with in these articles, have rendered it necessary practically to rewrite those chapters of the originally projected book already in print. Dr Middlemass and I had foreseen from the first that, in view of the large amount of attention that was being devoted to the study of the pathology of insanity in many countries, when the time came for the publication of the articles in book-form, they would require very thorough revision. The illustrations that accompanied these early articles are, however, all included in the present work, namely, plates vi., vii., viii., xiii., xiv., xv. and xvi. The first four of these appeared with the conjoint papers. Of the other plates in the book Nos. i., ix., x., xvii., xviii., xix., the series xxi. to xxvi., xxvii. (added to) and xxix. have accompanied other papers published by myself, whilst the following are new, Nos. ii., iii., iv., v., xi., xii., xx. (except some of the figures) and xxviii. Plate xxix. and the first four figures in xxvii. appeared in a paper written in collaboration with Dr David Orr, Pathologist at Prestwich Asylum.

* * * * *

I gladly avail myself of this opportunity of expressing my thanks to various persons to whom I am indebted in connection with the work of writing this book.

In the first place I have to express my indebtedness to the managers of the following Scottish Asylums, in whose laboratory a large part of the original researches here recorded were carried out, and under whose auspices this book has been written and published :

Royal Edinburgh Asylum,
Crichton Royal Institution, Dumfries,
Glasgow Royal Asylum,
Aberdeen Royal Asylum,
Stirling District Asylum, Larbert,
Barony Asylum, Lenzie,
Lanark District Asylum, Hartwood,
Inverness District Asylum,
Midlothian and Peebles District Asylum,
Perth District Asylum, Murthly,
The Murray Royal Asylum, Perth,

City of Glasgow District Asylum, Gartloch,
Kirklands Asylum, Bothwell,
Roxburgh District Asylum, Melrose,
Saughton Hall Asylum,
Haddington District Asylum,
Govan District Asylum.

I feel specially grateful to the members of the Executive Committee of the Laboratory of the Scottish Asylums for the consideration and patience they have shown under the delay in publication of this work for exactly a year beyond the date at which I thought I should be able to have it ready. In this respect I am also under an obligation to many of the other members of the medical staffs of the associated asylums, who have ungrudgingly allowed the preparation of reports upon cases in which they were interested to be indefinitely postponed, and who have, I believe, in many instances refrained from sending me material for report, that I might be as free as possible to complete the researches necessary for the purposes of this book.

I have to thank Mr C. W. Cathcart, Conservator of the Museum of the Royal College of Surgeons, Edinburgh, for kindly giving me the loan of the skull used in the preparation of plates ii., iii. and iv.

I am much indebted to Dr C. C. Easterbrook and Dr David Waterston for kindly supplying me with a number of cranio-logical data, and also to the latter for reading over the chapter on the skull, and making a number of valuable suggestions relative to it, most of which were adopted.

I am similarly indebted to the late Dr George Elder in regard to the chapter on the intracranial lymphatic system, cerebral circulation, and intracranial pressure. It happened that while I was preparing this part of my book in the autumn of last year, he was carrying out investigations upon the same subject in the Laboratory of the Royal College of Physicians, Edinburgh. He discussed with me many of the difficult problems that the subject presents, and very kindly read over the chapter after it was prepared for the press. He made many important suggestions, and, I believe, enabled me to amend some errors into which I had fallen. With certain of my conclusions he could not agree, but I think it best to give no indication of what these points were. I am solely responsible for the views expressed.

Lastly, I desire to tender my sincere thanks to Dr C. C. Easterbrook and Dr John R. Gilmour for the great amount of care they have bestowed upon the correction of the proofs.

* * * * *

The original subscribers will notice that two chapters included in the outline of the book, appended to the circular issued in February 1899, have been omitted, namely, those upon "morbid changes affect-

ing special parts of the nervous system," and "morbid changes affecting special organs or tissues." I sincerely regret this omission, which has simply been unavoidable. To have worked up these two chapters would have entailed at least six months' further delay in the publication of the book, and I therefore reluctantly abandoned them.

It is perhaps almost superfluous to say that this book is not primarily intended as a text-book for students of medicine. Its special purposes are to endeavour to awaken a more general interest in the study of the pathology of insanity in the asylums of this country, and to assist those who are anxious to carry out original researches in this department of medical science. One of the canons of the scientific method is to begin investigation at the point to which others have carried our knowledge, and never to waste time and energy by going over the old ground, unless there is good reason for suspicion that it has been imperfectly surveyed. I have endeavoured to show the reader the position in which our knowledge of the pathology of mental diseases stood about the middle of the present year, and I trust that my book may enable many who have not yet attempted, but who are nevertheless anxious, to do something to advance this work a little nearer to its great therapeutic ends, to understand where to begin. If it be thought to fail in these objects, it may perhaps yet succeed indirectly, on the principle that a man who publicly upholds erroneous views often advances truth by the amount of opposition and discussion which he arouses. If even in this way our knowledge of the Pathology of Insanity is in some small measure increased, the labour I have expended upon this work may not have been altogether in vain.

W. FORD ROBERTSON.

LABORATORY OF THE SCOTTISH ASYLUMS,
7 HILL SQUARE,
EDINBURGH, 22nd October 1900.

CONTENTS

CHAPTER I

	PAGE
INTRODUCTION	1

CHAPTER II

POST-MORTEM EXAMINATIONS—HISTOLOGICAL METHODS—	
Post-Mortem Examinations	4-11
Histological Methods. Methods of Fixing and Hardening—Section-Cutting	
—Methods of Staining—Special Processes	12-31
References	31

CHAPTER III

MORBID CONDITIONS OF THE SCALP—HÆMATOMA AURIS—	
Morbid Adhesion of the Scalp	32
Hypertrophy of the Scalp	33
Hæmatoma Auris	35
Bibliography. Description of Plate I.	48-50

CHAPTER IV

MORBID CONDITIONS OF THE SKULL—	
Introductory Note	51
Craniometry—Craniometrical Observations at Autopsy	54-60
Abnormalities in Form and Size. Characters of Cranial Diameters, Lengths, Arcs and Indices in the Insane—Cranial Capacity—The Microcephalic Skull—The Macrocephalic Skull—Asymmetry—Crania Progenea— Metopism, or Persistent Frontal Suture—Abnormalities of Clinoid Processes—Bilateral Elevation alongside Sagittal Suture—Absence of Glenoid Fossa of Temporal Bone—Absence of Normal Over-riding of the Dentary Arcades—Abnormalities of Palate	60-66
Changes in Thickness, Texture and Weight. Thickening—Thinning— Osteosclerosis—Osteoporosis—Alterations in Weight	66-69
Histological Changes. Tumours	68-69
Bibliography. Description of Plates II., III., IV. and V.	69-72

CHAPTER V

MORBID CONDITIONS OF THE DURA MATER—	
Note on the Normal Structure and Functions of the Dura Mater	73
Morbid Adhesion of the Dura to the Skull	77

	PAGE
Morbid Adhesion to the Pia-arachnoid	78
Thickening of the Dura	78
Thinning of the Dura	78
Bony Formations in the Dura	79
Degenerative Changes	80
Congestion	80
Inflammation of the Dura	80
Subdural False Membranes and Allied Morbid Conditions. <i>Review of Literature—Macroscopic Anatomy—Morbid Appearances observed in Superficial Horizontal Sections of the Dura Mater—Morbid Processes concerned in Subdural False Membrane Formation</i>	81-110
Bibliography. Description of Plates VI., VII., VIII., IX. and X.	110-115

CHAPTER VI

MORBID CONDITIONS OF THE PIA-ARACHNOID—

Normal Structure of the Pia-Arachnoid	116
Milkiness, Thickening, Opacity, and Allied Morbid Conditions	121
Morbid Adhesion to the Cortex	128
Bibliography. Description of Plates XI., XII. and XIII.	130-131

CHAPTER VII

MORBID CONDITIONS OF THE INTRACRANIAL BLOOD-VESSELS—

Introductory Note	132
Normal Structure of the Intracranial Blood-vessels	133
Pigmentary Deposits in the Vessel-Walls	138
Fatty Degeneration	139
Hyaline Degeneration	139
Hyaline Fibroid Degeneration	140
Endarteritis Deformans	144
Miliary Aneurisms	149
Cerebral Hæmorrhage	154
Embolism and Thrombosis	155
Endarteritis Obliterans	156
Periarteritis	156
Granular Degeneration of the Muscular Coat	157
Colloid Degeneration	158
Calcification	158
Diffuse Dilatation or Ectasis	159
État Criblé	159
Bibliography. Description of Plates XIV., XV., XVI., and XVII.	160-163

CHAPTER VIII

MORBID CONDITIONS OF THE NEUROGLIA—

Introductory Note	164
Development of the Neuroglia	165
Normal Histology. <i>Literature—The Neuroglia—The Mesoglia</i>	168-178
Functions. <i>The Neuroglia—The Mesoglia</i>	178-179
Reaction to Irritants; Rôle in Processes of Repair	179

CONTENTS

xiii

	PAGE
Hypertrophy and Hyperplasia of the Neuroglia in Disease	181
Pigmentary Degeneration	183
Other Degenerative Changes	183
Morbid Changes affecting the Neuroglia in Insanity	184
Morbid Changes affecting the Mesoglia Cells	187
"Miliary Sclerosis"	188
Bibliography. Description of Plates XVIII., XIX. and XX.	189-193

CHAPTER IX

MORBID CONDITIONS OF THE NERVE-CELLS—

Introductory Note	194
I. Normal Structure of the Nerve-Cell—	
(1) Terminology	195
(2) The Achromatic or Achromophile Part of the Protoplasm. The Gemmulae of the Protoplasmic Prolongations. The Spiral Vortices of Levi	197-200
(3) The Chromophile Part of the Protoplasm	200
(4) The Physiological Pigment	202
(5) Nucleus and Nucleolus	204
(6) The Pericellular Reticula of Golgi and others	208
(7) The Endocellular Reticula of Golgi. Lymph Canaliculi of the Nerve-cell protoplasm	211
(8) Morphological Classification of Nerve-cells	214
(9) Mode of Connection of Nerve-cells	216
(10) Nerve-cells of the Cerebral Cortex	217
II. Physiology of the Nerve-Cell—	
(1) The Neuron Theory	218
(2) Functions of the Achromatic Part of the Protoplasm	222
(3) Functions of the Chromophile Elements of the Protoplasm	222
(4) Functions of the Protoplasmic Prolongations	223
(5) The Law of Dynamic Polarisation	223
(6) Functions of the Cell-body	224
(7) Structural Changes accompanying Modifications of Functional State	225
(8) Physiological Regressive Changes	226
(9) The alleged Amœboidism and Plasticity of the Nerve-cell	227
(10) Lugaro's Theory of the Functional Contractility of the Gemmulae	228
(11) Lugaro's Hypothesis regarding the Distinctive Functional Values of the Intra-neuronic and Inter-neuronic Elaborations	229
III. Experimental Pathology of the Nerve-cell—	
(1) Changes following Section of the Prolongations	231
(2) Changes produced by various Poisons (including Bacterial Toxins)	234
(3) Changes produced by other experimental Lesions	234
(4) Proliferative Capacity of the Nerve-cell	238
(5) Post-mortem Changes in Nerve-cells	239
IV. Types of Morbid Change affecting the Nerve-cell—	
(1) Chromatolysis	241
(2) Achromatolysis or Plasmolysis	242
(3) Coagulation of the Achromatic Substance	243
(4) Intense Colourability of the Achromatic Substance	243
(5) Partial or Superficial Coagulation with Corpuscular Formation	243
(6) Pigmentary or Yellow-globular Degeneration	243

	PAGE
(7) Fatty Degeneration	246
(8) Vacuolation	246
(9) Invasion by Bacteria	247
(10) Varicose Atrophy	247
(11) Varicose Hypertrophy of the Axis-cylinder Process	251
(12) Displacement of the Nucleus	251
(13) Homogeneous Degeneration of the Nucleus	251
(14) Loss of Nerve-cells	251
(15) Granular Changes	252
V. General Pathology of the Nerve-cell	253
VI. Special Pathology of the Nerve-cells in relation to Mental Diseases	258
Morbid Conditions of the Medullated Nerve Fibres of the Brain in	
Mental Diseases	265
Bibliography	269
Description of Plates XXI. to XXIX.	275

CHAPTER X

MORBID VARIATIONS IN THE PHYSICAL PROPERTIES OF THE BRAIN—

Weight	278
Specific Gravity	280
Elasticity	281
Bibliography	281

CHAPTER XI

MORBID CONDITIONS OF THE INTRACRANIAL LYMPHATIC SYSTEM AND CEREBRAL CIRCULATION ; PATHOLOGICAL INCREASE OF INTRACRANIAL PRESSURE—

Introductory Note	283
Physiology of the Intracranial Lymphatic System	284
Physiology of the Cerebral Circulation	288
Condition of the Cerebral Circulation in different Physiological States	
of the Brain	303
Normal Intracranial Pressure	304
Morbid Conditions of the Intracranial Lymphatic System	306
Obstruction of Lymph-channels	306
Alterations in the Composition of the Cerebro-spinal Fluid	309
Variations in the quantity of Cerebro-spinal Fluid	310
Morbid Conditions of the Cerebral Circulation	310
Cerebral Congestion	310
Cerebral Anæmia	314
Pathological Increase of Intracranial Pressure	315
Bibliography	322

CHAPTER XII

CONGENITAL ABNORMALITIES OF THE BRAIN—

Absence of the Corpus Callosum	326
Absence or Abnormal Development of other parts of the Brain	326
Atypical Arrangement of the Convolution and Sulci	327
Microgyria	327

CONTENTS

XV

	PAGE
Heterotopia of the Grey Substance	327
Porencephaly	327
Microcephaly	328

CHAPTER XIII

FOCAL LESIONS OF THE BRAIN—

Gross Cerebral Lesions of Vascular Origin	331
Cerebral Tumours	333
Infective Granulomata	334
Sclerotic Areas	335

CHAPTER XIV

PATHOLOGY OF SOME OF THE MORE IMPORTANT CLINICAL TYPES OF MENTAL DISEASE—

Acute Insanity	337
General Paralysis of the Insane, or Paralytic Dementia	344
Syphilitic Insanity	355
Senile Insanity	358
Chronic Alcoholic Insanity	362
Epileptic Insanity	366
Idiocy and Imbecility	371

INDEX OF SUBJECTS	373
INDEX OF AUTHORS	377

LIST OF PLATES

PLATE	CHAPTER	PAGE
I. HÆMATOMA AURIS	iii.	50
II.-IV. CRANIOMETRIC POINTS	iv.	72
V. MORBID CONDITIONS OF THE CALVARIUM	iv.	72
VI.-X. NORMAL AND PATHOLOGICAL HISTOLOGY OF THE DURA MATER	v.	114
XI. DIAGRAMMATIC REPRESENTATION OF STRUCTURE OF THE PIA-ARACHNOID	vi.	130
XII.-XIII. NORMAL AND PATHOLOGICAL HISTOLOGY OF THE PIA- ARACHNOID	vi.	130
XIV.-XVII. NORMAL AND PATHOLOGICAL HISTOLOGY OF THE INTRA- CRANIAL BLOOD-VESSELS	vii.	162
XVIII.-XIX. NORMAL AND PATHOLOGICAL HISTOLOGY OF THE NEUROGLIA CELLS	viii.	192
XX. NORMAL HISTOLOGY OF THE MESOGLIA CELLS	viii.	192
XXI.-XXIX. NORMAL AND PATHOLOGICAL HISTOLOGY OF THE NERVE- CELLS	ix.	276

PATHOLOGY

IN RELATION TO

MENTAL DISEASES

CHAPTER I

INTRODUCTION.

PATHOLOGY is that department of biological science which treats of disease, or the disorder of structure and function in living organisms. But it goes deeper than the mere outward manifestations of such disorders, and considers their essential causes, the nature and course of the perverted vital processes upon which they depend, and the structural, physical, and chemical alterations associated with them. The facts regarding the various forms of disease which, as a progressive science, it endeavours to elucidate may be classified as follows:—

1. Etiology.
2. The Nature and Course of the Morbid Process (Pathogenesis).
3. Pathological Anatomy: (a) Macroscopic; (b) Microscopic (Pathological Histology).

This subdivision is applicable not only to pathology in general, but also to the pathology of any single disease. Some writers restrict the term *Pathology* to the science which treats of the etiology, nature and course of the morbid processes associated with disease, and therefore it has at present its wider and its narrower significance.

The present work deals with the pathology of that group of diseases of the nervous system to which the terms "insanity" and "mental diseases" have long been applied. This group is essentially a clinical one, and does not represent a distinct pathological division. Nevertheless, the consideration of the pathology of its component diseases in a separate treatise is amply justified in view of the great practical importance of the clinical division.

A systematic treatise upon the pathology of mental diseases ought to cover the whole ground represented in the above classification. It should explain all that is known regarding the causation of the

different forms of insanity, the morbid processes concerned with their production, and the special alterations to be observed in the nervous system, both with the unaided eye and under the microscope. I cannot, however, claim to deal with the subject in this complete manner here. It is to be borne in mind that the pathology of mental diseases is still at an early stage in its growth. The first division to make any substantial progress has naturally been that of pathological anatomy. Already there is an important and extensive array of facts of this nature capable of being recorded. But with regard to the etiology of the different forms of mental disease, and the nature of the morbid processes concerned in their production, there is much less definite knowledge. It is, therefore, almost inevitable that a work of this kind should deal chiefly with facts of pathological anatomy. At the same time, I have not considered nearly so fully as the present position of knowledge would justify, the morbid processes upon which the different forms of insanity and their clinical manifestations depend. This particular subject is one which is certainly not exceeded in difficulty by any other in the whole range of medical science, and I may therefore, perhaps, be permitted to leave its discussion largely to others better equipped for the task.

I have not attempted to frame any pathological classification of mental diseases, as I believe that far too little is yet known regarding their pathology, and more especially their etiology, to render possible the successful accomplishment of this object. I have regarded them simply as a clinical group, the pathology of which is to be considered apart from that of other nervous diseases merely for reasons of convenience and practical utility. When a complete and strictly scientific pathological classification of mental diseases is eventually constructed, it will, I venture to predict, be of a very different nature from that represented in some recent attempts to frame such a classification. The fact will be clearly recognised that mental diseases cannot be regarded as in themselves a pathological group, because the classification of diseases must always be based chiefly upon etiology and pathological anatomy, and not upon symptomatology. The ultimate classification will be one in which mental diseases are simply given their proper position among other diseases of the nervous system, and it certainly will not place them in one division. Indeed, it will probably put some of them beside other diseases with which as yet they are hardly even suspected to have any close relationship.

It would be of much interest to trace the history of the pathology of insanity from its origin up to the present day. I shall not, however, endeavour to do this here. I merely remark that the histological study of the subject appears to have been begun independently and almost simultaneously in this country and on the Continent. In our own

country the work may be said to have commenced early in the seventies with the researches of Batty Tuke at the Fife and Kinross District Asylum, and with those of Herbert C. Major, and other contributors to the West Riding Asylum Reports. What strikes me as most remarkable in regard to these earliest histological investigations upon the brains of the insane is the number and the importance of the observations that were made, notwithstanding the enormous disadvantages under which they were carried out, and the general accuracy of most of the inductions, as far as they went, in the light of later researches. During the last five or six years the pathology of insanity has indirectly been very greatly enriched by discoveries in the newly explored field of the experimental pathology of the nerve-cell. Already the contributions from this source have been very numerous and important, and they will be still more so when sufficient time has elapsed to permit of the further application of the new facts to the study of the morbid changes occurring in the human brain.

The general arrangement that I have adopted in this book is merely that which has seemed to me best adapted for the systematic exposition of its subject. It is essentially that which was decided upon by Dr James Middlemass and myself in 1894, when outlining our series of articles on the pathology of mental diseases, for publication in the *Edinburgh Medical Journal*. I have at places entered much more fully into questions of normal anatomy and physiology than may, perhaps, appear to some to be justifiable in a work of this kind. In this matter I have in most instances been guided simply by a desire to render clearly intelligible the immediately succeeding descriptions of morbid processes and alterations in structure.

CHAPTER II

POST-MORTEM EXAMINATIONS—HISTOLOGICAL METHODS.

I. POST-MORTEM EXAMINATIONS.

THE method of making an autopsy upon a person who has suffered from mental disease does not differ in any essential respect from that adopted in similar work in connection with a general hospital. Nor does the equipment of the post-mortem room require to be different in the two cases. As these matters are already fully dealt with in several standard text-books of general pathology, I do not propose to enter into them here, further than to reproduce the form for making the pathological records now in use at the Royal Edinburgh Asylum, which may perhaps also prove of service in other similar institutions.

In this form, which I compiled in 1896, I endeavoured to incorporate all that seemed to me at the time to be most useful in the various systems that had been advocated. Dr Clouston and his assistant medical officers kindly went over the original draft and made several valuable suggestions which were adopted. I was especially indebted in this respect to Dr C. C. Easterbrook, to whom many of the distinctive features of the form are really due.

At Morningside Asylum about one hundred and twenty of these forms, printed on foolscap paper, are bound into one volume in which the permanent records are made. Loose copies are kept in the laboratory, and upon one of these the facts observed by the pathologist while making the post-mortem examination are jotted down in pencil by an assistant. From these notes, extended by the pathologist himself immediately after he has finished the dissection, the permanent record is subsequently written out.

I used this form myself during the last fifteen months of my tenure of office as pathologist at Morningside Asylum, and found it to serve its purpose very satisfactorily. The only amendment that I could now suggest is the extension of the measurements of the skull in accordance with the scheme given in chapter iv.

No. _____

R. E. A. PATHOLOGICAL RECORDS.

	Vol.	No.	
Name			Form of Mental Disease.
Sex			
Age			
Case Book: vol.	page		Cause of Death.
Died			
Autopsy	Time		
Temperature of mortuary.			

EXTERNAL EXAMINATION.

Height	Circumference at Shoulders	Circumference of Head
Pupils		
P. M. Rigidity		
P. M. Lividity		
State of Nutrition		
Surface Abnormalities (Skin, etc.)		

LOCOMOTORY SYSTEM.

BONES, CARTILAGES, JOINTS, AND MUSCLES

CIRCULATORY SYSTEM.

PERICARDIUM. Fluid in Cavity

HEART. 1. GENERAL APPEARANCE (Surface, Size, Shape, etc.)

2. CAVITIES

3. VALVES	Tricuspid		Cone Diameter.
	Pulmonary	competent	(1.5 to 1.8 in.)
	Mitral		(1.1 to 1.2 in.)
	Aortic	competent	(1.2 to 1.4 in.)
			(.9 to 1 in.)

4. MUSCLE

5. WEIGHT. (M. 11 oz., F. 9 oz.)

AORTA. (a) Thoracic. (b) Abdominal.

OTHER ARTERIES AND VEINS

RESPIRATORY SYSTEM.

LEFT PLEURA. Fluid in Cavity

LEFT LUNG. Weight (M. 21 oz., F. 15 oz.)

RIGHT PLEURA. Fluid in Cavity

RIGHT LUNG. Weight (M. 24 oz., F. 17 oz.)

TRACHEA, LARYNX AND NARES

ALIMENTARY SYSTEM.

PERITONEUM. Fluid in Cavity

LIVER. Weight (M. 53 oz., F. 44 oz.)

Gall-bladder.

PANCREAS. Weight (M. 3 oz., F. $2\frac{3}{4}$ oz.)

LARGE INTESTINE

SMALL INTESTINE

No. _____

STOMACH

ESOPHAGUS, PHARYNX, FAUCES, AND MOUTH

URINO-GENERATIVE SYSTEM.

LEFT KIDNEY. Weight (M. $5\frac{1}{2}$ oz., F. 5 oz.)

RIGHT KIDNEY. Weight (M. $5\frac{1}{4}$ oz., F. $4\frac{3}{4}$ oz.)

URETERS

BLADDER

GENERATIVE ORGANS

BLOOD-GLANDULAR SYSTEM.

SPLEEN. Weight (M. 6 oz., F. $5\frac{1}{2}$ oz.)

ADRENALS

THYROID GLAND

LYMPHATIC GLANDS

NERVOUS SYSTEM.

I. BRAIN AND ITS ENVELOPES.

SCALP

EARS. Left

Right

SKULL. 1. Measurements

2. Thickness, texture, new formations, etc. (a) Calvarium. (b) Base

3. Hard Palate

DURA MATER. 1. Morbid adhesion to bone

2. Outer surface

3. Thickness, texture, etc.

4. Inner surface (*False membranes, rusty staining, granulations, adhesions to pia-arachnoid, etc.*)

5. Sinuses

PIA-ARACHNOID. 1. General appearance (*Milkiness, thickening, opacities, granulations, etc.*)

2. Vessels

3. Morbid adhesion to convolutions

4. Pacchionian bodies

No. _____

ARTERIES AT BASE

CRANIAL NERVES

WEIGHT OF ENCEPHALON. (M. 49 oz., F. 44 oz.)

FLUID IN CRANIAL CAVITY (*Amount and character*)

CEREBRUM. 1. External configuration, surface abnormalities, softening, atrophies, etc.

2. Cortex. (a) Vascularity
(b) Colour
(c) Consistence
(d) Breadth
(e) Layers

3. White Matter. (a) Vascularity
(b) Colour
(c) Consistence

4. Lateral Ventricles

Granulations on walls

5. Choroid Plexuses

6. Third Ventricle

7. Basal Ganglia

CEREBELLUM

PONS AND MEDULLA

Granulations on floor of fourth ventricle

Choroid Plexuses of fourth ventricle

PINEAL BODY

PITUITARY BODY

II. SPINAL CORD AND ITS ENVELOPES.

1. Spine
2. Meninges
3. Cord, nerve-roots and ganglia

III. SYMPATHETIC GANGLIA AND NERVES.**IV. SPINAL NERVES.**

No. _____

(a) ANNOTATIONS UPON CASE.

(b) RESULTS OF MICROSCOPIC EXAMINATION.

II. HISTOLOGICAL METHODS.

The histological technique for the study of the nervous system has now become so extensive and complicated that it requires for its complete description not a chapter, but a text-book. My purpose in introducing the subject here is threefold—(a) to enable the reader to understand the nature of the histological methods to which reference is frequently made in the succeeding chapters; (b) to place before the beginner of the practical study of the pathology of insanity the few preserving, section-cutting, and staining processes of which a knowledge is most needful to him; and (c) to describe certain methods of my own. As a reference book upon histological methods for the study of the nervous system, I would recommend Dr Jack's translation of Pollack's work (1). No pathological laboratory should, however, be without its copy of Bolles Lee (2).

METHODS OF FIXING AND HARDENING.

The importance of careful fixation and hardening of tissues intended for microscopic examination cannot be too strongly insisted upon. Imperfect or improper fixation is by far the commonest cause of failure to obtain good results with staining processes. Every effort should be made to secure the tissues in as fresh a state as possible. They should be placed in the fixing solution immediately after removal from the body, as exposure to the air undoubtedly greatly hastens the progress of post-mortem alterations. Another point of great importance is to use only exceedingly thin slices of tissue, not more than 1-16th of an inch in thickness. The only preserving fluid in the case of which an exception to this rule may be made is formalin, which has very remarkable penetrating powers. The quantity of fluid should be equal to ten or twenty times the volume of the pieces of tissue to be placed in it.

1. *Sublimate fixation*.—Place pieces of tissue in saturated solution (made with aid of heat) of corrosive sublimate in .5 per cent. sodium chloride solution (Heidenhain's fluid) for twenty-four hours; then wash for a few minutes in water; place overnight in 80 per cent. alcohol (which may be made up from methylated spirit), to which there has been added a sufficient quantity of alcoholic solution of iodine to give it a dark sherry colour. Change to 95 per cent. alcohol, or methylated spirits, containing a similar quantity of iodine. Next day change to 95 per cent. alcohol, or spirit, without iodine. Preserve in this. The tissues are now ready to be put through any of the processes required for the preparation of sections.

2. *Formalin hardening*.—Place pieces of tissue in 10 per cent. solution of formalin in water (formalin as sold being reckoned at 100);

change the solution next day. The bottle should be closely corked, and, if possible, rendered air-tight. This may be done quite effectively by rubbing the whole cork over with vaseline. At least ten days should be allowed for hardening if the tissues have afterwards to be passed through alcohol. An entire brain may be hardened and preserved in 10 per cent. formalin; but to ensure proper fixation of the deeper tissues, either the large vessels should be slowly injected with a quantity of the fluid, or the lateral ventricles should be cut into through the corpus callosum and slightly distended with cotton wool. The brain should be placed on a thick pad of cotton wool, and surrounded by a thinner layer. The jar in which it is contained should, as far as possible, be rendered air-tight.

3. *Chrome alum-copper hardening.*—Weigert's chrome alum-copper hardening fluid is composed of chrome alum $2\frac{1}{2}$ per cent., copper acetate 5 per cent., acetic acid 5 per cent., formalin 10 per cent. The chrome alum is first dissolved by boiling in the required amount of water, and then the acetic acid and copper acetate are put in. This solution is filtered when cold, and the formalin is then added. Use in the same way as 10 per cent. formalin solution.

4. *Bichromate hardening.*—Place thin slices of tissue in twenty times their volume of $2\frac{1}{2}$ per cent. solution of potassium bichromate in water. Renew fluid next day, and at least once afterwards.

5. *Bichromate and formalin hardening.*—This is generally to be preferred to simple bichromate hardening. Place tissues first in $2\frac{1}{2}$ per cent. potassium bichromate solution to which there has been added 5 per cent. of commercial formalin. Next day wash pieces shortly in water and place in $2\frac{1}{2}$ per cent. bichromate without formalin. Renew bichromate solution after twenty-four hours. The tissues should not be left more than twenty-four or forty-eight hours in the bichromate and formalin solution, as, if they are, they will become very brittle.

Special uses of the different Fixatives.—Corrosive sublimate is unquestionably the best fixative yet discovered for nerve-cells. It should always be employed for tissues in which it is specially intended to study these elements. Formalin is an excellent general fixing agent, although not quite so satisfactory as sublimate for nerve-cells. On account of its remarkable penetrating power, and the tough consistence it gives to the tissues, it is a reagent of great utility in neurohistology. Weigert maintains that solutions weaker than 10 per cent. will not fix myeline satisfactorily, that is to say to such a degree as to ensure that it will resist the solvent action of alcohol. But even 10 per cent. solutions occasionally fail in this respect, notwithstanding their prolonged action. I would therefore strongly recommend that Weigert's chrome alum-copper fluid, which is a much better fixative for myeline, should be used instead of a simple formalin solution for

tissues which are to be embedded in paraffin or photoxylin, or at least that they should be transferred from the formalin to the chrome alum-copper solution for a week or ten days before being subjected to the action of alcohol. The mordanting in bichromate solution required in the case of tissues to which the Weigert-Pal method for medullated nerve-fibres is to be applied, may be carried out after hardening in either of these fluids. The statement that has been made that 10 per cent. solutions of formalin prevent satisfactory staining of the Nissl-bodies is certainly quite erroneous. Nor does the action of the chrome alum-copper fluid interfere in any way with the application of basic aniline stains to the nerve-cells. As a general fixative for non-nervous tissues, I would recommend the bichromate and formalin solution, used in the manner described.

SECTION-CUTTING.

1. *Dextrine freezing method.*—The required dextrine solution is made as follows:—Dissolve one ounce of dextrine in two ounces of water by boiling. While the solution is still hot filter it through cotton wool. When cold add about 1 per cent. of carbolic acid.

This solution should be perfectly clear. Recently, however, there has come to the market a quality of "dextrine" which is not entirely soluble in water, and which therefore forms an opaque fluid. Pure dextrine should be obtained if possible.

Wash tissues from six to twenty-four hours in water to remove alcohol or potassium bichromate, and then place them overnight, or longer, in the dextrine solution. Cut sections with the aid of the Swift, Cathcart, or other form of freezing microtome. It is important to understand that dextrine solution may readily be frozen so hard that it cannot be cut. If this should occur stop the ether spray, and wait until the temperature of the frozen mass rises a little, when a good cutting consistence will be reached. Transfer the sections from the knife to a bowl of water by means of a wet brush. At least five minutes should be allowed for the dextrine to dissolve out, after which time staining may be proceeded with.

2. *Paraffin embedding method.*—The details of this process vary considerably as carried out by different workers. Its first stage is necessarily that of dehydration of the pieces of tissue. In order to avoid undue shrinkage it is very important that tissues which have been hardened in formalin or in bichromate solutions, should not be transferred at once to alcohol of full strength. After having been washed in water, they may, for example, be placed for twenty-four hours in 70 per cent. alcohol, and then for similar periods in 80 per cent., 90 per cent. and 95 per cent., before being passed on to absolute alcohol. Tissues that have been fixed in sublimate and preserved

in spirit may be transferred directly to absolute alcohol. Specimen tubes of half-ounce capacity will be found much more convenient than ordinary bottles for the purposes of this embedding process. With these preliminary explanations I would recommend that the various steps of the method be as follows:—

1. Dehydration in absolute alcohol for twenty-four hours.
2. Methylated chloroform (just sufficient to cover the piece of tissue) for one hour.
3. Methylated chloroform (larger quantity) for twenty-four hours.
4. Equal parts of methylated chloroform and paraffin (consisting of equal parts of hard and soft Cambridge paraffin) for twenty-four hours, in paraffin bath heated to about 50° C.
5. Paraffin (as above) for twenty-four hours, at just above its melting point, usually from 50° to 52° C.
6. Cast in the metal moulds sold for the purpose, or in paper boats. As soon as the paraffin has set, harden it off rapidly by immersion in cold water. Keep the blocks in chip boxes until required for cutting.
7. Cut the desired number of sections by means of the Cambridge rocking, or other suitable microtome.
8. Fix sections on albumenized slides.

Albumenized slides are prepared as follows:—Take the white of a fresh egg and add to it nine times its volume of water. Mix, and filter into a bowl. Clean several dozen slides. Holding in the left hand one of the slides, draw over one side of it the edge of another slide which has just been dipped in the albumen. The very thinnest possible film should be applied. Set the slide up to dry in a suitable tray, with the albumenized side turned down so that it is protected from dust. Coat the other slides in the same way. When they are dry store them in a dust-proof box.

To fix a paraffin section on one of these slides, float it upon water heated to just below the melting point of the paraffin. In this the section spreads out. At once take it up on a slide, being careful that the albumenized surface (which may be recognised from the fact that it does not fog when breathed upon) is turned towards it. Allow the section to dry overnight at the ordinary temperature, or lay it on the top of the paraffin bath for two or three hours.

The sections may most conveniently be freed from paraffin with the aid of a series of the stoppered glass vessels that are specially made for the purpose. These are of sufficient size to hold two small slides placed together. Three should be filled with benzole and three with absolute alcohol. They should be clearly labelled and numbered consecutively, beginning with those containing benzole. Two slides with sections affixed are placed back to back and immersed for a

couple of minutes in each of the vessels, from No. 1 onwards. From the third bath of alcohol they are transferred to a bowl of water. Sections of tissues that have been fixed in sublimate require in addition to be placed (after the third bath of absolute alcohol) for two or three minutes in a weak solution of iodine in spirit, in order to free them from any remaining mercurial deposit, and then transferred to a bowl of water to which have been added two or three drops of ammonia. As soon as the colour of the iodine has disappeared they should be washed in pure water.

Photoxylin method.—Photoxylin is, I think, to be preferred to celloidin. It is used in practically the same way, and for the same purposes. As obtained, however, it is damp, and must be thoroughly dehydrated before it can be successfully employed for embedding purposes. On account of the cotton-like form in which the substance is sold, the moisture it contains may be quickly removed by means of absolute alcohol. A quantity of photoxylin, sufficient to make up as much solution as is immediately required, should be placed in a watch-glass, or porcelain dish, and as much absolute alcohol poured over it as will serve to thoroughly soak it. After a minute, by which time the photoxylin will have begun to dissolve, pour off the alcohol. Dissolve the dehydrated photoxylin in equal parts of absolute alcohol and pure anhydrous ether. The solution should be thin enough to pour quite readily. Place the pieces of tissue, which must previously have been thoroughly dehydrated in absolute alcohol, in this solution for three days, or longer. During this time the bottle, or specimen tube, must be tightly corked in order to prevent evaporation of the ether and alcohol. On the day before the tissues are to be taken out of the embedding solution, remove the cork in order to allow of a certain amount of evaporation to take place. After three or four hours, when the solution has reached a thick syrupy consistence, close the bottle again. Next day, or after some days, lay the pieces upon flat glass (if it is intended to cut them in dextrine), and pour over them a quantity of the thick solution. Leave them for from four to eight hours, or until the photoxylin has attained a somewhat firm consistence. Then raise the photoxylin mass from the glass and cut out each piece of tissue with knife or scissors, leaving a narrow margin of photoxylin around each. Then place in 90 per cent. alcohol for at least twenty-four hours. The pieces may be kept in this for an indefinite time without suffering injury. Methylated spirit is used by some at this stage, but I am inclined to think that it alters the consistence of the photoxylin. In order to prepare a piece of the embedded tissue for cutting on the freezing microtome, it is first placed in water overnight, or until it sinks, and then in dextrine solution for forty-eight hours, or longer. In clearing photoxylin sections, origanum oil should

be used instead of clove oil, as the latter dissolves out the embedding material, and immediately causes a delicate section to break into fragments. If it is intended to cut the tissues with the sliding microtome, they must be set out, not upon glass, but upon blocks of wood adapted to the instrument.

METHODS OF STAINING.

1. *Toluidin Blue Method for Nerve-cells.*—Toluidin blue is probably the best stain at present known for the chromophile elements of the protoplasm. It is suitable for tissues fixed in sublimate, formalin, or the chrome alum-copper fluid. It is best applied to sections prepared by the paraffin process and fixed on slides. It is generally used in $\frac{1}{4}$ per cent. watery solution. A few drops of alcohol should be added. Sublimate sections require to be stained for from ten to fifteen minutes. Those prepared from tissues hardened in formalin should be given a considerably longer time. They may often with advantage be left to stain overnight. Decolourise and dehydrate in absolute alcohol. Watch the process of decolourisation under the microscope. As soon as the chromophile bodies are clearly differentiated, replace the alcohol by benzole, in which, provided dehydration is complete, the section rapidly clears. Wash in two or three changes of benzole, and then put on a drop of balsam in benzole, and cover.

Preparations stained and mounted in this way tend to fade after a few weeks or months, occasionally even in the course of two or three days. This specially tends to occur in the case of sections prepared from tissues that have been hardened in formalin. From observations of my own I am convinced that the chief cause of such fading of the stain is inclusion of moisture under the coverglass. To avoid this occurrence is extremely difficult if the sections are mounted in the way just described, because the benzole is cooled considerably below the temperature of the room, owing to its rapid evaporation, and consequently the moisture in the operator's breath, or even in the air of the room, readily condenses upon it. To ensure complete dehydration I advise the adoption of the following plan in all cases. After washing the section in benzole, replace this fluid by equal parts of turpentine and benzole, and set the slide upon the heater used in the methyl violet staining process. After one or two minutes pour off the turpentine-benzole, replace the slide on the heater, and at once apply a drop of Canada balsam and a coverglass.

2. *Thionin Stain for Nerve-cells.*—Thionin is used in the same way as toluidin blue and for the same purpose; but a more active decolourising agent than alcohol is required. The preparations are certainly very beautiful when mounted, but they fade even more

readily than those stained with toluidin blue. I believe that inclusion of moisture under the coverglass is in this instance also the chief cause of the alteration, and that it can be avoided by completion of the dehydration in hot turpentine-benzole in the way described.

Stain sections for five or ten minutes in saturated solution of thionin in water. Wash shortly in water. Decolourise in aniline-alcohol (aniline oil, 1 part; 96 per cent. alcohol, 9 parts); allow for some stain coming out during the next stage. Wash in two or three changes of absolute alcohol in order to remove aniline oil and to dehydrate. Clear in benzole, and then in turpentine-benzole on the heater. Mount in benzole-balsam.

3. *The Author's Methyl Violet Method for the Cortical Nerve-cells and Neuroglia.*—I described this method first in 1897 as a staining process for the neuroglia, but at the same time expressed the opinion that it would prove of value for the nerve-cells (3). A year later Dr David Orr and I gave a further description of it (4), altered in many points of detail (in accordance with the results of experimental observations made by both of us), and advocated its employment in the study of the nerve-cells of the cerebral cortex.

The tissues require to be fixed in corrosive sublimate, in the way already described, and cut by the dextrine freezing method. The subsequent stages of the process are as follows:—Transfer the sections from alcohol to 1 per cent. methyl violet 6 B in water. Allow them to stain for from five to ten minutes. Wash in water for ten or fifteen seconds. Place in *saturated* solution of iodine in 1 per cent. potassium iodide in water for ten minutes. Wash sections in water. They may remain in this for an hour or so without suffering harm, but the next stage may be proceeded with as soon as iodine ceases to come out of them. Take a section up from the water upon a perfectly clean slide. Carefully remove water from around it by means of a towel. Next lay the slide upon the table, and with a piece of smooth blotting or filter paper (folded double) blot the section in the same manner as one dries a sheet of wet manuscript. Immediately afterwards, without allowing it to completely dry in air, pour over the section some drops of a mixture of equal parts of turpentine and benzole. Renew this turpentine-benzole after a few seconds, and then place the slide upon the heater (described below), where it must remain at a temperature of about 60° C. until completely dehydrated. If the turpentine-benzole tends to evaporate off the section, add more by means of a pipette. When dehydration is complete the previously black and opaque tissue assumes a dark blue and faintly translucent appearance. Generally from ten to fifteen minutes is required. When the section seems dehydrated, remove the slide from the heater, allow it to cool, and then pour off the turpentine-benzole. Decolourise

in aniline-benzole (1 in 2). The aniline oil must be perfectly anhydrous. Renew aniline-benzole two or three times. Avoid breathing on the slide, as the smallest trace of moisture in the aniline-benzole will cause complete decolourisation of the section. When the dye ceases to come away, wash the section in several changes of pure benzole, and mount in balsam in benzole.

It is essential that the section should be completely dehydrated on the heater. Any spot in which moisture has been allowed to remain will be almost completely decolourised by the aniline-benzole. On the other hand it is important that the slide should be removed from the heater as soon as dehydration is completed, as the colour then begins to come out to some extent.

A heating apparatus of a very simple form is sufficient for the purposes of this method. I use a small spirit lamp placed below a tripod stand, on the top of which there is a thin metal plate, and upon this again two small iron bars laid parallel to each other, and at such a distance as just to allow the two ends of a microscopic slide to rest upon them. By such an arrangement heat is transmitted only by the two ends of the slide and the turpentine-benzole is driven to the centre.

I am indebted to Dr Orr for recently pointing out to me three important conditions upon which the success of this method largely depends, and which we did not fully understand in describing the method in 1898. The most important of these conditions is absence of over-hardening in spirit. The sooner the sections are prepared after the fixation and hardening are completed (fourth or fifth day) the better will be the results. After the tissues have been four or five weeks in spirit it is difficult, and often impossible, to obtain a satisfactory reaction. The second condition is the strength of the iodine solution. Saturated iodine in 1 per cent. potassium iodide gives a better result as regards the nerve-cells than the $2\frac{1}{2}$ per cent. solution which was formerly recommended. I still think, however, that the stronger solution fixes the stain better in the neuroglia fibrils. Lastly, he has clearly demonstrated to me the necessity of securing the tissues in a fresh state in order to ensure a good staining reaction. This, of course, applies to all staining methods, but in preparations by the methyl violet method the deleterious effects of post-mortem decomposition are specially manifest.

I have lately observed deterioration of some of my specimens prepared by this method, and have reason to believe that here also its essential cause is the inclusion of moisture under the coverglass. This may be avoided by exactly the same procedure as that recommended in the case of the toluidin blue method.

This staining method may also be applied to formalin-hardened

tissues, but the results are somewhat variable. As a rule the nerve-cells are not well stained. A very good view of the neuroglia is, however, generally obtainable. The sections stain much better if the piece of tissue is transferred from formalin to spirit for two or three days before being cut.

The results obtained with this method are illustrated in plates xviii. figs. 4 to 10; xix. figs. 17 and 18; xxvii. and xxviii.

4. *Author's modification of Heller's method of staining medullated Nerve-fibres.*—The only essential respect in which this method varies from Heller's original process is in the hardening agent employed. Heller (5) used tissues hardened in Müller's fluid; in this modification (6) they require either to be hardened in Weigert's chrome alum-copper fluid, or to be mordanted in this fluid for a week or longer after hardening in 10 per cent. formalin. The advantages claimed are a blacker reaction and simpler details of technique. The sections may be cut either by the dextrine freezing method, or by the photoxylin method. The procedure is as follows:—Place the sections in 1 per cent. osmic acid for half an hour (in the dark), then in 5 per cent. pyrogallie acid for half an hour, $\frac{1}{4}$ per cent. potassium permanganate for three to four minutes (brain sections for not more than one minute), 1 per cent. oxalic acid for three to five minutes. Wash the sections in water after treatment with each solution. Dehydrate, clear, and mount in balsam. In successful preparations by this method the medullated nerve-fibres are almost black, and other tissue-elements colourless or pale yellow.

5. *Hæmatoxylin and eosin staining.*—This long established process is still, I think, the most generally serviceable that we have for the study of non-nervous tissues, such as the dura mater, pia-arachnoid, and cerebral vessels. It is essential for its success that the tissues should be thoroughly mordanted in bichromate solution. The best results are obtained after hardening with bichromate and formalin in the way described. Tissues that have been hardened in 10 per cent. formalin alone, or in Weigert's chrome alum-copper fluid, can be sufficiently mordanted by being left in bichromate solution for a week or so. The action can be accelerated by the addition of a little formalin to this solution. Only sections by the dextrine freezing and photoxylin embedding methods are suitable; the results with paraffin sections are unsatisfactory. The procedure that I recommend is as follows:—

1. Stain sections for three to five minutes in Ehrlich's hæmatoxylin in a watchglass.
2. Wash in a bowl of water.
3. Transfer to second bowl of water. Allow sections to remain in this until the violet tint has changed to blue. If they do not quickly become blue, add a trace of an alkali to the water.

Sodium carbonate or bicarbonate is preferable to ammonia, which is apt to take out the colour.

4. Take section up on a slide. Dry off the water as far as possible from around the section with a towel.
5. Dehydrate in absolute alcohol.
6. Stain with $\frac{1}{10}$ per cent. eosin in absolute alcohol for two to three minutes.
7. Wash with absolute alcohol for a few seconds.
8. Clear in clove oil (origanum if photoxylin or celloidin sections are being stained).
9. Heat gently for a few minutes on heater.
10. Wash thoroughly with benzole to remove the volatile oil.
11. Benzole-balsam. Coverglass.

SPECIAL PROCESSES.

1. *Method of preparing surface sections.*—This method, which I described in 1896 (7), enables one to study a free surface under the microscope. I applied it originally to the study of the inner aspect of the dura mater, but I have also found it of great service for the examination of the outer and inner aspects of the pia-arachnoid. Dr J. A. H. Duncan has recently employed it in an investigation upon the pathological changes occurring on the pleural, peritoneal, and pericardial surfaces.

The necessary procedure will perhaps be best understood from a description of the method as applied to the dura mater. After hardening, square pieces of the dura about half an inch in size are cut with scissors and allowed to soak in water for a time. If bichromate of potassium solution has been the hardening reagent employed, one hour is sufficient. A few drops of a *thick* solution of dextrine in water are placed upon the section plate of an ether-freezing (Cathcart) microtome, and firmly frozen. A perfectly level surface is next obtained by cutting away a thin slice with a single sweep of the section knife. The smoothest surface is obtained by cutting slowly. A piece of the dura is taken up with forceps, and, after excess of water has been removed from it by laying the outer surface on a piece of filter paper, it is placed with its inner aspect undermost on the smooth, frozen surface, and gently pressed down with the finger. The ether spray is again put in action, so that the piece of tissue is also firmly frozen. The section plate is next slightly lowered, and successive slices of the dura are pared away, until only a very thin layer of tissue remains on the surface of the dextrine. The section plate is then raised so as to place this surface considerably above the plane in which the knife cuts, and a thick slice of the frozen solution is removed and placed in a basin of water, of course

carrying with it the required section of the dura, which is ready for staining a few minutes afterwards. The points of chief importance to attend to are to place the tissue upon a perfectly level, firmly frozen dextrine surface, and to have a very sharp knife. After some practice, very thin sections may be cut in this way. One has often to be content, however, with preparations of which only a portion is sufficiently thin for examination with high powers. Hæmatoxylin and eosin staining will be found of most general utility. In mounting the sections care must be taken that the inner surface is turned towards the coverglass. The stained section should be placed on a slide and examined without a coverglass with the low power of the microscope, by means of which it is usually easy to tell which surface is uppermost. For some purposes, however, it is of advantage to have the outer or cut surface towards the coverglass.

2. *Cox's modification of Golgi's sublimate method.*—There can be little question that this modification of Golgi's sublimate method is the best of this class that has yet been devised for the examination of the human brain. In virtue of the corrosive sublimate it contains, the solution employed rapidly fixes the tissues. Its power of penetration is, however, very limited, and therefore only very thin slices of tissue (not exceeding one-sixteenth of an inch in thickness) should be placed in it.

Cox's solution is composed as follows :—

2 per cent. potass. bichromate in water, 50 parts.

5 „ corrosive sublimate, 20 parts.

5 „ yellow potassium chromate, 16 parts.

After having been made up, it should be allowed to stand for a day, and then filtered through cotton wool. Pieces of tissue should be placed in about twenty times their volume of solution. On the following day the fluid must be renewed. The desired reaction requires about three months to develop; it is generally at its best after about six months. After a year or so there is some deterioration from excess of deposit.

I recommend the following procedure for obtaining sections :—Wash piece of tissue overnight in a large quantity of water, or in running water. Then place in a small quantity of absolute alcohol for half an hour, not longer. Cut sections on the Cathcart freezing microtome by Coats's method. Remove excess of alcohol from the piece of tissue by means of filter paper. Place a few drops of warm anise oil upon the centre of the section-plate, and at once lay on the piece of tissue. Now put the ether spray in action and freeze the anise oil. The piece of tissue becomes fixed to the section-plate. Have at hand a small wide-mouthed bottle, one-quarter filled with absolute alcohol, a watchglass containing absolute alcohol, and a

camel's-hair brush. With the brush drop some alcohol upon the piece of tissue, and also upon the upper surface of the section-knife. A knife with a long and straight blade is essential. Cut sections by a single slow sweep of the knife from heel to point. Remove each section from the surface of the knife to the watchglass by means of the alcohol-loaded brush. Keep the upper surface of the knife and the piece of tissue covered with alcohol. Blow the ether spray from time to time to keep the anise oil frozen. Transfer the sections to a second watchglass containing alcohol, and after two or three minutes to a bowl of water.

One of the various processes for blackening the originally steel-grey mercurial deposit should now be applied. Of the several methods I have tried, I think the best is that of G. Mirto (8). I employ it thus:—Place the sections for ten minutes in saturated solution of lithium carbonate (which must be filtered). Wash them in two changes of water, five minutes in each.

The sections should now be mounted in the following way. Place them for two minutes in a watchglass three-quarters filled with absolute alcohol. Transfer to a second watchglass of absolute alcohol for a similar period. Clear in two supplies of benzole, also placed in watchglasses. Transfer a section to a slide with the aid of a copper lifter. Blot rapidly with filter paper folded double, and at once put on a sufficient quantity of thin Canada balsam dissolved in benzole. Do not apply a coverglass. Lay the slides on the top of the paraffin bath (heated to the usual temperature) for an hour. If the balsam tends to dry off from any part of a section, put on a little more.

Methods of rendering the preparations permanent.—Preparations made in the way just described are unfortunately not permanent. In six months or so the black deposit generally shows distinct signs of granular disintegration, which, having once begun, steadily advances until the specimens become quite useless. Many efforts have been made to overcome this great defect, but for the most part without any substantial success. Obregia, Flechsig, and Golgi have each described processes for replacing the mercury by gold. I have been unable to obtain any satisfactory results with the method recommended by Obregia. With that advocated by Golgi—as briefly described in Jack's translation of Pollack's book (page 78)—I have, on the other hand, obtained some very beautiful purple-black preparations, which have now remained unaltered under a coverglass for over nine months. The toning solution I have used is one given in the *Dictionary of Photography* (7th edition, page 600), and is composed as follows:—

Chloride of gold, 1 grain.

Sulphocyanide of potassium, 12 grains.

Hyposulphite of soda, $\frac{1}{2}$ grain.

Distilled water, 4 ounces.

I cannot say if this is the solution recommended by Golgi himself. Pollack merely states that "the gold fixing bath is that which photographers employ in preparing prints upon aristo paper." The sections, immediately after having been cut and washed in water, were placed in this solution for five minutes. They were then washed well in water, dehydrated, cleared and mounted in balsam with a coverglass. While in a few instances I have, as indicated, obtained very satisfactory results with this process, in others the preparations have undergone rapid deterioration. So far I have been unable to ascertain the cause of these failures.

For a long time I have endeavoured to find out some process of replacing the mercury in Cox-preparations by platinum. I have had some success by treating the sections as follows:—

1. Place in saturated solution of lithium carbonate (filtered) for ten or fifteen minutes.
2. Wash shortly in water.
3. Place in equal parts of 1 per cent. chloroplatinite of potassium in water and 10 per cent. citric acid in water, for from one to two days. Keep in the dark. The chloroplatinite solution should be freshly prepared, or at least not more than a few days old.
4. Wash in water.
5. Place in equal parts of (a) saturated solution of iodine in 1 per cent. potassium iodide and (b) water, for five minutes.
6. Wash in water.
7. Place in a bowl of water, to which two or three drops of strong ammonia have been added, until the colour of the iodine disappears.
8. Wash in water.
9. Dehydrate. Clear in benzole. Mount in benzole balsam, with coverglass.

In sections treated in this way there is always a replacement of the mercurial deposit by platinum, and the preparations are permanent. In some sets of sections this replacement has to all appearance been complete, but in other instances it has quite evidently been only partial. This uncertainty of result is, of course, a serious fault in the method. Dr James H. Macdonald, while pathologist at the Crichton Royal Institution, carried out a long series of experiments with a view to the discovery of a method which would give a complete substitution. He has worked out the following process, which, although it might be premature to say it attains the full object aimed at, certainly comes very near to it:—

1. Wash sections in distilled water.
2. Place for 24 hours in $\left\{ \begin{array}{l} \text{Solution No. 1. } \text{M} \ 120. \\ \text{Solution No. 2. } \text{M} \ 30. \end{array} \right.$

Solution No. 1.

1 per cent. potassium chloroplatinite in distilled water.

Solution No. 2.

Sodium sulphite	$\frac{3}{4}$ oz.
Sodium hyposulphite	$1\frac{1}{2}$ oz.
Sodium chloride	$\frac{1}{4}$ oz.
Distilled water	10 oz.

3. Transfer sections directly to a watchglass containing 1 in 80 hydrochloric acid in water, and allow them to remain in this for two minutes; wash them for two minutes in a second bath of this fluid, and for another minute in a third.
4. Pass sections directly into $1\frac{1}{2}$ per cent. iodine in rectified spirit. Allow them to remain for five minutes.
5. Clear in Solution No. 2 for five minutes.
6. Wash well in distilled water.
7. Dehydrate. Clear in benzole. Mount in benzole balsam, with coverglass.

A brush should be used in lifting the sections. Needles are inadmissible.

3. *March's Method.*—The great importance of this method lies in the fact that it serves to demonstrate the existence of secondary degeneration of medullated nerve-fibres after the morbid process has proceeded a little way, and prior to the complete disappearance of the myeline.

The tissues are first hardened in Müller's fluid, or in potassium bichromate solution, for from one to four weeks. Exceedingly thin slices, not more than 2 mm. in thickness, are then placed in about twenty times their volume of a mixture of Müller's fluid (or $2\frac{1}{2}$ per cent. potassium bichromate) 2 parts, and 1 per cent. osmic acid 1 part. The bottle should be rendered air-tight and kept in the dark. After about ten days, or a longer period, the pieces are washed overnight in water, gradually dehydrated in alcohol and embedded in celloidin or photoxylin. The sections are generally mounted in the usual way, but some histologists think it better not to use a coverglass. The myeline of nerve-fibres undergoing secondary degeneration is blackened. Normal fibres and other tissue-elements remain of a yellowish colour. Fatty matter is, however, likewise blackened, and also the yellow pigment of nerve-cells to some extent. The penetrating power of the osmic acid in the above mixture is extremely feeble, and consequently it is very common to find that the black reaction has failed in the centre of the tissue.

Vassale (9) has devised a modification of this method that is at

present in general use in Italy. It consists in the substitution of the following fluid for that of Marchi:—

1 per cent. osmic acid, 1 part.

Müller's fluid (made with distilled water), 3 parts.

Nitric acid, 20 drops to every 100 c.c. of the mixture.

The advantages of this modification are especially that the reaction is more rapid (the pieces being ready for embedding by the fourth day, although longer action of the fluid should be allowed if possible), and that the ground is whiter.

Although Vassale's modification undoubtedly has these advantages, it does not serve to increase the penetrating power of the osmic acid. Dr David Orr has found that this object may be attained in a very important measure by the simple addition of a small quantity of acetic acid. This may be added either to the Marchi or to the Marchi-Vassale solution. Taking advantage of this property of acetic acid, Dr Orr has worked out a special modification of the Marchi method, and also an osmic acid block method for the normal medullated fibres (10).

Orr's Modification of Marchi's method, and method of staining the normal medullated Fibres en bloc.

(a) *Modification of Marchi's method.*—The tissues are hardened either in bichromate solution alone, or in the bichromate and formalin mixture for the first twenty-four hours, in which case the simple bichromate solution in which they are afterwards kept must be frequently changed in order to eliminate every trace of formalin. After the usual time allowed for hardening, pieces of tissue about one-eighth of an inch in thickness are placed in his acetic-osmic acid mixture, which is composed of 1 per cent. acetic acid 1 part, and 1 per cent. osmic acid 4 parts. A quantity of this fluid equal to about ten times the volume of the pieces of tissue should be used. The solution requires to be renewed on the fifth day. Penetration is completed in altogether about ten days. The pieces are then washed overnight in water and embedded in celloidin or paraffin. Dr Orr prefers the latter, as it enables one to obtain much thinner sections.

(b) *Method of staining the normal Medullated Fibres en bloc.*—The tissues are either first hardened in 10 per cent. formalin, or taken when fresh. In the former case blocks not exceeding one-eighth of an inch in thickness, after being washed shortly in water are placed in his acetic-osmic acid mixture for from four to six days. They are then embedded either in paraffin or in celloidin. Dr Orr in this process prefers to use the latter, as paraffin causes some shrinkage of the tissues. The sections are differentiated in one-twelfth per cent. potassium permanganate solution, washed in water and cleared in 1 per cent. oxalic acid. They are then again washed, dehydrated, cleared in benzole (or in turpentine-benzole) and mounted in benzole balsam.

The healthy medullated fibres are blackened, the other tissues remain colourless.

For fresh tissues he prefers to increase the strength of the osmic acid to 2 per cent. The staining solution is allowed to act for forty-eight hours. It must be renewed after the first twenty-four hours if much darkened. The tissue is next placed in 10 per cent. formalin for three days, then embedded in celloidin and subsequently differentiated and mounted in the way already described.

4. *Aniline Black Fresh Method of Bevan Lewis.*—The solutions required for this method are, (1) $\frac{1}{4}$ per cent. osmic acid in water, and (2) $\frac{1}{4}$ per cent. aniline black in water. Some varieties of "aniline blue-black" that are sold are quite unsuitable; the right dye may be obtained from Messrs Woolley, Sons & Co., chemists, Manchester. The sections are cut with the aid of a Cathcart, Swift, or other form of freezing microtome. I recommend that the various steps of the method should be carried out according to the following directions, which apply especially to the procedure necessary when the Cathcart microtome with plane is used.

The sections should be cut as soon after the removal of the brain from the body as is practicable. It is of great importance that water should not be allowed to get upon the piece that is to be cut, as, if it should do so, spicules of ice will form in the tissue when it is frozen, and render it impossible to cut good sections. Have ready two bowls of water. It is of great advantage, as pointed out by Middlemass (11), to add some pieces of ice in order to bring the temperature of the water down to near the freezing point. The risk of delicate sections breaking up is thereby diminished to a very important extent. The plane, which must be extremely sharp, should be cooled in this ice-cold water.

Take a piece of brain (including both cortex and white matter) about half an inch in length and in breadth, and about a quarter of an inch in thickness. Wet the section-plate of the microtome with cerebro-spinal fluid. Place the piece of tissue upon it, and blow the ether spray. While the tissue is being frozen, filter some osmic acid solution into a watchglass, making it about three-quarters full. When the piece of tissue is frozen, dip the cutting edge of the plane in water for a moment, then carefully dry the straight side on a towel laid across the knee, but leave a little water on the bevelled edge, which is to be turned uppermost in cutting the sections. Cut away a thick slice of the tissue in order to obtain a level surface. Again dip the plane in water, and then carefully dry its under surface as before. Now cut as thin a section as possible, and while it is still in the frozen state and adhering to the plane, dip it below the surface of the water in one of the bowls. Move the plane about gently in the water until the

section is detached. Dry the under surface of the plane before proceeding to make the next section. After thus cutting about half a dozen sections, lift each one separately out of the water with the handle of a mounted needle, and submerge it in the osmic acid solution for about fifteen seconds. Then transfer the section in the same manner to the second bowl of water. When the half-dozen sections have been thus treated, cut and fix another set, and so on until the number required have been passed through osmic acid. There is a certain degree of hardness of the tissue best for cutting, which can only be learned by experience. The piece of tissue must not be allowed to become soft once it has been frozen, until all the sections required have been cut. Allow the sections to wash in water for at least five minutes after they have been passed through osmic acid. Filter about an ounce of the aniline black solution into a small porcelain dish, and transfer the sections to it. Allow them to stain for one hour. Transfer to a bowl of water. After five minutes or so pass them into a second bowl. The water out of which they are mounted must be free from any trace of the dye. Take each section up on a clean slide. Dry the slide with a towel as far as it is possible to do so without injuring the section. Lay the slides against a suitable support, with the section turned downwards, in a place in which they will dry rapidly. When the sections are dry (say next morning), put a drop of thin balsam on each and cover with a clean coverglass.

5. *The Platinum method.*—I described this process in 1899 as a new method of obtaining a black reaction in certain tissue-elements of the central nervous system (12). The histological picture produced by it is entirely different from that of the sublimate and silver methods of Golgi. Its various features are fully described in the succeeding chapters (see plates xvii. and xx.).

The reaction obtained depends upon the fact that when platinum bichloride is slowly reduced in the presence of a tissue, the platinum, or "platinum black," tends to be deposited first in certain tissue-elements. The reducing agent employed is formalin. The progressive character of its activity in this histological process appears to be owing to its gradual conversion into formic acid, which is a more active reducer of platinum bichloride than the aldehyde corresponding to it. As might be expected, various additional factors come into play, and tend to disturb the continuous slow progress of the reduction, upon which a successful result depends. Among these disturbing factors there are at least three that can already be recognised, namely, the too rapid development of formic acid, accidental contamination of the fluid, and the state of the tissues. It is certain, however, that there are others of a more obscure nature. As the process generally requires from three to six months to carry out, it will

readily be understood that the technical details best calculated to ensure a successful result cannot be quickly determined. My own experimental observations on the subject are still in progress. The technique recommended here is that which has so far in my experience yielded the best results.

It is particularly to be noted that platinum bichloride, and not potassium chloro-platinite, is the salt required. It is obtained in gramme tubes, the contents of one of which should be dissolved in 200 c.c. of distilled water. This $\frac{1}{2}$ per cent. stock solution is probably best kept in yellow glass bottles, such as those in which Schering's formalin is sold.

Pieces of formalin-hardened tissue about one-sixteenth of an inch in thickness, and of any convenient size, are washed for an hour or longer in filtered distilled water, and then placed in the platinum-formalin solution, which I provisionally recommend should consist of $\frac{1}{2}$ per cent. platinum bichloride in distilled water, to which there has been added 2 per cent. of commercial formalin. This solution must be freshly prepared, and should be carefully filtered before the tissues are placed in it. Specimen tubes of one ounce and two ounces capacity are more suitable than bottles for the purposes of this method, as they can be more readily cleaned. It is absolutely necessary that the inside of the glass should be perfectly free from any foreign matter. The quantity of fluid should equal thirty or forty times the volume of the tissue. The bottle or specimen tube should be corked in the usual way and placed in a box or drawer, so that bright light is excluded from it. If platinum black begins to form within two or three days, it is probable that the glass is not perfectly clean, or that the formalin is too old and therefore too acid, or that the tissue itself is at fault. Blackening should not begin until five or six weeks have elapsed. It should be allowed to proceed until the tissue appears thoroughly blackened, in parts, if not over its entire surface. Some experience is, of course, required to enable one to know exactly when a piece is ready for cutting. If the supply of platinum bichloride appears to be exhausted (indicated by loss of the yellow colour) before the tissue is sufficiently blackened, half of the fluid in the bottle should be poured out and replaced by a corresponding quantity of $\frac{1}{2}$ per cent. solution of the platinum salt. Finally, the pieces are washed shortly in water, placed in dextrine solution for twenty-four hours, or longer, and then cut on the freezing microtome. The sections are dehydrated, cleared, and mounted with a coverglass in the usual way.

While the process just described seems to give the best results for the vessels and nerve-cells, higher percentages of formalin appear to be necessary for the display of the special selective action for the mesoglia cells, to which reference is made in chapter viii. For the purpose

of bringing out these elements, 10 per cent., or even 20 per cent., of formalin, previously neutralised by the addition of pure calcium carbonate, should be used.

This method is not applicable to formalin-hardened tissues only, as it can be successfully carried out, with slight modifications in the resulting reaction, upon tissues hardened in various other ways, more especially those that have been fixed in sublimate. It may also be applied to sections and to fresh tissues.

6. *Jores' method of preserving whole organs. Modifications of France and Shennan.*—These methods will be found of great service for the preservation of the natural appearance of abdominal and thoracic organs of which it is desired to make museum specimens. The directions for Jores' process are briefly as follows:—

- (1) Wash specimens for a short time only.
- (2) Fix for from twenty-four to forty-eight hours in 5 or 10 per cent. formalin added to—sodium chloride, 1 part; sodium sulphate, 2 parts; magnesium sulphate, 2 parts; water, 100 parts.
- (3) Place in 95 per cent. alcohol, or methylated spirit, for twenty-four hours, or until colour returns.
- (4) Preserve in equal parts of glycerine and water.

France (13) recommends that the organs should be placed, without preliminary washing, for from twenty-four to forty-eight hours in the following fixing solution—

Formalin 16 per cent. in water.

Acetate of potash .1 per cent.

Nitrate of potash .075 per cent.

They are then immersed in 80 or 90 per cent. alcohol for from twelve to twenty-four hours, and finally preserved in a fluid composed of glycerine 44 parts, water 100 parts, and acetate of potash 3 parts by weight.

Theodore Shennan (14) recommends a slight modification of Jores' original method, chiefly in the direction of more prolonged fixation by formalin and in the composition of the final mounting fluid. He has the salts made up in separate powders as follows:—

Sodium chloride	.	.	700 grains (1 per cent.).
Magnes. sulphate	.	.	1400 „ (2 per cent.).
Sodium sulphate	.	.	1400 „ (2 per cent.).

To make Jores' solution the three powders are dissolved in a gallon of tap water, and $7\frac{1}{2}$ oz. formalin added to make approximately a 5 per cent. mixture. After simply being rinsed in water, the organs are placed for from four to ten days in a suitable quantity of this solution,

which should be changed after two days if the organs are large. They are then washed in spirit until the natural colour comes back distinctly, generally about twenty-four hours. They are next transferred to equal parts of glycerine and water for a week, and finally preserved in

Glycerine	2 parts.
Water	3 parts.
Formalin	2 oz. to 1 gallon, or $\frac{1}{80}$ part.

The further details of the process, as well as a number of valuable practical hints, will be found in the original paper.

Dr Shennan informs me that he has lately adopted a further modification which he thinks gives still better results. He prepares the specimen as it is to be finally mounted, and then fixes it for only twenty-four hours in Jores' solution containing 10 per cent. of formalin instead of 5 per cent. In this way only the superficial layers are affected, and practically no blood is washed out. The fixing solution is replaced by spirit, in which the specimen remains for other twenty-four hours before being finally mounted in the glycerine and water mixture, with or without the addition of formalin.

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CHAPTER III

MORBID CONDITIONS OF THE SCALP—HÆMATOMA AURIS.

(PLATE I.)

THERE are at least two morbid conditions of the scalp that are so closely connected with mental disease as to require notice in any systematic account of its special pathological anatomy. One is morbid adhesion to the pericranium, and the other the apparently rare condition which has been termed "hypertrophy." The subject of hæmatoma auris, which, for a like reason, claims to be considered, is also most conveniently taken up at this stage.

MORBID ADHESION OF THE SCALP.

In the normal condition the epicranial aponeurosis, while closely united to the skin, is connected with the pericranium only by loose areolar tissue, so that, after the usual incision over the vertex has been made, the scalp can easily be separated from the subjacent structures by the hand. In some diseased conditions this areolar tissue becomes markedly indurated, giving rise to morbid adhesion of the scalp. In hospital cases this change is rare, though it is difficult to obtain exact statistics. In patients dying in asylums, on the other hand, it is exceedingly common. Statistics compiled by Dr Middlemass (1) and myself in 1894, from the records of cases examined up to that time by ourselves at the Royal Edinburgh Asylum, show that some degree of morbid adhesion occurred in 56 per cent. of all cases. A very marked degree of adhesion, such as to render detachment of the scalp impossible except by dissection, was found in 13 per cent. Taking the different forms of insanity, adhesion of the scalp was found to occur most frequently in general paralysis, in 77 per cent. of which cases it was present. Epilepsy came next with 57 per cent. It occurred in only 27 per cent. of cases of senile insanity. It was accompanied by thickening or condensation of the bones of the skull in 71 per cent. of cases, and frequently, though less commonly, by morbid adhesion of the dura to the skull. An analysis of 270 cases (86 of which were included in the foregoing series) examined by myself gives very similar results. There was some degree of morbid adhesion in 50 per cent., while its extreme form occurred

in 11 per cent. Such morbid adhesion of the scalp is evidence of the past occurrence of a proliferative process in the loose areolar tissue lying between the epicranial aponeurosis and the pericranium. In other words, it is the effect of sclerosis of this areolar tissue. Microscopic examination in a series of cases of insanity has shown that the connective tissue corpuscles of this tissue are often in a state of active proliferation. Such proliferative activity has, however, no immediate relationship to morbid adhesion, since it may be manifested in an otherwise normal tissue, as well as in one already sclerosed by past or long standing morbid change, while it may have entirely ceased in a tissue presenting evidence of severe sclerosis.

The comparative frequency of the occurrence of this sclerotic change in the sub-epicranial areolar tissue in the insane as compared with the mentally sound, is probably to be explained in the same way as the special proclivity of the latter to chronic morbid changes in the cranial bones and membranes of the brain. This interesting and important problem is considered in connection with the pathology of the dura mater.

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HYPERTROPHY OF THE SCALP.

The abnormality to which this name has been given was first described in 1884 by Poggi (1), who observed it in a patient in the asylum at Como. Four other cases have more recently been recorded,—two by T. W. McDowall (2), and two by J. J. Cowan (3), all of which occurred in adult male genitous idiots, two of them being also microcephalic. Poggi's patient, on the other hand, was a woman of sixty-six, who suffered from melancholia. The appearances described in the several cases are remarkably uniform, so that the general features of the condition may be readily stated. The scalp covering the upper and posterior part of the head is abnormally redundant, thick, lax, and mobile, and its surface presents a number of roughly symmetrical antero-posterior and transverse furrows and ridges. The hair is normal in appearance, or coarser than usual. The antero-posterior furrows, which are commonly about ten in number, occur on the top of the head; while the transverse ones, which do not usually exceed two or three, occur in the occipital region. In length, they vary from two or three up to six inches. The intervening ridges are about an inch in breadth. The depth of the furrows varies from one-eighth to three-eighths of an inch. The Italian case was somewhat exceptional in that the posterior surface of the head was most affected, and the antero-posterior and transverse arrangement of the folds and resulting

furrows was modified into a crescentic form with the concavity upwards. The results of a microscopic examination of the thickened scalp do not seem to have been yet recorded, but Poggi states that the skin of the folds in his case reached a thickness of 12 millimètres, and that of the furrows 4 millimètres. He believes the condition to be a congenital hypertrophy. Kundrat (M'Dowall) also regards it as hypertrophic. Kaposi (M'Dowall) further explains the abnormality by saying that "the brain had not advanced in growth, but the skin was sufficient for a normal skull, and had developed independently in accordance with its own capacity for growth. But because the contents to be surrounded remained too small, the normally large skin was forced to arrange itself in folds over the small skull, and in parts became atypic, *i.e.* hypertrophied, during development." M'Dowall, however, points out that the condition is very rare even in microcephaly, which would scarcely be the case if Kaposi's view were correct. He regards it rather as an indication of a retrogression to a lower type, of which examples are seen in many members of the carnivora.

It might be expected that the slighter degrees of this abnormality would be somewhat common. For my own part, however, I have not observed any indication of it in over three hundred cases of insanity examined after death.

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HÆMATOMA AURIS.

This condition, which is also known by the names of othæmatoma, auricular hæmatoma, and insane ear, is one the pathology of which has in past years given rise to much controversy. Even at the present day this controversy is not entirely ended, and for this reason it is necessary to enter into the whole question here in considerable detail.

Occurrence in the Insane and Mentally Sound.—The occurrence of sanguineous tumours of the auricle in asylum patients was first drawn attention to by Frederick Bird (1) in 1833. For a long time they were believed to be peculiar to the insane, but it has been shown by Strahan (14), Field (20), Vallon (10), Tomkins (16), Pilkington (17), and others, that they may also occur in persons in apparently perfect mental health. The last-named authority has even gone so far as to contend that the condition is not more common in the insane than in

the sane. The general opinion, however, is entirely against this view, and it is now almost universally admitted that othæmatoma is a rare occurrence in the mentally sound, while among asylum patients it may be observed with considerable frequency. A curious fact worthy of note is that othæmatoma has frequently been observed in otherwise healthy cats. Regarding the frequency of its occurrence in the insane, Campbell (15) found that out of 583 patients examined, deformity of one or both ears from this cause occurred in thirteen cases, a percentage of 2.23. Lennox Browne (8) found it in thirty-two patients out of 1424, or in 2.24 per cent. Langdon Down found it in 3.6 per cent. of male congenital idiots, but he states that it is seldom to be observed in idiocy developed during post-uterine life. It is important to note that the majority of his cases were also epileptics. Othæmatoma is more common in men than in women. Lennox Browne found it in 3.39 per cent. of male patients, and only in 1.11 per cent. of females. The left ear is more commonly affected than the right in the proportion of three to one, according to the same authority, who also states that both ears are affected in one-third of all cases, the left being then usually first involved. Hæmatoma auris has been observed in all the common forms of insanity. It is, however, especially prone to occur in general paralysis, epilepsy, and acute and chronic mania. All patients subject to attacks of excitement appear to be particularly liable to it. Its occurrence is generally regarded as warranting a bad prognosis as to the course of the pathological process going on in the brain. Clouston (31) states that he has "seen only four or five cases perfectly recover out of over eighty who had fully-developed hæmatoma auris, and four others who made partial recoveries after slight threatenings of hæmatoma, which might not have developed fully or were stopped by blistering fluid."

External Appearances.—Othæmatoma commences most frequently about the helix as a tense, ovoid, fluctuating swelling of a livid colour, which may remain limited to a small area, or extend so as to involve the whole of the cartilaginous portion of the ear. The swelling increases gradually until, in the course of a few hours to several days, it may attain the size of a hazel-nut, or even of a hen's egg. Rupture of the cyst occasionally occurs at this stage. In these cases, or when the cyst is opened artificially, the contents are found to be composed either of fluid blood that has not undergone much change, or of a pale gelatinous material which is simply decolourised blood-clot. After from one to three weeks the tumour begins to undergo shrinkage. This process, unless interrupted by the occurrence of new hæmorrhages, generally continues until great deformity is produced, in severe cases the ear ultimately appearing as a shrivelled and shrunken mass.

Perichondritis auriculæ is a condition which requires to be dis-

tinguished from othæmatoma. It does not seem to occur specially in the insane. According to Pietersen (19) only a small quantity of effusion occurs and the swelling persists, but no further deformity results.

Views that have been advanced regarding its Pathology.—In 1846 Leubuscher (2) advanced the theory that othæmatoma is an erysipelas of the ear, which leads to hæmorrhage between the cartilage and the perichondrium. Two years later Franz Fischer (3) described the occurrence of cysts in the cartilage, or between it and the perichondrium, and maintained that the blood effusion in hæmatoma auris takes place primarily into such cysts. In 1860 Gudden (4) endeavoured to show that othæmatoma is entirely traumatic in origin, resulting from forcible separation of the perichondrium from the cartilage, and hæmorrhage from the vessels that are thereby ruptured. He maintained that Fischer's cysts are also the result of injuries. In 1863 Virchow (5) lent the weight of his authority to Fischer's views. In the following year Pareidt (6) also confirmed Fischer's theory, and at the same time gave a fuller description of the softening process in the cartilage, and made the observation that the walls of the cyst frequently contain new vessels. In 1865 L. Meyer (7), before becoming acquainted with Pareidt's work, arrived at similar conclusions, as the result of extensive observations mainly upon the ears of the mentally sound. In addition, however, to primary softening of the cartilage, he described the occurrence of "enchondromata," which undergo secondary softening and thus lead to the formation of cysts. He attached very great importance to these enchondromata in relation to hæmatoma auris. In 1891 Tischkow (23) recorded some observations which support the theory that othæmatoma is primarily due to degenerative changes in the cartilage. My knowledge of his work is limited to that obtainable from the three reviews of his monograph (which is in Russian) mentioned in the Bibliography. From these it would appear that his view is merely that degeneration and vascularisation occur in certain areas of the cartilage, and that, with or without the aid of traumatism, rupture of the new vessels takes place. There is no mention of the formation of cysts previous to the effusion of the blood. In 1892 Pellizzi (21) announced the discovery of streptococci in the effusion in recent othæmatomata, and contended that they are the cause of the lesion. He found that the organisms were practically identical with the *streptococcus erysipelatis*, and he maintained that all cases are initiated by cutaneous erysipelas. His theory is therefore virtually a revival of Leubuscher's view. In this paper he mentions the fact that Vassale made several cultures from the fluid in an othæmatoma, all of which remained sterile. In another paper published in the following

year, Pellizzi (22) gave an account of some experimental observations "upon the influence of vasomotor paralysis and section of the sensory nerves, on the development of the inflammation and abscess produced by the streptococci of othæmatoma of the insane." The chief conclusions derived from these experiments, which were conducted upon rabbits, were that section of the sympathetic in the neck diminishes the effects of inoculation into the ear (at least for the first few days after the section), and that on the other hand section of the sensory nerves aggravates these effects. He maintained his opinion that "othæmatoma is a clinical manifestation analogous to erysipelas." In the same year Goodall (24) quite independently observed the occurrence of the *staphylococcus pyogenes aureus* and *albus* in the effusion in three cases of hæmatoma auris, and the latter organism alone in two others. He claimed that an etiological significance was to be attached to their presence. Shortly afterwards Dr Middlemass (26) and I contended that there was strong histological evidence in favour of the view that the proclivity of the insane to othæmatoma is due to a peculiar degenerative change in the cartilage of the ear, and that the specific infective theory is untenable. In 1896 Pellizzi (27) published another paper, in which he discussed the relation of hæmatoma auris to traumatism, and maintained, in accordance with his previously expressed opinions, that almost always in the insane the primary cause of the lesion is a local infection. In the same year I published an account of further researches upon the histological changes occurring in the ear-cartilages of the insane and mentally sound (28), on the ground of which I supported the view of the etiology of hæmatoma auris originally advanced by Fischer; and D. A. Welsh (29) described a bacteriological investigation upon the subject, the results of which tended to confirm his opinion, based upon general considerations, that the infective theory is erroneous.

Numerous other theories, in addition to those indicated above, have been advanced to explain the occurrence of othæmatoma. Mabile (13), Cobbold (25), and many others have expressed the belief that it is the outcome of special degenerative changes in the vessels of the perichondrium, or of those of the subcutaneous connective tissue. Numerous other writers, including Pietersen (19), and Alexander Robertson (9), have advocated the view that the undoubted predisposition of the insane to this lesion is the result of disease of the vasomotor fibres of the cervical sympathetic, in consequence of which a condition of local hyperæmia and of liability to vascular rupture is produced. Othæmatoma has further been ascribed to "otitis externa," inflammation of the cartilage, a congestive state of the head or brain, disease of the restiform bodies, etc.

Preliminary changes in the Ear-Cartilages.—As already indicated,

my own investigations convince me of the accuracy of the view of the pathology of hæmatoma auris originally advanced by Fischer and subsequently supported and extended by Virchow, Pareidt and L. Meyer. I have, however, been unable to find any evidence of the occurrence of the enchondromata described by Meyer. Before I give an account of these investigations, which deal chiefly with the changes that occur in the tissues prior to the development of othæmatoma, it is necessary to direct attention to certain features of the normal structure of the ear-cartilage. The stain that I have found most satisfactory for the general study of the morbid as well as of the healthy cartilage, is picrocarmine, employed in the usual way.

The yellow or elastic cartilage (plate I. fig. 1) contained in the external ear is generally regarded as being in the adult a non-vascular structure, nourished only by the vessels of its perichondrium, though it is known that some arterioles pass through it from behind forwards in order to reach the anterior aspect of the ear. Meyer has, however, stated that some of these perforating vessels give off branches which ramify in the cartilage. For my own part, I have not been able to obtain any microscopic evidence of the accuracy of this observation. The perichondrium is a very tough and dense fibrous tissue membrane of considerable thickness. It blends gradually with the cartilage, so that in transverse sections it is impossible to say where the one ends and the other begins. In the healthy condition the two structures can only be separated from each other with difficulty. If a portion of the perichondrium is forcibly torn from the cartilage with forceps, it will be found on microscopic examination that the separation has occurred at a deep level, so that the membrane carries with it at numerous spots, cells that can be recognised as belonging to the cartilage. In the examples that I have seen of detachment of the perichondrium as the result of a morbid process, the line of separation has always been at this same level. Transverse sections of the ear give the impression that vessels are only numerous in the outer layers of the perichondrium and practically absent in its deeper portion. It might therefore be questioned if simple detachment of the perichondrium is followed by effusion of blood beneath it, as has been asserted. I have been able to demonstrate, however, by the use of surface sections of the perichondrium forcibly torn off from the healthy ear-cartilage, that a small number of capillaries do exist even in close proximity to the cartilage-cells, so that it must be admitted that separation of the perichondrium involves tearing across of vessels.

The degenerative lesion that has been found by the observers above named to affect the ear-cartilage is capable, I think, of a more complete and precise description than they have given of it, although I am not fully acquainted with the work of Tischkow on the subject.

According to my own observations, which extend to considerably over a hundred different ear-cartilages, the following are the various stages that the lesion typically presents.

Although the initial change begins in the cartilage-cells, the earliest deviation from the normal that is readily recognised under the microscope, is the disintegration and disappearance of the yellow elastic fibres (fig. 2). They break up into minute droplets, which, while they remain, preserve an affinity for picric acid in picrocarmine preparations, but soon entirely disappear. This change may affect small or large areas, sometimes involving the whole breadth of the cartilage. The cartilage-cells of the tissue involved always show marked degenerative changes (fig. 3). Pareidt and Meyer are agreed that these are not essentially of a fatty nature. The cases that I have examined entirely bear out this view, although granules that blacken with osmic acid may occasionally be seen. What appears to be the essential morbid change may frequently be observed in the cartilage-cells near the edge of the areas devoid of elastic fibres, as well as within them. It shows itself first in the development in the protoplasm of fairly large globules which give the cell a vacuolated appearance (fig. 7). These globules are not blackened by osmic acid, and remain unstained in picrocarmine preparations. Their presence is associated with more or less marked shrinking of the nucleus, and latterly with loss of its affinity for carmine. As the result of this vacuolar degeneration, the whole cell ultimately breaks down and disappears. It is, however, usually much later in completely disappearing than the elastic fibres. When merely the latter are lost, the cartilage is reduced to the form of hyaline-cartilage or white fibro-cartilage. In some instances white fibres are very distinct, while in others they are apparently absent. One form of this fibrillation, generally combined with more or less complete degeneration of the cartilage-cells, is peculiar in that its direction is always at right angles to the perichondrium. The changes are as a rule most advanced in the centre of the degenerated area. Here the cartilage-cells first entirely disappear, leaving a homogeneous or slightly granular or fibrillated substance which stains faintly with carmine. If such an area is small and connected directly with the perichondrium, it may become penetrated by vessels at this stage, the whole area ultimately becoming replaced by vascular fibrous tissue (fig. 4). But as a rule, and always when the degenerated area is large, the central portion liquefies, so that a cyst is formed (fig. 9). This breaking down of the homogeneous or granular substance is generally accompanied by the formation of large globules which stain with carmine, and which are not blackened by osmic acid. The cyst comes ultimately to be filled with clear fluid. Some portion of it is usually in immediate connection with the perichondrium, from which,

or occasionally perhaps from contiguous perforating arteries, vessels pass in, extending in time more or less completely round the wall (fig. 5). In the course of these changes small round cell infiltration of the cartilage or of the perichondrium practically never occurs, and thickening of the latter, such as might be expected to accompany chronic inflammatory change, is also entirely absent. The original change in the cartilage can only, I think, be looked upon as degenerative in character, and in the subsequent penetration of the part by vessels we have to recognise nature's effort to repair the damage inflicted by the lesion.

From an early stage these degenerated areas can be readily observed with the unaided eye on section of the fresh cartilage. The opaque pale yellow appearance of the healthy tissue is replaced by grey semi-transparent gelatinous spots. Cysts, when present, can be recognised without any difficulty. The degenerated areas are usually multiple, and may be very numerous. They may be rounded, elongated, or irregular in form (fig. 9). When advanced they are generally associated with a degree of local swelling of the cartilage. They may affect any portion of the cartilage, but they are certainly most frequently developed in its anterior half. A long narrow strip immediately subjacent to the anterior perichondrium is somewhat frequently to be observed. Cysts may be minute or may extend over a large portion of the ear-cartilage, not infrequently measuring $\frac{1}{2}$ in. or more in different directions. When large they are always slit-like, and contain only watery fluid which never distends them.

In order, if possible, to determine more precisely than has hitherto been done, the relationship of this morbid change in the ear-cartilage to hæmatoma auris, I have, in the course of the investigation already referred to, made a comparison of the condition of the left ear-cartilage in two series of fifty cases, one being from the insane and the other from the mentally sound. Taking first the results of the examination of the series from the mentally sound, I found that there were only two out of the fifty in which this degenerative lesion was entirely absent. But although it had thus to be recorded as present in forty-eight cases, in the majority of these it consisted merely in the loss of the elastic fibres and slight degeneration of the cartilage-cells in exceedingly minute areas. It had proceeded to the development of a cyst in only eight cases. In no instance had the wall of a cyst become vascular. In eleven cases small areas of the cartilage were replaced by vascular fibrous tissue. There was no example of true hæmatoma, though one case showed a small quite recent blood-extravasation in an area of granulation tissue. The fifty cases from the insane, although not altogether consecutive, were quite unselected, so that they form a fair comparison with those from the mentally

sound. In this series there were likewise only two cases in which the degenerative change could not be found. With respect to the severity of the lesion, however, there was a difference of the most marked kind. It had advanced to a cystic stage in thirty of the cases as contrasted with eight in the former series. In eight out of these thirty cases there was vascularisation of the cyst-wall. Four of these were examples of recent othæmatoma. In eight other cases there were areas of vascular fibrous tissue in the cartilage. The series included two old hæmatomata. Striking as these numerical differences undoubtedly are, they do not convey a full idea of the preponderance of this degenerative change in the ears of the insane over those of the mentally sound. In the number of the separate areas of morbid change, and in the extent of tissue involved, there was a contrast of the most marked kind. It can, I think, scarcely be disputed that these statistics entirely bear out the theory long ago advocated by the four German investigators already named. At the same time, they supply new data that throw additional light upon the pathology of hæmatoma auris.

Each of the four recent hæmatomata in the above series—or five in all, as in one case both ears were affected—showed a cavity which was entirely subperichondrial, while the cartilage was extensively affected by the preliminary morbid change already described in all its stages. The two old-standing hæmatomata, as well as a third one not included in the series, showed cicatricial tissue and portions of cartilage bounded likewise by a perichondrial layer. In a case of choreic insanity, not included in the above series, I found in the left ear a condition which demonstrated in a very convincing way the accuracy of the German theory. In the lower half of the cartilage there was an extensive cleft-like cyst, measuring about 1 in. in a vertical direction, and about $\frac{1}{2}$ in. in length in a horizontal section of the ear. The cartilage was much broken up, some small pieces being completely detached. The cavity, which was in no way distended, contained clear watery fluid. On microscopic examination, the cartilage presented all the stages of the degenerative change that has been described. The cyst was entirely subperichondrial, and at places its walls contained numerous vessels, many of which were much degenerated. There had certainly been no large hæmorrhage into the cyst, although indications of a small recent extravasation were to be observed in one part of the wall. It is evident that a slight injury to this ear would have resulted in the development of a typical othæmatoma.

Conclusions regarding the Pathology.—On the ground of these observations I conclude that, in the typical othæmatoma commonly seen in asylum patients, the hæmorrhage usually takes place from new vessels in the walls of a cyst that has developed in the ear-cartilage as

the result of a chronic degenerative change, less commonly from the vessels of new tissue which replaces a portion of the cartilage independently of the formation of a cyst, and, though probably only very rarely, from those of the perichondrium which have been ruptured in consequence of fracture of the cartilage at a degenerated spot, an occurrence to which reference will be made presently. I also conclude that the frequency of hæmatoma auris in the insane as compared with the mentally sound is owing to a corresponding difference in the severity with which this degenerative change affects the ear-cartilage in the two classes of individuals.

A most important question still is, What determines the hæmorrhage from the vessels within the cartilage? It is commonly believed that new vessels are specially prone to rupture. This generalisation is, however, I think, scarcely accurate. Observations upon the morbid changes occurring in the dura mater of the insane incline me to believe that new vessels have no special tendency to give way if they are in a healthy condition. They are, however, more liable to impairment of nutrition than the original vessels of the tissue, and I maintain that when they rupture independently of traumatism it is in consequence of degenerative changes that they have undergone. Now, there is abundant evidence of the occurrence of degeneration of the new vessels that form in the ear-cartilages. The morbid change that they specially exhibit consists in a glassy swelling of the fibrous tissue immediately outside their endothelium (fig. 5). It is one that agrees essentially with the hyaline fibroid degeneration that so commonly affects the intracranial vessels. This lesion in its early stages implies softening of the affected tissues, and therefore diminished power of resistance to the normal blood-pressure, and special liability to rupture. I think that there is good ground for believing that hæmorrhage may occasionally occur from these morbid vessels quite independently of traumatism. At the same time, it is easy to understand that a slight injury which would not result in the rupture of healthy vessels, may determine the giving way of these morbid ones.

When rupture of vessels occurs in the wall of one of these ear-cysts, blood is slowly poured out, gradually distending the cavity. Although the cysts are often of considerable size before hæmorrhage takes place into them, there is conclusive microscopic evidence that when they become distended with blood they enlarge by gradual separation of the perichondrium from the cartilage at the margins of the cavity. How this separation is effected it is somewhat difficult to say precisely. It is known that the effusion comes to be under a considerable degree of tension, owing, there can scarcely be any question, to the continued oozing from the ruptured vessels. Hence the cavity tends to enlarge in the direction of least resistance. As

already indicated, the weakest spot is in the deeper layers of the perichondrium, and it is therefore along a line in this position that the cavity extends. The continuous undue strain to which the tissues are subjected probably causes those at the angle formed by the cartilage and the perichondrium to become weakened, and to give way after some hours, so that a gradual detachment of the perichondrium results.

The extravasated blood appears to be somewhat slow to coagulate, or to coagulate imperfectly. It is probably for this reason that the effusion often continues to increase for several days. As already stated, however, separation of the perichondrium is attended by rupture of some capillaries, and to the blood effused from these the progressive enlargement of hæmatoma may in part be due. Even at an early stage it is sometimes found, if the cavity is laid open, that the contents are not fluid blood, but are of a pale clear gelatinous character. This fact has to some authorities presented a difficulty in the way of accepting the view that the process is a hæmorrhagic one at all. But this is exactly the condition of the contents that we should expect to find after coagulation of the blood has taken place. The great rapidity with which red corpuscles break down and disappear under certain conditions is as yet very imperfectly realised. Abundant microscopic evidence of the fact is, however, furnished by a study of the microscopic changes following hæmorrhage into the subdural space. When the blood in an othæmatoma coagulates, it is deposited on the walls of the cyst, while a quantity of clear fluid remains in the centre (fig. 10). Vessels penetrate the fibrin from the wall of the original cyst, or directly from the perichondrium (fig. 6). A thick layer of granulation tissue is formed which undergoes higher development, and after a time begins to contract, leading generally to great distortion and puckering of the pinna. The cyst usually becomes completely closed, and there remains a mass of cicatricial tissue usually containing numerous islets of cartilage, and sometimes pieces of tissue having osteoid characters. As already stated, in the cases of old othæmatoma that I have observed, the cicatricial tissue was always limited by cartilage or perichondrium.

When hæmorrhage takes place in a vascularised area in the cartilage not associated with a cyst, the effused blood is probably capable of pushing its way below the perichondrium so as to form a typical hæmatoma. It is doubtful, however, if this occurs very often, because it seems probable that such hæmorrhages are generally rapidly arrested and of small size. At the same time, there is reason to believe that small hæmorrhages occur in these areas with some frequency, for many of the patches of fibrous tissue that may be found in the ear-cartilages, especially of the insane, are of greater extent than can

be easily accounted for by the mere vascularisation of a degenerated area.

The loss of the elastic fibres which attends the degenerative change greatly diminishes the elasticity of the cartilage, and consequently renders it very liable to fracture when it is bent. The series of cases examined presented several examples of this accident in association with degeneration. In none of these was it attended with hæmorrhage when the degenerated area had not become vascularised. At the same time, it must be admitted that a fracture across such an area is liable to cause some detachment of the perichondrium; and this, as has already been contended, implies rupture of vessels, so that a typical hæmatoma may develop. Fracture across an area that has become vascular must be much more liable to produce the same result. The examinations that I have made, however, most strongly favour the view that, although hæmatomata may arise, especially after traumatism of considerable severity, from vascularised areas, and in consequence of fractures at spots where the cartilage is degenerated without vascularisation, yet, vascularised cysts are in the great majority of instances the starting-point of the lesion.

One or two points still require a word of explanation. It is well known that hæmatoma is far more common in the left ear than in the right. Several cases in which I have examined both ears microscopically have shown most distinctly that the degenerative lesion usually affects the left ear much more severely than the right, and in this fact we must, I think, recognise the explanation of the special proclivity of the same ear to hæmatoma. As to the primary cause of the degeneration of the cartilage, it would be impossible in the meantime to do more than theorise. But it can be shown that the insane are specially prone to chronic morbid changes in all the coverings of the brain, from the pia-arachnoid to the scalp; and I think we are warranted in attributing their special proclivity to this lesion in the ear-cartilage to the same abnormal nutritional state which seems to be in some way dependent upon the subjacent morbid brain. Indeed, this degenerative lesion of the cartilage in its more severe forms is especially met with in those cases in which these other morbid changes are most pronounced, such as general paralysis.

It has also been stated that othæmatoma always occurs on the anterior aspect of the ear, and never on the posterior. There are, however, distinct fallacies underlying this statement. For one thing, the effusion is not in front of the perichondrium, as has often been supposed. It is, however, certainly the case that the preliminary degenerative changes are most common on the anterior half of the cartilage, and that it is generally the anterior perichondrium that becomes detached when the cavity of an othæmatoma enlarges. Yet

this is by no means always so. The true explanation of the anterior projection of the tumour is, I think, to be found in the fact that the general shape of the ear is concave forwards, so that the swelling must occur chiefly on the anterior aspect. If a recent hæmatoma is examined, it may be observed that at the point of the ear which is normally concave backwards, namely, the hollow corresponding to the antihelix, a similar posterior swelling occurs.

Criticism of other views.—It is evident that if we accept Fischer's theory as to the origin of hæmatoma auris, we must reject each of the others that have been advanced, except in so far as some of them may help to explain the primary cause of the degenerative lesion. We certainly, however, can no more admit Gudden's contention, that the degeneration of the cartilage is due to traumatism, than we can accept his view that all othæmatomata arise entirely from this cause. Investigation seems still to be required to determine whether or not the degenerative changes in the ear-cartilages have any etiological relationship to morbid conditions of the vessels of the perichondrium and adjacent tissues. But we must in any case reject the theory that the hæmorrhage in typical othæmatoma is merely the result of degeneration of these vessels. If the blood escaped from the vessels of the subcutaneous fibrous tissue, it would not be subperichondrial in position; and there is abundant histological evidence that much more extensive lesions than mere structural alterations in the capillaries of the perichondrium precede the development of hæmatoma auris.

The theory of the infective origin of othæmatoma must also, I think, be rejected as entirely erroneous. Notwithstanding the deservedly high position that Pellizzi now holds among the workers in the domain of pure neurology, it seems to me that in his excursion into this closely adjacent field he has assumed a position that is logically untenable. It is to be remarked that the evidence upon which he founds his conclusion does not include any systematic histological investigation of the changes occurring in the tissues involved. Indeed, he seems to have been unaware of the observations of Fischer and others upon the preliminary changes in the ear-cartilages. The case against the infective theory from the bacteriological point of view has been very clearly stated by D. A. Welsh, from whose important contribution to this controversy I quote the following passage:—"The organisms so frequently present must be either the cause or an accident of the condition. In the former case, either they must have the power of producing those early degenerative changes in the cartilage which precede the formation of the hæmatoma, or they must by their presence determine the occurrence of the hæmatoma from a degenerated patch already present, or from healthy cartilage.

"There is, however, absolutely no proof that micro-organisms are at all related to simple cartilage degeneration, and the completely negative results of the examination for bacteria which I made of the pieces of cartilage are strongly against this alternative.

"Hence, if the presence of micro-organisms is not to be considered purely accidental, it must be shown that they are the direct cause of the hæmatoma. This is the position for which Pellizzi contends, and which Goodall is inclined to support, but in my opinion it is quite untenable, for the following reasons:—(1) The cases quoted by Pellizzi, Goodall, and myself show that no single organism can be regarded as the specific cause, since at least three different varieties have been found. (2) The results of Vassale, Goodall, and myself further show that organisms are by no means constantly present, but that there is a considerable proportion of cases which, when examined with all due care, give purely negative results. (3) By inoculation of pure cultures, Pellizzi has consistently failed to reproduce the condition, causing simply inflammation and suppuration in varying degrees of severity. (4) The organisms hitherto discovered are all identical with well-known pyogenic forms which, so far as I am aware, have never been found to produce any condition analogous to hæmatoma auris. It is obvious, then, that the evidence on which is based this theory of a casual relation is very fragmentary, and, even in the absence of any more probable hypothesis, could hardly be accepted. It is possible, however, to find a perfectly rational and sufficient cause for the occurrence of othæmatoma altogether apart from the action of micro-organisms. . . . The conditions which precede and which determine the formation of the hæmatoma may be consistently explained by a series of pathological changes which are essentially degenerative in their nature and are quite independent of bacteria.

"The conclusion, therefore, to which the evidence most strongly points is, that the relation of micro-organisms to othæmatoma is purely accidental. It is not the presence of organisms that determines the formation of the hæmatoma, but, on the contrary, it is the hæmatoma that affords a subsequent nidus for organisms. Nor is it difficult to understand how such access may be obtained. Any subcutaneous effusion is more or less liable to become inoculated, and, in the insane, this liability is considerably increased, more especially when such an exposed part as the ear is affected. For, owing to the carelessness or restlessness or actual violence of the patient, or owing to his fingering the damaged part, there may readily be produced an abrasion which may become the channel of infection. In support of this view, I should refer to the second case described by me. The first examination of that case gave a purely negative result, showing that, at its commencement, the hæmatoma was practically sterile. A second

examination, however, by precisely similar methods, revealed the presence of streptococci in great abundance, showing that a later infection had occurred."

L. Scabia (32) has recently disputed the contention of Pellizzi that othæmatoma is due to infection by the micro-organism of erysipelas. He concludes, from evidence which it must be maintained is wholly insufficient, that the lesion is caused by the common pyogenic streptococcus.

Conditions giving rise to Othæmatoma in the Mentally Sound.—When it occurs in the mentally sound, othæmatoma is in almost every instance known to have followed an injury to the ear. This is usually of a severe character, being commonly received in boxing, playing football, or wrestling. Naturally the opportunities of examining such othæmatomas microscopically are extremely rare. I have as yet only studied one example, which was sent to me by Dr G. M. Robertson from Murthly Asylum. A patient in that institution, in falling in an epileptic fit, sustained a severe contusion of one ear. He died next day. In the fresh state the ear presented in its upper half the usual appearances of a severe bruise with much ecchymosis. On cutting into this part, it was found that the subcutaneous connective tissues were infiltrated with recently effused blood, which lay chiefly in front of the cartilage. There was a fracture of the cartilage about $\frac{1}{2}$ in. in length near its outer edge. Microscopic examination showed that the blood was entirely outside the perichondrium. The cartilage presented some small areas of early degenerative change, but no vascularisation. It is clear that this was an extreme case of traumatic othæmatoma, and one that probably would not have followed the usual course. Considering the frequency with which vascularised areas occur in the ear-cartilages of the mentally sound, I think that it is most probable that the majority of the typical othæmatomata that develop in them after a traumatism arise from rupture of new vessels that have formed in the cartilage. The injury is probably frequently attended by fracture through the vascularised area and some separation of the perichondrium. At the same time there is sufficient reason to believe that extensive degeneration of the ear-cartilages and the formation of vascular cysts may occasionally occur quite apart from mental disease. Dr Oliver (30) of Newcastle has lately described a very interesting case of double hæmatoma auris, which seems to me to bear out this opinion. Although there was no history of mental aberration, there was a very distinct one of anæmia from insufficient food, alcoholism, and traumatism. The patient, a woman aged thirty-six, was struck a violent blow on each ear by the closed fist of another woman. The ears swelled up almost immediately, and when seen a week later they presented the typical appearances of

a recently developed othæmatoma. It appears probable that in this case the general mal-nutrition had induced extensive degeneration of the cartilage of the ears, which had gone on to the formation of vascular cysts, into which blood was effused as the result of the traumatism.

Summary.—It may be useful to briefly sum up what seem to be the essential facts regarding the pathology of this interesting lesion.

Hæmatoma auris is predisposed to in the insane by the occurrence in a severe form of certain morbid changes in the ear-cartilage. These affect small or large areas. They consist in degeneration of the cells, loss of the elastic fibres, and breaking down of a portion of the hyaline basis of the cartilage, so that a cyst is formed. If the area is small a cyst does not usually form. New capillaries (derived from the perichondrium) develop in the walls of these cysts or in the small degenerated areas. The early stages of these morbid changes are extremely common in the mentally sound as well as in the insane. Their advanced stages and extensive development are, however, only common in the latter. Vascular-walled cysts occur in the ear-cartilages of about ten per cent. of the insane. The new capillaries are very prone to degenerative changes, especially to one that is probably identical with the hyaline fibroid degeneration so common in the intra-cranial vessels. The great majority of othæmatomata are the result of hæmorrhage into one of these intra-cartilaginous cysts from the new vessels in its walls. It is probable that the hæmorrhage may sometimes occur spontaneously in consequence of degenerative changes in the vessels. Usually, however, a slight traumatism initiates the effusion. The blood is somewhat slowly poured out until it distends the cyst, which then enlarges by separation of the perichondrium from the cartilage. The hæmatoma may thus continue to increase in size for several days. It forms a large, tense fluctuating swelling, the skin over which is generally somewhat congested. In other cases similar results may be brought about by hæmorrhage from the new vessels in a small vascularised area not associated with a cyst. Fractures are very liable to occur at degenerated spots, owing to diminution of the elasticity of the cartilage. Rupture of new vessels is thus sometimes brought about. It is probable also that fractures through degenerated areas which have not become vascular may result in hæmorrhage from the vessels of the perichondrium and the development of a typical hæmatoma. It is, however, only the hæmorrhages into previously developed cysts that commonly attain to a large size.

The effused blood coagulates upon the walls of the cavity and becomes penetrated by vessels. A thick layer of granulation tissue is formed and subsequently develops into dense fibrous tissue. The contraction associated with the formation of this leads to great distortion and shrinkage of the pinna. Occasionally suppuration occurs in a recent othæmatoma.

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DESCRIPTION OF PLATE I.

All the preparations from which the drawings were made were transverse sections of the ear-cartilage stained with picrocarmine.

- Fig. 1. Portion of normal cartilage and perichondrium. ($\times 450$.)
- Fig. 2. Small degenerated area showing disintegration of elastic fibres and loss of cartilage-cells. From a case of general paralysis. ($\times 450$.)
- Fig. 3. Edge of a larger degenerated area showing loss of elastic fibres and degeneration of cartilage-cells. From a case of alcoholic insanity. ($\times 450$.)
- Fig. 4. Area of vascular fibrous tissue in cartilage. From a case of general paralysis. ($\times 100$.)
- Fig. 5. Vascularised wall of a large cyst in cartilage. *a.* Perichondrium. *b.* Cartilage devoid of elastic fibres. *c.* Granulation tissue with vessels showing thickened and hyaline walls. *d.* Cavity of cyst. From a case of general paralysis. ($\times 450$.)
- Fig. 6. Anterior wall of somewhat recent hæmatoma. *a.* Perichondrium. *b.* Thin layer of cartilage. *c.* Vascular fibrous tissue. *d.* Inner layer formed of blood-clot which is becoming vascularised. From a case of general paralysis.

- Fig. 7. Edge of degenerated area showing vacuolation of protoplasm of cartilage-cells. Osmic acid preparation. From a case of general paralysis. ($\times 450$.)
- Fig. 8. Normal cartilage, perichondrium and extra-perichondrial fibrous tissue. ($\times 2$.)
- Fig. 9. Degenerated cartilage showing a large cyst. The spot marked (*a*) is that from which Fig 5 was drawn. ($\times 2$.)
- Fig. 10. Somewhat recent hæmatoma showing degeneration of cartilage and detachment of anterior perichondrium. From a case of general paralysis. ($\times 2$.)

PLATE I.

Fig. 1.

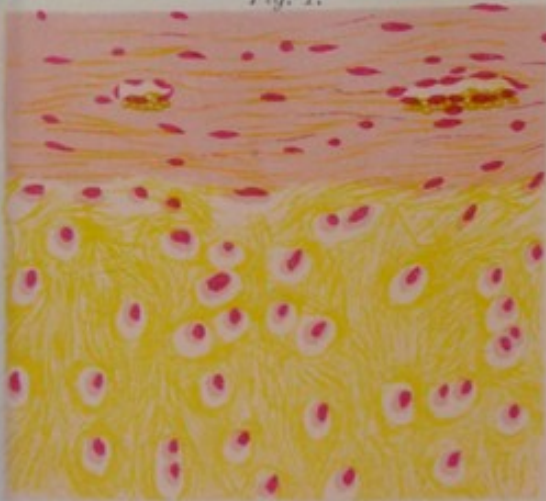


Fig. 2.



Fig. 3.



Fig. 4.



Fig. 5.

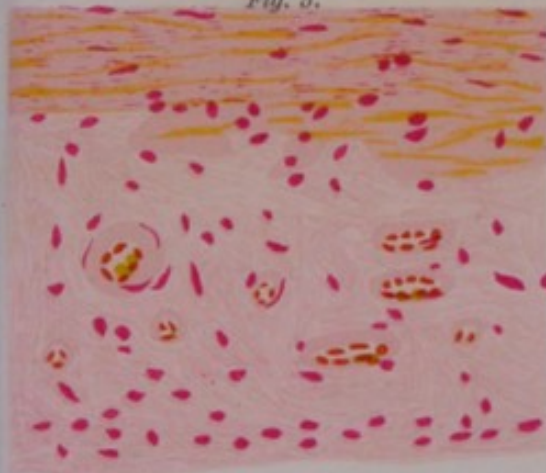
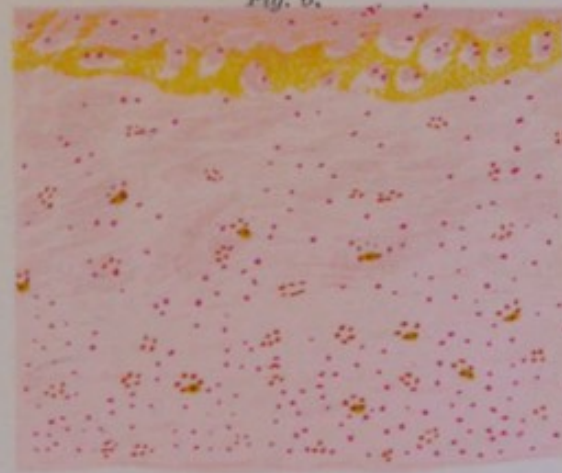


Fig. 6.



a
b
c
d

Fig. 7.



Fig. 8.



Fig. 9.



a

Fig. 10.





CHAPTER IV

MORBID CONDITIONS OF THE SKULL.

(PLATES II., III., IV., AND V.)

MORBID conditions of the skull are essentially of two classes. Firstly, there are variations in form and size overstepping the limits of the typical or normal; and, secondly, there are changes in the structure of the bone, evidenced by abnormalities in thickness, consistence, and histological characters. Those of the first class are for the most part peculiarities of individual growth determined by conditions that are established especially in late intra-uterine and early extra-uterine life. Those of the second class, on the other hand, are in a large measure independent of development, being capable of initiation at almost any period of life, as the result of various morbid influences.

The form and size of the skull are of interest and importance, chiefly because it is believed that their characters are largely determined by those of brain-development. As Macalister (40) expresses it, "Brain-shape determines skull-shape, and is the mould on which the skull is developed." Granted that this is so, then, since the paramount influence for good or bad in early brain-development is heredity, the morphological characters of the skull become in some measure an indication of the natural qualities of the brain. The general truth of the dictum that the growth of the skull is dominated by that of the brain, scarcely admits of dispute. It is attested by a large array of observed facts, both of a physiological and of a pathological nature. At the same time there are unquestionably other, though usually less potent, influences that play their part in the shaping of the skull, and serve to render it a less accurate index of the natural qualities of the brain than it would otherwise be. Virchow has attached great importance to localised premature synostosis as a cause of malformations of the skull. Much of his teaching regarding this matter has, however, been proved to be erroneous, and it is now certain that premature closure of sutures is a factor of much less importance in this connection than was once supposed.

Craniology, which concerns itself with all that relates to the morphological characters of the skull, is now an important science,

precise in its methods of investigation, rich in accumulated facts, and with a very extensive literature of its own. It has various special branches, of which the study of the cranial anomalies associated with mental diseases may be regarded as one. Another, and at certain points closely related branch, forms a department of criminal anthropology.

It is to be borne in mind that there are three different conditions under which the human skull may be studied. In the first place, in the living subject an approximate estimate may be made of a few of its more important measurements; in the second place, at post-mortem examinations a much larger series of observations may be made, alterations in texture and thickness may be noted, and portions of the bone may be preserved for future histological examination; in the third place, the skull may be examined in the macerated and dried state, in which alone an accurate and complete series of measurements can be made.

Although the abnormalities of form and size that manifest themselves in the skulls of asylum patients have for long been investigated by numerous observers, it cannot be said that, in this country at least, sufficient data have yet been collected upon which to base trustworthy conclusions regarding the large majority of the questions that naturally demand answer in any systematic account of the craniology of the insane. A large proportion of the observations that have been recorded have been made upon the living subject, and there has been a distinct attempt on the part of several writers, each of whom has generally had a particular set of measurements of his own to recommend, to place the study of the skull in mental diseases upon a scientific basis by the employment of such cephalometric methods. I have no desire in any way to disparage the making of observations of this kind. They have their own scientific and practical value. But it can scarcely be too strongly insisted, for there are many writers who do not seem to appreciate the fact, that measurements made upon the head of the living subject cannot supply the data required by human craniology, but only such as belong to the wider science of anthropology.

Some observers have made a more extensive but, as far as I know, still incomplete series of measurements at post-mortem examinations. Records of the complete examination of dried skulls of insane persons, the exact nature of whose disease was known, are, in our own country, exceedingly few, although such exist, as, for example, the excellent study of the skull of a microcephalic idiot recently published by Cunningham and Telford-Smith (8). Not, however, until such studies have been greatly multiplied can we possess a scientific craniology of the insane.

The great difficulty that has hitherto stood in the way of the

pursuit of exact craniometric observations in relation to insanity in this country is, of course, the practical impossibility of obtaining for study any considerable number of dried skulls of asylum patients. This difficulty does not appear to exist to the same extent in many other countries, where, more especially in Italy, there are museums containing large collections of skulls of persons who have died in asylums. Some of these collections have been very thoroughly studied by competent craniologists. Unfortunately, however, the papers in which the results of such studies are recorded have very commonly been published in a class of journal that does not obtain a wide circulation, and consequently I have found it impossible to get access to more than a comparatively small number of them. At the same time, conclusions derived from the examination of the skulls of the insane of one country can scarcely be regarded as fully applicable to the insane of another country, owing mainly to the differences in the racial characteristics of skulls and in the clinical classifications of mental diseases employed. At most only a very limited number of such conclusions can be of universal application. A thoroughly satisfactory craniology of the insane in this country must be one based upon extensive comparison of the skulls of patients who have died in our own asylums with those of the sane of the same class.

Although the obstacles that lie in the way of such investigations are very great, and have not yet been overcome, I am convinced that they are not insurmountable. I have long been inclined to believe that all the measurements essential to a strictly scientific craniology could be made at post-mortem examinations, although it is only quite recently that I have put the matter to a practical test. The one specially important point in the skull that is not made accessible in the ordinary way of performing a post-mortem examination is the basion. If this could be reached without serious difficulty, all the really essential measurements could be taken.

I am indebted to Dr David Waterston, whose advice I sought regarding this matter, for demonstrating to me that the basion can be readily reached in the post-mortem room subject either through the mouth or nose. He has devised a special limb for Hepburn's craniometer by means of which the basi-bregmatic height and the basi-nasal length may be quickly and accurately measured at an autopsy without any additional disfigurement of the head. I quote from his recent paper (71) on the subject the following description of his method:—

"The difficulties to be overcome are met with, first, in exposing the essential bony points; and, second, in measuring the intervening distances.

"1. The bony points on the vault are easily accessible, as it is only necessary to make the usual transverse incision across the head, from ear to ear, and to reflect the flaps forwards and backwards a little further than usual, so as to expose the

nasion in front and the occipital point behind. The temporal muscle should also be reflected from its fossa on either side.

"But a little dissection is necessary to expose the point on the base of the skull from which measurements of the height and of the prognathism of the skull require to be taken, and the ordinary calipers are of a shape unsuitable for taking the measurements.

"The basion is best reached from the anterior aspect, where it is only separated from the pharyngeal cavity by the mucous membrane and some ligamentous bands. The mouth should be opened to its full extent, and the posterior wall of the pharynx examined with the forefinger, and the bony prominences there carefully identified. At the level of the hard palate a prominent bony transverse ridge is readily felt: this is the anterior arch of the atlas vertebra, and on its centre is a well-marked tubercle. About half an inch above this the pharyngeal tubercle of the basi-occipital bone is felt, and between these two points lies the basion. A sharp-pointed knife is now to be passed along the forefinger, and a transverse incision about an inch and a half in length made between the bony points, dividing the mucous membrane, the anterior ligament between the atlas and the occiput, and the fibres passing from the odontoid process to the same region. In fact, the under surface of the anterior margin of the foramen magnum is cleared, and, practically, this is found to be a very easy matter, when the bony points have been made out. As a preliminary, it is advisable to swab out the mouth with a small sponge moistened with spirit, and a rubber glove is useful in protecting the hand from any sharp edges of the teeth, without seriously affecting the tactile sense.

"2. In taking the measurements, a suitable kind of caliper must be used; and the form of instrument devised and described by Dr Hepburn¹ is very good, as, by it, measurements of asymmetry can be taken.

"An additional limb must, however, be used to take the measurements from the basion, in place of one of the curved limbs of this instrument. This limb must be shaped so that its free end can be brought against the basion from the mouth or nose, while at the same time the rest of the instrument is free to move, so that the other limb can be made to touch the bregma."

For a description of this instrument and of the way in which it is used, the reader is referred to Dr Waterston's paper. I have myself made a number of observations with it, and found it to serve its purpose perfectly.

So thoroughly am I satisfied that it is practicable to make upon the skull of the insane at autopsy all the measurements of essential importance in modern craniology, that I think it is worth while to go into the subject somewhat fully here, and to endeavour to frame a working scheme for such researches in asylums.

CRANIOMETRY.

The following are some of the most important points in the skull from which measurements are taken in making craniological observations (plates ii., iii., and iv.) :—

1. *Nasion, or nasal point.* The centre of the naso-frontal suture.
2. *Glabella, or nasal eminence.* The slight prominence on the outer surface of the frontal bone, just above the nasion.

¹ Hepburn, *Proc. Royal Soc. of Edin.*, vol. xxii., 1899.

3. *Bregma*. The point of junction of the coronal and sagittal sutures.

4. *Lambda*. The point of junction of the sagittal and lambdoid sutures.

5. *Opisthion*. The centre of the posterior margin of the foramen magnum.

6. *Basion*. The centre of the anterior margin of the foramen magnum.

7. *Ophryon*. The centre of the supra-orbital line, or line drawn across the narrowest part of the forehead. It lies just above the glabella.

8. *Occipital point*. The point in the middle line of the occiput farthest from the glabella.

9. *Alveolar point*. The centre of the anterior margin of the upper alveolar arch.

10. *Subnasal, or spinal point*. The centre of the inferior border of the anterior nasal aperture, at base of anterior nasal spine.

11. *Dacryon*. The point of junction of the fronto-maxillary and fronto-lachrymal sutures.

12. *Pterion*. The region near the anterior part of the temporal fossa, where the frontal, parietal, squamous temporal, and ali-sphenoid approach each other in varying proportions in different individuals, generally by an H-shaped suture.

13. *Stephanion*. The point of crossing of the temporal ridge and the fronto-parietal suture.

14. *Asterion*. The point behind the mastoid process where the parietal, occipital, and temporal bones meet by a tri-radiate suture.

15. *Mental point*. The centre of the lower border of the inferior maxilla.

Sir William Turner, who is admittedly the highest authority upon craniology in this country, prescribes the following as the observations required for the complete comparative study of a series of human skulls:—

Collection.	Greatest parieto-squamous breadth.
Age.	<i>Cephalic Index</i> .
Sex.	Horizontal circumference.
Cubic capacity.	Frontal longitudinal arc.
Glabello-occipital length.	Parietal " "
Basi-bregmatic height.	Occipital " "
<i>Vertical Index</i> .	Total " "
Minimum frontal diameter.	Vertical transverse arc.
Stephanic diameter.	Length of foramen magnum.
Asterionic diameter.	Basi-nasal length.

Basi-alveolar length.	Orbital height.	
<i>Gnathic Index.</i>	<i>Orbital Index.</i>	
Interzygomatic breadth.	Palato-maxillary length.	
Intermalar „	Palato-maxillary breadth.	
Nasio-mental length.	<i>Palato-maxillary Index.</i>	
<i>Nasio-mental complete facial Index.</i>	Lower jaw. {	Symphysial height.
Nasio-alveolar length.		Coronoid „
<i>Maxillary upper facial Index.</i>		Condylod „
Nasal height.		Gonio-symphysial length.
Nasal width.		Inter-gonial width.
<i>Nasal Index.</i>		Breadth of ascending ramus.
Orbital width.		

Although slightly different series of measurements have been recommended by other authorities (*e.g.* Mantegazza, 43; Benedikt, 4), we probably could not do better than adopt the above scheme in making craniometrical observations upon dried skulls from persons who have been insane.

The *capacity* is commonly ascertained by completely filling the cranium with sand, shot, or other suitable material, and estimating the quantity used in cubic centimetres. The *glabello-occipital length* is the distance between the glabella and the occipital point. The *basi-bregmatic height* is the distance between the basion and the bregma. The *vertical* (or *altitudinal*) *index* is obtained from the formula—

$$\frac{\text{Basi-bregmatic height} \times 100.}{\text{Glabello-occipital length.}}$$

Crania of which the vertical index is below 70, are termed *tapeinocephalic*; those in which it is above 75, *akrocephalic*; and those in which it is between 70 and 75, *metriocephalic*. The *minimum frontal diameter* is taken immediately behind the external orbital process. The *cephalic* (or *latitudinal*) *index* is obtained from the formula—

$$\frac{\text{Greatest parieto-squamous breadth} \times 100.}{\text{Glabello-occipital length.}}$$

Crania of which the cephalic index is below 70, are termed *hyperdolichocephalic*; those in which it is between 70 and 75, *dolichocephalic*; between 75 and 80, *mesaticephalic*; between 80 and 85, *brachycephalic*; above 85, *hyperbrachycephalic*. The *horizontal circumference* is taken with a tape measure passed across the glabella in front and the occipital point behind. The *frontal longitudinal arc* extends from the nasion to the bregma. The *parietal longitudinal arc* extends from the bregma to the lambda. The *occipital longitudinal*

arc extends from the lambda to the opisthion. The *vertical transverse arc* is measured from the upper edge of each external auditory meatus. The *basi-nasal length* is the distance between the basion and the nasion. The *basi-alveolar length* is the distance between the basion and the alveolar point. The *gnathic* (or *alveolar*) *index* is obtained from the formula—

$$\frac{\text{Basi-alveolar length} \times 100.}{\text{Basi-nasal length.}}$$

Skulls of which the gnathic index is below 98, are termed *orthognathic*; those in which it is above 103, *prognathic*; and those in which it is between 98 and 103, *mesognathic*. The *inter-zygomatic breadth* is the greatest breadth between the zygomatic arches. The *intermalar breadth* is one regarding which there is a want of agreement among the authorities as to the exact points from which it should be measured. It is not, however, a very important measurement. The *nasio-mental length* is the distance between the nasion and the mental point. The *nasio-mental complete facial index* is obtained from the formula—

$$\frac{\text{Nasio-mental length} \times 100.}{\text{Interzygomatic breadth.}}$$

Skulls in which this index is below 90 are termed *chamæprosopic*; those in which it is above 90, *leptoprosopic*. The *nasio-alveolar length* is the distance between the nasion and the alveolar point. The *maxillary upper facial index* is obtained from the formula—

$$\frac{\text{Nasio-alveolar length} \times 100.}{\text{Interzygomatic breadth.}}$$

Skulls in which this index is below 50 are said to have a *chamæprosopic* upper face; those in which it is above 50 are said to have a *leptoprosopic* upper face. The *nasal height* is the distance from the nasion to the subnasal point. The *nasal width* is the greatest width of the anterior nasal aperture. The *nasal index* is obtained from the formula—

$$\frac{\text{Nasal width} \times 100.}{\text{Nasal height.}}$$

The *orbital height* is the distance between the centre of the upper margin of the orbit and the centre of its lower margin. The *orbital width* is measured from the point of junction of the fronto-lachrymal suture and lachrymal crest to the most distant point from this on the outer border of the orbit. The *orbital index* is obtained from the formula—

$$\frac{\text{Orbital height} \times 100.}{\text{Orbital width.}}$$

The *palato-maxillary length* is the distance from the inner lamella of the alveolus between central incisors to the nasal spine of the palate bone. The *palato-maxillary breadth* is the distance between the inner lamellæ of the alveolar arch, opposite second molars. The *palato-maxillary index* is obtained from the formula—

$$\frac{\text{Palato-maxillary breadth} \times 100.}{\text{Palato-maxillary length.}}$$

Skulls in which this index is below 80 are termed *leptostaphyline*; those in which it is above 85 are termed *brachystaphyline*; and those in which it is from 80 to 85 are termed *mesostaphyline*.

The following have been given as some of the *average measurements of the normal British skull*:—*Cranial capacity*, male 1500 c.c., female 1325 c.c.; *circumference* 503 to 534 mm.; *length*, male 186.2 mm., female 178.7; *greatest breadth*, male 144 mm., female 138 mm.; *cephalic index*, 78; *vertical index*, 75; *gnathic index*, 94. It is mesaticephalic, metriocephalic and orthognathic.

Craniometrical Observations at Autopsy.—With the exercise of a little ingenuity probably almost all of the measurements enumerated in the foregoing scheme could be accurately made upon the skull at a post-mortem examination, without any dissection being necessary that would involve disfigurement. But so complete an examination in such circumstances would undoubtedly be very troublesome to carry out, and would require the expenditure of much time. I therefore think that in making craniometrical observations at autopsies we should be content, except in special cases, with ascertaining the more important and easily obtainable measurements. Provided that these include certain that must be regarded as essential, they can furnish the data for a thoroughly scientific craniology. The following is the scheme that I recommend should be followed in making such investigations, not only upon the insane, but also, for purposes of comparison, upon the sane of the same class.

Place of examination.	Minimum frontal diameter.
Date.	Stephanic diameter.
Name of subject.	Asterionic diameter.
Nationality.	Greatest parieto-squamous breadth.
Sex.	<i>Cephalic index</i> .
Age.	Horizontal circumference.
Form of insanity.	Frontal longitudinal arc.
Cause of death.	Parietal " "
Glabello-occipital length.	Occipital " "
Basi-bregmatic height.	Total " "
<i>Vertical index</i> .	Vertical transverse arc.

Basi-nasal length.	Asymmetry (b) Stephanic.
Basi-alveolar length.	(c) Parietal.
Gnathic index.	(d) Asterionic.
Asymmetry (a) Frontal.	Cubic capacity.

For the purpose of making these measurements, which, with the exception of the cubic capacity and basi-nasal and basi-alveolar lengths, must be taken before the calvarium is removed, certain dissections beyond those that are commonly made at a post-mortem examination are necessary. The anterior flap must be carried far enough down to bring the naso-frontal suture into view. Laterally the temporal muscle must be carefully reflected from the bone as far as the level of the zygoma, and the upper edge of the external auditory meatus must be exposed. The posterior flap must be dissected far enough down to bring into view the asterion and the occipital point. The basion must be reached in the way already described.

I have included the asymmetry of the skull in the above scheme, as it is of special importance in relation to insanity, and as a simple means of exactly registering its amount has recently been devised. I have excluded the palate measurements for reasons which are explained in the section upon palatal deformities.

The craniometer that I at present use, and the one I would specially recommend, is that recently devised by Dr David Hepburn (72).¹ Besides being a very convenient and accurate instrument for taking the measurements of length, it permits of an exact registration of the degree of asymmetry presented by the skull in various regions. With the addition of a Waterston limb it enables one to obtain the basi-bregmatic height and the basi-nasal length at post-mortem examinations.

The degree of asymmetry should be recorded as left or right, plus the number of centimetres by which the one side exceeds the other in the four positions named, *e.g.*:—Left frontal + 1·3; left stephanic + 0; left parietal + 1·5; right asterionic + ·2.

The tape line employed for measuring the circumference and the length of the arches should be graduated in centimetres and millimetres.

Probably the best method of estimating the cubic capacity of the cranium at a post-mortem examination is that of Zanke (69-70). After the brain has been taken out, the dura detached from the base and the foramen magnum plugged, the basal portion of the skull is filled with water, which is then collected in a vessel. To this is added the amount of water required to fill the calvarium. The total amount gives the capacity of the cranium. For the application of

¹ This instrument is made by Mr Andrew H. Baird, 39 Lothian Street, Edinburgh.

this method it is necessary that the calvarium should be removed by a straight saw-cut. The foramen magnum and other apertures at the base may readily be plugged with putty, which should be carefully pressed down with the finger until its upper surface corresponds to the position of the openings.

ABNORMALITIES IN FORM AND SIZE.

Characters of Cranial Diameters, Lengths, Arcs and Indices in the Insane.—As already maintained, the skulls of the insane in this country have not yet been sufficiently studied by strict craniological methods to permit of precise statements being made regarding the special morphological features that they exhibit. At the same time the observations that have already been made in this country and abroad fully justify the important general conclusions that the skulls of the insane present deviations from the limits of the normal as regards form and size far more commonly than those of the general population, that they exhibit certain special anomalies more frequently, and that they occasionally present gross abnormalities of form or size, some of which are never, others only very exceptionally, co-existent with a normal brain.

Among the important signs of "degeneration and pathological diathesis," Benedikt (3) includes shortening of the median arch of the parietal bones (which he regards as a certain sign that the individual was an epileptic), disproportionate evolution of the occipital part of the skull, under-typical height of the skull, and shortening of the post-auricular part of the sagittal axis (an alteration which is more commonly hemilateral than bilateral). The same authority says that he has "demonstrated that a positive and negative excess of the cephalic index is indicative of degenerated and pathological cases." Morselli (46) puts this last point somewhat differently, stating that he finds that in insanity there is very commonly an exaggerated individual cephalic index as compared with the normal cranial type of the population.

It is to be hoped that precise craniometric data will soon be collected regarding the skulls of the insane in this country in sufficient numbers to allow of the construction of a more exact craniology of insanity than it is yet possible to frame. In the meantime only some of the more conspicuous and easily detected abnormalities that have been observed require some reference here.

Cranial Capacity.—Those who have investigated the matter seem to be agreed that the average cubic capacity of the skull is greater among the insane than the sane. This conclusion seems all the more striking when it is considered that among the cases of insanity included in the statistics there has been a considerable proportion of

abnormally small skulls of idiots and imbeciles. On the other hand, however, the inclusion of some hydrocephalic skulls may have helped to raise the average in the insane. More extensive investigations, taking into account among other things the different clinical types of insanity, seem to be required upon this subject.

The Microcephalic Skull.—A very complete description of the microcephalic or idiot skull, based upon the study of nineteen examples, has somewhat recently been given by Sir George Humphry (32). His paper will probably remain the most authoritative work on the subject for a considerable time to come, and should without fail be consulted by anyone into whose hands a specimen of this kind should chance to come for investigation. He summarises the characters of the microcephalic skull as follows:—"The brain-case is small or contracted in all its dimensions, in the base as well, though less than in the vault; and it is most so in the fore part, the frontal bone being sloped back and narrow, with deep temporal fossæ behind the external angular processes, and with curved orbital plates, which narrow the ethmoidal fossæ. The parts in the interior are contracted and often thickened. The occipital condyles are rendered prominent by the sloping of the squamous and basilar parts of the bone behind and in front. The superciliary ridges are thrown into prominence, and the frontal sinuses are large. The facial bones, smaller than normal and less wide, with a narrow dental arcade, though proportionately large, are prognathous, the upper incisive alveolar processes and teeth being especially so. The angle of the jaw is more open than usual. The foramina at the base are usually small."

The circumference of the nineteen skulls examined ranged from 12 in. to 19.5 in. and averaged 16.7 in. The exact size-limits of the microcephalic skull do not appear to have yet been fixed by craniologists. Ireland (35) considers that the name microcephalic should be given to all heads below 17 in. or 431 millimetres in circumference. Shuttleworth (59) objects to such limitation of the term on the ground that there is a characteristic form as well as size of microcephalic heads. With regard to the capacity of skulls of this nature it may be mentioned that French craniologists apply the term microcephalic to those in which it is 1150 cubic centimètres and under. Virchow maintained that microcephaly is caused by premature ossification of the cranial sutures. In 1891 Lannelongue, although only partially admitting the truth of Virchow's teaching, advocated craniectomy in such cases for the relief of pressure upon the brain by the skull. Since attention was thus specially directed to the possible importance of premature synostosis in the production of microcephaly, numerous authorities have recorded the results of observations upon the subject. Practically all of them are agreed that premature

synostosis does not occur in microcephaly, or at least that the microcephalic condition is determined long before synostosis occurs, and that no undue pressure is exerted upon the brain by the bone. It is now certain that the imperfect development of the skull is the result and not the cause of the associated imperfect brain development. Among those whose observations bear out this conclusion are Langdon Down (19), Humphry (32), Cunningham and Telford-Smith (8), Telford-Smith (58), Giacomini (73), Funaioli (22), and Kempson (37).

Descriptions of microcephalic skulls will also be found in papers by Urquhart (67) and Baistrocchi (6).

The Macrocephalic Skull.—To Professor Humphry (32) craniology is also indebted for a very complete description of the special characters of the macrocephalic skull, which on account of its being in the great majority of instances caused by hydrocephalus is also commonly termed hydrocephalic. The only other disease with which macrocephaly appears to be associated is the rare condition which is known as hypertrophy of the brain. Humphry sums up his description of "the macrocephalic or hydrocephalic skull" as follows:—"The brain-case is expanded in all directions, to some extent in the base, but much less than in the vault. The forehead bulges forwards, beetling over the face; the orbital plates are in the young flattened and pressed down, and the superciliary ridges are elevated and depressed. The temporal fossæ are shallowed, and the occipital condyles are not prominent. The face, though in many larger than ordinary and widened, the dental arcade being wide, and the rami of the maxilla being slanted outwards to accommodate the condyles to the separated position of the glenoid fossæ, is relatively small, retired beneath the forehead, and devoid of prognathism."

The hydrocephalic skulls examined by Humphry consisted of five from children and five from adults. In the latter the greatest circumference, which was situated above the level of the glabella and occipital spine, ranged from 23.5 in. to 25.5 in. At the level of the glabella and occipital spine it ranged from 21.5 in. to 23.5 in. and averaged 22.6 in. Descriptions of hydrocephalic skulls will also be found in the papers of Campbell Clark (17), Tamburini (74) and Giuffrida-Ruggeri (29). As in the case of the microcephalic skull, the exact size-limits separating the normal skull from the macrocephalic do not appear to have yet been authoritatively fixed. Testut (65), however, states that crania of which the capacity reaches 1950 cubic centimetres and above, are classified as macrocephalic.

Asymmetry.—No cranium is strictly symmetrical, and considerable degrees of asymmetry are common in skulls of normal individuals. Benedikt (3) states that even the highest degree of asymmetry may have no pathological significance, because there may co-exist with it a

complete compensation. The most nearly symmetrical skulls have been observed in some cases of idiocy. Hasse (34) maintained that the normal asymmetry of the skull consists simply in a greater development of the left half of the calvarium and upper face, in correspondence with the commonly greater development of the left cerebral hemisphere. This view has been disputed by many authorities, more especially by Giuffrida-Ruggeri (30), who contends that it is entirely erroneous. According to his observations asymmetry of the calvarium only in rare instances takes the form of a special prominence of all the bones on one side; ordinarily it consists in a more or less evident plagiocephaly, or greater projection of the frontal region on the one side and of the occipital on the other. Tedeschi (66) found that this plagiocephaly generally consisted of prominence of the right side in the frontal region and of the left side in the occipital. Giuffrida-Ruggeri (30), on the other hand, though able to confirm the statement that the asymmetry is generally of a plagiocephalic type, found that it most commonly consisted in the anterior part of the cranium being less developed on the right side than on the left, and in the parietal bosses being further back on the right side than on the left.

Although asymmetry of the cranium is not, therefore, to be regarded as necessarily an indication of an abnormal brain, high degrees of it, and certain special forms, are undoubtedly far more common in the insane than in the mentally sound. It has been observed that high degrees are very common in the criminal class. Lombroso has attached considerable importance to asymmetry of the skull as a sign of degeneracy. The observations of Fränkel (24) have shown that plagiocephaly is more pronounced in the insane and criminals than in the general population. Giuffrida-Ruggeri (30) has especially drawn attention to the occurrence of asymmetry of the internal aspect of the cranium, and to the fact that it does not always correspond to that of the external surface.

An extensive investigation upon the occurrence of asymmetry of the cranium in asylum and general hospital patients in this country is much needed. Its results would be of considerable scientific interest and practical importance. In Hepburn's craniometer we have now an instrument by means of which such observations can be rapidly and accurately made at post-mortem examinations.

Crania progenera.—L. Meyer (41) applied this name to skulls presenting a special kind of deformity which he observed in a number of cases of idiocy and imbecility. It consists in abnormal prominence of the lower jaw and forehead, defective development of the occipital region, and narrowing of the face. He attributed it to arrest of development of the occipital bone.

Other named varieties of cranial deformity include the following:—The scaphocephalic skull, the top of which is keel-shaped; the oxycephalic, acrocephalic or dome-shaped skull; the leptcephalic or narrow skull; the trigonocephalic skull, in which the frontal region is narrow and the occipital abnormally wide; and the chæmocephalic or platicephalic skull, the characteristic feature of which is flatness of the upper aspect. Clapham and Clarke (11) have drawn attention to a form of cranium which they regard as peculiar to insanity, and which they have therefore termed "the insane type." Its special feature consists in the greatest transverse diameter being in the anterior third, instead of behind the middle point as is normally the case.

Metopism, or persistent frontal suture.—Although this abnormality is by no means uncommon in skulls of mentally normal individuals, it has been shown to occur with special frequency in congenital forms of insanity. S. Bianchi and Marimo (1) found it in 13·72 per cent. of such cases, and in 25 per cent. of male idiots and imbeciles. Giuffrida-Ruggeri (28) states that it has been observed that the condition is most common in Europeans, some other races presenting it in relatively very small percentages, so that to a certain extent the tendency to it is a racial characteristic.

Abnormalities of clinoid processes.—Raggi (54) has made an extensive investigation of this subject. He distinguishes three types of abnormality, viz., (a) absence; (b) fusion of the anterior clinoid processes with the posterior; and (c) isolated fusion of the middle process with the anterior or with the posterior. He found the middle clinoid processes absent in 53 per cent. of the insane, and in 34 per cent. of the mentally sound. It is to be remembered that in the anthropoid apes this middle clinoid process is wanting. He observed union of the anterior and posterior processes without participation of the middle processes in 34 per cent. of the insane, and in 11 per cent. of normal individuals. The crania of the insane which showed this abnormality presented also numerous degenerative characters.

Bilateral elevation alongside sagittal suture.—Benedikt (4) regards this somewhat rare abnormality as significant of profound perversity of brain function.

Absence of glenoid fossa of temporal bone.—Giuffrida-Ruggeri (30) found this abnormality in 13 lunatics out of 1000. He regards it as a reversion to a lower mammalian type.

Absence of the normal over-riding of the dentary arcades.—Attention seems to have been first directed to this abnormality by Sir William Turner (62), who observed it in 11 out of 15 Australian crania examined. He regarded the tendency to the condition in these skulls as a racial feature. In 1894 Camuset (10) recorded the results of

an investigation upon the occurrence of this anomaly in the living subject. He found that the dentary over-riding was wanting in 1.58 per cent. of normal Europeans, and in 20.42 per cent. of the insane. Among the latter the percentage was considerably higher in men than in women. Giuffrida-Ruggeri (26) found that out of 115 crania of the insane in the museum at Reggio-Emilia, over-riding was complete only in 52.18 per cent. In 47.82 per cent. the arcades met more or less exactly in their anterior segments.

These observations seem to prove that this anomaly, which the researches of Turner justify one in regarding as atavistic in character, is much more common in the insane than in the mentally sound.

Abnormalities of the Palate.—Much discussion has taken place during recent years regarding the importance of deformities of the hard palate as stigmata of degeneration. Apparently all of the numerous extensive series of investigations into the question that have been recorded have been made upon the living subject, or at least with the soft tissues in position, either by means of simple inspection or with the aid of casts. Such observations, valuable as they are for clinical and anthropological purposes, do not supply craniological data, which alone are here being specially considered.

As the question rests at present, viewed from its clinical and anthropological standpoints, there is a complete divergence of opinion among those who have studied it. On the one hand it is maintained that palates of which the vault is unusually high, narrow, or otherwise markedly deformed, are much more common in those who have a bad initial neurotic heredity (and therefore in cases of idiocy, congenital imbecility, epilepsy, adolescent mania, etc.) than in the general population; on the other hand it is asserted that these abnormalities of the palate do not preponderate to any marked extent in idiocy, imbecility, etc., and that they have not been proved to be stigmata of degeneration.

The former view has been supported especially by Langdon Down (19), Clouston (15), Talbot (64), Ireland (35), Peterson (53), and Charon (18), and the latter by Claye Shaw (60), Norman W. Kingsley (an American dentist), and Channing (9).

It scarcely admits of dispute that the element of by far the greatest importance in any palatal deformity is that contributed to it by the superior maxillary and palate bones. Modifications in the conformation of the palate by individual differences in the thickness of the soft tissues, which may depend upon acquired as well as developmental conditions, are of comparatively trivial moment. It is therefore obvious that what is required to settle this vexed question is a large series of statistics of strictly craniometric data regarding the vault of the palate in the normal individual and in various forms of insanity. Here, however, we are unfortunately faced

by a special difficulty. Craniologists have never had any reason to attribute to the form of the hard palate the great importance that has been attached to it within recent years by alienists, and the measurements that they generally regard as sufficient for ethnological investigations are obviously quite inadequate for those of a pathological nature. The length and breadth of a palate and the index derived from them are data that are not necessarily affected by variations in the characters of the palatal vault. The addition of the palatal height and of a vertical palatal index would, to some extent, supply what is needed, but the results would still remain unaffected by the form of the arch to which the clinician, rightly or wrongly, attaches so much importance. This question as to what would constitute a complete craniometric examination of the palate is one that requires an authoritative answer, for it is certain that only by means of such investigations, and not merely by a study of palatal deformities as they present themselves clinically, no matter how accurate be the method by which they are recorded (25), will the subject be placed upon a sound and scientific basis.

CHANGES IN THICKNESS, TEXTURE, AND WEIGHT.

No one who has made an extensive series of post-mortem examinations, both in a general hospital and in an asylum, can have any doubt as to whether the cranial bones of the insane are more commonly affected by structural alterations than those of the mentally sound. In my own experience distinct evidence of such alterations has been present in the former in a considerable majority of cases, while in the latter it has existed only very occasionally.

The classification of the structural alterations chiefly of importance in relation to insanity adopted here, though not a strictly pathological one, is that which I think serves best for descriptive purposes. For obvious reasons these morbid conditions are most readily studied in the upper portion of the skull, and indeed most of the observations recorded on the subject refer especially to this portion. There seems, however, sufficient reason to believe that although all the bones of the cranium (in its narrower sense, as distinguished from the face) are commonly affected together, the calvarium as a rule suffers much more severely than the base.

Thickening.—The thickness of the cranial bones varies within considerable limits as an individual feature in perfectly normal conditions. Its pathological variations, whether in the way of increase or diminution, must therefore within these limits be incapable of accurate appreciation. For this reason all statistics of morbid thickening of the skull must be regarded as of somewhat uncertain value. They are at best only individual appreciations of

a matter regarding which there is necessarily in many instances a large element of doubt. Nevertheless, most of those who have examined a large series of cases regard thickening as the most common morbid change affecting the cranial bones of the insane (plate v. fig. 2). It occurs in various degrees, generally being only slight. It may involve the whole cranium, but specially tends to affect the vault. Not infrequently it is confined to the frontal portion, less commonly to the occipital or other region. The consistence of the thickened bone may be normal, but is usually much increased (osteosclerosis), the diploë being at the same time diminished or entirely lost. Occasionally it is diminished (osteoporosis). Thickening is sometimes accompanied by the development of large irregular bosses, or of more or less numerous, small excrescences on the inner aspect. These bony outgrowths occur especially in the frontal region (plate v. fig. 1).

Bevan Lewis (39) has found the cranial bones thickened in 25·8 per cent. of cases of insanity. He states that "the thickened dense skull-cap is frequent in epileptic subjects and in chronic insanity." The statistics compiled by Bullen (2) show that hypertrophied calvaria occur in maximum number in epilepsy, and that bony growths on the inner aspect are present in only about 1 per cent. of all cases of insanity. Beadles (7) observed thickening of the calvaria in 51 cases out of 234. Statistics compiled by Dr Middlemass and myself (44) from the records of 304 cases examined by us at Morningside Asylum, show some increase in thickness to have been present in 50·7 per cent. of all cases. The records of 289 cases examined by myself (only 92 of which were included in the preceding series) give a percentage of 51·5. Notwithstanding the element of uncertainty that enters into statistics of cranial thickening, I am strongly inclined to believe that these figures are nearer the truth than the smaller percentages of most other observers. Of 149 cases in which I observed thickening, the condition was limited to the frontal region in 6, and to the occipital region also in 6. In many instances it was more marked in one or both of these regions than elsewhere. In all chronic forms of insanity the alteration was very common; in all cases of short duration it was extremely rare. In 61 instances it was accompanied by appreciable condensation of the bone, in 10 by softening. The highest degrees of thickening occurred in cases of senile insanity and in senile secondary dementia, but the largest proportion of thickened crania was recorded in general paralysis (46 out of 65).

Thinning.—Atrophic thinning of the calvarium is of much less frequent occurrence than thickening. Beadles (7) found it in less than 2 per cent. of cases. The statistics of Dr Middlemass and

myself give a percentage of 9.9. In my own cases it is recorded as present in 8 out of 289, or in rather less than 3 per cent. Six of these were in cases of senile insanity.

Osteosclerosis.—This condition, as it occurs in the skull, is also known as *hyperostosis cranii* and *cranio-sclerosis*. It consists in condensation of the bone, generally but not always accompanied by thickening of it. The diploë becomes replaced by cancellous tissue so that the bone assumes an ivory-like appearance and consistence, and at the same time is greatly increased in weight (plate v. fig. 1). Hamilton (33) states that the bone may be so thickened as to measure from 1 to 2 in. on section, that the cranial capacity may be encroached upon, and that the nerves and vessels of the skull may suffer compression. Such extreme degrees of osteosclerosis appear, however, to be rare even in the insane, who are undoubtedly far more prone to its slighter manifestations than are the general population. Bevan Lewis (39) found the cranial bones indurated, dense and heavy in 33.4 per cent. of cases. My own statistics show condensation to have been present in 85 cases out of 289, or in about 29 per cent. In 61 of these the bone was at the same time thickened. The condition occurred in highest proportion in cases of general paralysis (in which disease it seems to be almost constant), next in senile insanity.

Osteoporosis.—This is probably the correct term by which to designate the condition of thickening of the bones of the cranium accompanied by softening. In my series of 289 cases there were 15 in which this alteration was observed. In three of them the softening was so marked that the bone sawed like rotten wood. All of these three were cases of secondary dementia which had reached senility. Of the remaining 12, two were cases of the same nature, eight of senile insanity, and two of epilepsy.

Alterations in weight.—Fränkel (23) has made investigations into the absolute and relative weight of the calvarium, and comes to the conclusion that in general paralysis the weight is greater than in any other form of mental disease. Peli (50) confirms this, but associates epileptics with paralytics. He states, in addition, that the calvaria of females are relatively heavier than those of males; that those of the insane are heavier than those of the sane, and that the range of variation is greater in the insane.

I have been unable to find any published record of observations upon the histology of the above morbid changes as they occur in the cranial bones. Research in this field would probably throw some light upon their essential nature, which is still a matter of doubt. Some writers assume that sclerosis and thickening of the cranial bones as they occur in the insane are essentially of an inflammatory

character, but the necessary proof is certainly wanting. For my own part I am inclined to adhere to the view which I have already advanced in conjunction with Dr Middlemass (44), that they are probably more correctly to be regarded as mere nutritional changes. The grounds for this belief are fully stated in the succeeding chapter in connection with the discussion of the pathology of the chronic changes that affect the dura mater in the insane.

Tumours of the cranium hardly call for special notice in connection with insanity. I give, however, an illustration (plate v. fig. 4), of a rapidly growing osteoma which occurred in a case examined by myself at Morningside Asylum, and which was the immediate cause of an attack of acute insanity, as well as of death. It was situated on the inner surface, over the upper half of the left coronal suture, and was composed of two separate portions, each of which consisted of an irregular cauliflower-like excrescence. The upper and larger portion was about an inch in length and half an inch in breadth. It projected about a quarter of an inch from the general level of the bone. The lower portion, which was separated from the upper by about a quarter of an inch of healthy bone, was a quarter of an inch in diameter. Both were very hard, but some of the excrescences could be moved slightly, owing to the extreme narrowness of their pedicles. Both tumours had penetrated the subjacent dura, pia-arachnoid and cerebral cortex, and at places had even reached the white substance. The posterior ends of the first and second frontal convolutions were the portions of the brain implicated. The patient was a woman aged forty-nine, with a strong hereditary predisposition to insanity. Her symptoms, which began to manifest themselves only six weeks before death, consisted of mental enfeeblement, delusions, absolute sleeplessness, cerebral vomiting, and latterly general convulsions. There was nothing in the character of the convulsions to enable one to localise the seat of irritation.

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DESCRIPTION OF PLATES II., III., IV., AND V.

PLATE II. Lateral aspect of normal human skull. From a photograph.

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|--------------|---------------------|---------------------|-----------------|
| 1. Nasion. | 4. Lambda. | 9. Alveolar point. | 12. Pterion. |
| 2. Glabella. | 7. Ophryon. | 10. Subnasal point. | 13. Stephanion. |
| 3. Bregma. | 8. Occipital point. | 11. Dacryon. | 14. Asterion. |
| | 15. Mental point. | | |

PLATE III. Upper aspect of normal human skull. From a photograph.

- | | |
|------------|------------|
| 3. Bregma. | 4. Lambda. |
|------------|------------|

PLATE IV. Lower aspect of normal human skull. From a photograph.

- | | |
|---------------|------------|
| 5. Opisthion. | 6. Basion. |
|---------------|------------|

PLATE V. Four calvaria (internal aspect), showing morbid conditions. From a photograph.

Fig. 1. Calvarium from a case of advanced general paralysis. Man, aged forty-five. Shows severe general sclerosis, absence of diploë, and numerous small excrescences in frontal region.

Fig. 2. Calvarium from a case of senile insanity. Woman, aged seventy-eight. Shows great thickening in frontal region. The bone is not condensed.

Fig. 3. Calvarium from a case of idiocy. Boy, aged twelve. Shows thickening, sclerosis and very pronounced asymmetry.

Fig. 4. Calvarium showing osteomatous growths underlying left coronal suture. From case described in text.

PLATE II.

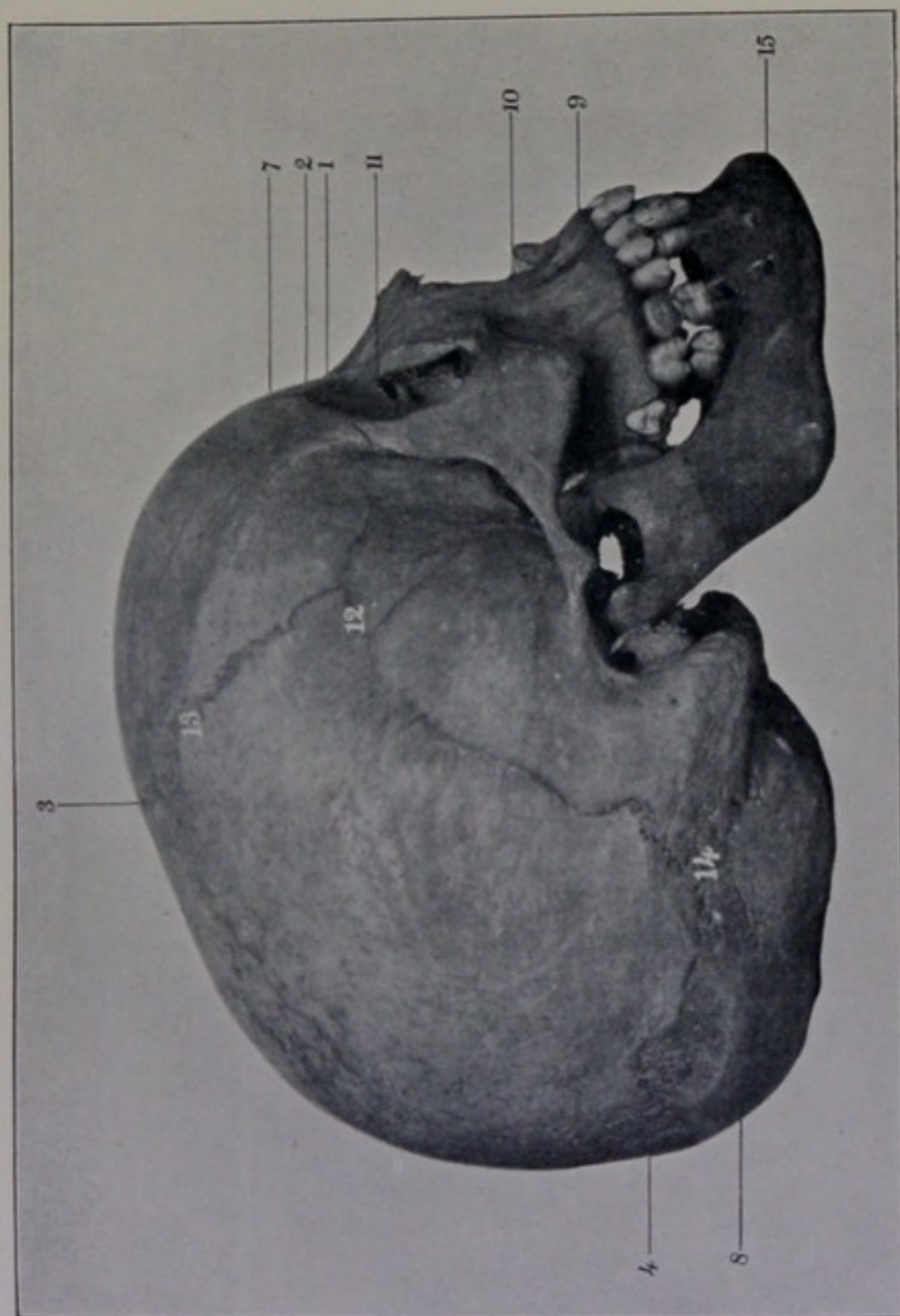




PLATE III.

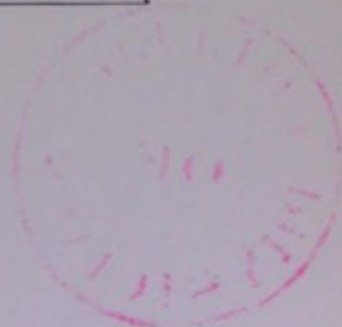




PLATE IV.

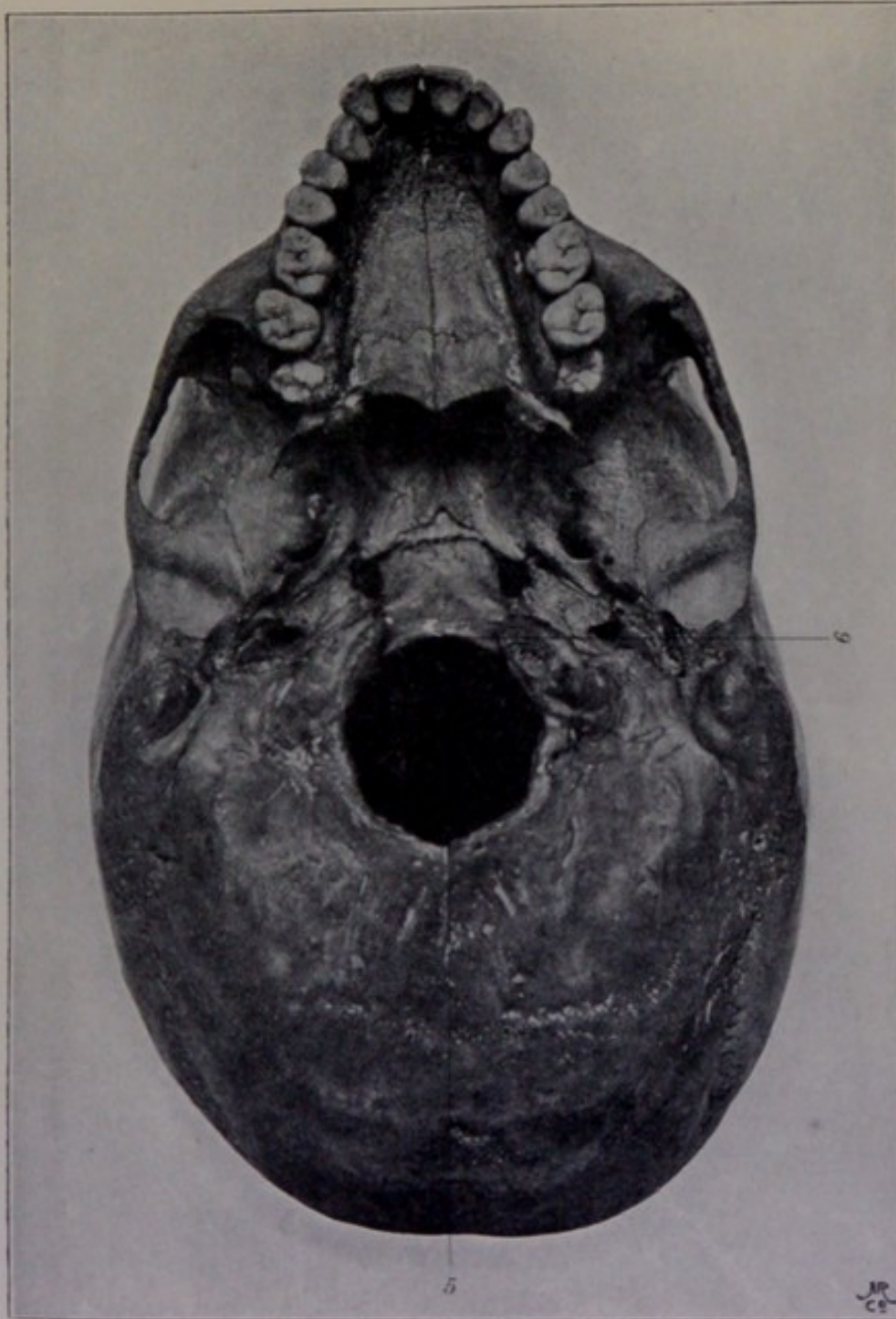




PLATE V.



Fig. 1.



Fig. 2.



Fig. 3.



Fig. 4.

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62



CHAPTER V

MORBID CONDITIONS OF THE DURA MATER.

(PLATES VI., VII., VIII., IX., and X.)

OF the many morbid conditions that may affect the dura mater, the one that is of paramount interest and importance in connection with insanity is the formation of subdural false membranes, and to this subject the greater portion of this chapter is therefore devoted. Chiefly on account of their bearing on the pathology of this process, it is necessary to consider in some detail certain points regarding the structure and functions of the dura. It is to be understood that throughout this section it is the intracranial dura mater that is referred to, except when the spinal membrane is expressly mentioned.

NOTE ON THE NORMAL STRUCTURE AND FUNCTIONS OF THE DURA MATER.

The dura mater is usually described as composed of two layers of dense fibrous tissue running in different directions, and some authorities even mention a definite relationship between the thickness of the one and of the other. While this is, no doubt, the most frequent arrangement, and the constant one near the venous sinuses, in other situations all the fibres of the membrane are often found to run in one direction, and to form only a single layer, while again three distinct layers may sometimes be seen. When two layers occur their relative breadths vary greatly in different instances.

Many writers in describing the microscopic characters of intracranial subdural false membranes mention the elastic fibres of the dura. According to Sappey, however, elastic fibres exist only in the spinal membrane. From my own observations I can corroborate this statement, and I may add that they occur there in very large numbers. The dural sheath of the spinal cord has therefore a considerable degree of elasticity.

The next point is one of special importance in relation to subdural false membrane formation, namely, the normal vascular arrangements of the dura. While the main arteries lie towards the outer aspect, the large veins are situated near the centre, between the two layers, when these occur. Capillaries are very few in number, except at the

outer and inner aspects of the membrane. In the latter situation, just below the surface endothelium, there is an exceedingly rich capillary network, which can be satisfactorily examined only in superficial horizontal sections. It presents structural features of a highly specialised character, without a clear knowledge of which it is impossible to rightly understand the pathology of the formation of subdural false membranes. Although the vessels forming this superficial network are in structure mere capillaries, they are of remarkably large size, many of them being in their normal condition three or four times the diameter of an ordinary capillary vessel (figs. 2, 12, 32, and 33). They lie in grooves which run for the most part in a direction parallel with the connective tissue fibres of the membrane. These grooves, which vary considerably in size and depth, form a system of perivascular canals. The only writer upon subdural false membranes who, as far as I have been able to ascertain, seems to have been aware of the existence of these channels, is Obersteiner (44), though he attaches no importance to them in this relation. Their outer wall is lined by endothelial cells, the nuclei of which can be clearly seen in superficial horizontal sections stained with hæmatoxylin and eosin, while their outlines can be readily observed in silver preparations (fig. 35). It is difficult to determine whether or not a similar layer overlies the capillary, which is more or less completely surrounded by the canal. Some pathological conditions favour the view that there is such a layer. The appearance that these perivascular canals normally present in superficial horizontal sections will be best understood by reference to the illustrations. They are commonly seen as a narrow channel on each side of the vessel, but when shallow they are represented only by the nuclei of their endothelial cells (fig. 33). Strands of dural connective tissue are attached at intervals to the capillary wall, passing obliquely across the canal. Occasionally the connection is more close, so that for a certain distance the vessel is only incompletely surrounded by the canal. Obersteiner mentions the occurrence of communicating branches of these perivascular canals. I have found such branches exceedingly difficult to recognise even in silver preparations, but have been able to observe appearances confirmatory of their existence. Perivascular canals undoubtedly also occur in the deeper tissues of the dura, but I am unable to speak very definitely about their arrangement. They appear to be absent from some of the vessels.

While each capillary of the surface network has normally a uniform calibre, at the points of junction the vascular channels occasionally present peculiar ampullary enlargements.

Anatomists do not now describe a parietal arachnoid, but there are some writers who refer to a subendothelial layer of loose con-

nective tissue on the inner surface of the dura. I have already (48) committed myself to the view that the endothelium in its normal condition lies immediately upon the dense fibrous tissue of the dura, but I have since observed in superficial horizontal sections some appearances that I can only reconcile with the presence of a very delicate sub-endothelial layer of loose connective tissue. It is only very occasionally that such appearances can be recognised, and therefore it is probable that the arrangement exists only locally. In bichromate hardened preparations, stained with hæmatoxylin and eosin, the surface endothelial cells (figs. 32 and 33) show a large oval nucleus the groundwork of which stains somewhat faintly with the former dye. In its centre there is a more deeply-stained, large oval nuclear network. This central portion, with ordinary powers, commonly appears as if composed of minute, closely-set, dark granules. The normal cell-plate, which is of large size, can rarely be distinguished in hæmatoxylin and eosin preparations. The nuclei of the endothelial cells of the perivascular canals have the same characters as those of the surface endothelium.

On either side of the superior longitudinal sinus there may be seen quite distinctly with the unaided eye long fibrous tissue buttresses, extending outwards and obliquely forwards or backwards over the inner surface of the dura. Similar, but much smaller, dense fibrous tissue strands, not, however, projecting beyond the general level of the surface, occasionally occur in other parts of the dura. Their existence is to be borne in mind, as they require to be distinguished from certain very similar strands that form as a result of morbid changes.

The nerves of the dura mater have recently been very fully described by Acquisto and Pusateri (51). They distinguish two sets, namely, non-medullated vaso-motor fibres which accompany the meningeal vessels, and medullated sensory fibres which course through the dura in all directions. The latter form irregular plexuses, some of the branches given off from which terminate in little club-shaped swellings near the endothelium of the inner surface.

There is another point regarding the structure of the dura to which reference requires to be made here in order to obviate a possible source of misunderstanding with regard to some of the conclusions of this chapter. It is that the flattened or lamellar corpuscles that are found in this membrane as in other fibrous connective tissue structures, cannot be sharply distinguished morphologically from the endothelial cells of the surface and of the perivascular canals. This circumstance might give rise to a question as to whether certain proliferated cells are connective tissue corpuscles or endothelial elements. Such a question, however, is probably a gratuitous one, for it is now held by many high authorities that these cells differ from each other in no respect except in the position in which they are found. For my own part, I am now

convinced that this view is the correct one. The contention that endothelium is of epiblastic origin, and is therefore allied to epithelium and essentially different from the mesoblastic connective tissue corpuscle, is inconsistent with the results of pathological observation. It can be shown that endothelial cells lining free surfaces are capable, like connective tissue corpuscles, of forming fibroblasts. Moreover, both are subject to the same types of degenerative change, which, on the other hand, are different from those that affect epithelium. On these, as well as on other grounds that might be stated, I think we are warranted in believing that endothelial cells and connective tissue corpuscles are essentially the same tissue-elements.

There can be little doubt that the perivascular canals of the dura are lymph-channels. Obersteiner states that they communicate with the subdural space by means of stigmata on the visceral surface of the dura, and "that on the other side, they open into the real blood-vascular system." I have endeavoured to find these stigmata in superficial horizontal sections of silver preparations, but I have been unable to observe any distinct openings. The arrangement that appears to me to exist is that a certain number of the canals, but more especially certain wide expansions of them, instead of being bridged over by the surface endothelium, are closed in only by their own endothelial cells, as represented in fig. 34.

In a previous publication (50) I expressed the opinion that Obersteiner is in error in believing that the perivascular canals open into the blood-vessels. I am now obliged to alter this opinion. There is experimental evidence (see chapter xi.) which proves that fluid injected into the subdural space is capable of finding its way through the dura into the veins of the skull. The consideration of this experimentally demonstrated fact, and of many pathological phenomena that may be observed, some of which will be described presently, lead me to conclude that the perivascular canals of the dura constitute one of the channels by which the cerebro-spinal fluid is carried into the general circulation. According to this view, a large proportion of the fluid contained in the spaces of the pia-arachnoid (which is constantly being replenished by the flow from the adventitial lymph-channels of the intracerebral vessels) filters into the subdural space, passes into the perivascular canals at the inner surface of the dura, is collected into larger channels in the substance of the membrane, and finally discharged into the veins of the skull.

At the outer aspect of the dura, between the membrane and the bone, there are, in the adult at least, numerous small but distinct spaces which contain lymph. They are of interest here because morbid changes may occur in them similar to those that take place at the inner surface.

The cerebral dura mater has at least three distinct functions. Firstly, it protects and supports the brain; secondly, it is the internal periosteum of the cranial bones; and, thirdly, it conveys away cerebro-spinal fluid from the cranial cavity.

MORBID ADHESION OF THE DURA TO THE SKULL.

Normally in the adult the calvarium, after it has been sawn through in the usual way, can be detached from the subjacent dura by slight force. The union between the bone and the membrane at the base is much more intimate, and consequently slight degrees of morbid adhesion are there more difficult to appreciate. I shall deal only with the condition as it affects the dura at the vertex. Morbid adhesion in this situation is exceedingly common in the insane. As a rule, it is slight and patchy, rarely reaching to such a degree as to necessitate removal of the membrane along with the calvarium. It is commonly most marked under the frontal bone and alongside the sagittal suture, and is often confined to these situations. Occasionally it occurs as a small isolated patch. Bevan Lewis (43) found morbid adhesion of the dura to occur in 15 per cent. of those dying insane. Bullen (52) found it in 16.6 per cent. of cases. Statistics compiled by Dr Middlemass and myself (48) show a considerably higher percentage, namely, 44.1. In my own series of cases the condition was present in 34 per cent.

Bullen found that it was most common in dementia, and least so in general paralysis and epilepsy. The statistics of Dr Middlemass and myself show it to occur in 63.3 per cent. of cases of senile insanity, in 59.5 per cent. of secondary dementers, in 36 per cent. of epileptics, in 35.7 per cent. of general paralytics, and in 25 per cent. of cases of alcoholic insanity.

Most authorities, including Bevan Lewis, regard morbid adhesion of the dura to the bone as the result of bygone inflammation. Dr Middlemass and I have expressed doubt as to the accuracy of this view, pointing out that the condition is not usually associated with much thickening of the membrane, and that it may be developed to a marked degree in cases in which there was no history of headache. We advanced the opinion that such adhesion is, as a rule, due to the circumstance that new bone is being deposited by the periosteal surface of the dura. Similar firm adhesion occurs in the skull of the child so long as the bone is actively growing. In the insane it is commonly associated with thickened bone (60.8 per cent. of cases), and both conditions are most frequent in the same region, namely, the frontal. Some cases of adhesion are doubtless due to inflammation, but this process is generally evidenced by the presence of a layer of new tissue on the outer surface of the dura.

MORBID ADHESION TO THE PIA-ARACHNOID.

This condition, unlike the preceding, is a somewhat rare one. It is usually seen over only a very small area as a dense fibrous-tissue connection. Its occurrence is probably most common on the under surface of the temporo-sphenoidal lobes. I exclude all cases of subdural false membrane formation, and also the undue adhesion between the dura and the pia-arachnoid that is so common on either side of the superior longitudinal sinus. The latter is rather the result of a morbid condition of the pia-arachnoid, and therefore requires to be considered under diseases of that membrane. Apart from the formation of subdural false membranes, obliteration of the subdural space seems to be an exceedingly rare occurrence. Bevan Lewis (43) met with localised fibrous bands between the dura and the pia-arachnoid in .6 per cent. of cases. The statistics of Bullen (52) show a much smaller percentage. Those of Dr Middlemass and myself (48) give a considerably higher figure, viz. 3 per cent. In my own more recent series of cases such fibrous adhesions were present in 7 out of 290, or in 2.5 per cent. This form of local adhesion is clearly the result of an inflammatory process. Its early stage, which may occasionally be met with, is represented by a small patch of adhesion by recent lymph.

THICKENING OF THE DURA.

General thickening of the dura is a condition that it is certainly difficult to recognise, owing to the somewhat variable thickness of the normal membrane. But experience enables one to pronounce it to be present in many cases. It occurs especially in general paralysis, but is common also in senile insanity. It is almost constantly associated with undue opacity of the membrane, especially around the middle meningeal arteries, recognisable on holding it up to the light. The dense strand of dura mater which is normally found in the groove which lies below the ridge limiting the middle cerebral fossa anteriorly must not be mistaken for this local thickening and opacity. The causes of dural thickening are fully explained under the subject of subdural false membrane formation. As already stated, localised thickenings, due to inflammatory deposits between the membrane and the bone, are occasionally met with.

THINNING OF THE DURA.

In judging of the presence or absence of general thinning of the dura we meet with the same difficulty as in the case of thickening. Nevertheless, after all due allowance has been made for naturally delicate duras, cases undoubtedly occur in which there is a degree of atrophic thinning. The change is of much less frequent occurrence

than general thickening. Dr Clouston (53) has described two very remarkable cases in which the pressure transmitted from a cerebral tumour caused localised thinning of the dura at several points and the protrusion of small herniæ of brain substance.

BONY FORMATIONS IN THE DURA.

These occur with some frequency, but it is questionable if they are more common in the insane than in other persons. Two varieties may be distinguished—(a) those that form in the true substance of the dura; and (b) those that sometimes develop in old inflammatory deposits on its outer surface. Hard concretions are on rare occasions found in old hæmatomata of the dura, but it is doubtful if they are composed of true bone. The most common forms of bony growth are those which arise in the substance of the dura itself. In the majority of cases they are seen in the falx, usually embedded in the fibrous tissue, but occasionally lying on the free surface. They are generally small, flattened and smooth, occasionally appearing as little melon seed-like bodies. They may, however, be an inch or more in diameter, and some cases have been described in which the whole falx was changed into bone. Sometimes they are in the form of spiculæ. Jeannerat (54) and Camuset (38) regard these growths as being due to an ossifying pachymeningitis. The former found them most common in epilepsy and chronic mania, while the latter believes they are most frequent in general paralysis, in which disease he found them in nine cases out of 100. Dagonet (55) met with them 16 times in 250 cases of insanity. They were most frequent in epilepsy, and next in dementia and general paralysis. They occurred mainly in the falx. Dr Middlemass and I found them in 6 cases out of 294. In every instance they were in the falx. In one of these the bony growth was somewhat nodular, and was associated with two similar but larger and rapidly-growing tumours attached to the skull, which had compressed and irritated the brain, causing acute mania and rapid death (see p. 69). These were undoubtedly true osteomata, but the common type of bony nodule occurring in the dura cannot be regarded as of the nature of a tumour. It is more probable that this is of chronic inflammatory origin, though some examples may perhaps be correctly regarded as merely developmental anomalies, resulting from the inclusion of osteoblastic cells in parts of the dura which are not normally concerned with the production of bone. It is rare that there is any evidence of these bony growths having irritated the subjacent brain. Camuset made a microscopic examination of one, and found it to contain true, though irregularly disposed, Haversian canals. Bony plates in old inflammatory deposits on the outer aspect of the dura occur only very rarely.

DEGENERATIVE CHANGES.

Degenerative changes are of very common occurrence in the dura mater in various forms of insanity, and, though mostly microscopic, are of great pathological importance. They are intimately related to the development of subdural false membranes, and will be considered along with that subject.

CONGESTION.

There are considerable variations in the degree of distension of the dural vessels as seen on post-mortem examination in different cases. Congestion manifests itself most markedly on the two surfaces near which are situated the chief vascular areas. On the outer aspect it shows itself in engorgement, especially of the smaller vessels, and in extravasation of blood on the surface as a result of their laceration in the process of detaching the membrane from the bone. On the inner surface the distended capillaries give rise to a bright red blush, which, with a hand lens, can be resolved into an irregular vascular network. Numerous larger distended vessels may also be recognised with the unaided eye. Microscopic examination of superficial horizontal sections of duras presenting this appearance, proves that, while in some instances the bright red tint is due merely to extreme distension of the capillary network lying immediately subjacent to the inner surface, it is also very commonly associated with an extensive new formation of capillaries on the surface, the cause of which is explained in connection with the subject of the development of subdural false membranes. These new vessels are mostly of large size, and when congested have a varicose appearance under the microscope.

It is difficult to define the exact significance of simple dural congestion in the insane. It is undoubtedly in them a common appearance at post-mortem examinations, but it is probable that it is frequently related rather to the mode of death than to the special morbid cerebral conditions that are present. It is, however, a constant occurrence in general paralytics dying in a congestive attack. Excepting perhaps in this class of patients, there is little or no histological evidence that congestion of the dura mater is common in the insane during life. The frequency of the occurrence of subdural false membranes in various forms of insanity has been regarded by many as proof that such chronic congestion does commonly occur. But a careful study of the origin of these formations proves that they depend upon essentially different factors.

INFLAMMATION OF THE DURA.

Many authorities still regard subdural false membranes as the result of a pachymeningitis. As I am convinced that this view is an erroneous one, I exclude these formations from among the manifesta-

tions of dural inflammation. Apart from conditions which may be broadly defined as either traumatic or infective, and which have no special claim for discussion here, this morbid change seems to be of rare occurrence, except in very limited areas. Evidence of it in the insane is chiefly to be recognised in the local adhesions that may occasionally be observed between the dura and the pia-arachnoid, in some of the bony growths that occur in the substance of the dura and in the localised deposits of new fibrous tissue that are in rare instances to be found on the outer aspect of the membrane.

SUBDURAL FALSE MEMBRANES AND ALLIED MORBID CONDITIONS.

Review of Literature.—Under the term “subdural false membrane,” I include all those morbid conditions that have been described by different authors under the various names of “hæmatoma duræ matris” (Virchow, 14); “pachymeningitis hæmorrhagica interna” (König, 37); “meningeal hæmorrhage” (Baillarger, 4); “arachnoid cysts” (Quain, 13; Wilks, 22, 23 and 25); “false membranes of the arachnoid” (Aubanal, 8); “meningeal apoplexy” (Prus, 10); “blood cyst of the dura mater” (Bauchet, 11); “subdural hæmatoma” (Ormerod, 39); and “false membranes under the dura mater” (Clouston, 36). “Subdural membrane” is the term that has been adopted by G. M. Robertson (45), and it has the great advantage that, unlike most of the others, it may be used without implying belief in any particular etiological theory.

The subject is one that has given rise to a now long-standing controversy. The majority of writers have endeavoured to explain all the different phenomena to be observed by one or other of two theories. Around these almost the whole of the controversy has been waged. They are, first, *the inflammatory theory*, usually associated with the name of Virchow (14), and, second, *the primary hæmorrhagic theory*, which has been specially advocated by Huguenin (33). The supporters of the inflammatory theory maintain that the process begins as an exudation, upon the inner surface of the dura, of a layer of fibrinous lymph which becomes organised, the false membrane increasing subsequently both by the deposition of fresh layers of the same kind, and by the occurrence of hæmorrhages from the new vessels that develop in it. The advocates of the primary hæmorrhagic theory, on the other hand, maintain that inflammation plays no part in the process, and that all the phenomena may be explained as the result of an effusion of blood into the subdural space. Several authorities, including Calmeil (1), Bayle (2), and Heschl (12), argued for the inflammatory theory before Virchow wrote, and it has since been supported by Charcot (16), Lancereaux (17), Christian (30),

Kremiansky (24), Rindfleisch (28), Camuset (38), Ziegler (42), and others.

Prescott Hewitt (9) was the chief early authority who supported the hæmorrhagic theory. Virchow's views were pretty generally accepted for some time after his paper appeared in 1856, but in 1877 Huguenin's contribution to the controversy, which is undoubtedly one of the most important that has appeared, gave a fresh impetus to the theory of primary hæmorrhage. Wilks (22, 23 and 25), Sperling (26), and others, however, had previously combated Virchow's teaching, the two authorities named supporting their opinions by experiments upon animals. They injected blood into the subdural space, and found that a typical false membrane was formed. At the present day Virchow's theory seems still to be pretty generally accepted on the Continent, though with many important exceptions. In this country the majority of authorities, including Greenfield (34), Wiglesworth (40 and 41), and Bevan Lewis (43), support the primary hæmorrhagic theory. Other supporters of the latter are Baillarger (4), Brunet (15), Laborde (21, 29 and 32), Prus (10), Lelut (3), Aubanal (8), Boudet (5), Rilliet and Barthez (7), Legendie (6), König (37), Crichton Browne (31), and Bondurant (46).

The advocates of the inflammatory theory maintain that their view is fully supported by the naked-eye and microscopic characters of the typical lesions that may be observed, and that the hæmorrhages so frequently found occur subsequently to the formation of a false membrane, from the vessels of which the blood has escaped. Very numerous arguments against the inflammatory theory and in support of the hæmorrhagic have been adduced, especially by Huguenin, Bevan Lewis, and Wiglesworth.

Bevan Lewis urges against it the following considerations:—1. The cyst is readily removable from the dura; it is only slightly adherent, or not at all; 2. in the majority of cases there is no evidence whatever of the existence of pachymeningitis—(a) the dura is not thickened or softened or vascular, (b) no organic connection exists between the two; 3. in early stages the characters are purely those of a simple extravasation of blood into the arachnoid cavity (subdural space); 4. there is the co-existence in this affection of a recognised vascular disease and vasomotor disturbances which render hæmorrhage frequent, *e.g.* the othæmatoma, or "insane ear." Wiglesworth (40) states that in one-sixth of the large number of cases of the disease which he has observed there was fluid blood, or this combined with recent clot, without the presence of any trace of membranes on the inner surface of the dura; that the membrane resembles in microscopic character an organising thrombus; that the dura mater shows no signs of inflammation, and that the membrane can almost

always be stripped off from the dura with ease, leaving the inner surface smooth and shining. In another paper (41) he says: "If the membrane were the primary thing and the hæmorrhage secondary, although we might get the membrane without the blood, we could not get the blood without the membrane," which condition, however, he says he has frequently observed. Others have pointed out that the so-called inflammatory membrane is often really a dense coagulum formed at the periphery of a blood-clot. Thus Baillarger (4) maintains that a delicate and transparent false membrane forms on the superior surface of the blood-effusion, and another similar one on the inferior surface, and that these two unite at the circumference into one layer, which is often prolonged for a considerable distance. It should be mentioned that Obersteiner (44) holds that subdural membranes may develop either from a primary hæmorrhage, or as a result of inflammation of the dura. In 1877 Clouston (36) maintained that neither of these theories satisfactorily explained the formation of false membranes under the dura in the insane.

In 1893 a new theory was advanced by G. M. Robertson (45). In his own words it is as follows:—"We believe that the all-important element in the production of subdural membrane formation is sudden lowering of the intracranial pressure, and the effect of this is analogous to a dry cupping of the dura mater." He held that this sudden lowering of pressure arose from vasomotor derangements in the cerebrum, which caused vascular spasms and contraction of the brain. These vascular derangements, he believed, occurred specially in certain forms of mental disease, notably general paralysis and senile insanity. He maintained that the sudden lowering of pressure caused distension of the superficial vessels of the dura and the occurrence of numerous minute hæmorrhages from them. He adduced, in support of his contentions, very numerous and elaborate arguments, drawn partly from phenomena he had observed, partly from considerations more or less theoretical, and also from actual experiments he had made.

Regarding the later stages of the morbid process, the various authorities are fairly agreed. The inflammatory exudation, or the blood-clot, becomes replaced by granulation tissue, the vessels of which, derived always from the dura, are extremely liable to rupture. In this way new blood-clots are formed either within the membrane, below it, or on the surface, and lead to the development of more granulation tissue. Thus the membrane increases in thickness, though, as already stated, the advocates of the inflammatory theory maintain that it also grows as the result of the exudation of new layers of inflammatory lymph from the dura. Very careful descriptions of the naked-eye appearances of subdural membranes have been

given by various writers, among whom Wigglesworth (40 and 41) specially deserves mention.

According to the advocates of the inflammatory theory, "the first morbid sign is the appearance of very thin fibrinous deposits on the internal surface" (Ziegler, 42). Those who hold the hæmorrhagic theory maintain that this is either a white or a decolourised blood-clot, and that the earliest stage is represented by a layer of freshly coagulated blood. The occurrence of rusty staining on the inner surface of the dura without the presence of a separable false membrane, seems scarcely to have been noticed until G. M. Robertson specially drew attention to it, and claimed that, in many cases, it represented an important stage in the pathological process.

Fully developed subdural false membranes are generally described as being of a soft gelatinous character. Frequently they are highly vascular. They may form a very thin layer, or attain to half an inch or even more in thickness. They may be distinctly laminated. They frequently present small, more rarely large, recent hæmorrhages into their substance. They may have a rusty colour, owing to the presence of hæmatoidin granules. Bevan Lewis (43) states that in old membranes calcareous matter may occasionally be found.

In some cases the false membrane is formed of two layers, which enclose fluid. This is the cystic variety. It assumes various forms. It may be localised to a small area, or extend over the whole of one side of the brain, and may even be developed on both sides. The walls of the cyst may be thin or thick. The contents may be recently effused blood, disintegrating blood, or rarely, almost clear fluid. These cysts are generally explained as a late result of either a large primary hæmorrhage, or of a large secondary hæmorrhage between the false membrane and the dura (Bauchet, 11). Subdural false membranes are always adherent to the dura, though they are as a rule easily detached. They are almost never adherent to the pia-arachnoid. They are usually unilateral, but are also frequently bilateral. About these points there is general agreement.

Regarding the source of a primary hæmorrhage into the subdural space, Crichton Browne (31), Huguenin (33), Bevan Lewis (43), and Wigglesworth (40) are all agreed that it is usually to be found in a pial vein. G. M. Robertson (45), on the other hand, holds that the hæmorrhage usually occurs from the superficial dural vessels.

Subdural false membranes are most frequent over the upper and lateral aspects of the brain. But many cases have been described in which they were confined to the basal fossæ. Bevan Lewis and Wigglesworth both say that they have never seen either recent clots or organised membranes in the cerebellar fossa.

Various explanations have been offered to account for the fre-

quency of hæmorrhage from the new vessels in a false membrane. Pirotais (19) states that it is owing to the fact that they have a great tendency to fatty degeneration. Lancereaux (17) holds the same opinion. Rindfleisch (28) gives another explanation. He says that in the normal capillaries of the dura, which lie in dense tissue, the blood pressure is excessive, while the new capillaries of the membrane, which communicate with them, are in a soft tissue that cannot withstand the pressure that is transmitted to them. Hence they dilate and rupture.

All authorities are agreed that subdural false membranes are much more common in the insane than in the sane. Regarding their occurrence in the insane, the following statistics may be quoted: Wigglesworth (41) observed 54 cases in 637 post-mortems (8.47 per cent.); Crichton Browne (31) found them in 5 per cent. of his cases; Bevan Lewis found them in 81 cases out of 1565, or in 5.2 per cent. It is generally agreed that they occur most commonly in the insane of a somewhat advanced age, and that they are found in the great majority of instances in patients in whom the mental disease has been of long standing. The form of insanity that furnishes the largest proportion of cases is general paralysis.

Regarding the occurrence of subdural membranes in the mentally sound, according to Althaus (35), they occur "in the old, decrepit, worn-out, intemperate," and are "not infrequently associated with low forms of pleuro-pneumonia, pneumothorax, pleurisy, pericarditis, emphysema, rheumatic fever, delirium tremens, leucæmia, pernicious anæmia, scurvy, hæmophilia, and various forms of Bright's disease of the kidneys." Many other writers speak of having observed cases in these or in other bodily diseases, among which should be specially mentioned typhus fever and those associated with chronic alcoholism. G. A. Sutherland (47) has specially directed attention to the occurrence of hæmatoma of the dura mater in infantile scurvy. As evidence of the degree of frequency of the occurrence of subdural false membranes in the mentally sound, it may be mentioned that Kremiansky (24) obtained the material for his authoritative work entirely from patients who died in a general hospital.

Many authorities have endeavoured to give a satisfactory explanation of the special frequency of subdural false membranes in the insane. Wigglesworth (41) thinks it is due to "wasting of the hemispheres and general or localised congestion of the meninges." He believes that the hæmorrhage is often simply compensatory. Crichton Browne (31) and Huguenin (33) hold practically the same view. G. M. Robertson's explanation has already been stated.

The various descriptions that have been given of the microscopic anatomy of subdural false membranes may be summed up as implying

that they may be composed of white or red blood-clot, or of fibrin threads entangling numerous leucocytes (inflammatory exudation), or of granulation tissue. When of the last-named structure they usually contain very numerous, large, thin-walled, often varicose capillaries, and more or less abundant hæmatoidin granules.

Greenfield (34) observed on the free surface of the false membrane a layer of endothelial cells. König (37) states that many of the cellular elements in organising membranes are "due to the proliferation of the epithelium of the dura." Fatty changes in the vessels have been observed by Pirotais (19), Lancereaux (17), and others. Congestion of the dural vessels is mentioned by many writers as occurring whenever there is a false membrane, and those who believe in the inflammatory theory maintain that there is in addition always a small-cell infiltration of the superficial dural tissues. G. M. Robertson has drawn attention to the frequent occurrence of dilated vessels and deposits of hæmatoidin granules near the inner surface of the dura in cases in which there is no false membrane. The same writer has described the frequent presence of very delicate fibrinous films on the inner surface of the dura in association with congestion. Obersteiner (44) states that "not rarely, in old people especially, concentrically laminated, glancing concretions, *corpora arenacea*, are found in the dura." He says they consist of phosphate and carbonate of lime. He also mentions that they may be found in subdural false membranes. Thomson and Dawson (49) have described a case of general paralysis in a child in which there was a subdural false membrane presenting some very exceptional features. It lined the entire inner aspect of the dura, being even prolonged into the spinal canal. It was fully a quarter of an inch thick in places. A similar false membrane in part separated the dura from the bone. The microscopic structure of both was that of vascularised fibrous tissue. The layers of the subdural false membrane nearest to the brain had in some places acquired a homogeneous hyaline appearance. In the substance of the dura, there were networks of fibrin containing round cells in their meshes.

In 1895 Dr Middlemass (48) and I gave an account of some researches upon the origin of subdural false membranes, carried out with the aid of surface sections of the dura mater. This new method of observation was at first beset with great difficulties which we did not know how to overcome. We were able to obtain only a comparatively imperfect demonstration of the morbid changes occurring at the inner surface of the dura, and consequently we were led into some erroneous conclusions regarding their nature. We were able, however, to ascertain the fact, which subsequent researches have fully confirmed, that the special subdural membrane formation of the insane is

preceded by a process of obliteration of capillaries at the inner surface of the dura and the development of new vessels. After publication of this paper I continued the same line of research, studying not only duras from the insane, but also a large number from general hospital cases. By gradual improvements in the method of preparing surface sections, and the study of duras by this means, especially in the stage immediately prior to the development of a false membrane, I was able, I believe, to fully elucidate the pathological processes at work. The results of these researches were recorded in the *Journal of Pathology and Bacteriology* in 1896 (50).

1. *Macroscopic Anatomy.*

My own observations lead me to the conclusion that we must divide subdural false membrane into two classes. On the one hand, there are those that are the result of a simple hæmorrhage into the subdural space, most commonly from a pial vein. On the other hand, there are those that develop in consequence of a widespread morbid process occurring in the dura itself. This process, in its initial stage, can only be recognised with the aid of the microscope; but it has certain common intermediate stages, prior to the development of a false membrane, which manifest themselves in such a way as to be readily observable at a post-mortem examination. The morbid appearances referred to, occur at the inner surface, and are essentially of three different kinds, viz., granulations, yellow or rusty staining, and a peculiar silvery appearance.

Granulations are exceedingly common. They appear as minute asperities on the inner surface of the dura. They are so small that they are very apt to be overlooked, if the surface is not examined with care. When present, they are usually specially abundant and large over the body and lesser wings of the sphenoid and the upper surface of the tentorium cerebelli, but are often easily recognisable over the whole of the inner surface. They are most numerous and prominent in senile insanity and general paralysis. Those lying over the sphenoid are very commonly associated with a marked hyper-vascularity of the surface, especially round the sella tursica. *Yellow or rusty staining* is due to the presence of granules of hæmatoidin near the surface. This substance requires to be present in considerable quantity before it is observable with the unaided eye. Many duras from the insane which appear at the post-mortem to be free from any pigmentary deposit, are found, on microscopic examination, to contain hæmatoidin granules in abundance near the inner surface. *The silvery appearance* is one that is exceedingly difficult to describe satisfactorily. It may also be likened to ground or frosted glass. It occurs at any part of the internal surface, usually being only slightly developed and affecting small areas. In two

of my cases, however, it affected almost the entire inner surface of the dura, in one to a very marked degree.

In association with false membranes and these related morbid conditions, the dura is very frequently slightly thickened and indurated by general overgrowth of its connective tissue.

Mere congestion of the inner surface of the dura mater cannot be regarded as a preliminary stage in the formation of subdural false membranes. It may exist quite independently of the morbid conditions, presently to be described, that lead to hæmorrhage from the dural vessels, though in association with these morbid conditions it has considerable importance in relation to the formation of false membranes. It may be due to the distention of new capillaries that have developed in the way subsequently explained, but this condition is scarcely distinguishable, with the unaided eye, from congestion of the original superficial dural capillaries. Exception to this statement must be made, however, in the case of the hyper-vascularity so common over the body and lesser wings of the sphenoid, in association with granulations. Microscopic examination proves that this is always due to the presence of new capillaries.

Subdural false membranes differ greatly as regards situation, extent of surface they cover, thickness, colour, and numerous other characters. A common form is one which is reached by an insensible gradation from mere rusty staining. In many cases in which rusty staining is specially well marked, it will be found on careful investigation that a delicate layer of tissue containing most of the pigment can be raised from the surface at certain places. Equally delicate false membranes entirely devoid of pigment granules may, however, occur. At the opposite extreme from such delicate new formations there are false membranes which may attain to more than an inch in thickness, and extend over the whole of the inner surface of the dura.

The most common situations for localised subdural false membranes are one or both sides of the vault, and one or both middle fossæ of the base. Bilateral development in these situations is, in my experience, the rule rather than the exception. Any part of the inner surface may, however, be affected. The cerebellar fossa enjoys a remarkable though by no means complete immunity. The spinal dura is frequently involved. The entire surface of the intracranial dura, generally excepting that of the cerebellar fossa, is affected in a considerable proportion of cases.

In thickness subdural false membranes commonly vary from a layer of extreme tenuity to one of about $\frac{1}{16}$ or $\frac{1}{8}$ of an inch. Although many much thicker false membranes than this have been described, their occurrence is quite exceptional, at least if we exclude the recent clot found in cases of rapidly fatal subdural hæmorrhage resulting from

rupture of a large vessel. In consistence subdural false membranes are nearly always exceedingly soft. Many of them might be accurately described as gelatinous, but all except some very thin examples are sufficiently firm to be separated from the dura as a coherent layer. False membranes of leathery consistence have been described, but are certainly extremely rare.

As regards colour the variations are specially numerous. Some of the most delicate membranes are quite devoid of colour. Generally, however, a portion of such films has a reddish appearance, or may be manifestly a red blood-clot. Others have a reddish hue throughout, owing to the fact that they are permeated by capillaries. Combined with this there is in most instances a yellow or rusty tint, varying greatly in intensity in different membranes and in different parts of the same membrane.

Many false membranes attached to the inner surface of the dura are obviously nothing more than recent small blood-effusions that have coagulated in the form of a thin layer. In such instances all that attracts attention at first is perhaps a minute portion of red clot. But if the neighbourhood of this clot is carefully examined, more especially after the dura has been hardened in bichromate solution, it can be demonstrated that in every instance a colourless clot extends a long way beyond the red clot.

Some very large subdural false membranes, obviously of hæmorrhagic origin, show a somewhat dense, pale encapsuling layer lying upon the cerebral hemisphere on the one hand and on the inner surface of the dura on the other, while in the centre there is a reddish brown, diffuent mass, or sometimes blood which has undergone little change.

Subdural false membranes are always adherent to the dura, but in almost every instance may be easily detached. They practically never form any true adhesion to the pia-arachnoid.

It may be useful to add here some descriptions of the morbid appearances presented by the inner aspect of the dura in actual cases. The following are selected from my own reports in the Pathological Records of the Royal Edinburgh Asylum.

1. General paralysis. Man, aged 46. In the anterior and middle basal fossæ there was well marked rusty staining, but no separable false membrane. There were also well marked granulations, especially at the vault.

2. General paralysis. Woman, aged 48. At the vault there were some fine granulations, hyper-vascularity evidently due to the formation of new vessels, and faint rusty staining. There were similar morbid appearances over the sphenoid, without the rusty staining.

3. General paralysis. Woman, aged 42. Over the convexity of the hemispheres the inner surface of the dura showed distinct hyper-

vascularity, evidently from formation of new vessels. There was no false membrane. Over the sphenoid there were some fine granulations.

4. Alcoholic insanity. Man, aged 59. Near the summit of the vault on both sides there were some minute points of recent hæmorrhage and numerous granulations. Granulations were also numerous over the sphenoid.

5. Chronic melancholia; phthisis. Woman, aged 45. At the vertex on the right side there were numerous minute points of red clot, and around these a very delicate, coherent, colourless, gelatinous false membrane could be raised. There were some granulations over the body of the sphenoid.

6. Senile insanity; pneumonia; Bright's disease. Woman, aged 67. Over the greater part of the right side there was a thin, pale, transparent, fairly tough, easily separated false membrane. It was most distinct over the convexity of the hemisphere. There was slight rusty staining in the middle fossa. On the left side the dura was hyper-vascular, and numerous granulations studded the surface, especially near the superior longitudinal sinus and over the sphenoid.

7. Senile insanity. Man, aged 72. There was a universal, thin, gelatinous, pale or blood-red, and at places slightly yellow, false membrane. Through the paler portions, networks or arborisations of small, deeply congested vessels could be seen. There were granulations over the sphenoid.

8. Senile insanity; double pneumonia. Man, aged 60. There was a recent false membrane covering the whole of the inner surface, with the exception of that of the cerebellar fossa. It was nowhere more than $\frac{1}{16}$ th of an inch in thickness, and for the most part it was much thinner. It was chiefly composed of recent blood-clot of a dark red colour, but largely also of fibrin of a pale or slightly rusty character.

9. Senile insanity; chronic Bright's disease. Man, aged 72. In the subdural space on the left side, overlying the convexity of the hemisphere, there was a thick false membrane. At its thickest it was about a $\frac{1}{4}$ of an inch across. It was for the most part of a rusty red colour and soft. On the external and internal aspects there was a thin, coherent, pale, tough fibrinous film. The false membrane was easily raised from the dura and from the pia-arachnoid, but was distinctly more firmly attached to the former. In the centre its consistence was almost fluid. The false membrane was continued into the basal fossæ as a delicate, very deeply rusty stained film.

The following statistics, compiled from the records of 290 post-mortem examinations made by myself at Morningside Asylum, will give some idea of the frequency of the occurrence of these morbid conditions in the insane. Separable false membranes were found

attached to the cerebral dura mater in 71 cases (25·5 per cent.); 8 of them were obviously the result of recent large hæmorrhages, the source of which was ascertained in six instances. In 5 of these it was a pial vein, while in the remaining case a hæmorrhage into the substance of the brain had burst through the pia-arachnoid. There were 4 examples of the cystic variety of false membrane. In 13 instances the false membranes were formed of recent small blood-clots. In addition to the 71 cases in which false membranes were present, there were 72 in which were recognised the morbid appearances already described as frequently being present prior to the development of a false membrane. They consisted sometimes of granulations alone, more commonly of these combined with yellow or rusty staining, and in about a dozen instances of the frosted glass appearance.

Subdural false membranes probably occur in largest proportion in cases of general paralysis and senile insanity, but they and their allied morbid appearances are very common in practically all forms of chronic insanity.

2. *Morbid Appearances observed in Superficial Horizontal Sections of the Dura Mater.*

(a) *Morbid changes in the endothelial elements.*—These are both proliferative and degenerative. They occur especially in the insane, in whom they are often of a very marked character, frequently leading to the formation of several layers of cells on the inner surface of the dura. They are of special importance in relation to subdural false membrane formation, though existing quite commonly apart from it. Of 60 cases examined microscopically, in 38 there was distinct evidence of proliferation of the surface endothelium. In a like number, and for the most part in the same cases, there was proliferation of the endothelial cells of the perivascular canals. As a rule, the condition when present in the one situation occurs also in the other. In both it may either be general or specially localised to small areas (figs. 36 to 42). These proliferative changes also occasionally affect the endothelium of the perivascular canals of the deep dural vessels. Localised cellular aggregations on the surface constitute one form of granulations. The proliferated endothelial cells in the peri-vascular canals are probably identical with the cellular aggregations that have been observed near the surface in transverse sections of the dura by the advocates of the inflammatory theory, and regarded by them as of the nature of a small round-cell infiltration of the connective tissues. For my own part, I am perfectly confident that I am accurate in stating that these cellular aggregations are in almost every instance the result of proliferation of the endothelial cells of the perivascular canals. When examined in thin superficial horizontal

sections deeply stained with hæmatoxylin, their endothelial character is in most cases perfectly evident, although their nuclei are much smaller than those of the normal endothelial cells. As a rule, they contrast markedly with the wandering leucocytes that may occasionally be observed among them (figs. 38 and 39).

The degenerative changes that occur in the endothelial cells, especially in association with proliferation, are of several varieties. Fatty changes, both in the nucleus and cell-plate, are exceedingly common. They are usually slight, but occasionally they are marked, sometimes leading to the formation of large globules of fat on the inner surface, or in the perivascular canals. Many of the proliferated cells seem to break down and disappear in this way.

Another important change is that which produces the peculiar silvery or frosted-glass appearance that I have described. It begins as a vacuolation of the nucleus. The vacuoles gradually increase in size until the cell appears as a glassy or vitreous-looking body (fig. 46). In the early stages the cell-plate can also occasionally be seen to contain small vacuoles, but the change is chiefly a nuclear one. It affects extensive areas of the surface endothelium (fig. 47), and also that of the perivascular canals (fig. 48). Degenerated endothelial cells of this kind may often be seen in large numbers in subdural membranes. The homogeneous glassy substance does not stain with eosin, and only faintly with hæmatoxylin. It is not blackened by osmic acid. I have suggested the name "vitreous degeneration" as an appropriate one for this endothelial change (50). The term "vitreous," however, describes merely the microscopic appearance presented by these degenerated cells, and must not be taken to imply any indurative change in their consistence, which, indeed, there is evidence to show, is semi-fluid. There is also conclusive evidence that this change may develop with great rapidity, and that it specially tends to arise in the moribund state. In those cases in which a silvery appearance is recognisable with the unaided eye, the entire endothelium of the surface and of the perivascular canals over extensive areas may be completely transformed by it. When the change is developed to its extreme degree, the affected cells become shed, leaving a surface studded with small, clear globules, which are not stained by hæmatoxylin or eosin, and are not blackened by osmic acid. When marked degrees of vitreous degeneration affect the endothelium of the perivascular canals, the enclosed vessel becomes compressed, and its lumen obliterated. Its slighter degrees may produce the same result when the change affects the proliferated cells in this situation (fig. 49).

Hyaline degenerative endothelial changes also occur and lead to the formation of concentric bodies, the whole subject of which is, however, considered further on.

(b) *Morbid changes in the superficial vessels.* *Development of new capillaries.*—A common change is one that consists in a slight thickening and granularity of the capillary wall, which at the same time stains abnormally deeply with eosin. Osmic acid preparations show that part of this granularity is due to slight fatty changes. Large globular masses, which blacken with osmic acid, are sometimes found within the superficial capillaries, completely blocking them. Their exact origin is doubtful. Around these granular capillaries hæmatoidin masses may often be observed either in the perivascular canal, or in the intervacular areas, but still subjacent to the surface endothelium (fig. 20). In transverse sections hæmatoidin granules may also quite commonly be observed at some distance from the inner surface (fig. 3). The proliferation of the endothelial cells of the perivascular canals, already described, is generally accompanied by some degree of this thickened and granular condition of the capillary wall, though the latter often occurs in the absence of the former. These proliferated endothelial cells frequently compress the capillaries, interfering partially or completely with the passage of blood through their lumen. This result is chiefly produced by the localised proliferations in the perivascular canals, which in some cases are very numerous (figs. 40 and 41). Vitreous degeneration of the endothelial cells of the perivascular canals also, as already stated, occasionally leads to compression and obliteration of the contained vessels (figs. 48 and 49). Another change that may result in compression of these capillaries is overgrowth of the connective tissue of the dura around the perivascular canals. Such overgrowth is a natural consequence of slow endothelial proliferation when not accompanied by degeneration. When it occurs it is not confined to the walls of the perivascular canals, but affects the dura throughout, leading to a condition of general thickening.

The fibrous tissue immediately outside of the perivascular canals also occasionally undergoes a change that is probably identical with the hyaline fibroid degeneration so common in the vessels of the pia-arachnoid and brain. The process does not appear to be a very common one in the dura, but nevertheless it seems to be one of the causes of compression and obliteration of these superficial vessels.

Great variations occur in the amount of blood contained in the dural vessels. In many cases the large majority of them are empty. In others they are greatly distended, more or less completely obliterating the perivascular canals. It is probable that these differences depend chiefly upon the mode of death in each case.

Associated with the above morbid changes, recent capillary hæmorrhages from the superficial dural vessels are very frequently to be observed. They appear most commonly to depend upon fatty

degeneration of the vessel-walls, accompanied by congestion. Distension and rupture of a vessel also frequently occurs behind a point at which it has become compressed. When such hæmorrhages are very small, the effused blood may not pass beyond the perivascular canal. Hæmorrhages from these causes are by no means confined to the inner aspect of the dura. They may very frequently be seen in deep horizontal sections. They are especially common near the superior longitudinal sinus.

In constant association with the chronic obliterative changes, a development of new capillaries takes place on the inner surface of the dura (figs. 40 and 41). Why this occurs is not perfectly clear. All that can be said is that the new vessels are required to carry on the nutritional functions of those that have been obliterated. There is complete demonstration of the fact that they shoot out quite independently of the previous occurrence of hæmorrhage. When the obliteration has been recent the new vessels may sometimes be seen in process of development, usually spreading over the surface in the form of a leash. Very rarely a new capillary can be seen to have formed in a perivascular canal of a vessel that has been closed by changes further back in its course. These new vessels are often developed in very large numbers, sometimes forming over extensive areas quite a network on the surface. They become covered over by the surface endothelium, which tends to proliferate in their immediate vicinity (fig. 37). They are often of very large size. They have no perivascular canals. They frequently show great congestion (fig. 42) and a degree of fatty degeneration. When they are simultaneously affected by these two conditions, hæmorrhages tend to occur from them at a multitude of points (fig. 44). Granular hæmatoidin frequently lies around them (figs. 4, 31, 37, and 43), sometimes in very large quantity. Its presence is evidence of previous hæmorrhage. Hæmatoidin may undoubtedly be formed very rapidly, probably within twenty-four hours. Much of the pigment of this kind that so commonly lies outside of the perivascular canals of the original superficial capillaries (fig. 39) in duras from the insane, seems to be derived from blood extravasated from new capillaries. It finds its way into these canals owing to the fact that it tends to travel with the lymph-stream.

(c) *Phenomena following effusion of blood upon the internal surface of the dura.*—These phenomena may be studied with great facility in superficial horizontal sections and are of much interest, not only on account of the light that they throw upon the processes concerned in subdural false membrane formation, but also because of their bearing upon questions of general pathology.

It is to be understood that the following observations apply specially

to small blood-effusions, which alone can be studied in superficial horizontal sections.

When such an effusion takes place into a subdural space in which there is no excess of fluid, a thin layer of red and white blood-clot forms in the neighbourhood of the point from which the blood escaped, the red clot occupying the centre and the white clot spreading out as a delicate surrounding film, which generally extends much further than is appreciable to the unaided eye. As the dura presents a highly vascular surface, and the pia-arachnoid a practically non-vascular one, the reactive changes that the presence of the clot induces in the surrounding tissues result in the penetration of the clot by vessels from the dura alone, to which it consequently becomes adherent, while shedding of the endothelium of the arachnoid surface, transudation of cerebro-spinal fluid, and probably also the movements of the brain, assist in effecting its detachment from the inner wall of the space. At the same time, small clots formed from hæmorrhages from the dural vessels will practically always be found adherent to the dura, even when there has not been sufficient time for their penetration by vessels. Small clots of this kind can be shown to be continuous with coagulum within ruptured vessels and perivascular canals. This is probably the true explanation of their attachment to the dural surface. The red corpuscles rapidly break down into granular *débris*, a certain portion of which is generally converted into hæmatoidin granules. The fibrin threads are at first very distinct (fig. 57), but they soon become less evident, and the coagulum assumes under the microscope a somewhat homogeneous appearance (figs. 58 to 61). It usually remains slightly striated and granular. This granular appearance may, in part, be due to the products of disintegration of leucocytes and red corpuscles, the latter of which, it can be shown, are always present even in the white portion of the fresh clot, though it may be in only very small numbers. A continuous sheet or film is thus formed which often presents little trace of the original threads of which it consisted. From an early stage the clot shows signs of undergoing contraction. This leads to the formation of openings in the film, so that a fenestrated appearance is produced. Many subdural false membranes, when stripped from the surface of the dura and examined in horizontal view, are found to have essentially this structure, the only difference being that the larger clot in contracting has assumed the appearance of many inaccurately superimposed flattened networks or fenestrated membranes, instead of that of one such layer. In the thinner films the contraction may continue until the fenestrated sheet becomes a network. The cords of this network have usually a longitudinally striated appearance, and generally show a strong, but varying and unequal, affinity for both eosin and hæma-

toxylin (figs. 60, 61 and 62). They tend to split across and then to further contract and curl up (fig. 60). Long before these changes have proceeded thus far, the fibrinous coagulum begins to be penetrated by new capillaries, which shoot out from the dura (figs. 59 and 60). This outgrowth of vessels may probably begin within a few hours of the occurrence of the blood-effusion. In a case in which it appeared evident, from the history, that blood had begun to be poured out into the subdural space from a pial vein only seven hours before death, new capillaries were found penetrating the clot. Another effect upon the dural tissues of the presence of a fibrinous film seems to be rapid proliferation of the surface endothelial cells, a condition which, however, is often already established to a marked degree in those cases in which hæmorrhage from the superficial dural vessels is specially liable to occur shortly before death. Under certain circumstances, especially in the case of thin fibrinous films, a large number of the new capillaries become obliterated. The cause of this obliteration is somewhat difficult to understand. Many of the appearances suggest that it may be due to compression of the new vessels by the contracting fibrin which can be seen to envelop them with a sheath (fig. 60). These obliterated capillaries, which frequently assume a homogeneous hyaline appearance, but usually remain more or less striated, may be seen very frequently in superficial horizontal sections, often presenting little or no evidence of the clot that caused their development (fig. 62). They may be lying on the surface of the dura, or the endothelium may have grown over them. When subendothelial in position, being not infrequently traceable into patent dural vessels, they produce appearances that naturally suggest their development from original dural capillaries, as the result of a morbid change. This was the view taken of these appearances, in the paper by Dr Middlemass and myself on this subject (48). I have no doubt now that this view was in large part erroneous, and that these "hyaline capillaries" most commonly arise in the way I have just described. Some of the changes that take place subsequently to the above are exceedingly difficult to follow. Fatty degeneration appears to play no part in the process of disintegration of the fibrin. What becomes of the cords of the contracted coagulum, I have been unable to determine with certainty. The obliterated capillaries after being covered over by the surface endothelium are probably ultimately replaced by fibrous cords, which are often indistinguishable from the smallest of the dense fibrous tissue strands, which, as already mentioned, normally traverse the inner surface of the dura in some parts. When the new capillaries do not suffer obliteration they become the vessels of the granulation tissue that develops on the surface of the dura, replacing the blood-clot and forming an organised false membrane.

(d) *Hyaline changes*.—The term hyaline is used here merely in a general descriptive sense, implying a substance which under the microscope has a homogeneous glassy appearance and stains deeply with eosin in hæmatoxylin and eosin preparations, but gives no waxy reaction. Irregular and globular masses, cords, rods, networks, and fragments of a substance of this kind may very frequently be observed in superficial horizontal sections of the dura, as well as in subdural false membranes. While the origin of many of these hyaline bodies can be stated with certainty, that of others is difficult in the extreme to understand. Some of the appearances presented are most conflicting. It would be endless to enter into a discussion of all the various possibilities that they suggest, and I shall confine myself to a brief statement of the present position of my own views as to their most probable origin.

The cords of the networks formed by contracting fibrinous films on the surface of the dura often assume a hyaline appearance, staining very deeply with eosin. At the same time, they are usually slightly longitudinally striated (figs. 19 and 61). Capillaries that have penetrated a fibrinous false membrane, and have afterwards been obliterated in the manner already described, frequently show a similar hyaline sheath (fig. 62). At a later stage these vessels assume the appearance of homogeneous hyaline rods, covered over by the surface endothelium. The dense fibrous tissue strands which in some parts of the dura lie just below the surface endothelium, may assume a hyaline appearance. The hyaline rods which can occasionally be seen to lie on each side of a superficial dural vessel, also probably arise from a peculiar change in the fibrous tissue immediately external to the endothelial wall of the perivascular canal (fig. 17). The hyaline material that forms concentric bodies is developed chiefly from endothelial cells in the manner described in the next subsection. The substance produced by vitreous degeneration of the endothelial cells may undergo a further change by which it assumes the appearance of hyaline material. It may occur as irregular masses on the surface, or as rods which fill the perivascular canals.

(e) *Concentric bodies*.—I distinguish two varieties of these structures. There is first the more usual form, which is characterised by its commonly spherical shape and hyaline appearance (figs. 22 and 50). Concentric bodies of this kind vary greatly in size. Commonly they are two or three times the diameter of a normal superficial dural capillary, but not infrequently they are double this size. They usually have a very strong affinity for eosin. As a rule they have a narrow or broad capsule which stains more lightly, and is either homogeneous or distinctly fibrous and laminated. Their concentric markings, which are merely thin darker or lighter lines as seen under the microscope,

may be few in number or numerous. The second variety is what I term the concentric body of the starch grain form (fig. 55). It is much smaller than the typical hyaline concentric body, though it likewise varies considerably in size. It has usually an oval shape, which is also assumed by the one or two concentric markings that it commonly shows. In hæmatoxylin and eosin preparations concentric bodies of this kind stain of a violet colour, and have an opaque appearance. Very rarely, however, a portion of their structure may be seen to have hyaline characters. Their general appearance suggests at once the simile of a starch grain. They are, as a rule, accompanied by much granular débris.

Concentric bodies of the large hyaline form are much the more common. I have found them in 41 out of 60 duras examined microscopically. In some cases they are present in very large numbers. They may occur in groups or singly. They are by no means confined to the insane, though they certainly occur in such patients in far greater numbers than in the mentally sound, so far as I have seen. They may be found in duras that show practically no other morbid change. They are certainly most common in old people, but probably may form at any age. It is in senile insanity that they are found in greatest numbers. They occur chiefly at the inner surface, but also sometimes in the spaces that exist between the dura and the cranium. I have observed them only very occasionally in the deeper tissues of the dura. They occur also, and often in very large numbers, on the surface of the pia-arachnoid (especially in association with the milky change that is so common in this membrane in the insane), in the Pacchionian granulations, choroid plexuses, and endotheliomata of the dura, as well as in psammomata. Their occurrence has long been recognised by pathologists, but the earlier observers misunderstood their essential nature and origin. The following are some of their reactions:—They stain deeply with eosin and hæmatoxylin, generally showing a much greater affinity for the former when double staining with these dyes is employed. They also stain deeply with carmine and many of the aniline dyes. They are slightly darkened but not blackened by osmic acid, although occasionally this reagent may demonstrate the presence of a few fatty granules in them. They have a dark brown colour in silver preparations, exactly resembling that assumed by portions of the endothelial cell-plate. As they occur in the dura they are seldom affected by the action of mineral acids, but in some situations, as in the choroid plexuses, they commonly contain carbonate of lime, on account of the presence of which an evolution of gas occurs. Findlay (56), who has recently given an excellent account of these formations as they occur in the choroid plexuses, states that

it is necessary to use strong hydrochloric acid in order to obtain effervescence.

Most of the older writers on the subject, including Obersteiner, have described concentric bodies as being composed essentially of carbonate and phosphate of lime, but it is now certain that calcareous infiltration is merely a secondary and comparatively unusual occurrence. They essentially consist of hyaline degenerative material.

Concentric bodies of the starch-grain form can be clearly traced from the nucleus of a single endothelial cell. They do not develop only from the surface cells, though these are probably their most common source. I have frequently observed them in the perivascular canals deep in the substance of the dura.

The process of the development of hyaline concentric bodies is much more easily followed on the surface of the pia-arachnoid than on that of the dura, as in the former situation there are no rods of hyaline material to complicate the appearances. They develop on the surface of the pia-arachnoid as the result of a coalescence of certain of the endothelial cells that have undergone hyaline degenerative change, which is specially prone to occur in the proliferated cells that constitute granulations. The cell-plate becomes first affected, assuming a homogeneous appearance, and generally a slightly increased affinity for eosin in hæmatoxylin and eosin preparations. The nucleus has at first an increased affinity for hæmatoxylin, but as the morbid change advances it gradually loses this affinity, becoming homogeneous, and staining with eosin in the same way as the degenerated cell-plate, with which it ultimately blends. A homogeneous globule is thus developed from a single endothelial cell. This may become a small concentric body, but more commonly, owing to the circumstance that several endothelial cells in a granulation are usually affected simultaneously, the hyaline globules developed from several adjacent endothelial cells coalesce into one large mass. This being apparently of a semi-fluid consistence assumes a spherical form. Concentric rings appear subsequently, evidently owing to shrinkage. In many developmental forms there is an irregular central mass which stains more deeply with eosin than the peripheral portion. It may be that this central mass corresponds to the nuclei of the degenerated cells, but the point is doubtful. This deeper staining of the central portion, as already indicated, is often maintained in the fully developed concentric body. It may be fairly conclusively demonstrated, and it may indeed be accepted as certain, that hyaline concentric bodies develop in the same way from the surface endothelial cells of the dura, and also occasionally from those of the perivascular canals (fig. 41). As in the pia-arachnoid, they develop specially from the localised aggregations of proliferated endothelial cells that form granu-

lations. But there are other morbid appearances in the dura, evidently associated with the formation of concentric bodies, which cannot be explained so simply. Many of the hyaline rods already described show what appear to be transition forms in the development of concentric bodies. They evidently split across, the segments contracting into rounded masses. Some of the appearances presented are exceedingly difficult to interpret, and I am still uncertain as to the explanation of many of them.

I think there can be little doubt that most of the hyaline rods that develop into concentric bodies, though in appearance identical with others that may often be traced into continuity with vessels, with dense strands of fibrous tissue, and even with fibrinous films on the surface, are those having their origin either (1) from a vitreous degeneration of the endothelial cells of a perivascular canal, as already described (a process which I have been able to trace clearly in one case); or (2) from the surface endothelial cells, the hyaline material developed from them having run together in the form of a rod instead of collecting into globular masses. The latter is the only explanation I could offer of such appearances in subdural false membranes as that shown in fig. 54. Histological evidence is, I think, strongly against their development in any instance from contracting fibrinous films and the obliterated new vessels that these often contain. From our early studies of the pathology of the dura, Dr Middlemass and I were led to maintain that these concentric bodies develop from dural capillaries that have undergone hyaline degeneration. While there is no doubt that we were wrong in regarding this as their typical mode of development, and although my own later observations led me to conclude that the opinion we had expressed was entirely erroneous, the recent observations of Findlay (56) upon the changes in the tissues of the choroid plexuses, seem to prove that concentric bodies are capable of forming from vessels that have undergone hyaline degeneration. Therefore it cannot be excluded that hyaline concentric bodies occasionally develop from hyaline capillaries in the dura.

I have never seen any evidence of retrogressive or disintegrative changes in these bodies. When once formed they seem to remain indefinitely. It may be, however, that some of the hyaline material is removed by leucocyte action. After a time a distinct fibrous capsule develops round them.

(f) *Mulberry bodies*.—I have applied this name to certain curious structures that may occasionally be seen on the surface of the dura in superficial horizontal sections (fig. 56). They consist of groups of rounded or oval cells of a homogeneous appearance, which stain of a deep purple colour in hæmatoxylin and eosin preparations. The individual cells are pretty uniform in size, being about twice the

diameter of a red blood corpuscle. Each group usually has a comparatively faintly-stained gelatinous capsule. Isolated cells with a similar capsule may occasionally be seen, but the mulberry form is the typical one.

Findlay (56) has traced these bodies in the choroid plexuses from single endothelial cells, and believes that the pathological alteration giving rise to them is one closely allied to hyaline degeneration. He further maintains that they develop into hyaline concentric bodies.

(g) *Granular patches in the fibrous tissue.*—In superficial horizontal sections stained with hæmatoxylin and eosin there may frequently be seen, scattered over the surface, numerous small irregular patches which stain deeply with both dyes, and have an opaque and faintly granular appearance (fig. 11). They usually occur in the centre of the inter-vascular areas, suggesting that they result from imperfect nutrition. They are generally quite easily recognised under the low power. The connective tissue corpuscles of the part are fattily degenerated, and stain very faintly. Most of the granules outside of the cells do not, however, give a fatty reaction. Many of them stain deeply with eosin. The endothelial cells are generally denuded over these areas. When present they usually show advanced vitreous degeneration. Similar patches may frequently be observed at a deeper level in horizontal or transverse sections. They are exceedingly common at the inner surface of duras from general hospital patients, as well as in those from the insane.

A gross lesion, representing a further stage in this granular change, has been described by Dr Middlemass and myself (48). An example is shown in fig. 10, in which part of the degenerative material has undergone a hyaline change. These larger patches, which, however, are somewhat rare, are readily recognisable with the unaided eye, appearing as dark, opaque, slightly depressed spots, when the membrane is held up to the light.

3. *The Morbid Processes concerned in Subdural False Membrane Formation.*

As already indicated, I maintain that in considering the morbid processes concerned in the formation of subdural false membranes, it is necessary at the outset to distinguish between two classes of cases that occur. In the first place, there is a class in which false membranes develop as the direct outcome of a widespread morbid process in the tissues of the dura itself; and, in the second place, there is a class in which they are formed as a result of a hæmorrhage into the subdural space, which takes place quite independently of this morbid process in the dura. In the first class we have a morbid

condition which, while it is very common in the insane, is comparatively rare in the mentally sound. In the second class we have one that is probably almost as common in the mentally sound as in the insane.

It will be most convenient to consider first the development of false membranes that are to be included in the latter class. The causes of the hæmorrhage are merely those that give rise to intracranial hæmorrhage in general. Many of the larger effusions, which, however, are comparatively rare, have their source in a pial vein. The cases of this kind that I have seen have distinctly suggested that an important factor in leading to the rupture of the vessel was its partial obstruction by fibrous overgrowth of the tissues of the pia-arachnoid, where they join the dura at the side of the superior longitudinal sinus. As this condition of the pia-arachnoid is in its extreme degrees practically confined to the insane, hæmorrhage from this cause may be almost special to them.

The blood may also escape from a pial artery, an artery at the base, a venous sinus, an intra-cerebral vessel, or one near the inner surface of the dura. To take, for example, a fairly large hæmorrhage, one of the first effects of the presence of the blood in the subdural space is to set up very active proliferation of the cells of the endothelium lining the subdural cavity. Many of the proliferated cells are shed and pass into the effusion, in which they may be afterwards recognised in large numbers. After a certain interval coagulation of the blood takes place. This commences on the walls of the subdural space, so that a white clot forms at the periphery and envelops the red clot which forms later. The peripheral white clot, probably mainly owing to the effects of pressure, often forms quite a dense membrane. In the case of small hæmorrhages the clot is spread out as a thin layer, the red portion occupying the central area, and the white appearing as a delicate surrounding film which gradually becomes more and more attenuated until it is lost to view on an apparently normal surface. The microscope reveals the fact that it extends much further than the unaided eye can trace it. If, as occasionally occurs, especially in chronic insanity, there is marked excess of fluid in the subdural space, the effused blood becomes mixed with it, and after a time its fibrin coagulates out upon the walls of the cavity, often forming a film which extends over the entire surface, including that of the spinal dura. At first the clot is not adherent to either wall. Very soon, however, new capillaries shoot out into it from the dura, so that vascular connections are formed by which it adheres to the outer wall of the space. Vessels very seldom penetrate it from the inner wall, for the reason that there are practically no capillaries near the outer surface of the pia-

arachnoid, from which it also tends to become separated as previously described. The cerebral aspect of the clot becomes covered over with endothelial cells, continuous with those of the surface of the dura or pia-arachnoid at its margin. Thus the false membrane does not lead to the obliteration of any portion of the subdural cavity, but forms for it a new outer wall. The subsequent stages are practically identical with those of organisation of a thrombus in a vein, the clot, if vital processes continue, in time becoming entirely replaced by granulation tissue. In very large hæmorrhages the red clot in the centre is apt to break down before the process of organisation has reached it, and in this way a typical "arachnoid cyst" is produced. After false membranes formed by comparatively small hæmorrhages have become vascularised, they closely resemble those that are produced by the other morbid process presently to be described, and the further changes that may occur in them are also probably very similar.

Coming now to what I regard as the special subdural false membrane formation of the insane, we have a process to consider which is in certain respects essentially the same as the preceding, but in others entirely different. It is the same, in that a part of it consists in the occurrence of hæmorrhage into the subdural space, and all its consequences. It is different, in that it generally consists in the occurrence of multiple hæmorrhages, in that these are due to definite morbid changes in the tissues of the dura (from which the blood is always effused), and in that it may result in the formation of a thin false membrane even without the occurrence of hæmorrhage. It is to be understood, however, that no sharp distinction can be made between the two classes. They merge into one another, and there are many cases which cannot properly be wholly assigned to either group. Yet I think it will be evident presently that the classification is a scientific and necessary one.

Before sketching this process, however, I must diverge for a moment to direct attention to a matter which, to my view, has very important bearings upon the pathology of subdural false membrane formation in the insane, but which does not seem to have been grasped by previous writers on the subject. I think that it can be shown that, with very few exceptions, all the false membranes found in the subdural space of the insane are the development of a few days preceding death. Of the 18 subdural membranes from the insane examined microscopically in the course of a systematic research upon this subject, only 3 showed a structure of fully-developed granulation tissue. All the others showed a basis of fibrin threads, which pointed to a very recent origin. To these 15 cases there have to be added 13 others in which there was microscopic evidence of the

presence of false membranes of a fibrinous structure, giving a total of 28 cases out of 31 in which the false membrane was undoubtedly of recent development. The appearances presented by the other 28 subdural membranes that occurred in my cases, but which were not examined microscopically, were such as to warrant, when taken in conjunction with the results of the microscopic examination of similar false membranes, the conclusion that they also were, with only one or two exceptions, of very recent growth. Many of them, as already stated, were simply recent blood-clots. Moreover, the accounts given of the naked-eye appearances of subdural membranes by various writers, *e.g.* Wigglesworth (40 and 41), are in most instances clearly descriptions of membranes mainly of a fibrinous character. Numerous more recent occasional observations of my own have tended to confirm the opinion that these formations are mostly of a fibrinous nature. It seems to me, therefore, that the great majority of the false membranes that occur in the subdural space of the insane are formed in the course of a few days or a few hours preceding death.

In the general hospital cases examined (putting aside 5 in which there was head injury), it was found that in 9 out of 15 there was either naked-eye or microscopic evidence of hæmorrhage (often exceedingly slight) having occurred from the vessels of the dura very shortly before death. Now, since in several cases new capillaries had begun to shoot into these recent effusions, they cannot be entirely attributed to the severe congestion attending an asphyxial mode of death. Therefore I think we must further recognise that there are certain factors furnished by the moribund condition which predispose to hæmorrhage from the dura in all patients. These factors are, I believe, merely the fatty and other molecular changes that occur in the walls of the dural vessels in common with many other tissues of the body, to some extent in the last stages of practically all diseases not resulting in sudden death, but especially in acute illnesses attended with high temperatures, and in the last stages of chronic diseases, towards the termination of which there is prolonged and great bodily enfeeblement.

At the same time, we have to account for the undoubted fact that subdural false membranes appreciable to the unaided eye are far more frequently met with at post-mortem examinations upon the insane than at those upon general hospital patients. From the investigations I have made, I conclude that this is due to the circumstance that the insane are specially prone to a chronic morbid condition of the dura mater, on account of which these same pathological factors which cause hæmorrhages from the dural vessels in the mentally sound shortly before death, make their influence felt in them at a much earlier stage and to a much more marked degree. This chronic

morbid condition, the chief features of which have already been described, is an exceedingly complex one, and several of the morbid changes included in it have undoubtedly an important influence in preparing the way for the development of false membranes. But by far the most important of these changes in this relation is beyond doubt the development of new capillaries on the inner surface of the dura. It can be shown by means of superficial horizontal sections that in the great majority of duras from the insane such new vessels have been developed to some extent, and that in many, over extensive areas, they are so numerous as to form a close network. A certain amount of granulation tissue develops around them. Thus a delicate false membrane may be formed quite independently of the occurrence of hæmorrhage. The fatty and other molecular changes to which I have referred, probably tend to affect these new capillaries to a greater degree than the original dural vessels. The examination of an extended series of osmic acid preparations has satisfied me that fatty changes are constantly present in both sets of vessels in association with recent capillary hæmorrhages. They are seldom established to a marked degree, but probably only slight degenerative changes in the new capillaries are sufficient to render such already delicate vessels unable to withstand the normal blood pressure. The presence of congestion of the dura from any general cause is, of course, in such cases an important additional factor favouring rupture of the vessels. The intense patchy congestion of the inner surface of the dura which is frequently to be observed over areas from which there has been recent blood-effusion, is to be attributed, I think, to weakening, from degenerative changes, of the walls of either original or new capillaries, so that the vessels become dilated by the normal blood-pressure. For some reason not very easy to understand, the numerous new capillaries so commonly developed over the body and lesser wings of the sphenoid very rarely rupture. They form, with their surrounding new fibrous tissue and proliferated endothelial cells, a coherent false membrane, which, however, I have not counted as such in my statistics.

It is from the blood that escapes at a multitude of points from these new capillaries, when they have become affected by degenerative changes, that the typical subdural false membranes of the insane are formed. While this is so, the fact is not to be lost sight of that hæmorrhages are also very prone to occur, a few days or a few hours before death, from the original vessels of the dura which remain pervious. Indeed, it is certain that many false membranes are formed in this way in the insane, as well as in the mentally sound. In the former, however, though it is doubtful if the tendency to fatty and other molecular changes in the moribund state is more pro-

nounced, hæmorrhage is certainly prone to occur from the original dural vessels to a greater extent, and at an earlier period. This I maintain is owing to the previously established chronic morbid changes in the dural vessels in the insane. The proliferation of the endothelial cells of the perivascular canals indicates a morbid nutritional state that must at the same time affect the capillary walls and cause them to be weakened. Again, the flow of lymph along the perivascular canals must be greatly interfered with by the proliferated and degenerated endothelial cells, hæmatoidin granules, etc., that accumulate in them. This obstruction must in itself produce an abnormal condition of matters which will be an additional source of weakness to the contained capillary. Further, these morbid accumulations in the perivascular canals, even when they do not completely block the contained capillary, must partially obstruct it at many points, and thus retard the blood-flow, causing congestion and increase of pressure, and consequently greater liability to rupture when degenerative changes are added. An interesting additional cause of hæmorrhage from the original dural vessels shortly before death is their compression by vitreous change in the endothelial cells of the perivascular canals. In several of my cases minute surface hæmorrhages appeared to have occurred on the proximal side of obstructions produced in this way. One of these was a case of purpura hæmorrhagica, in which there were numerous small recent blood-effusions on the inner surface of the dura mater.

The changes that take place in these blood-effusions into the subdural space I have already fully described, and need not consider further. The false membrane increases in size as the result of new hæmorrhages alone. Such hæmorrhages occur with great frequency from the new vessels. They are, I think, sufficiently accounted for by the enfeebled state of all the vital processes of the patient. In consequence of this, fatty changes occur in these vessels, as in the new capillaries that were developed on the surface of the dura, and cause weakening of their walls. In addition to distinct hæmorrhages into the intervacular areas, in almost every organised false membrane isolated red blood corpuscles are to be observed scattered about without any apparent rupture of the neighbouring vessel-wall. Hæmorrhages also continue to occur from the new vessels formed previous to the primary effusion. The frequency with which recent extravasations are to be observed between a false membrane and the dura is thus to be explained. Some forms of lamination seen in subdural membranes are to be accounted for by coagulation of successive blood-effusions in this situation. In other cases the lamination is due to coagulation of successive extravasations on the arachnoid surface of a false membrane.

The study of duras from the series of general hospital cases has, I

think, conclusively proved that all the chronic changes that I have described are comparatively rare in the mentally sound. In no case did new capillaries appear to have formed on the surface independently of the occurrence of recent hæmorrhages. Deposits of hæmatoidin granules near the surface of the dura and localised endothelial proliferations were also practically absent. A slight degree of general proliferation of the surface and perivascular endothelium was frequently observed, and concentric bodies of both varieties were occasionally seen. As already indicated, fatty changes, vitreous degeneration, and recent capillary hæmorrhages were found very frequently.

Most organised false membranes contain copious hæmatoidin granules of an orange or brownish-yellow colour. They give rise to the rusty appearance which is so prominent a feature in many cases. I have only seen this substance in these membranes in the amorphous form, and never as rhombic plates. Its development from red blood corpuscles can be studied in many preparations, and the process is of considerable interest. My observations on the point have inclined me to the opinion that its formation is always the result of leucocyte action. The mere fact that leucocytes may be seen in abundance with entire red corpuscles, disintegrating red corpuscles, or these granules in their protoplasm, does not, of course, prove this contention; but the following considerations must, I think, carry with them much weight. I have frequently observed in recent blood-effusions into the subdural space many leucocytes containing hæmatoidin granules, together with others filled with entire or disintegrating red corpuscles, while not a single hæmatoidin granule could be seen outside of the leucocytes. In the same clot granular débris, produced from disintegration of red corpuscles, was present in great abundance, and since it is impossible to believe that the leucocytes could show a selective action, and pick out all the hæmatoidin granules from among this débris, I am forced to the conclusion that the hæmatoidin must have been formed within the leucocytes from some of the granular débris or entire red corpuscles which they could be seen to be taking up. I think that this may explain, in part, the curious fact that in organised subdural false membranes, while the extravasated red blood corpuscles are scattered throughout the intervacular areas, the hæmatoidin granules become aggregated just outside the vessels. I suggest that what has occurred is that leucocytes have taken up red corpuscles, or the débris that results from their disintegration, and changed them into hæmatoidin. They have then, as it were, attempted to return to the circulation with their load, but, finding it impossible to carry it through the capillary wall, they have left it behind them at the side of this vessel. In many instances, however, the occurrence of aggregations

of hæmatoidin around a vessel is to be explained merely from the fact that hæmorrhage was localised to a corresponding area.

There is conclusive evidence that the endothelial cells are likewise capable of taking up granular matter. Much of the hæmatoidin lying in the perivascular canals can in some cases be observed to be in the protoplasm of these tissue-elements.

How far the primary hæmorrhagic theory is true, and to what extent its advocates have been unaware of the profound morbid changes that occur in the dura, must appear quite evident from what has already been said. The inflammatory theory is, I maintain, entirely disproved by the phenomena revealed by superficial horizontal sections of the dura mater. These show that the initial changes in the tissues of the dura leading to the special subdural false membrane formation of the insane are of a totally different kind from those that the advocates of this theory have supposed. The cellular infiltration that they have pointed to in support of their views is clearly due to a chronic proliferation of endothelial cells, and not to migration of leucocytes, and all the appearances presented by fibrinous membranes can be shown to be merely those assumed by blood-clots in the course of the various changes that they undergo.

Regarding G. M. Robertson's dry-cupping theory, I am now convinced that, considering the microscopic evidence that can be adduced of antecedent morbid changes in the tissues of the dura, no such factor as he suggests is required to account for the development of subdural false membranes. That such vascular spasms as his theory requires do actually occur is far from being proved. At the same time, I am not prepared to deny that such conditions, and especially the normal variations in the intracranial pressure, may be, in some degree, a contributory cause of rupture of the degenerated vessels at the inner surface of the dura. The delicate fibrinous films to which he has specially directed attention are proved by the study of superficial horizontal sections to result from ordinary hæmorrhages.

A point of great importance, to which reference must be made here, is the relation that exists between the morbid changes in the dura, leading up to the subdural false membrane formation of the insane, and those that produce the thickening, milkiness, and opacity of the pia-arachnoid that is so common in such patients. The two conditions are specially developed in the same forms of mental disease, notably senile insanity, general paralysis, and alcoholic insanity, and are indeed practically always associated with each other. As is maintained in the next chapter, the morbid process in this alteration of the pia-arachnoid consists essentially in a slow hyperplasia of the connective tissues of the membrane, and marked proliferative and degenerative changes in the endothelial cells of

the arachnoid trabeculae and outer aspects of the membrane; and in its typical form it cannot rightly be regarded as an inflammatory one, but is rather to be looked upon as degenerative in character. In the endothelial proliferation on the inner surface of the dura and in the perivascular canals, which is undoubtedly the chief morbid condition leading to the development of new capillaries, and in the slow overgrowth of the connective tissue of the dura leading to slight general thickening of the membrane, we have exactly similar morbid processes to those that produce this change in the pia-arachnoid. The chronic changes that occur so commonly on the two sides of the subdural space in the insane are therefore, primarily, but the manifestations of the same pathological process.

It is still necessary to answer the question, What is the cause of the chronic proliferative and degenerative changes in the dural tissues which prepare the way for the formation of the subdural false membranes of the insane? It is clear that this chronic disease of the dura constitutes only one of a whole series of morbid changes that are specially prone to affect the coverings of the brain in the insane. Among these are to be included, from within outwards, milkiess and thickening of the pia-arachnoid, this morbid change in the dura which is primarily of the same nature, thickening and other changes in the cranial bones, adhesion of the scalp to the pericranium, degenerative changes in the cartilages of the ear which lead to the development of hæmatoma auris, and, lastly, coarseness and thickness of the hair. In 1895 Dr Middlemass and I, following a view that had long been taught by Dr Clouston, maintained that they are to be regarded as, in part at least, due to an abnormal trophic condition which is in some way reflected upon the surrounding tissues by the morbid energising of the subjacent brain which constitutes insanity. But with the recent important advances in our knowledge of the intra-cranial lymphatic arrangements (see chapter xi.), there has emerged a new and more precise explanation of these morbid alterations, which may be applied at least to those of them that affect the skull, dura mater, and pia-arachnoid. Through these structures the cerebro-spinal fluid passes on its way to the general circulation. This fluid, which is the lymph of the brain, is derived from the cerebral capillaries; it bathes the cerebral tissues and receives from them the products of their metabolism. Probably these products are in part returned to the cerebral capillaries by processes of diffusion, but in part also they must be carried away in the lymph which flows through the membranes of the brain into the dural and cranial veins. Now if, as must occur in all well-marked cases of acquired insanity, the metabolism of the cerebral tissues becomes abnormal, the cerebro-spinal fluid must be altered in composition and cease to be suitable for the healthy nutrition of the

endothelial cells and connective tissue fibres which form the walls of the channels by which it is carried away. Consequently these tissue-elements undergo proliferative and degenerative changes, such as have just been described as occurring in the dura mater, and such, as we shall see in the next chapter, take place also in the pia-arachnoid.

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DESCRIPTION OF PLATES VI., VII., VIII., IX. AND X.

PLATE VI.

- Fig. 1. Transverse section of normal dura mater, stained with hæmatoxylin and eosin. The letter *a* indicates the inner surface. ($\times 300$).
- Fig. 2. Superficial horizontal section of normal dura mater, stained with hæmatoxylin and eosin, showing capillaries and perivascular canals of inner surface. ($\times 450$).
- Fig. 3. Transverse section of dura mater, stained with hæmatoxylin and eosin, from a case of dementia of forty years' duration. It shows increase of capillaries near the surface (*a*), dilatation of the deeper vessels, and deposit of pigment especially near the surface. ($\times 300$).
- Fig. 4. Superficial horizontal section of the dura mater, stained with hæmatoxylin and eosin, from a case of general paralysis. The dura showed faint rusty staining, but no false membrane.
 - (a) Dural capillary showing one branch degenerated and completely closed, the other with greatly thickened walls.
 - (b) New capillaries showing delicacy and irregularity of wall, abnormal distribution, absence of perivascular canal, and hæmatoidin granules lying in close relation to them. ($\times 450$).
- Fig. 5. Transverse section of dura mater with delicate false membrane, stained with hæmatoxylin and eosin, from a case of general paralysis. It shows (*a*) the new membrane on the inner surface, and (*b*) the dura. The capillaries of the new membrane are numerous and comparatively large. There is abundant hæmatoidin. The dural vessels are dilated, but there are no evidences of inflammatory change in the tissues of the dura mater. ($\times 300$).

- Fig. 6. Horizontal view of a delicate subdural false membrane similar to that shown in the preceding fig., stained with hæmatoxylin and eosin. From a case of general paralysis. The structure is essentially that of granulation tissue. The capillaries are very large, and there are numerous hæmatoidin granules, as well as some recently extravasated red blood corpuscles, in their vicinity. ($\times 450$).
- Fig. 7. Transverse section of dura mater with fibrinous subdural false membrane, stained with hæmatoxylin and eosin. From a case of general paralysis.
 (a) False membrane. Note that it contains no vessels.
 (b) Dura mater. ($\times 300$).
- Fig. 8. Horizontal view of the same membrane as shown in the previous fig., stained with hæmatoxylin and eosin. It has the characters of white blood-clot. Note the numerous delicate fibrin threads, and the leucocytes and occasional red blood corpuscles. ($\times 450$).

PLATE VII.

- Fig. 9. Horizontal view of a thin subdural false membrane showing fibrous development, stained with hæmatoxylin and eosin. From a case of general paralysis. The vessels are diminished in size in comparison with those seen in fig. 6, and the cells in the intervascular areas are mostly spindle-shaped. ($\times 450$).
- Fig. 10. Transverse section of dura mater, stained with hæmatoxylin and eosin. From a case of general paralysis. Shows a localised area of degenerative change in the fibrous tissue. For description see text. ($\times 300$).
- Fig. 11. Superficial horizontal section of dura mater, stained with alum carmine and eosin. From a case of organic brain disease. Shows small areas of a degenerative change affecting the fibrous tissue, evidenced by deeper staining with eosin. ($\times 450$).
- Fig. 12. Superficial-horizontal section of normal dura mater, stained with alum carmine and eosin, showing normal capillary and perivascular canal. ($\times 450$).
- Fig. 13. Superficial-horizontal section of dura mater, stained with alum carmine and eosin. From a case of senile insanity. Proliferation of endothelial cells of perivascular canal. ($\times 450$).
- Fig. 14. Superficial-horizontal section of inner surface of dura mater, stained with alum carmine and eosin. From a case of senile insanity. Local proliferation of endothelial cells of perivascular canal, dilatation and rupture of capillary behind obstruction.
- Fig. 15. Longitudinal view of capillary of inner surface of dura mater, from a case of general paralysis, showing hyaline thickening of wall and aggregation of cellular elements (leucocytes or endothelial cells?). Alum carmine and eosin. ($\times 450$).
- Fig. 16. Longitudinal view of smaller capillary from same case, showing similar hyaline change. Alum carmine and eosin. ($\times 450$).
- Fig. 17. Longitudinal view of capillary of inner surface of dura, from a case of general paralysis, showing hyaline thickening of wall of perivascular canal, and collection of cells in the canal. Alum carmine and eosin. ($\times 450$).
- Fig. 18. Longitudinal view of capillary of inner surface of dura, from a case of general paralysis, showing hyaline transformation and aggregation of cell-elements. Alum carmine and eosin. ($\times 450$).
- Fig. 19. Hyaline rod from inner surface of dura. From a case of general paralysis. Alum carmine and eosin. ($\times 450$).

- Fig. 20. Longitudinal view of capillary of inner surface of dura, from a case of general paralysis, showing slight hyaline thickening of wall. The perivascular canal contains some hæmatoidin granules. Alum carmine and eosin. ($\times 450$.)
- Fig. 21. Transverse section of inner portion of dura mater, from a case of dementia, showing a granulation. Hæmatoxylin. ($\times 100$.)

PLATE VIII.

- Fig. 22. Superficial horizontal section of dura, from a case of general paralysis, showing a group of hyaline concentric bodies at inner surface. Alum carmine and eosin. ($\times 450$.)
- Figs. 23, 24, and 25. Hyaline rods from inner surface of dura, representing early forms in the development of concentric bodies. Alum carmine and eosin. ($\times 450$.)
- Fig. 26. Concentric body in a fibrinous subdural false membrane, from a case of melancholia. Hæmatoxylin. ($\times 450$.)
- Fig. 27. Transverse section of inner portion of sphenoidal dura, from a case of dementia, showing two concentric bodies projecting from the surface. Hæmatoxylin. ($\times 300$.)
- Fig. 28. Diagrammatic representation of the formation of hæmatoidin granules from red blood corpuscles through ingestion by leucocytes. Hæmatoxylin and eosin.
- Fig. 29. Transverse section of inner portion of dura mater, from a case of dementia in which there was rusty staining but no false membrane, showing projection of dilated (new?) capillaries into the subdural space. Hæmatoxylin. ($\times 300$.)
- Fig. 30. Superficial horizontal section of dura, from a case of senile insanity, showing vessel with surrounding hæmorrhage. Alum carmine and eosin. ($\times 450$.)
- Fig. 31. Superficial horizontal section of dura, from a case of general paralysis, showing new capillaries and hæmorrhage from them. Alum carmine and eosin. ($\times 450$.)

PLATES IX. AND X.

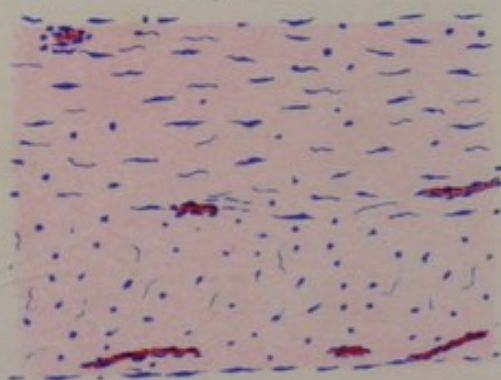
All the drawings have been made from surface sections of the dura mater. The preparations were stained with hæmatoxylin and eosin, excepting that from which fig. 34 was drawn.

- Fig. 32. Normal superficial dural capillary and perivascular canal. Note nuclei of endothelial cells of surface. From a general hospital patient who died suddenly from rupture of aortic aneurism. ($\times 500$.)
- Fig. 33. Normal superficial dural capillary with shallow perivascular canal. From same case as the preceding. ($\times 500$.)
- Fig. 34. Silver preparation counterstained with alum carmine, showing surface endothelium limited by edge of perivascular canals, which are covered over only by their own endothelial cells. This arrangement only occurs at certain spots, the surface endothelium being generally carried over that of the perivascular canal. From a case of senile insanity. ($\times 500$.)
- Fig. 35. Silver preparation counterstained with hæmatoxylin and eosin, showing endothelial cells of superficial perivascular canal. The surface endothelium is denuded. From a case of senile insanity. ($\times 500$.)
- Fig. 36. Endothelial granulations. From a case of congenital imbecility. Patient aged 49. ($\times 500$.)

- Fig. 37. Endothelial granulations, new capillaries, hæmatoidin granules, and hyaline concentric bodies on the surface of the dura. From a case of senile insanity. ($\times 400$.)
- Fig. 38. Superficial dural capillary, showing general proliferation of endothelial cells of perivascular canal. From a case of senile insanity. ($\times 400$.)
- Fig. 39. Do., with hæmatoidin granules lying outside of perivascular canal. From a case of senile insanity. ($\times 400$.)
- Fig. 40. Localised proliferation of endothelial cells of perivascular canal obliterating original vessel, and new capillaries coursing over surface. From a case of general paralysis. Patient aged 46. ($\times 500$.)
- Fig. 41. Do., showing also hyaline concentric bodies. Note the slight general proliferation of the surface endothelium. From a case of senile insanity. ($\times 500$.)
- Fig. 42. Congested new capillaries on surface of dura, and proliferation of endothelial cells. From a case of senile insanity. ($\times 500$.)
- Fig. 43. New capillaries and hæmatoidin granules on surface of dura. From a preparation fixed with osmic acid. Note the marked distinction between the pale nuclei of the endothelial cells and those of the deeply stained leucocytes. From a case of early general paralysis. Patient aged 26. ($\times 500$.)
- Fig. 44. Minute hæmorrhage from new capillary on surface of dura. From a case of senile insanity. ($\times 500$.)
- Fig. 45. Types of surface endothelial cells in a case of senile mania. Some of them show slight nuclear changes, and the cell-plate is visible in two. Normally it cannot be distinguished in hæmatoxylin and eosin preparations. ($\times 600$.)
- Fig. 46. Surface endothelial cells showing vitreous degeneration. From a case of dementia. Patient aged 49. ($\times 600$.)
- Fig. 47. Advanced vitreous degeneration of surface endothelium. From a case of purpura hæmorrhagica. Patient aged 26. ($\times 500$.)
- Fig. 48. Advanced vitreous degeneration of endothelial cells of perivascular canal. Those of the surface have been shed. Note also the extravasated red corpuscles among the degenerated endothelial cells. From a case of senile insanity. ($\times 500$.)
- Fig. 49. Localised proliferation of endothelial cells of perivascular canal, a number of the cells forming which have become affected by vitreous degeneration. From a case of senile insanity. ($\times 500$.)
- Fig. 50. Group of hyaline concentric bodies on surface of dura. From a case of senile insanity. ($\times 500$.)
- Fig. 51. Atypical forms of hyaline concentric bodies. From various cases. ($\times 500$.)
- Fig. 52. Semi-diagrammatic representation of mode of development of hyaline concentric bodies from endothelial cells. For description see text. It is doubtful whether or not the more deeply stained central portion that may frequently be seen in those bodies really corresponds to the nuclei of the cells. A perfectly homogeneous globule certainly frequently precedes the stage represented in *f*. ($\times 500$.)
- Fig. 53. Developmental form of hyaline concentric body, corresponding to stage represented in fig. 52 *d*. From a case of senile insanity. ($\times 500$.)
- Fig. 54. Concentric body, and hyaline rod evidently contracting into same form. From a delicate fibrinous false membrane in cervical region in a case of choreic insanity. ($\times 400$.)
- Fig. 55. Concentric bodies of the starch grain form. From a case of senile melancholia. ($\times 500$.)
- Fig. 56. Mulberry bodies. From a case of senile mania. ($\times 500$.)

PLATE VI.

Fig. 1.



a

Fig. 2.

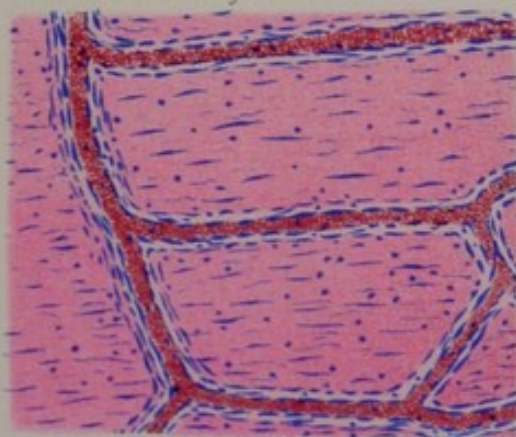
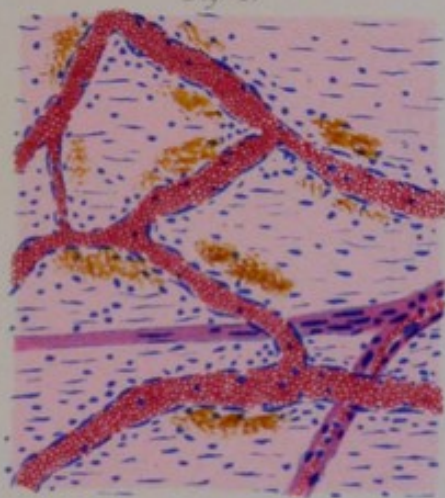


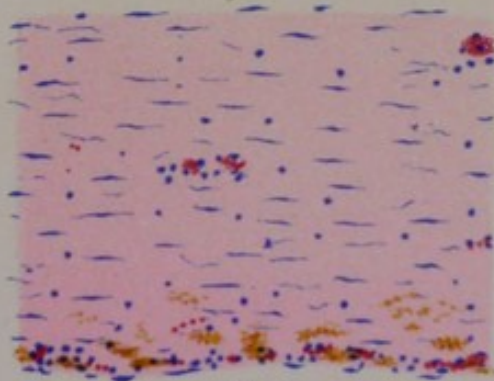
Fig. 4.



b

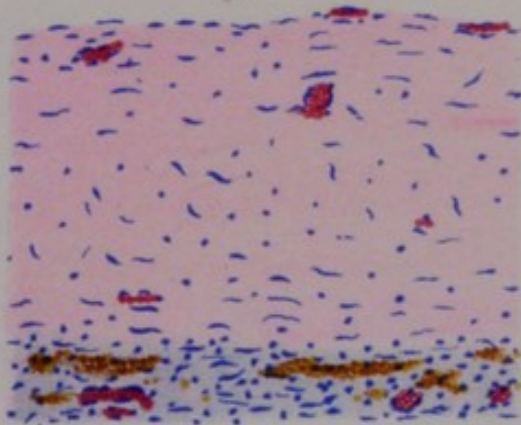
a

Fig. 3.



a

Fig. 5.



b

a

Fig. 6.

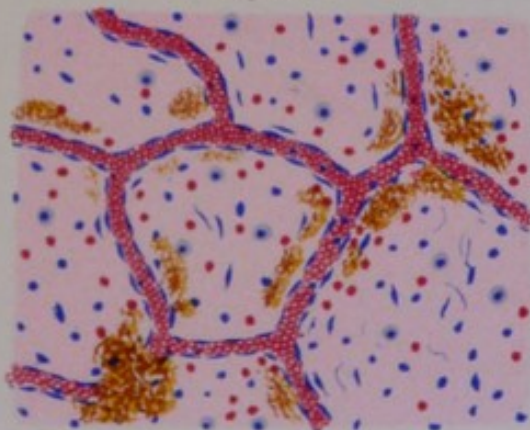


Fig. 8.

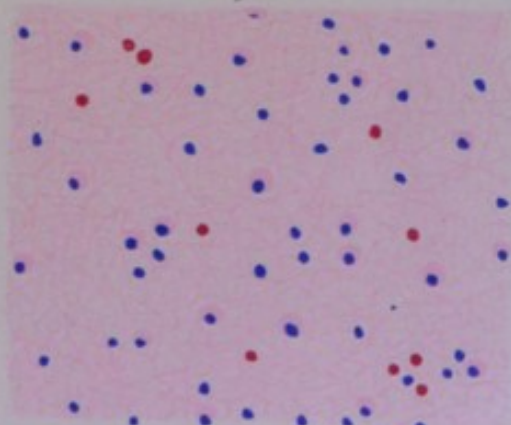
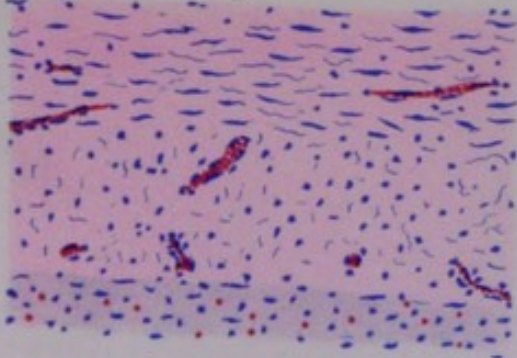


Fig. 7.



b

a



PLATE VII.

Fig. 9.

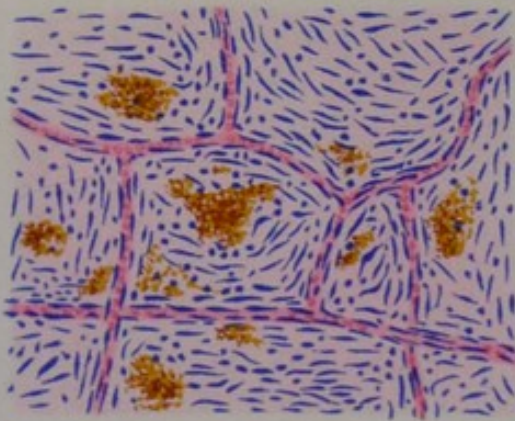


Fig. 10.

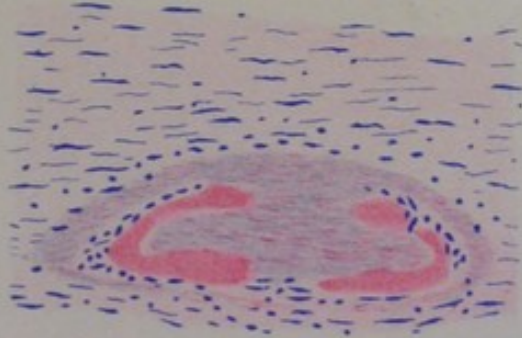


Fig. 11.

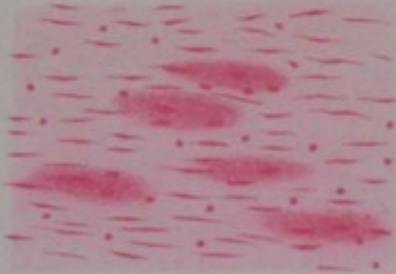


Fig. 12.



Fig. 13.

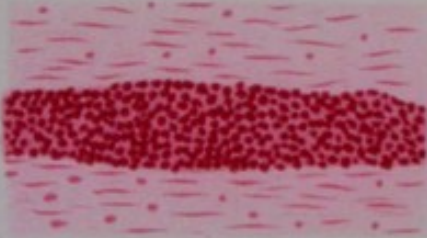


Fig. 14.

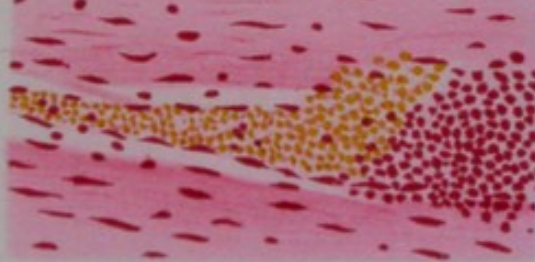


Fig. 15.



Fig. 16.



Fig. 17.



Fig. 18.

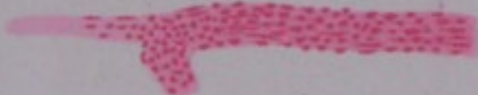


Fig. 19.



Fig. 20.



Fig. 21.

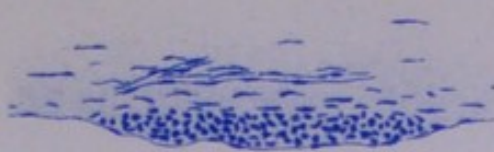




PLATE VIII.

Fig. 22.



Fig. 23.

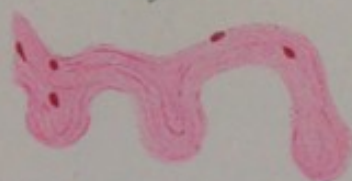


Fig. 24.



Fig. 25.

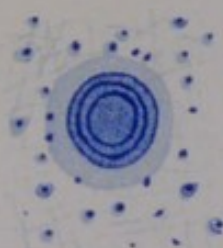


Fig. 26.



Fig. 27.

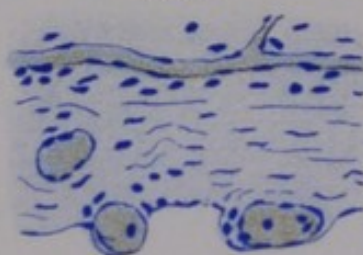


Fig. 28.



Fig. 29.

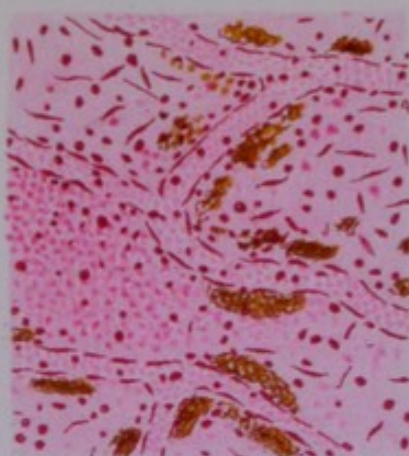


Fig. 30.



Fig. 31.

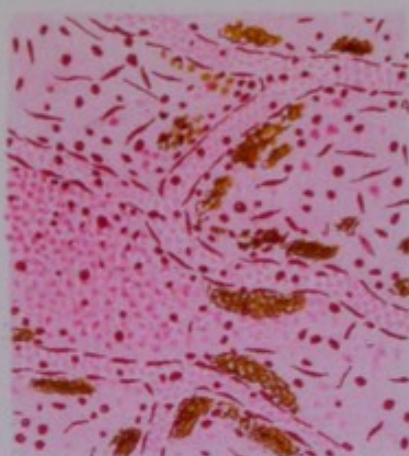




PLATE IX.

Fig. 32.



Fig. 33.

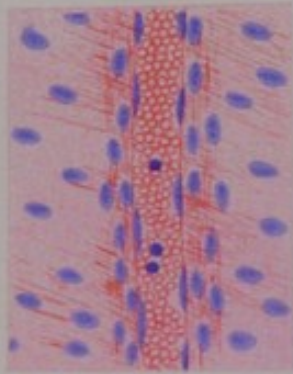


Fig. 34.

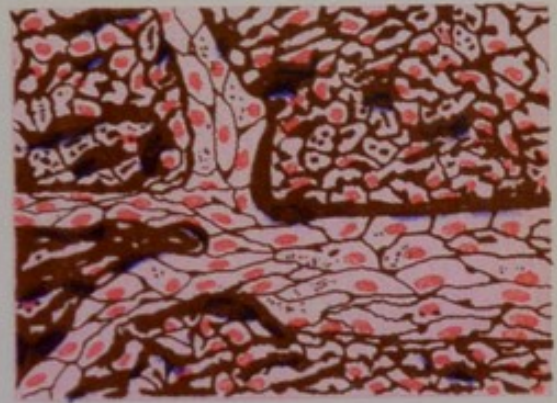


Fig. 35.



Fig. 36.

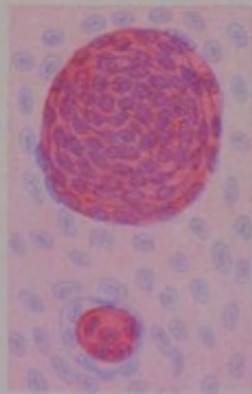


Fig. 37.

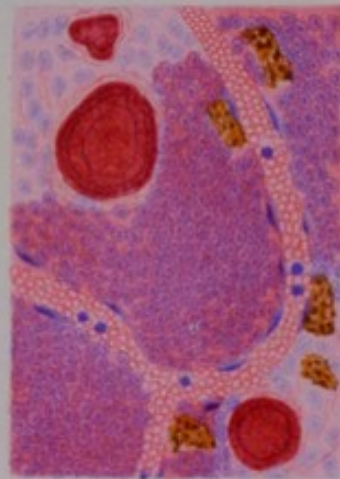


Fig. 38.

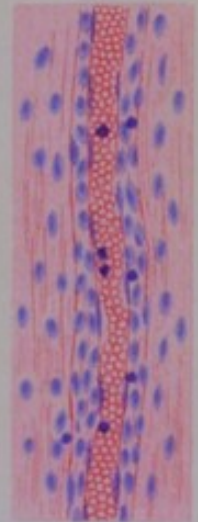


Fig. 39.

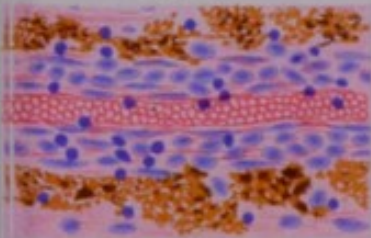


Fig. 40.



Fig. 41.

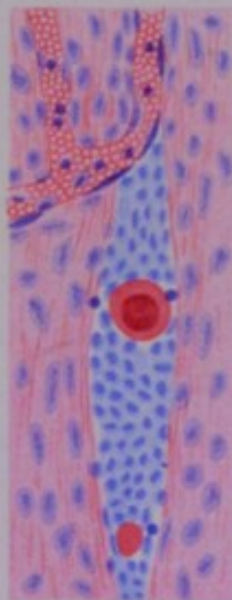


Fig. 42.



Fig. 43.

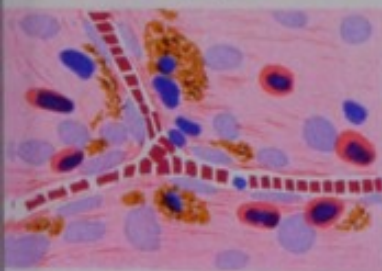


Fig. 44.

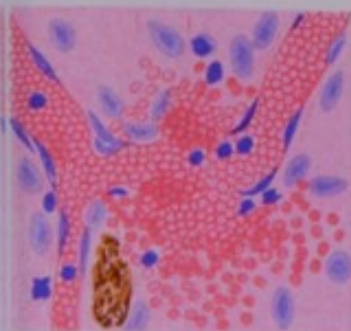


Fig. 45.



Fig. 46.



Fig. 47.



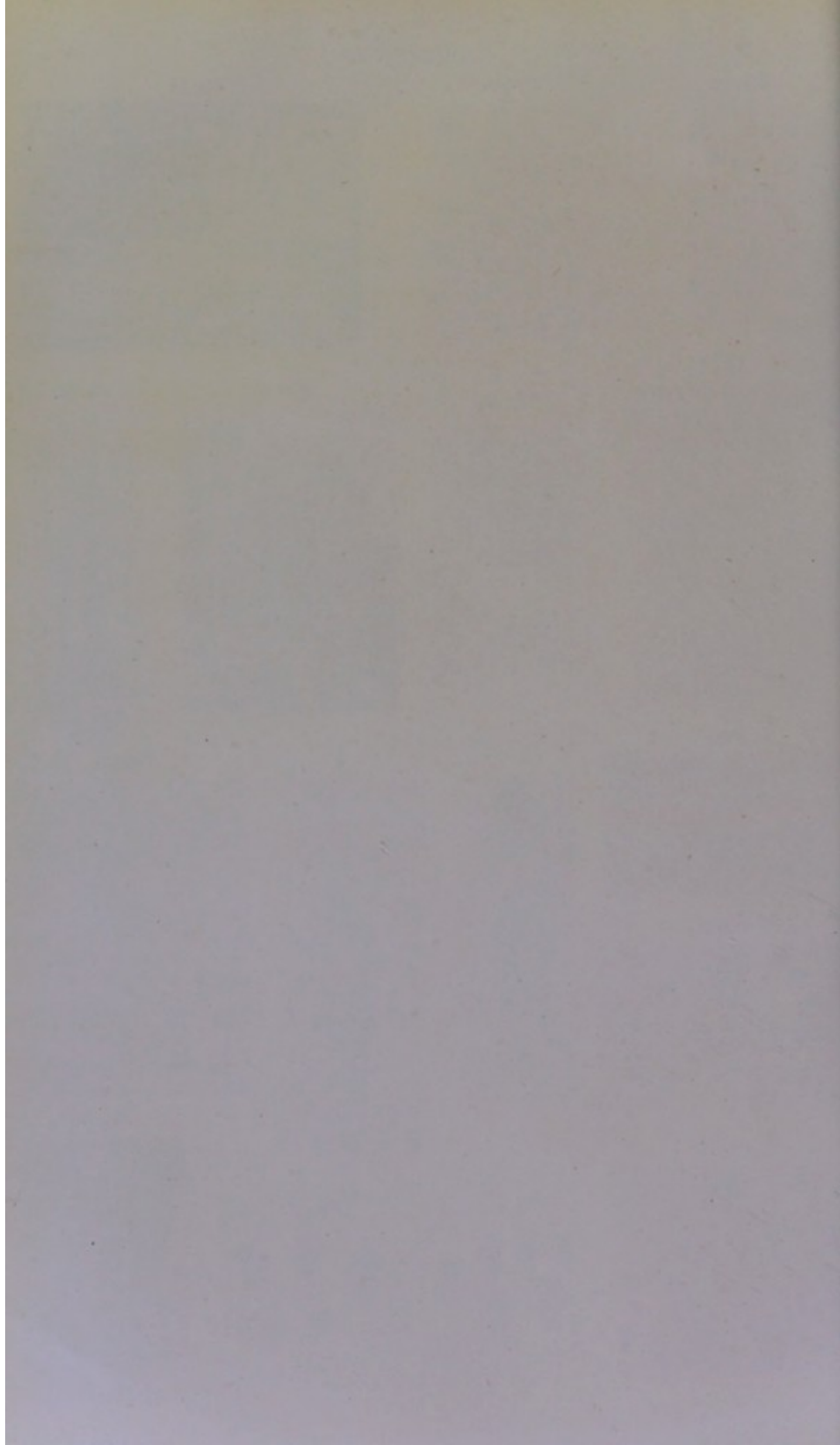


PLATE X.

Fig. 49.

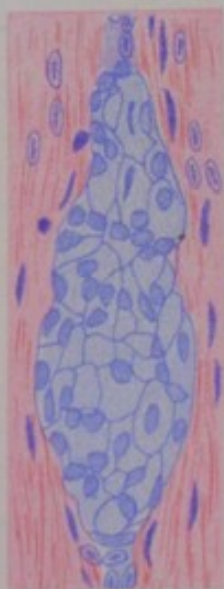


Fig. 48.



Fig. 50.

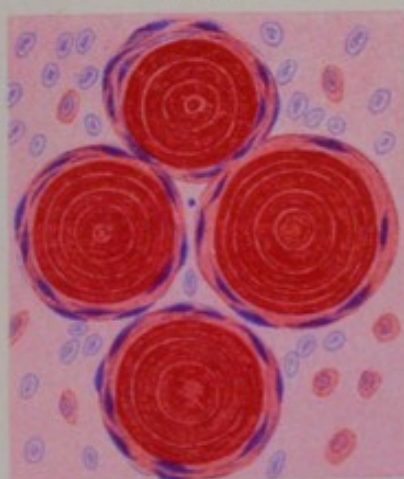


Fig. 51.

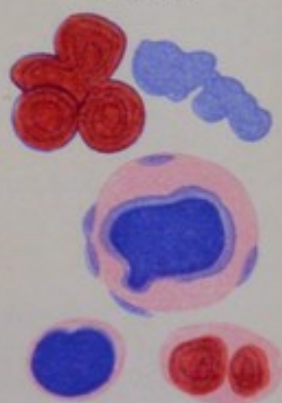


Fig. 52.



Fig. 54.



Fig. 55.

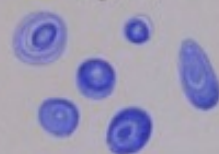


Fig. 53.



Fig. 56.

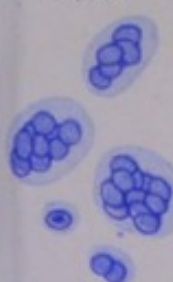


Fig. 57.

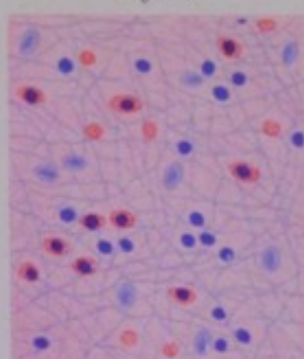


Fig. 58.

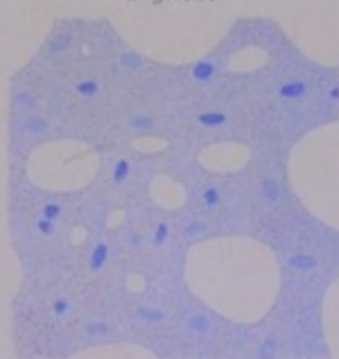


Fig. 59.

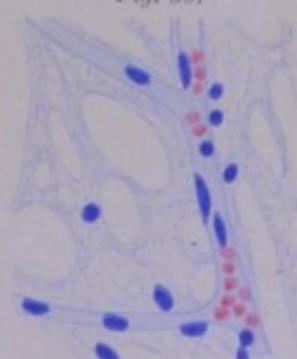


Fig. 60.



Fig. 61.

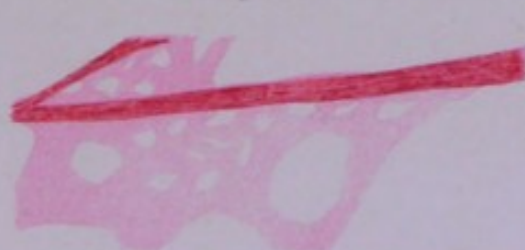
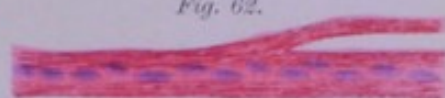
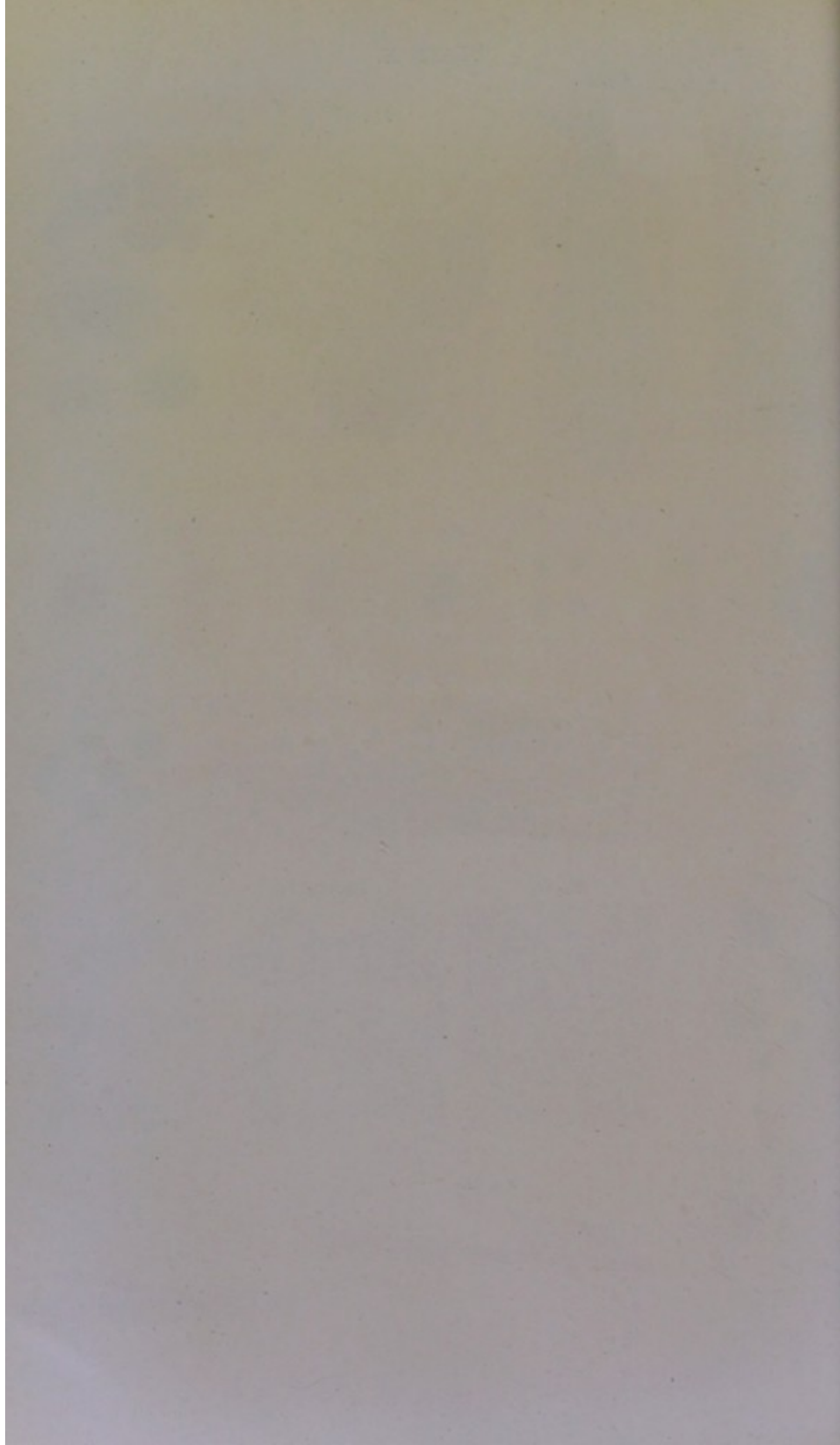


Fig. 62.





- Fig. 57. White portion of small recent blood-clot on surface of dura, showing fibrin threads, endothelial cells, leucocytes, and red blood corpuscles. From a case of senile insanity. ($\times 500$.) This and the succeeding figures are intended to illustrate the changes that occur in minute blood-effusions upon the surface of the dura.
- Fig. 58. Fenestrated fibrinous film on surface of dura, resulting from changes in small recent blood-extravasation. From a case of general paralysis. ($\times 500$.)
- Fig. 59. New capillaries in contracting fibrinous film on surface of dura. From a case of senile insanity. ($\times 500$.)
- Fig. 60. Contracting fibrinous film on surface of dura, and new capillary which has penetrated it. Note how the contracting fibrin ensheaths the vessel. Observe also the curling up of some of the fibrinous cords. From a case of general paralysis. ($\times 500$.)
- Fig. 61. Contracting fibrinous film on surface of dura, forming striated cords. From a case of chronic Bright's disease. ($\times 500$.)
- Fig. 62. New capillary which has penetrated a thin blood-clot on the surface of the dura and subsequently become obliterated. It is surrounded by a sheath formed by the contracting fibrin. From a case of malignant disease of the abdomen. ($\times 500$.)

CHAPTER VI

MORBID CONDITIONS OF THE PIA-ARACHNOID.

(PLATES XI., XII., AND XIII.)

THE morbid conditions of the leptomeninges that can be regarded as in any way specially related to insanity are few in number, but nevertheless of much importance. The most common, and at the same time the most important, is that which manifests itself to the unaided eye as milkiness, thickening, opacity and other abnormal appearances presently to be enumerated. It is necessary to take these changes together as they are the result of essentially the same pathological process. Consideration of the morbid conditions of the pial vessels is included in the succeeding chapter.

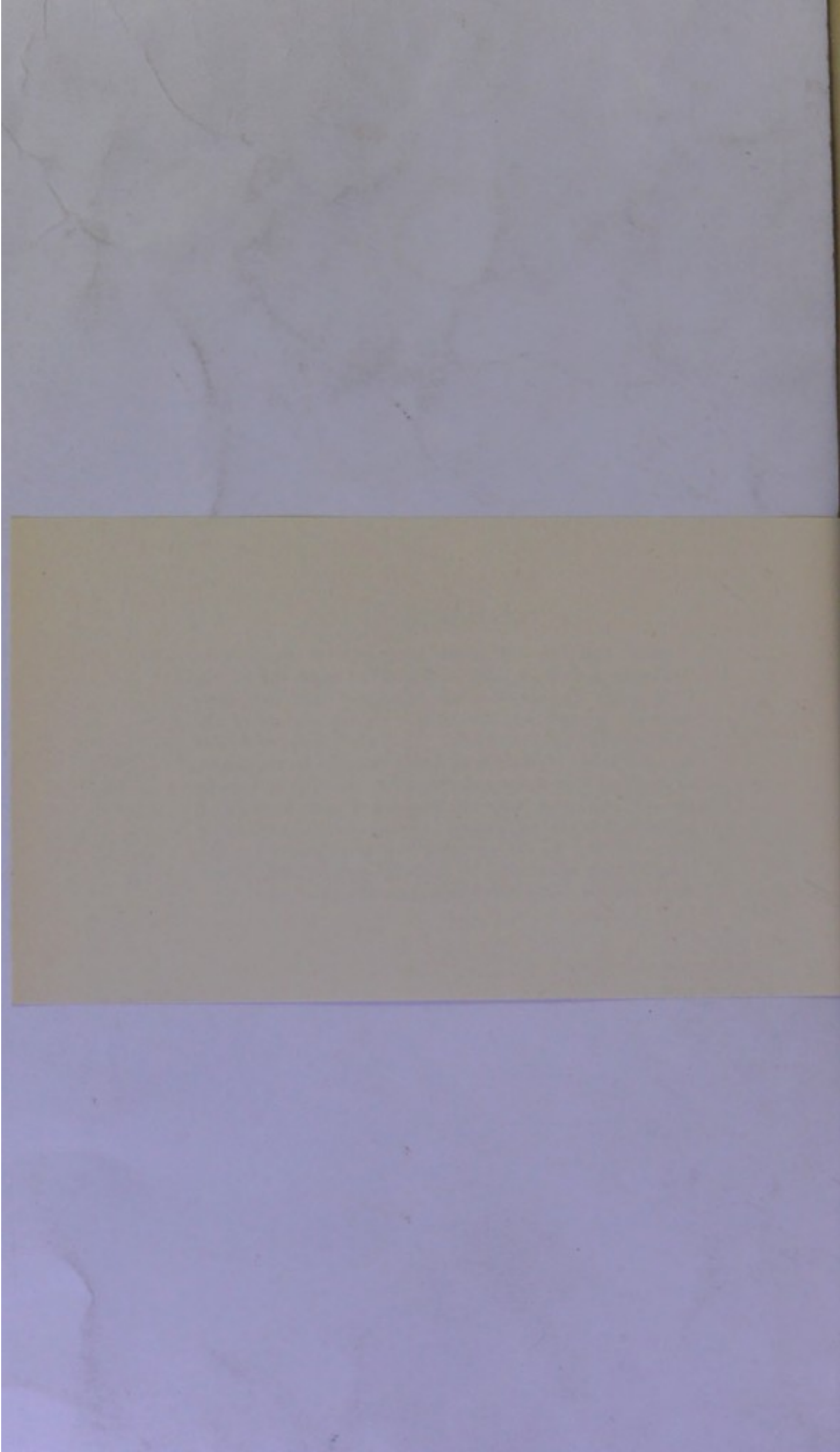
In 1895 Dr James Middlemass and I (13), in a paper dealing with the subject of this chapter, were obliged to dissent from the descriptions commonly given of the structure of the soft membranes of the brain, as well as from the views most generally held regarding the histological changes and the nature of the pathological process associated with milkiness, thickening, etc., of them. Of the general accuracy of the views that were then advanced, subsequent observation has only served to convince me more thoroughly.

NORMAL STRUCTURE OF THE PIA-ARACHNOID.

It is usually taught that the leptomeninges consist of two distinct membranes—an outer delicate, non-vascular layer of fibrous tissue which bridges the sulci without dipping into them, and an inner vascular membrane which closely invests the whole of the cerebral surface. Between these two layers there is said to be a considerable space (the “sub-arachnoid space”) traversed by numerous trabeculae, a spongy lymph-sac being thus formed which contains the cerebro-spinal fluid. Batty Tuke (6) has dissented from this commonly-received view of the constitution of the pia-arachnoid, maintaining that it should be looked upon as only one membrane, of which the so-called arachnoid is merely the outer layer. If I understand him aright, he bases this view upon the belief that over a convolution the two layers are intimately bound together, leaving no spaces containing cerebro-spinal fluid. He is otherwise in accord with the usual descriptions of the microscopic structure, except that he holds that the vessels course between the two layers instead of in the inner layer.

ERRATUM, page 116.

Batty Tuke, in the paper here referred to, says:—
“Between each convolution a pia-matral space exists, and it is easily demonstrable by injections that they communicate freely with one another on the surface of the cerebrum by wide channels.” I have interpreted this sentence, taken together with other passages in the paper, as implying that these communicating channels lie only in the sulci, although near the surface. I now understand, however, that *channels passing over the convolutions* are really implied. The views regarding the arrangement of the lymph-spaces maintained by this authority in 1882, do not therefore, essentially differ from those expressed here.



While I think that Batty Tuke's description of the pia-arachnoid as one membrane is a step towards a more correct conception of its constitution, I venture to maintain that in certain other respects his view, like that generally taught, is a mistaken one. It can be demonstrated that his statement regarding the distribution of the vessels is only correct for the large arteries, and his contention that the two layers of the membrane are intimately bound together over the convolutions, leaving no so-called sub-arachnoid spaces, may also be disproved by special methods of examination. By the employment of these methods it can be shown that the membrane has peculiarities of structure that appear to have escaped general notice, a knowledge of which must, I think, lead to the adoption of a view of its constitution differing from that at present commonly taught. According to the present teaching there are three structures composing the pia-arachnoid,—an outer layer of dense fibrous tissue; an inner layer of a similar kind, but differing from it in being highly vascular; and an intervening trabecular tissue, which, according to Batty Tuke, is absent over the convolutions. I think that it can be shown that, as maintained by Dr Middlemass and myself in 1895, there is essentially only one structure throughout, and therefore only one membrane.

The minute anatomy of the pia-arachnoid seems to have been studied almost exclusively by means of transverse sections. These, however, fail to demonstrate the arrangement of the lymph-spaces—a matter of the utmost importance. For the satisfactory examination of either the normal structure of the membrane, or the morbid changes that occur in it, it is necessary to use ordinary horizontal, superficial horizontal and oblique sections. The facts regarding the structure of the normal human cerebral pia-arachnoid, revealed by the employment of these methods, are as follows.

The basis of the membrane is white fibrous tissue collected for the most part into distinct bundles or trabeculæ. The individual fibres vary considerably in thickness. As a rule they are remarkably long. Numbers of them in some portions of the membrane cross each other at or near a single point, in such a way as to produce a radial arrangement (plate xii. fig. 1). Elsewhere the fibres, or bundles of fibres, form a more or less open meshwork (plate xii. fig. 2). The inter-spaces vary greatly in size, but are everywhere distinct, except at the centres of the radial systems of fibres. These structural features are very clearly revealed by the platinum method. In hæmatoxylin and eosin preparations, on the other hand, the cellular elements are brought into prominence, while only the general arrangement of the bundles of connective tissue fibres can be distinguished. Surface sections stained by the latter method show upon the outer aspect a continuous layer, generally single, of somewhat flattened endothelial

cells, each containing a large, oval nucleus (plate xiii. fig. 35). Cells of essentially the same type occur in considerable numbers throughout the membrane (plate xiii. fig. 40). Many of them are distinctly placed upon the surface of the trabeculæ, but it is doubtful if they here form a continuous layer. I am now strongly inclined to believe that they do not. Hæmatoxylin and eosin preparations further show that the trabeculæ are arranged in the form of inaccurately superimposed and partially united, slightly flattened networks, lying for the most part parallel to the cerebral surface. The meshes of these networks form freely communicating spaces which contain cerebro-spinal fluid (plate xiii. fig. 40). These spaces are largest in the centre of the membrane, a circumstance that explains its seeming division into two separate layers. In the sulci some of them are specially large, and about the base of the brain and along the upper surface of the corpus callosum there are some still larger cavities which form the arachnoid cisterns. Below the endothelium of the outer surface there is no distinct horizontal layer of compact fibrous tissue that can be properly regarded as a separate membrane. What is typically found is simply a layer of connective tissue of the same thickness as the subjacent trabeculæ, and formed by their arches. The same arrangement of trabeculæ and intervening lymph-spaces is maintained to the inner surface immediately external to the cortical tissue. Thus the membrane has throughout the structure of a spongy lymph-sac. Though the vessels lie chiefly in the deeper portion of the membrane, they may occur in any part of it. In almost every superficial horizontal section some may be seen a little below the outer endothelial layer. The veins especially tend to lie near the outer surface. Therefore the statement that the so-called arachnoid is a non-vascular structure is quite erroneous. The majority of the arterioles are large, being for the supply of the subjacent cerebral tissues. I am now convinced that capillaries are virtually absent from the normal pia-arachnoid. Around the large vessels, near the inner aspect of the membrane, the endothelial cells are more numerous, and the lymph-spaces smaller and more elongated than elsewhere, so that the tissue seems to have a denser structure. It is doubtless chiefly this circumstance that has led to the belief that there is an inner layer of a distinct structural character. Horizontal sections, however, prove that the structure is essentially the same throughout. The junction of the pia-arachnoid with the cerebral tissues is formed, apart from the vascular connections, by a slight interlacement of the connective tissue and glia fibres. The existence of an intervening special layer of endothelial cells, described by some, is not borne out by the study of deep surface sections of the membrane. The "epi-cerebral space," still described in many text-books, is, I believe, a purely artificial production.

Some of the above structural features are diagrammatically represented in plate xi.

There is a fact regarding the structure of the arterioles of the pia-arachnoid which, I think, helps us to understand the true constitution of the membrane. It is that, in comparison with the arterioles in other situations, their adventitia is extremely thin and inconspicuous. Indeed, in many instances it is practically invisible, the vessel appearing as if bounded by its muscular coat. Beyond this there are seen the lymph-spaces and trabeculae which form the essential structure of the membrane. This trabecular tissue practically forms for these vessels a common adventitia. From a consideration of these features of structure, Dr Middlemass and I have advocated the view that the whole extra-vascular structure of the pia-arachnoid may be looked upon as the conjoined and hypertrophied adventitial coats of the pial vessels, the lymphatic spaces of which have undergone a special development so as to form a spongy lymph-sac. In further support of this view, there is the fact that the trabecular tissue is directly continuous with the relatively very thick adventitial coats of the cortical arterioles. The main object of this special development of the lymphatic spaces of the adventitia of the pial arterioles is probably to give to the brain the protective advantages afforded by its envelopment in a thin water-cushion. The arachnoid cisterns and the so-called sub-arachnoid spaces of the cord are merely the result of special local enlargement of numerous spaces, and do not represent any essential structural difference. The arachnoid in these situations is supposed to be distinguished from the subjacent pia in being non-vascular. Even if this supposition were accurate, which, strictly speaking, it is not, the argument based upon it is quite fallacious, for as far as nutrition by blood-vessels is concerned, the whole pia-arachnoid is practically non-vascular. The vessels it contains are almost entirely arterioles and venules, going to and coming from the nervous tissues. Capillaries, as has been said, are virtually absent. The membrane is nourished not by capillaries of its own, but by the lymph which transudes from those within the brain, and which is conveyed to it by way of the adventitial lymph-channels of the larger intra-cerebral vessels.

These facts regarding the microscopic anatomy of the pia-arachnoid lead to the conclusion that it can only be correctly looked upon as consisting of one membrane. If this view is accepted, it is obvious that there is much in the present terminology that should be altered. The best name to apply to the whole membrane, since it is the only one that can be employed without risk of confusion, is probably that used above, viz., "pia-

arachnoid." The term "pia-mater" in its usual acceptation should certainly be abandoned. But it might conveniently be applied to the whole membrane synonymously with "pia-arachnoid," in which sense indeed it is now often used. The meaning of the term "arachnoid" should be extended so as to include all the trabecular tissue which stretches from the outer to the inner aspect of the membrane. "Sub-arachnoid" is anatomically inaccurate, and should therefore be disused. The terms "arachnoid trabeculae," "arachnoid spaces" and "arachnoid fluid" should be employed instead.

There are some additional points regarding the structure of the pia-arachnoid which still require to be mentioned here. As in the case of the dura mater, the question as to whether in certain pathological processes the endothelial cells or the connective tissue corpuscles are involved, must be regarded as an entirely gratuitous one. The two are essentially identical; the endothelial cells lining the arachnoid spaces, as well as those of the outer surface, are but connective tissue corpuscles in a special position, and performing in part a special function. They present no important morphological difference, they behave in the same way under abnormal nutritional conditions, and are each capable of forming fibroblasts.

In horizontal and oblique sections, broad bands of dense but delicate white fibrous tissue, with numerous long spindle-shaped nuclei, may very occasionally be observed. They are perfectly normal constituents of the pia-arachnoid, but their occurrence is not sufficiently common to make it easy to determine their exact relationships.

Pigment cells are exceedingly abundant in the pia-arachnoid of some of the lower animals. In the sheep and ox, for example, they are sometimes so numerous as to give to the frontal lobes a dark grey, and in parts even a black aspect. Under the microscope they appear as more or less distinctly branching corpuscles, the protoplasm of which is filled with dark brown granules. They are generally placed at or near the outer surface, and are to be regarded as merely specially modified endothelial cells. In the human subject they are not infrequently to be observed, more especially in the membrane covering the anterior aspect of the pons and medulla, to which indeed they sometimes impart a distinctly grey tint.

In superficial horizontal sections of perfectly normal membranes there may occasionally be seen rounded or oval aggregations of small, often slightly elongated, endothelial cells. They differ from the pathological granulations, described below, in having towards their periphery a regular concentric arrangement of their cells, as well as of the subjacent fibrous tissue. Further, the cells show no degenerative changes, and the formations are little, if at all, raised above the general surface.

It is to be borne in mind that the pia-arachnoid is normally adherent to the dura mater underneath the superior longitudinal sinus, where the large pial veins, supported by a certain amount of fibrous tissue, pass into this blood-channel, and where also the Pacchionian granulations penetrate the dural tissues.

MILKINESS, THICKENING, OPACITY AND ALLIED MORBID CONDITIONS.

The normal pia-arachnoid presents a smooth glistening surface, and, except for numerous vessels which are seen lying chiefly in its deeper parts, it is transparent, and perfectly free from any cloudiness or opacity. Over the convexity of the cerebrum, the Sylvian fissure, and the anterior part of the superior vermiform process of the cerebellum, it is normally much thicker than over other parts of the encephalon, where it is an exceedingly delicate membrane. In persons dying insane it is the exception to find the soft membranes retaining this transparent and delicate structure. As a rule they present a more or less thickened and milky aspect. The appearances vary greatly in different cases. The slightest degree of the change appreciable to the naked eye is usually a faint milkiness, confined to the convexity, without any distinct thickening. With the advance of the morbid process the milkiness becomes more and more marked, and the membrane is distinctly thickened. Except in certain classes of cases, these morbid appearances are almost limited to a definite area, which corresponds pretty accurately to those situations in which the membrane is normally thicker than elsewhere. They are practically always most marked alongside the superior longitudinal sinus, while at the lateral aspects of the hemispheres they gradually shade off into apparently healthy membrane. The meninges over the frontal and occipital poles, and over the internal and inferior aspects of the hemispheres, are seldom much affected. The milkiness is usually specially pronounced over the sulci and alongside the veins which course near the outer surface, as they pass towards the superior longitudinal sinus. In these situations it often appears as opalescent spots and streaks. Along with this cloudy change there are frequently perfectly opaque white patches, usually of small size, but occasionally large. These patches also occur especially over the sulci and in the neighbourhood of the large veins. In some cases there is added to the cloudy appearance a distinct smoky tinge, and in others a more or less rusty hue. The arachnoid fluid is, as a rule, considerably increased in quantity. The term "œdema" scarcely seems a suitable one to apply to this condition, as in the majority of instances the fluid is merely compensatory of brain atrophy. When the brain is removed, and the fluid drains away, the cloudy appearance, if slight, tends to disappear.

This circumstance must not, however, be taken as indicating that the morbid appearance is due to actual milkiness of the arachnoid fluid, careful examination of which in such cases shows that it is always either clear or only faintly turbid. When marked thickening is associated with great increase of fluid, cysts are frequently developed. They almost invariably occur at the vertex, and are usually small, but may be the size of a hazel-nut, or even larger. They are always in the pia-arachnoid, and never between the membrane and the brain, and contain fluid of the same character as that which distends the sinuses. When the morbid changes are advanced, the membrane is generally remarkably tough. This is especially noticeable when the Sylvian fissures are opened up for examination of the branches of the middle cerebral arteries. The fact is then also clearly demonstrated that the outer portions of the membrane are those most distinctly affected. Marked thickening and toughening of the membrane is commonly associated with great increase of the adhesions normally existing between it and the dura, immediately adjacent to the superior longitudinal sinus. Accompanying this cloudy change there is frequently to be observed a finely granular appearance on the surface of the membrane. It is especially common in the neighbourhood of the Sylvian fissures. More rarely there are distinct, but still very minute granulations. These were apparently first observed in 1826 by Bayle (1), who described them as "rounded, excessively delicate asperities."

In advanced general paralysis these morbid appearances are seen in their most extreme degree. In this disease, and also in syphilitic insanity, they extend over the whole surface of the brain, though they are still always most marked over the convexity. In this situation the cloudiness and thickening, along with the congestion which in these cases usually attends them, are often so marked as to entirely obscure the outlines of the convolutions. In such instances, if the arachnoid fluid is very abundant, a curious appearance, which has been likened to that of a jelly-fish, is produced over the convexity of the brain. Cysts, small hæmorrhages, and a diffuse smoky tinge are specially apt to be added to the other morbid appearances in general paralysis. Very commonly in this disease there is some adhesion of the apposed surfaces of the membrane on the internal aspect of the frontal lobes just beneath the corpus callosum. This condition is comparatively rarely to be observed in other forms of mental disease, excepting perhaps syphilitic insanity.

Another morbid change which must be placed in the same category is the formation of osteoid plates. They are common in the spinal membrane, rare in that of the brain. They most frequently occur on the posterior aspect of the cord, and are often present in large numbers.

They usually appear as flattened, irregular plates of a white or grey colour, and firm bony or cartilaginous consistence. They may be so small as to be scarcely recognisable by the unaided eye, or they may be so large as to cover completely the whole breadth of the spinal cord. According to Krømer (4) they are sometimes so numerous and lie so closely together that they form a fenestrated canal. The edges are often serrated, and large pointed processes may project from them. These appearances have given origin to the name "*corps étoilés*," by which these bodies are known in France. They may be embedded in the membranes, or may appear to lie on its outer surface. In the membranes of the brain, where they have similar characters, they are found almost exclusively on the anterior portion of the convexity (Krømer).

It is agreed on all hands that milky cloudiness occurs far more commonly, and to a more pronounced degree, in the insane than in the mentally sound. Bevan Lewis (10) found it in 50 per cent. of those dying insane, Batty Tuke and Woodhead (8) in 58 per cent., and Bullen (9) in 49·3 per cent. The statistics of Dr Middlemass and myself (13), in which were included the slighter degrees of the change, give a percentage of 73·5. The condition is constant in general paralysis and in senile, syphilitic and alcoholic insanities. It is almost always present in some degree in acute insanities, even when they have been of very short duration. It is absent in many cases of epilepsy and secondary dementia. Opaque patches in the membranes and a granular appearance on their surface are found most commonly in senile insanity, in which disease, indeed, they are seldom absent. Bevan Lewis, however, regards the latter condition as most frequent in general paralysis. Osteoid plates are, as already stated, rare in the intra-cranial membrane, but common in that of the spinal cord. Krømer observed them altogether in 20 per cent. of cases of insanity, but they only occurred nine times in the cerebral pia-arachnoid in 996 cases. He further remarks that the more carefully the spinal arachnoid is examined in healthy people, the more frequently are these structures found. There is, he says, no form of mental disease in which they specially occur. Voisin (5) met with them in 75 per cent. of cases of general paralysis.

Regarding the occurrence of cloudiness of the pia-arachnoid in the mentally sound, Bevan Lewis states that in some degree it is usually found in people dying in middle age, and that it increases with advancing years. According to Ziegler (12) it is also found in connection with chronic venous engorgement and with certain morbid states of the blood, as alcoholism and chronic nephritis. All forms of acute meningitis are, of course, to be excluded from this category, as they have a different pathology from the morbid conditions under considera-

tion. The purulent infiltration of the meninges occasionally unexpectedly discovered in the insane at autopsy, the pathology of which has been thought to be different from that of the ordinary forms of purulent meningitis, owing to the absence of the usual symptoms, can now, I think, only be regarded as identical with this condition. Most of the cases are associated with pneumonia, to which the purulent meningitis is probably secondary. The typical clinical picture is masked by the cerebral disease already established.

Before passing to the description of the microscopic changes it will be well to state briefly the various opinions that have been expressed as to the pathology of milkiness and thickening of the pia-arachnoid. Bayle (1), writing in the early part of the present century, regarded the condition as a chronic meningitis, which he believed must play the principal rôle in the etiology of insanity. Bevan Lewis (10) is of opinion that in its extreme degrees "we must infer an inflammatory agency." In its slighter manifestations, and especially in senile atrophy of the brain, he thinks it may occur apart from inflammatory action. In all cases he attributes much importance to the effect of frequent congestive conditions or chronic hyperæmia. Ziegler (12) describes two separate conditions, one affecting mainly "the arachnoid and sub-arachnoid tissues," and the other involving chiefly "the pia and underlying nerve-tissue." The former he terms "chronic arachnitis or external leptomeningitis," and the latter "atrophic meningo-encephalitis." Though thus committing himself in his terminology to an inflammatory theory, he states that he doubts if the first form is always inflammatory, and that the second in its inception is mainly dependent upon degenerative changes. Batty Tuke and Woodhead (8) also practically adhere to the inflammatory theory of Bayle, though they attach considerable importance to "occasional pathological congestion superadded to the normal mechanical obstruction produced by the peculiar anatomical relations of the vessels to the longitudinal sinus." Batty Tuke, in his more recent work on "The Insanity of Over-exertion of the Brain" (7), further attributes the morbid change to "a deposit of waste and plastic exudates. As these accumulate and diffuse the membrane becomes thick, tough, and on section is found to consist of a mass of material which looks like an immense increase of the normal trabeculæ." Ziegler states that the condition which he terms "chronic arachnitis" is due to fibrous thickening, endothelial hyperplasia, and more rarely to cellular infiltration. In early cases of "atrophic meningo-encephalitis," in which he thinks the changes may be degenerative only, the white turbidity is due "to accumulation of small granules and globules of fat, fatty and broken down cells and occasional fat granule cells." In many cases from the first, and in all advanced cases, the most important change is, he states, the small-cell

infiltration that pervades the pia mater, and to a less degree the sub-arachnoid tissues. Other authorities are pretty generally agreed in describing the microscopic changes as consisting in an infiltration of the tissues with round cells, and in an increase in the fibrous elements.

Microscopic changes.—These consist essentially in proliferation and degeneration of the endothelial cells of the trabeculæ and outer surface, and in slow hyperplasia of the fibrous tissues. The connective tissue overgrowth is directly proportional to the degree of milkiness and thickening. It affects the whole membrane, but the outer and less vascular parts chiefly (plate xiii. fig. 41). The new fibres tend to be thicker and coarser in structure than normal. Opacities are due to an extreme degree of this overgrowth occurring locally, and resulting in more or less complete obliteration of the arachnoid spaces (plate xiii. fig. 34). The endothelial proliferation may be very marked, slight, or entirely absent. Like the fibrous hyperplasia, which results from it, it is usually most pronounced in the outer portions of the membrane. In the majority of cases it is a well-developed condition, and its absence is exceptional. The proliferated cells frequently form dense aggregations in the arachnoid spaces. As observed in transverse sections they have been commonly mistaken for the small round cells of an inflammatory exudation. Their endothelial character, however, is, I maintain, beyond question. The nuclei, though often somewhat smaller, are otherwise morphologically identical with those of the normal endothelial cells of the trabeculæ and of the outer surface. This point is admitted by Ziegler for the earlier stages of the morbid process in a certain number of cases. In the more advanced stages, and in many cases from the first, he believes that there is also a small round-cell (leucocyte) infiltration. The results of my own observations oblige me to differ from this view. In my experience it is only in advanced general paralysis and in syphilitic insanity that this morbid condition of the pia-arachnoid is associated with leucocyte infiltration of the tissues. In other cases, even when there is an extreme degree of milkiness and thickening, the cell-elements preserve the endothelial type, and collections of round cells upon the vessel-walls or elsewhere are only very rarely to be observed. In several cases of early general paralysis that I have examined, leucocyte infiltration has also been absent, and even in some advanced cases it has occurred only locally.

The endothelial cells of the outer surface, in addition to showing general proliferation, frequently present numerous small localised aggregations (plate xiii. figs. 36, 37, and 38). These constitute the granulations of the pia-arachnoid. Their endothelial character was recognised by Meyer (2) in 1862. In transverse sections they appear as oval masses of cells extending about an equal distance above and below the general level of the surface.

The degenerative changes, which may affect either the previously healthy or the proliferated cell, are of various kinds. One of the most common is of a pigmentary character. It occurs especially in the cells of the trabeculæ in senile insanity, independently of proliferation. It manifests itself by the presence of numerous minute yellow granules in the cell-body. These granules are slightly darkened, but not blackened, by osmic acid, and do not disappear in the presence of the usual solvents of fat. They are therefore not of a fatty nature. They are lighter in colour, larger and not so numerous as the granules in the normal pigment cells. Moreover, every cell in a large area may be affected, while the normal pigment cells are never numerous in the pia-arachnoid of the human cerebral hemispheres. Therefore, I conclude that this is a degenerative change, though at the same time it is one that may have a physiological basis in the normal pigment cells, just as in pigmentary degeneration of nerve-cells the granules that replace the protoplasm are merely an increase in a normal element.

Another common change is hyaline degeneration. As in the dura, it specially occurs in cells that have undergone proliferation. It may also affect strands of the fibrous tissue. On the outer surface it occurs chiefly in the centre of granulations, and tends to go on to the formation of concentric bodies, the process of development of which has been described in the preceding chapter (plate xiii. figs. 38 and 39). In surface sections of the pia-arachnoid from cases of senile insanity, these bodies may often be observed in very large numbers, and in all stages of development. They are always most numerous on the upper surface of the hemispheres. Hyaline degeneration of the endothelial cells of the trabeculæ results in the formation of homogeneous globules which stain only very faintly with eosin in hæmatoxylin and eosin preparations. These globules may occasionally be observed in great numbers. They are undoubtedly capable of developing into concentric bodies, but it is somewhat rare to find these formations in the arachnoid spaces.

Vitreous degeneration of the endothelial cells of the trabeculæ is also very common. Its characters are essentially the same as in the dura mater. In some cases almost every cell is affected.

The proliferated and degenerated cells of the trabeculæ are constantly being shed and carried away in the arachnoid fluid, coverglass preparations of which always show large numbers of them, usually in a more or less shrivelled and disintegrated state. Simple breaking down into granular débris is probably the most common change that these proliferated endothelial cells undergo. A point of considerable importance is that osmic acid preparations, whether of sections or of coverglass specimens of the arachnoid fluid, prove that fatty changes do not occur to any great extent in this milky condition of the pia-

arachnoid. The same opinion has already been expressed by Adler (3), though, as I have mentioned, an opposite statement is made by Ziegler.

Extravasated red corpuscles are frequently to be observed in the arachnoid spaces. Hæmatoidin granules and crystals often occur, especially in senile insanity, in association with miliary aneurisms of the pial vessels. These morbid elements, resulting from recent or old-standing hæmorrhage, are the chief cause of the smoky or rusty tint that the pia-arachnoid occasionally presents in the fresh state. In many cases granular débris of various kinds is present in great abundance. It probably arises chiefly from disintegration of extravasated red and white blood corpuscles, and from degeneration of endothelial cells.

The osteoid plates that are so common in the spinal membrane are, I think, the result of a retrograde metamorphosis in arachnoid opacities. They arise by a peculiar change in the dense fibrous tissue of which these opacities are composed, very similar to that which occurs in the intramembraneous development of bone. They may, therefore, probably be correctly termed "osteoid." In my experience their infiltration with calcareous salts is rare. With few exceptions, they are unaffected by the action of mineral acids.

As stated in the previous chapter, these tissue-changes are essentially of the same nature as those that occur on the opposite side of the subdural space in the same kind of cases. The differences are due to differences in the structure of the two membranes. In the pia-arachnoid there are no capillaries to be obliterated, and therefore new formation of vessels is comparatively rare, although it may occasionally be observed to have taken place in association with occlusion of arterioles.

Nature of the morbid process.—I have endeavoured to show that the tissue-changes associated with thickening, milkiness and allied morbid conditions in the pia-arachnoid, consist essentially of proliferation and degeneration. Sometimes the one is in the ascendant, sometimes the other. Occasionally only one is distinctly represented. The leucocyte infiltration that occurs in advanced general paralysis, and in syphilitic insanity, is clearly a superadded and independent phenomenon which may be left out of account in considering the essential nature of the morbid process.

It will be seen that we are here faced by the same difficulty as that with which we were met, in considering the pathology of the corresponding changes in the dura mater. Are we entitled to speak of such a proliferative and degenerative process as inflammatory? This depends upon our definition of inflammation. By many authorities the term has been employed in a sense sufficiently wide to include the process in question; by others it has been limited to

phenomena which are essentially different. It is further to be borne in mind that there is a tendency among pathologists at the present day "to allow the idea of inflammation to drop completely," because of the apparent impossibility of arriving at a unity of opinion as to the definition of the term (Thoma, 15). For my own part, I think that we should not speak of these morbid changes in the pia-arachnoid as inflammatory, mainly for the reason that if we do so, we are certain to convey a wrong impression regarding their essential nature. The term "chronic meningitis" was based upon the belief that the numerous cellular elements present were the products of an inflammatory exudation, and if the expression is retained, so, with many, will be the erroneous interpretation of the existing tissue-changes. In the meantime, I think, we should be content to refer to the morbid condition merely by the naked-eye appearances that it presents.

The essential cause of these chronic morbid changes that so commonly affect the pia-arachnoid of the insane has already been partly considered in the preceding chapter. It is more fully discussed in chapter xi., in connection with the subject of the lymphatic system of the brain. It will be sufficient to state here that I maintain that the proliferative and degenerative changes that have been described are essentially the result of an alteration in the composition of the cerebro-spinal fluid, consequent upon the pathological state of the subjacent nervous tissues. As has already been contended, the pia-arachnoid is dependent upon this fluid, and not directly upon its blood-vessels, for its nutrition. Any morbid alteration in the composition of the cerebro-spinal fluid must therefore be liable to affect the membrane injuriously. In the cases in which a distinct leucocyte infiltration of the tissues is added to the typical alterations, there is beyond question an inflammatory process at work.

MORBID ADHESION TO THE CORTEX.

Bevan Lewis (10) has specially drawn attention to the occurrence of morbid adhesion of the pia-arachnoid to the cerebral cortex in various forms of chronic insanity. He considers that in general paralysis of the insane, the condition forms so important a feature as to constitute to the pathologist the one distinctive sign indicative of this disease. He found it in 77.1 per cent. of cases of this nature. It is chiefly evidenced by laceration of the cortex on stripping off a portion of the membrane, which, instead of readily separating from the nervous tissues, as in the normal condition, carries a more or less thick layer of them with it. Bevan Lewis attributes this morbid adhesion to neuroglial overgrowth, but admits that softening of the outer layers of the cortex may be a factor in the case. He further

attributes absence of such morbid adhesion in advanced senile insanity, and in some cases of general paralysis, to the fact that in the later stages "the organisms have succumbed to a fatty liquefaction, and so been removed from observation."

That the degree of adhesion normally existing between the pia-arachnoid and the cerebral cortex is greatly increased in chronic insanity, and especially in general paralysis, is a fact of which every pathologist who has studied the matter must be fully satisfied. There are two factors in the production of the normal degree of adhesion, viz., (a) the interlacement and attachment of the glia-fibres to the connective tissue fibres of the pia-arachnoid, and (b) the blood-vessels which pass from the membrane into the substance of the brain. The latter factor is by far the more potent one, as must appear from a consideration of the existing histological arrangements. Before the normal pia-arachnoid can be stripped off, the glia-fibres must be broken away from their attachments to its connective tissue fibres, and the vessels must be drawn out from the cortex, and at the same time broken across at a greater or less distance from their point of entrance to the brain. There are likewise two factors in the production of an abnormal degree of adhesion of the pia-arachnoid to the cortex,—(a) increase in the number and strength of the glia-fibres, and (b) increase of the connective tissue fibres of the adventitia of the vessels. The vascular factor is again by far the more important one.

I have entered into these details because I am thoroughly convinced, from my own observations, that Bevan Lewis is in error in attributing the eroded appearance of the convolutions, observed on stripping off the pia-arachnoid in some cases of general paralysis, to morbid adhesion between the membrane and the cortex. The histological evidences of increased adhesion that have been enumerated occur quite independently of this special morbid appearance, which, I maintain, depends essentially upon another cause, which Bevan Lewis admits to be a factor in the case, namely, softening of the cortical tissues. In cases of general paralysis, the erosion is to be observed almost exclusively near the summits of the convolutions. But the histological changes upon which increased adhesion of the membrane depends, occur to quite as great, and often to a greater, extent in the sulci. This would not be the case if the laceration were owing to these changes. Moreover, these changes are often equally developed in other forms of insanity without laceration of the cortex occurring on removal of a portion of the pia-arachnoid. Further, if a normal brain is allowed to soften from post-mortem change, the whole membrane, both in the sulci and over the convolutions, strips off with adhesion and laceration of the cortex, just as occurs near the top of some convolutions in certain cases of general paralysis. Lastly, there

is macroscopic and microscopic evidence of a tendency to the occurrence of softening in the cerebral cortex, near the summits of the convolutions, in cases of general paralysis. For these reasons I think we must attribute to this softening, and not to the morbid adhesion between the membrane and the brain, the cortical erosions that may commonly be produced in cases of this disease at autopsy. In consequence of this softening the weakest point has been removed from the cortico-pial junction to the cortex itself; but without such softening the weakest point remains at the cortico-pial junction, notwithstanding the presence of the highest degrees of vascular sclerosis and of neuroglial overgrowth.

I have not observed erosions of the convolutions so frequently in general paralysis as Bevan Lewis has found them. This, however, is accounted for partly by the fact that I have removed the pia-arachnoid only from a comparatively small portion of the hemispheres. These erosions are undoubtedly of considerable pathological interest, but the practice of stripping off the entire membrane in order to discover whether or not they can be produced at any spot, is not one to be recommended, for it involves injury to the cortex that is most detrimental to its subsequent histological study.

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DESCRIPTION OF PLATES XI., XII. AND XIII.

PLATE XI.

Diagrammatic representation of human cerebral pia-archnoid in transverse section, showing arrangement of trabeculae and lymph-spaces. Note that the spaces exist throughout the membrane, but that they are largest in its centre

PLATE XI.

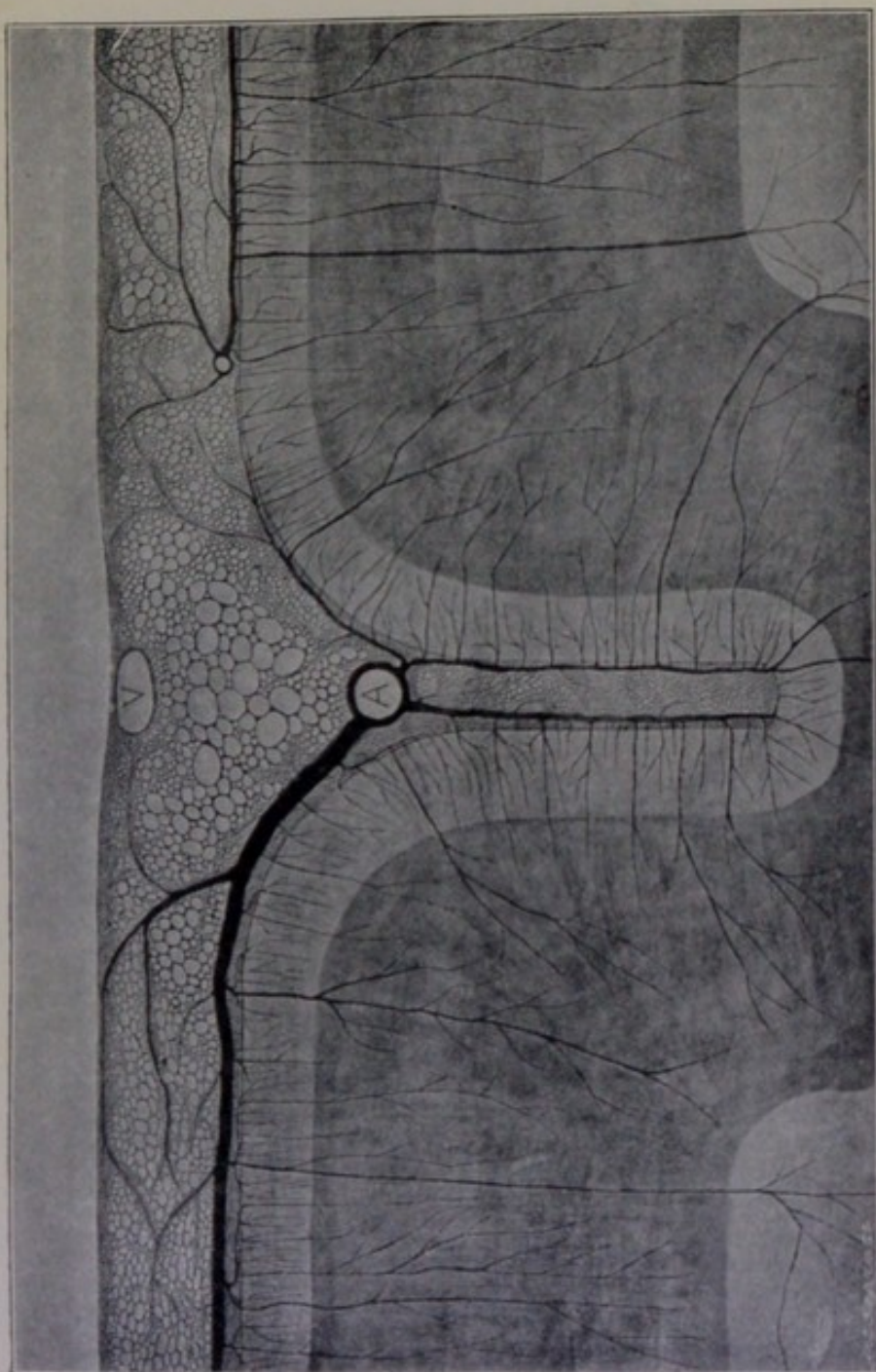




PLATE XII.

Fig. 1.

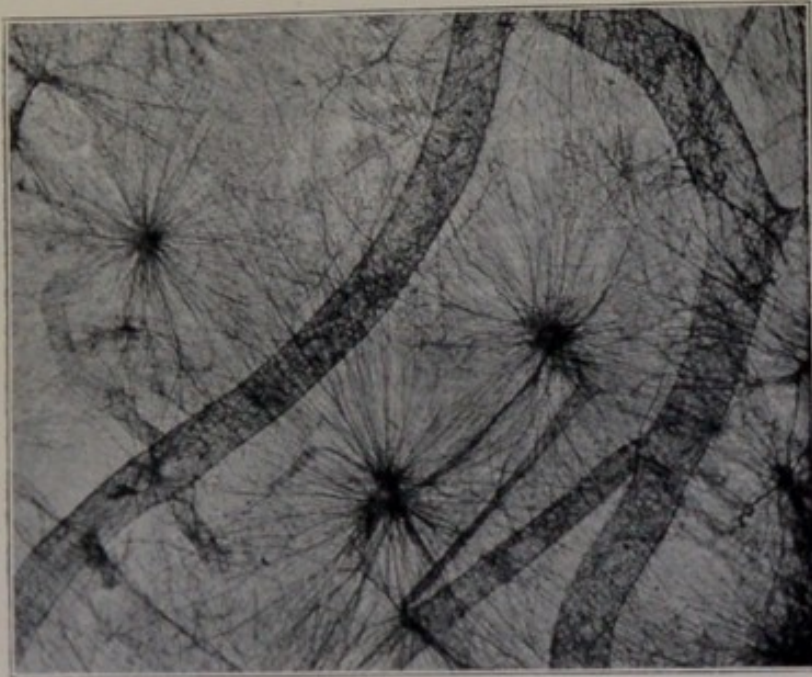
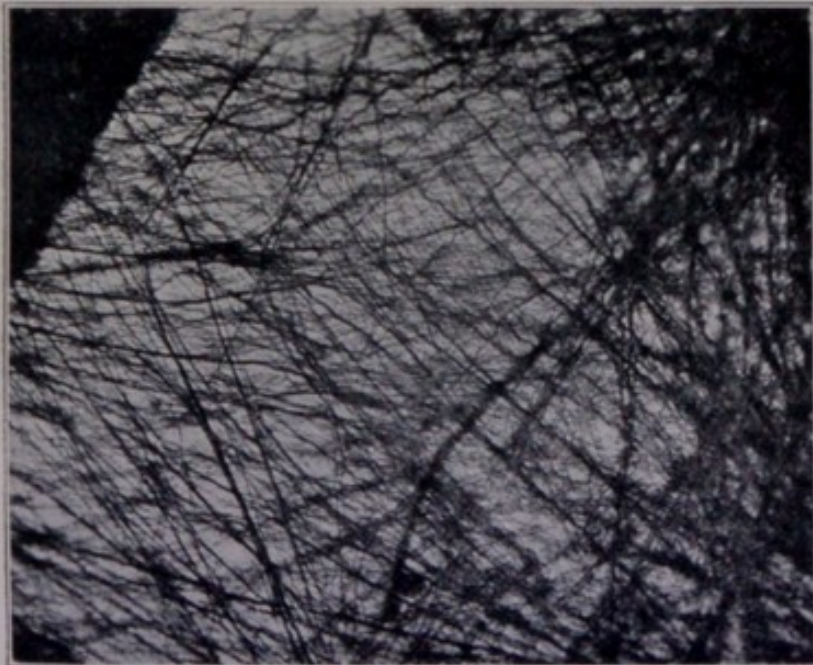


Fig. 2.



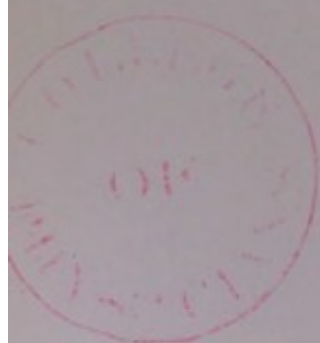


Fig. 32.

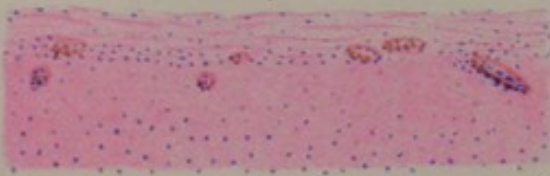


Fig. 33.

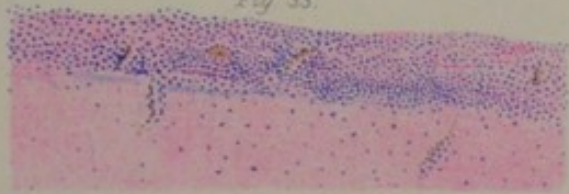


Fig. 34.

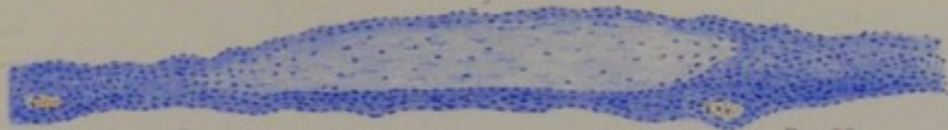


Fig. 35.

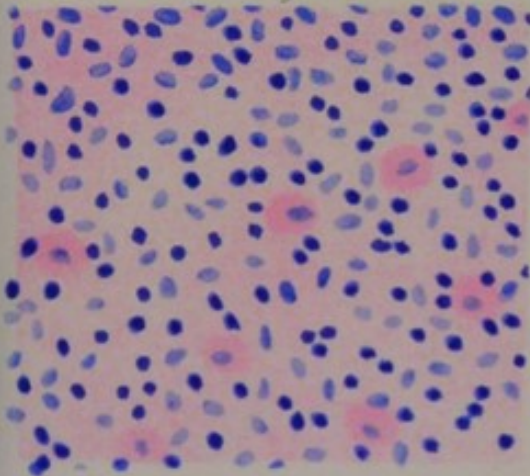


Fig. 36.

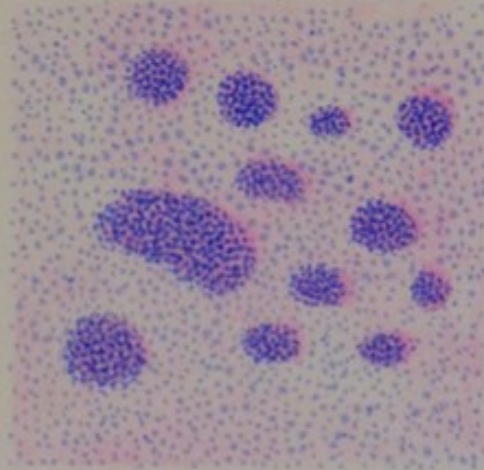


Fig. 37.

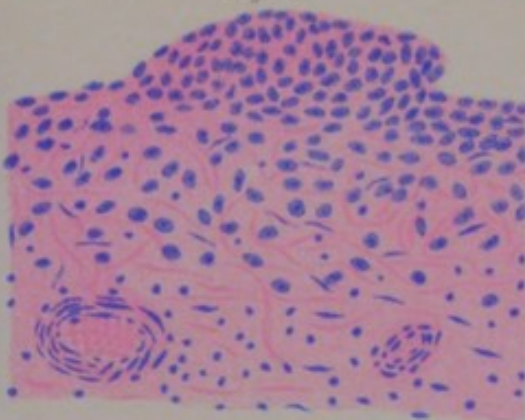


Fig. 38.

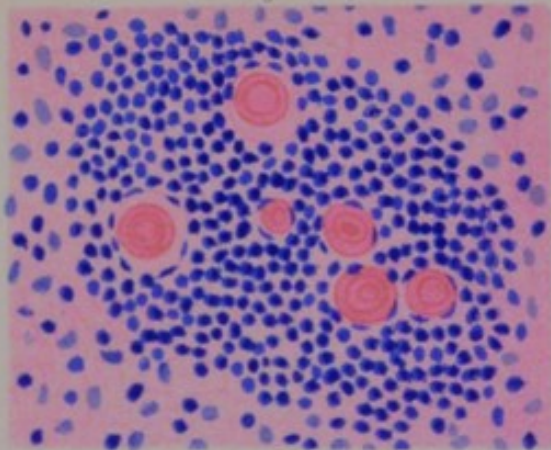
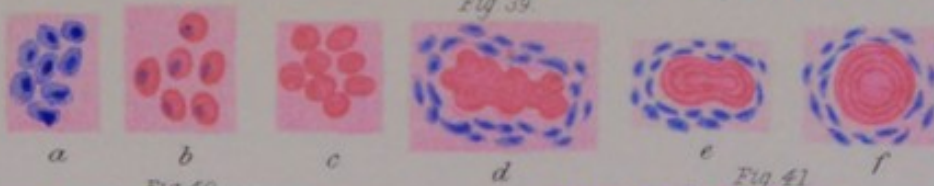


Fig. 39.



a

b

c

d

e

f

Fig. 40.

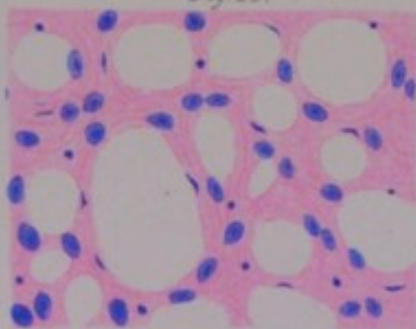
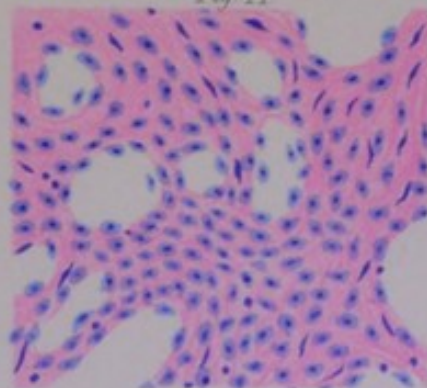


Fig. 41.





and in the upper portion of the sulcus. A, artery. V, vein. The venules are not represented.

PLATE XII.

- Fig. 1. Horizontal view of pia-arachnoid of dog, showing radial arrangement of connective tissue fibres. Platinum preparation. From a photomicrograph; objective, Leitz No. 3; ocular, No. 1.
- Fig. 2. Horizontal view of pia-arachnoid of dog, showing connective tissue fibres and the open character of the feltwork formed by them. Platinum preparation. From a photomicrograph; objective, Zeiss 4 mm.; ocular, Leitz No. 1.

PLATE XIII.

- Fig. 32. Transverse section of normal pia-arachnoid with subjacent brain. Hæmatoxylin and eosin. ($\times 100$.)
- Fig. 33. Transverse section of pia-arachnoid from a case of general paralysis of the insane, showing thickening and cellular infiltration. Hæmatoxylin and eosin. ($\times 100$.)
- Fig. 34. Transverse section of pia-arachnoid from a case of senile insanity, showing a small fibroid area. To the naked eye the area appeared as an opaque spot. Hæmatoxylin. ($\times 100$.)
- Fig. 35. Superficial horizontal section of outer surface of normal pia-arachnoid, showing nuclei of endothelial cells, the plates of some of which can be indistinctly seen. Hæmatoxylin and eosin. ($\times 450$.)
- Fig. 36. Superficial horizontal section of outer surface of pia-arachnoid from a case of senile insanity, showing localised proliferations of endothelial cells, constituting granulations. Hæmatoxylin and eosin. ($\times 100$.)
- Fig. 37. Transverse section of pia-arachnoid from a case of senile insanity, showing the structure of a granulation. It is seen to consist of a localised proliferation of the endothelial cells on the outer surface. Hæmatoxylin and eosin. ($\times 450$.)
- Fig. 38. Superficial horizontal section of outer surface of pia-arachnoid from a case of senile insanity, showing a granulation containing several concentric bodies. Hæmatoxylin and eosin. ($\times 450$.)
- Fig. 39. Semi-diagrammatic representation of the development of concentric bodies from endothelial cells on the surface of the pia-arachnoid.
- Fig. 40. Horizontal section through trabeculæ of normal pia-arachnoid, showing fibrous tissue and nuclei of endothelial cells. Hæmatoxylin and eosin. ($\times 450$.)
- Fig. 41. Horizontal section through trabeculæ of pia-arachnoid from a case of senile insanity, showing proliferation of endothelial cells and increase of fibrous tissue. Hæmatoxylin and eosin. ($\times 450$.)

CHAPTER VII

MORBID CONDITIONS OF THE INTRACRANIAL BLOOD-VESSELS.

(PLATES XIV., XV., XVI., AND XVII.)

MORBID conditions of the intracranial blood-vascular system naturally divide themselves into two classes, one consisting of derangements of the circulation apart from actual structural changes in the vessel-walls, and the other embracing such structural changes and their consequences. The former class will be considered in chapter xi., and, therefore, only the latter is dealt with here.

Of the great importance of these organic vascular changes, not only in mental diseases, but in nervous diseases in general, there can be no question. Nevertheless, as yet, they are far from having been fully worked out, and at the present day, when the whole field of neuro-pathology has but recently been so widely opened up for detailed investigation, owing to the invention of improved means of observation, and to the discovery of new facts which always tend to lead on to others, there is special need of diligent study in this comparatively neglected portion of it.

The morbid conditions of the vessels selected for description in this chapter are those that appear to me to be of chief importance in mental diseases. I make no attempt to give a systematic or exhaustive account of cerebral vascular lesions. To do so is rather the province of the writer upon general neuro-pathology. I doubt, however, if the present state of knowledge upon the subject is sufficiently advanced to justify such a task being undertaken, for a hundred important questions that careful research alone can solve still require answer.

None of the vascular lesions found within the brain in insanity are peculiar to this class of diseases. Nevertheless, certain of them are beyond doubt very commonly developed in the insane to a degree to which they rarely attain in the mentally sound. All mental disturbance is ultimately due to disordered or arrested functional activity of cortical neurons, and therefore any influence that intracranial vascular disease may have in the production of insanity must be exercised through these cell-elements. In many cases of mental disease the vascular lesions are probably of too slight a character to cause any appreciable interference with the nutrition of the nervous structures. In another set of cases, though developed to a degree sufficient to produce such an

interference, they cannot be regarded as a primary cause of the insanity, as there is proof that they arise subsequent to its onset. At the same time, such secondary vascular disease doubtless often plays an important part in the production of the later mental symptoms, and may probably in certain cases have considerable influence in preventing or retarding recovery. Thirdly, there is a class of cases in which we are entitled to regard the disordered or arrested action of certain of the cortical neurons as primarily due to morbid changes in the walls of the cerebral vessels. In this category we must place at least the vascular form of syphilitic insanity, and those cases of paralytic insanity in which there has been rupture, obliteration, or plugging of cerebral vessels. In all cases of senile insanity the vascular lesions must also, though not to the same extent in every instance, be looked upon as a primary cause of the cerebral disorder.

Note on the Normal Structure of the Intracranial Blood-vessels.

In time past the normal histology of the intracranial blood-vessels was the subject of much disputation among the various authorities. To-day, however, the points regarding which there can reasonably be any distinct difference of opinion are few in number and of comparatively trivial moment.

The peculiar vascular arrangements of the dura have already been described (chapter v.). Attention has also been directed to certain special features of the pial vessels (chapter vi.), which, however, require fuller description here.

The small vessels of the pia-arachnoid consist only of arterioles and venules. Notwithstanding the usual statement to the contrary, the membrane is, I maintain, devoid of capillaries. Microscopic examination fails to reveal any vessels that can be rightly regarded as of this nature. All the blood that courses in the pial arterioles has to pass through the nervous substance before being discharged into the pial venules. Regarding the significance of this arrangement, much might be said. For one thing, I think it might be shown that the absence of pial capillaries obviates a serious danger to which the cerebral tissues would otherwise be subjected, namely, that of a progressive short-cutting of their blood-supply.

Most of the small pial arterioles have a single layer of muscular fibres, but in some this middle coat is wanting. Its absence is compensated for by a comparatively thick adventitia (fig. 58). The pial arterioles with a single or double layer of muscular fibres have, as a rule, an extremely delicate adventitial coat, which indeed is often so tenuous as to be recognisable only with difficulty in hæmatoxylin and eosin preparations (figs. 57 and 59). It is, however, never really

absent. Even when its connective tissue fibres cannot be recognised, it is generally represented by an occasional flattened connective tissue corpuscle lying upon the muscular coat. Moreover, it is clearly revealed by the platinum method. Here and there, arachnoid trabeculae are attached to the vessel-walls, and as they pass for some little distance along them render the adventitia locally quite a thick coat (fig. 57). The intima consists of a continuous layer of flattened endothelial cells and of a delicate stratum of fibrous tissue between this and the muscular coat. The pial veins are remarkable for their large calibre, and for the delicacy of their walls, which contain no muscular fibres.

The arterioles of the pia-arachnoid pass into the substance of the brain in a direction vertical to the plane of the surface of the convolutions. At the point at which they leave the membrane their adventitia becomes considerably increased in thickness by connective tissue fibres continuous with those of the pia-arachnoid (fig. 59), and their lumen is generally diminished by about one-third. These intra-cerebral arterioles are referred to as cortical or medullary, according to their distribution. The larger of them have a well-developed muscular coat, usually consisting of a single layer of fibres (fig. 56). Their generally thick external coat contains a lymph-channel, which, according to the evidence of platinum preparations, is formed merely by open spaces between the connective tissue fibrils. This lymphatic channel pervades the whole of the adventitia, and occurs in the walls of the larger intra-cerebral venules as well as in those of the arterioles. The path followed by the lymph is described in chapter xi. Some of the earlier observers described a separate hyaline membrane lying external to the adventitia. I am satisfied that the structure that has been regarded as of this nature is merely the outer denser portion of the adventitia which tends to be specially conspicuous at the branchings of the vessels. Platinum preparations show it to be fibrillar in character, and not homogeneous. The smaller intra-cerebral arterioles are entirely devoid of muscular fibres. They consist only of a prominent adventitial coat, composed of longitudinally arranged connective tissue fibres and connective tissue corpuscles, and of an intima formed by flattened endothelial cells. Both of these coats are continued in the capillaries, which thus differ from those of other organs. Key and Retzius seem to have been the first authorities to direct attention to this special structural feature of the cerebral capillaries. Although their view has been disputed by several other writers, it has been supported by Greenlees (21a), Bevan Lewis (30), Obersteiner (39), Lapinsky (31), and others. Bevan Lewis and Lapinsky have independently pointed out that two varieties of nuclei are to be observed in the walls of these vessels, one oval and the other round, and belonging respectively to the intima and adventitia. The latter observer

has described these nuclei very minutely, pointing out that, among other distinctive features, the round ones project from the capillary wall and stain deeply with carmine, while the elongated ones do not project and stain faintly. Similar distinctive features are often recognisable in preparations by the fresh method of Bevan Lewis (fig. 44).

Complete confirmation of the presence of this special adventitial coat in the cerebral capillaries is furnished by the platinum method (57), which reveals its fibrillar element. Some of the appearances presented by the intra-cerebral arterioles, capillaries and venules in preparations by this method are shown in plate xvii. The blackened fibres vary greatly in thickness. Many of them are of a sufficient size to be distinguishable with the low power of the microscope. Others are so minute as to be recognisable only with very high powers. In the larger arterioles they appear as long strands of smooth contour, straight, wavy, or sharply zig-zagged (fig. 69). For the most part they lie in the long axis of the vessel. Sometimes they wind obliquely round it. They form anastomoses with each other, and also divide into branches. The finer fibrils, composed partly of these branches, often form a sort of reticulum or plexus (fig. 70). On each vessel there are generally from one to three fibres, which are much larger than the others (fig. 69). In the smaller arterioles, and in the capillaries, the fibres are as a rule more delicate than in the larger arterioles, although even in the smallest vessels the occurrence of a thick fibre is common. Sometimes only a single strand can be seen upon a capillary, but it is probable that in such instances the black reaction has been incomplete. In the venules the fibres are in general more delicate than in the arterioles, and anastomose more freely. In the arterioles that possess a middle coat, the connective tissue fibres of the adventitia and those of the intima are seen to be intimately connected with each other, appearing, indeed, almost like a single fibrous tube. Probably the muscular fibres ought therefore to be regarded not as an intervening layer, but merely as embedded in the fibrous tissue wall. Single fibres may very commonly be observed to extend from one arteriole or capillary to another adjacent to it (figs. 72, 73, and 74). These connecting fibres are generally, though not always, comparatively thick. At the point of their attachment they often present a distinct thickening, beyond which the fibre divides into numerous spreading branches (fig. 73). They evidently serve to support the small arterioles and capillaries, and to fix them in position. They occur in large numbers, being indeed almost as numerous as the capillaries. In platinum preparations of the pia-arachnoid all the connective tissue fibres—both of vessels and trabeculae—are blackened in a similar way to those of the intra-cerebral vessels.

These connective tissue fibres are all of a highly elastic character. They do not, however, precisely correspond, either in reaction or in appearance, to ordinary yellow elastic fibres. There are strong reasons for regarding them as a specially modified form of connective tissue fibre, probably occurring only in the vessels of the central nervous system and in the pia-arachnoid.

There is considerable difference of opinion as to the extent to which ordinary yellow elastic fibres are present in the cerebral vessels. In the arterial trunks and larger branches they unquestionably form a prominent internal elastic lamina. But it is generally taught that there is no such elastic lamina in the intra-cerebral and small pial arterioles. Findlay (18) has, however, conclusively demonstrated this layer in the small arterioles of the choroid plexuses, and, although the vessels of these organs may be somewhat exceptional in this respect, the fact renders it at least probable that careful examination by suitable methods would prove that yellow elastic fibres are continued much further into the ramifications of the cerebral arteries than is generally supposed.

In the deeper layers of the cortex the larger arterioles may occasionally be observed to present a curious convoluted or kinked condition, to which little attention seems yet to have been paid, although Batty Tuke (46*a* and 47) described it many years ago. From the manner in which branches are sometimes given off from these kinks, it may be inferred, I think, that they are normal formations, and not the result of post-mortem relaxation of the vessels. They doubtless have some physiological importance, but regarding this matter nothing seems to be known.

The cerebral capillaries are fairly uniform in size. The majority of them have a diameter of about 6μ . In 1891 Kronthal (28) asserted that, with the aid of a method in which the tissues were first macerated in lactic acid and then stained with picrocarmine, he had succeeded in demonstrating the existence of exceedingly fine capillaries in the brain, some of which had a diameter of only 2.5μ . Lapinsky (31) afterwards described capillaries of still smaller size, some being not more than 1.4μ in diameter. Preparations by the platinum method show with perfect clearness that no such minute capillaries exist, and that what these observers have regarded as such, are really the adventitial fibres which connect and support adjacent capillaries.

In the adventitia of the vessels in healthy brains, whether from the human subject or from the lower animals, there may frequently be seen little granules or masses of a homogeneous substance, which may be almost colourless, especially in early life, but are usually of a pale chrome-yellow shade. It occurs in the adventitia of the larger vessels, appearing usually on its outer surface, more rarely within the lymph-

spaces. On the capillaries it occurs almost exclusively at the side of the rounded nuclei. In the perfectly normal state this pigment is present only in very small amount, and on many vessels it cannot be observed. It becomes greatly increased in quantity as a physiological senile change, tending at the same time to assume an orange tint. It is slightly darkened by osmic acid, but is not blackened by it in the same way as fat. It further differs from fat in respect of its affinity for certain stains, and in being insoluble in the usual solvents of this substance, such as xylol. One or two observers, including Batty Tuke (46*a* and 47) and Obersteiner, have recognised the existence of this adventitial pigment, but it has misled a great number of others, who have looked upon it, especially when present in abnormal quantity, either as fat or granular hæmatoidin.

The existence of nerves in the pial arterioles, though for a time denied, has now been fully established, more especially by the observations of Obersteiner (41), Gulland (21), Morison (34), and Huber (23), each of whom used a different method for their demonstration. According to Gulland, the fibres are in the walls of the vessels and have the usual appearance of perivascular nerve-plexuses. Huber states that both medullated and non-medullated nerve-fibres are present. The former accompany the large arteries. The latter occur as rich plexuses in the adventitial and muscular coats. Morison believes that the fibres terminate in the other tissues of the membrane, as well as in its vessels. He also describes the occurrence of small unipolar ganglion cells in the course of the larger fibres.

The question of the extent to which the cerebral vessels anastomose with each other is one that has given rise to some discussion. Heubner (22) has maintained that the communications between the pial arteries are very free, taking place between those of one millimètre in diameter. Duret (53), whose views have the support of Charcot (14*a*), has, on the other hand, asserted that these anastomoses of the pial vessels are unimportant, and that the arteries between which they occur never exceed one-fourth of a millimètre in diameter. In specimens of the pia-arachnoid examined in horizontal view, in which the course of every vessel can be followed, I have observed these arterial anastomoses to occur with considerable frequency. Four or five of them may often be seen in a preparation consisting of about a square half-inch of the membrane. As I have seen them, they always occur between arterioles containing only a single layer of fibres in their muscular coat. It is generally agreed that there are no anastomoses between the intra-cerebral vessels except by capillaries. Charcot (14*a*) has further insisted that even this form of anastomosis does not exist between the central and the cortical arterial systems.

There is one other feature in the arrangement of the cerebral

vessels, which, though it is, I am convinced, of great importance in relation to cerebral pathology, has not, so far as I am aware, been specially drawn attention to by others. It is, that the outermost layer of the cortex is not supplied by lateral branches from the larger cortical arteries, but by a special system of very short vessels. They contain no muscular fibres in their walls, which differ from those of capillaries only in the much greater thickness of their adventitia. They break up into a capillary network in the first layer of the cortex, and partly in the second, and return their blood by way of minute venules, which are indistinguishable from the afferent vessels, except by the fact that they may be seen to discharge into the pial veins. This system of vessels is pre-eminently the seat of an important morbid change that very commonly affects the cerebral vessels.

PIGMENTARY DEPOSITS IN THE VESSEL-WALLS.

The occurrence of yellow pigmentary deposits on the tunica adventitia of the cerebral vessels of persons dying insane, seems to have been first described by Batty Tuke (46*a* and 47) more than twenty-five years ago. He pointed out that two different kinds of pigment are commonly present, one of which is a normal constituent of the vessel-wall, while the other consists of masses of hæmatoidin. He stated that the former becomes darker with age, and that it is not affected by the ordinary tests for fat. To his very full description of these histological features there are to-day practically no new facts of importance to be added.

Pigmentary deposits are most commonly to be observed upon the outer aspect of the adventitia, but they may be in the adventitial lymph-channel, or in the immediately adjacent nervous tissues. They occur most abundantly on the arterioles (figs. 48, 49 and 50), but the walls of the venules and capillaries are also frequently studded with them (fig. 51). As already stated, the normal adventitial pigment becomes much increased in amount as the result of a physiological senile change, but apart from senility it undoubtedly undergoes marked increase in various chronic cerebral diseases. It is seen in greatest abundance in cases of senile insanity. By far the greater proportion of the pigmentary deposits that occur in the walls of the cerebral vessels of the insane, is unquestionably of this non-hæmatogenous nature. That this is so is sufficiently evidenced by the facts that the substance is for the most part of a much paler colour than hæmatoidin, and that in many instances it has a wax-like appearance (fig. 49), which hæmatoidin never assumes. At the same time granular deposits of the latter substance, in or near the walls of the vessels, are undoubtedly common in insanity, and have a much greater

pathological importance, as they are a witness of antecedent hæmorrhage. Unfortunately in many cases it is extremely difficult to distinguish between the two forms, owing to the fact that in pathological conditions the adventitial pigment frequently assumes an orange tint, in consequence of which it very closely resembles granular hæmatoidin. In my experience the chemical tests for the latter substance cannot be applied satisfactorily to microscopic sections. Notwithstanding this difficulty in distinguishing accurately between these two forms of pigment, it may be affirmed that granular hæmatoidin is very commonly present in the adventitial lymph-space, or immediately external to the vessel-wall, in various forms of chronic insanity, but especially in senile insanity and general paralysis.

FATTY DEGENERATION.

Many of the observers who have described the occurrence of fatty changes in the cerebral vessels have evidently included in this category the appearances presented by the paler shades of adventitial pigment. This circumstance probably explains why the cerebral vessels have come to be regarded as specially prone to fatty degeneration. I have examined the cortical vessels in osmic acid preparations from thirty-five cases of insanity, and, apart from softenings, have found true fatty changes only in four, and in no instance were they well marked. I therefore conclude that the vessels of the brain have no special proclivity to fatty degeneration, and that when the condition does occur in them as a general change it is, as in the vessels of other organs, mostly of recent development and of little significance. On the other hand, as a local morbid change, secondary to other pathological conditions, fatty degeneration is common in the vessels of the brain and its membranes, but probably not more so than in those of other organs. Such secondary fatty degeneration tends specially to occur in the thickened intima in endarteritis deformans, and in all the coats of vessels involved in local softenings.

HYALINE DEGENERATION.

In the two immediately preceding chapters, hyaline degeneration has been described as a very common morbid change affecting the endothelial cells (or connective tissue corpuscles) and connective tissue fibres of the membranes of the brain. These two tissue-elements, the latter of which is a product of the former, are the essential components of the pial and intra-cerebral blood-vessels, and in them also are very commonly affected by this special pathological alteration. The essential characters of hyaline degenerative material are a homogeneous, translucent appearance,

more or less strong affinity for eosin, and failure to give the staining reactions of waxy and colloid substance. Occasionally, however, it has a slightly granular appearance, which may be due either to the fact that it is formed of small particles, or that it has undergone secondary changes. In consequence of such secondary changes, it also sometimes becomes modified in its staining reactions, as, for example, in some concentric bodies of the dura mater.

It is convenient to distinguish two forms in which hyaline degeneration may affect the pial and intra-cerebral vessels, namely, an acute and a chronic. The acute form is comparatively rare, and occurs chiefly in and near cerebral tumours. It is characterised by extreme, and generally widespread, homogeneous swelling of the connective tissue fibrils, more especially of the capillaries, which in consequence are often obliterated. The chronic form is one of the most common morbid changes to which the cerebral vessels are subject. It occurs especially in the adventitia in hyaline fibroid degeneration, and in the intima in endarteritis deformans, both of which are described below.

HYALINE FIBROID DEGENERATION.

In the year 1872, Gull and Sutton (20) published their classic paper upon "Arterio-capillary Fibrosis" and its relation to chronic Bright's disease. They described as a general disease of the vascular system, specially liable to occur after the middle period of life, a peculiar "hyaline fibroid" change, affecting the outer coat of the small arteries and the walls of the capillaries. To its occurrence in the kidney they attributed granular contraction of that organ. They found that it could be most conveniently studied in the vessels of the pia mater, and on this account their descriptions of its microscopic characters are chiefly based upon appearances observed in this membrane. The accuracy of their observations, and of the conclusions that they based upon them, has been keenly disputed by numerous authorities in this country.

The only part of the subject that concerns us here is that which regards the implication of the cerebral vessels by the morbid change in question. High authorities have declared their conviction that the morbid appearances described by Gull and Sutton, were entirely due to the effect of the preserving reagents employed, and it would appear that there are still pathologists who maintain this view. On the other hand, investigators equally competent have stated that they are able to confirm the original observations. On the Continent little attention seems to have been paid to Gull and Sutton's work, but under other names morbid changes in the cerebral vessels, identical with the hyaline fibroid degeneration of the English authors, have there also been described.

In 1896 I contended (56) that the description given by Gull and Sutton of hyaline fibroid degeneration of the pial vessels is in every detail, as far as it goes, in accord with morbid changes that actually occur, and that the view that the abnormal appearances in question are produced by the action of certain reagents is wholly untenable. Further observation has only tended to confirm and strengthen these opinions.

Some observers, while acknowledging that there is such a change as hyaline fibroid degeneration, have said that it occurs so commonly in otherwise healthy individuals that it can have no pathological importance. The same argument might with equal force be urged against the importance of atheroma. In their slighter degrees both are exceedingly common, but have little or no effect upon the health of the individual. It is only when the morbid changes are far advanced, or specially active, that grave disturbances are produced by them. From my own observations I am convinced that hyaline fibroid degeneration is one of the most important vascular lesions associated with insanity.

The pathological process at work in the production of this alteration in the adventitia of the pial and intra-cerebral vessels is clearly identical with that which affects the extra-vascular tissues of the pia-arachnoid and dura mater in the same cases. In the membranes it is characterised by proliferation of endothelial cells (or connective tissue corpuscles), formation of new fibrous tissue, and degeneration both of the original and of the new endothelial cells and connective tissue fibres. Exactly the same morbid changes may be observed in the adventitia of the pial and intra-cerebral vessels in this hyaline fibroid disease. The process is essentially a slow sclerosis, accompanied in varying degrees by retrogressive changes, of which hyaline degeneration is the most prominent. It is caused by an abnormal condition of the cerebral lymph, or cerebro-spinal fluid. This fluid bathes the adventitia of the intra-cerebral vessels and the tissues of the pia-arachnoid and dura, and supplies them with the materials they require for their nutrition. When from any cause its composition is altered, it is no longer capable of fulfilling this function in a normal manner. Consequently the tissues undergo morbid changes. These probably take the form of hyperplasia, or degeneration, according as the lymph has irritant properties, or is merely deficient in the necessary nutritive materials. As has already been contended, there are at least two common causes of alteration in the composition of the cerebral lymph. The first is disturbance of the general nutrition, such as occurs, for example, in chronic Bright's disease, and the second abnormal metabolic changes in the nerve-cells, or other tissues of the brain. Probably both of these have considerable importance in the causation of hyaline fibroid degeneration of the cerebral vessels.

Although simple hyaline degeneration of the connective tissue fibres and corpuscles appears most commonly to be the initial alteration, I am now convinced that it is an error to assume that it is invariably so. In some instances a pure hyperplasia of the adventitia may continue for a long time without being interrupted by degenerative changes. There is, however, every reason to believe that the hyaline substance is capable of being gradually removed by leucocytic action or in other ways, and replaced by fibrous tissue.

In the arterioles and venules of the pia-arachnoid, hyaline fibroid degeneration is most easily recognisable when it assumes the form of a hyaline swelling of the adventitia (figs. 61 and 62). The whole of this coat is often converted into a broad homogeneous band of regular outline, which stains more or less deeply with eosin in hæmatoxylin and eosin preparations, and faintly with the aniline dye in those by the fresh method of Bevan Lewis. It must be borne in mind, however, that increase in the number of the cellular elements of the adventitia and fibrous thickening of this coat are also manifestations of the same morbid process. When either the hyaline or the fibroid change is very marked in the arterioles, there is generally some degeneration of the middle coat. The muscular fibres are granular, and many of their nuclei have lost their affinity for hæmatoxylin (figs. 62 and 63). Osmic acid staining proves that some of these granules are of a fatty nature. The majority of them, however, do not give a black reaction. On the other hand they have a strong affinity for eosin.

Precisely the same microscopic characters are presented by hyaline fibroid degeneration in the intra-cerebral vessels. The capillaries, owing to the existence of their special adventitial coat, are liable to be affected as well as the arterioles and venules. The short vessels given off from the pial arterioles for the supply of the first and second layers of the cortex, as well as the corresponding venules, are specially prone to the alteration in a very severe form (figs. 54, 55 and 60). The same remark applies, though to a less extent, to the small vessels sub-jacent to the ependyma of the lateral ventricles.

Hyaline fibroid degeneration may be observed in the cerebral vessels of practically all persons dying after middle life. But apart from chronic alcoholism, senility and various chronic forms of mental disease, it is as a rule slight in degree and probably of little pathological significance. In this form it does not appreciably diminish the lumen of capillaries, although it must cause some slight interference with the flow of lymph in the adventitial lymph-channels of some of the intra-cerebral arterioles and venules. In simple senility and in chronic alcoholism, hyaline fibroid degeneration is always a well developed change, affecting especially the pial arterioles and venules,

and the short vessels of the first and second layers of the cerebral cortex. In various forms of chronic mental disease, but especially in senile insanity, general paralysis and alcoholic insanity, it almost constantly occurs as a very severe and widely distributed lesion. In some cases of senile insanity it is to be observed in its extreme form. In such instances almost every arteriole and venule in the soft membranes presents distinct hyaline or fibroid thickening of the adventitia; practically all the short vessels of the first and second layers of the cortex are also greatly thickened, the lumen of many of them being at the same time obliterated; the other arterioles, capillaries and venules of the brain are likewise affected, but the extreme degrees of alteration generally occur only locally. I have, however, seen one or two cases of undoubted senile insanity in which there was a general capillary thickening exactly resembling that which occurs in advanced general paralysis.

The most serious results of this lesion are probably those produced by the implication of the short vessels of the first and second layers of the cortex. To enable one fully to realise the important extent to which these vessels are affected, it is necessary to examine them in thin surface sections showing the inner aspect of the pia-arachnoid after it has been stripped off from the fresh brain and properly hardened. In the type of case under consideration, preparations of this kind show hundreds of these thickened and obliterated short vessels that have been drawn out from the nervous tissues. It is evident that this local lesion must profoundly affect the functional activity of the nervous tissues of the first layer of the cerebral cortex, and to a certain extent also that of the second layer. Indeed it can be shown that it is always accompanied by degeneration of the nerve-fibres of the first layer, and by distinct overgrowth of its neuroglia.

Another common result of hyaline fibroid degeneration is the development of atrophic areas in various parts of the brain from local obliteration of capillaries. These areas are usually of small size, but occasionally they are extensive. Sometimes they are seen as distinct softenings. But more commonly they appear as patches of sclerosis, that is to say of neuroglia overgrowth. Further, the mere thickening of the walls of the capillaries, apart from actual obliteration, must interfere in an important manner with the exchange of materials between the blood and the lymph, and thereby affect the nutrition of the nervous tissues. Lastly, the changes in the adventitia of the intra-cerebral arterioles and venules must seriously obstruct the passage of the lymph through the adventitial lymph-channels.

In advanced general paralysis there is always well-marked hyaline fibroid degeneration of the vessels of the brain and its soft membranes.

The special feature is the wide distribution and the severity of the change in the small vessels. Over extensive areas of the cortex and white matter, almost every capillary is greatly thickened and unduly cellular. The short vessels of the first layer of the cortex are always severely affected. It will probably be denied by many that the capillary changes in senile insanity and general paralysis are pathologically the same. For my own part, I am now convinced that they differ only in respect of the activity of the morbid process. In general paralysis the lesion develops more rapidly, and generally involves a much larger number of vessels. Proliferation of the connective tissue corpuscles of the capillary adventitia is more marked, and the degenerative changes in the fibres take place more readily. Added to the hyaline appearance there is generally slight granularity. The changes are in many instances accompanied by some migration of leucocytes, and are then virtually of an inflammatory character. But this extreme intensity of the morbid process is exceptional, and otherwise the changes do not differ in any essential feature from those to be observed in cases of senile insanity. Moreover, as I have already mentioned, some cases of the latter disease show a diffuse capillary change in the cortex, corresponding in every particular to that which is so constant in general paralysis. As in senile insanity, the lesion of the capillaries frequently causes their local obliteration, and consequent atrophy of the tissues. Softenings from this cause tend specially to occur in the deeper layers of the cortex. When the capillary changes are very severe the whole cortex is often slightly softened, notwithstanding the neuroglia overgrowth that is generally present.

In alcoholic and other forms of chronic insanity, hyaline fibroid degeneration is, as a rule, much less marked than in senile insanity and general paralysis. In acute forms of insanity occurring in persons under middle age, it is seldom a prominent change. Nevertheless there is generally evidence that the morbid process has set in both in its proliferative and degenerative phases, and often with sufficient intensity to cause serious obstruction to the flow of lymph in the adventitial lymph-channels of the intra-cerebral vessels. This subject of the obstruction of the lymphatic channels is more fully dealt with in chapter xi.

ENDARTERITIS DEFORMANS.

It is well known that the proliferative and degenerative changes in the intima, usually referred to by the term "Endarteritis Deformans" or "Atheroma," very commonly affect the large cerebral arteries in a severe form in persons advanced in years, quite apart from conditions of mental disease. From this fact it has been inferred by some writers

that atheroma of the cerebral vessels has no special importance as a cause of insanity. There are at least two grounds upon which this inference is unwarranted. In the first place, although exact statistics bearing upon the question do not seem to be available, there is now a considerable weight of opinion in support of the view that these high degrees of atheroma of the large cerebral vessels are much more commonly to be observed at post-mortem examinations in asylums than at those performed in general hospitals. In the second place, it is to be pointed out that the extent to which the large cerebral vessels are affected by this morbid change is no certain index of the severity of the lesion in the small pial and intra-cerebral arterioles. Although as a rule the large trunks and their branches are affected in fairly corresponding proportion, not infrequently the former present well-marked changes while the latter show almost none, and *vice versa*. It is therefore clear that we cannot, by reference to the condition of the large vessels alone, judge of the importance of atheroma as a factor in the production of cerebral disease. We must take into account the extent to which the small branches are affected. This can be done only by careful microscopic examination. Some thickening of the intima of the pial and intra-cerebral arterioles is doubtless common in aged persons who have not been the subjects of mental disease; but in a large proportion of cases of senile insanity atheromatous changes in these vessels are so pronounced, and so widely diffused, as to be obviously incompatible with the normal functional activity of the brain. Moreover, in many of these cases there is extensive destruction of the nervous tissues which can be proved to be dependent upon the vascular lesion. It can be shown that miliary aneurisms, the great majority of cerebral hæmorrhages, and a large proportion of atrophic cerebral softenings are essentially results of endarteritis deformans of the small cerebral arterioles. We are, therefore, clearly justified in regarding this form of vascular lesion as one of the most important factors in the production not only of insanity, but also of other diseases of the central nervous system.

The characters of atheroma of the large arteries are described in all text-books of general pathology, and hardly claim special notice here (fig. 68). I shall, therefore, confine myself to a description of the condition as it manifests itself in the small pial and intra-cerebral arterioles. The tissue-changes do not here differ in any essential particular from those in the larger vessels. Nevertheless, they present certain special features that very materially help us to understand the true nature of the pathological process.

The earliest deviations from the normal that can be recognised consist of slight increase in the number of the endothelial cells or connective tissue fibres of the intima, or of hyaline degeneration of

this coat. The new connective tissue fibres are very readily detached from the muscular coat, and may frequently be seen to be partially separated from it in microscopic preparations. It is impossible to be certain how far such separation is artificial. At this stage the muscular coat may be normal, but generally it shows signs of commencing granular degeneration, similar to that which, as already stated, tends to accompany severe degrees of hyaline fibroid change. In the later stages the fibrous thickening of the intima is increased, in extreme instances even to the complete obliteration of the lumen of the vessel. This new tissue may or may not contain numerous endothelial cells. It is exceedingly prone to hyaline and fatty degenerative changes. When the thickening of the intima exceeds the slightest appreciable degree, it is always accompanied by distinct granular degeneration of the muscular coat.

In these small arterioles the intima is generally affected to a like extent over a considerable tract. The localised or unilateral thickening that is the rule in the larger vessels, is rarely to be observed. There is, however, a special tendency to thickening at the point at which the small arterioles are given off from the larger vessels. In the peripheral portion of the new tissue, close to the degenerated muscular coat, there is very commonly a distinct encircling space, which, although probably exaggerated by hardening in bichromate solutions, is certainly not artificial (fig. 66). In the living state it appears to contain clear fluid along with some fatty granules. These are very readily removed by solvents of fat, so that they are not seen in sections that have been passed through clove oil and mounted in benzole balsam. Independently of the occurrence of a space of this kind, fatty matter is very commonly present in the outer layers of a thickened intima. Sometimes the connective tissue is locally replaced by hyaline material, doubtless formed by swelling of its fibres. In association with thickening of the intima and degeneration of the muscular coat, there is very commonly some local dilatation of the vessel. One type of this condition consists of a close succession of very slight, rounded expansions, affecting especially the muscular coat, and giving the vessel a beaded appearance. It has been termed by Löwenfeld (33) the *Rosenkranzform des Muscularisrohres*. The lumen of the vessel does not always follow this local bulging of the muscular coat; on the contrary, it may be uniformly narrowed by the thickening of the intima. In such instances there is a space between the concavity in the muscular coat and the fibres of the intima, similar to that referred to above. Another type of local dilatation is constituted by the miliary aneurism.

Proliferative changes of the same nature as those that affect the intima of the arterioles provided with a muscular coat, can be re-

cognised in the small arterioles devoid of this coat. There are the strongest reasons for believing that they also affect the capillaries and venules, but in these vessels they are difficult to distinguish from hyaline fibroid degeneration. Both conditions tend to produce fibroid thickening, but in the one case it is by proliferation of the endothelium of the intima, in the other by proliferation of the cellular elements of the adventitia.

Complete obliteration of an arteriole, whether in the pia or in the brain, is very commonly followed by the development of new capillaries in its neighbourhood. These new vessels are very prone to rupture.

The question of the essential nature of the pathological process in endarteritis deformans has given rise to the expression of numerous different views. Probably most authorities regard the condition as consisting of a chronic inflammation with secondary degenerative changes. Others maintain that it is primarily a degeneration, and that the new formation of fibrous tissue is merely the result of a reparative action. According to another view it arises secondarily to changes in the *vasa vasorum*. Thoma (49), on the ground of a long series of experimental observations, believes that fibrous thickening of the intima is the result of slowing of the blood-current, owing to disturbances of the circulation in distant districts, especially in the capillaries, and to slight weakness of the vessel-walls, in consequence of which there is impeded that contraction of the muscular coat by which the lumen is adapted to the diminished current. He thinks that in many cases the connective tissue formation serves to adapt the lumen of the vessel to the blood-current.

Against each of these views objections may be urged which, I think, go far to prove that none of them fully account for the changes that occur. In opposition to the inflammatory theory, it may be stated that there is microscopic evidence that the first change may be a hyaline degeneration of the original tissue-elements of the intima. Against the view that the condition is primarily degenerative there is the fact that at what has every appearance of being an initial stage, it may manifest itself as a very active proliferation of the surface endothelium. To those who attach special importance to changes in the *vasa vasorum*, it is to be pointed out that exactly the same morbid alterations affect the intima of small arterioles devoid of nutrient capillaries. Although Thoma's theory has undoubtedly a considerable weight of incontrovertible evidence in support of it, and may be admitted as a correct explanation of some of the phenomena to be observed, I venture to maintain that it does not account for all of them. It seizes upon what is at most only a subsidiary concomitant pathological factor and gives it a primary and exclusive import-

ance. Consequently it is insufficient and misleading. Its conception of endarteritis deformans as an expression of nature's attempt to adapt the lumen of the arteries to a slackened blood-current, is certainly not in accord with the phenomena to be observed in the cerebral arterioles. In these vessels the end towards which the morbid changes are progressing is manifestly not compensation of circulatory disturbances, but obliteration of the lumen.

It seems to me that we have to recognise in endarteritis deformans a morbid process similar to that in hyaline fibroid degeneration. The latter, it has been contended, depends upon an abnormal condition of the cerebral lymph, whereby it is rendered unsuitable for the healthy nutrition of the tissues composing the adventitia. Similarly endarteritis deformans depends upon an abnormal condition of the blood, whereby it is rendered unsuitable for the healthy nutrition of the tissues composing the intima. In both, the immediate result is either new formation of tissue or degeneration, in accordance with the nature of the nutritional abnormality. In the adventitia degenerative changes predominate, in the intima those of a proliferative character. In the latter situation, however, the new tissue is very liable to secondary degenerative changes, especially at the point furthest from the source from which it derives the materials for its nutrition, that is to say, at its outer portion. Granular degeneration of the muscular coat, which constantly follows thickening of the intima, may in part be due to the abnormal condition of the blood, but it seems more probable that it depends chiefly upon the fact that the thickening of the intima has interfered with the free access of its nutritional supplies. The whole pathological process is generally an exceedingly slow one, probably often beginning early in middle life and progressing intermittently. It evidently varies greatly in its intensity at different times, probably even remaining entirely quiescent for considerable periods. Its gravity is not to be measured merely by the amount of the fibrous thickening of the intima. Of much greater moment is the acuteness of the degenerative changes. It is when these progress rapidly that miliary aneurisms specially tend to form, and cerebral hæmorrhage is prone to occur.

Probably the disease may be correctly regarded as a chronic inflammation, for it seems certain that in the development of the new fibrous tissue there is an irritative action going on, as well as a purely reparative one. Little valid objection can therefore be offered to the term "endarteritis deformans." "Arterio-sclerosis" cannot be limited to this pathological change in the intima, because hyaline fibroid degeneration is likewise a sclerotic process.

Regarding the nature and causes of the abnormal conditions of

the blood that give rise to endarteritis deformans, we as yet know very little. The subject is one that presents a highly important field for future investigation, more especially in the department of chemical pathology.

Very similar views regarding the pathology of endarteritis deformans have already been expressed by numerous authorities, among whom there specially require to be mentioned Oettinger (42) and Martinotti (38). The latter has obtained some valuable experimental evidence in support of his conclusions.

Endarteritis deformans of the small arterioles of the pia-arachnoid and brain, occurs as a prominent morbid change in practically all of the senile insane. It is, however, in the more limited class of senile insanity that it may most commonly be observed in its extreme form. In numerous cases of this disease, the majority of these small arterioles are considerably narrowed by it, while many of them are nearly obliterated, and some of them completely so. As the result of such complete obliteration, areas of cerebral atrophy very commonly develop. It is to be remarked here that in a considerable proportion of cases of senile insanity the chief vascular lesion is not atheroma, but hyaline fibroid degeneration.

In my experience endarteritis deformans is not a well marked change in alcoholic insanity, if not associated with senility. Nor have I found it present to any important extent in general paralysis. I have only seen three cases of this disease out of nearly a hundred in which the large cerebral arteries were atheromatous. It is true that slight fibrous and cellular thickening of the intima of the cerebral arteries and their branches is practically constant in this form of insanity, but that it is pathologically identical with endarteritis deformans there is strong reason to doubt. It has recently been contended by Straub (45) that it is not, and my own observations, so far as they go, certainly bear out his opinion.

MILIARY ANEURISMS.

The subject of miliary aneurisms of the cerebral vessels and the morbid process leading to their development, is one of great pathological interest and considerable clinical importance. It has a distinct claim to consideration here on account of its close connection with paralytic and senile insanity.

Miliary aneurisms were first described in the year 1851 by Virchow (51) in the pial arterioles, though they had previously been figured by Cruveilhier in his Atlas as apoplectic foci. They were also described by other observers previous to 1866, but Charcot and Bouchard (12, 13, 14), who began to publish their researches in that

year, were undoubtedly the first to insist on the frequency of their occurrence within the substance of the brain, and to recognise their great importance in relation to cerebral hæmorrhage. A very good description of miliary aneurisms will also be found in a paper published by Byrom Bramwell (10) in 1886.

Though specially associated with advanced age, miliary aneurisms also frequently develop in middle life, and they have been found, though only rarely, in youth. It is known that they are not confined to the brain and its membranes, but may occur in other parts of the body. Within the cranium they may be single, in small numbers, or very numerous. According to Charcot and Bouchard, they are most common in the basal ganglia, next in the pons, then in the grey matter of the convolutions, more rare in other parts of the brain. These authorities state that all miliary aneurisms are visible to the naked eye. While this statement may be true of those occurring in the substance of the brain, it is certainly inaccurate as regards those that affect the pial vessels. Little is said by Charcot and Bouchard about the occurrence of miliary aneurisms in the soft membranes, and they give the impression that it is uncommon. In three cases of senile insanity, however, in which only a small number of miliary aneurisms could be observed in the substance of the brain, I found them in very large numbers in the thickened pia-arachnoid of the convexity of the hemispheres. In the latter situation the great majority of them were too small to be detected with the unaided eye, and it was only on microscopic examination of thin horizontal sections that they were recognised. I am, therefore, inclined to believe that miliary aneurisms are more common in the pia-arachnoid than is generally supposed, and would maintain that they can never be pronounced absent by naked eye examination alone. I have also found isolated aneurisms on microscopic examination of this membrane in several cases in which they could not be observed at the post-mortem.

The small arterioles that have only a single layer of muscular fibres in their walls are the vessels that most commonly dilate. According to some writers, aneurisms may also develop on the capillaries, but if they do, it is certainly only very rarely. The larger miliary aneurisms, which are easily recognised in the fresh state with the unaided eye, appear usually as highly characteristic, dark red bodies of about the size of the head of a common pin. They are generally rounded in form, but may be more or less elongated.

Charcot and Bouchard have asserted that the rupture of these aneurisms is the immediate cause of the extravasation of blood in the very great majority of cases of hæmorrhage within the brain, and this dictum is now pretty generally accepted. It is not so, however,

in the case of their theory as to the morbid process leading to the development of miliary aneurisms. This theory, though it has received the support of many high authorities, has been disputed by other equally competent observers. Charcot and Bouchard stated that their observations led them to believe that miliary aneurisms were the result of a diffuse periarteritis, the first stage of which was characterised by a multiplication of nuclei in the outer coat of the vessel. This inflammatory condition, they said, caused atrophy of the muscular coat, and so rendered the vessel-wall liable to yield to the blood-pressure. In the later stages the excess of nuclei disappeared, and the vessel became thickened and fibrous. It was in the early stage alone that it tended to dilate. This morbid process, they maintained, though it frequently spread to the middle and internal coats, was sharply distinguished from that which led to atheromatous degeneration of the arteries, and which was rightly called endarteritis. This view of the etiology of miliary aneurisms has been opposed by, among others, Zenker (52), Eichler (17), and J. J. Brown (7), who attribute them to atheroma; by Roth (43), who holds that they are the result of amyloid degeneration; by Kromayer (27), who assigns them to colloid degeneration of the media. Eppinger (16) opposes Charcot and Bouchard's teaching on different grounds, contending that "miliary aneurisms" are not true aneurisms at all, but merely examples of ectasis or dilatation, in which all the coats of the vessel are present. He further denies that such conditions have anything to do with cerebral hæmorrhage.

I have studied the miliary aneurisms and associated vascular changes in the pia-arachnoid in the three cases of senile insanity above referred to, using thin horizontal sections of the bichromate hardened membrane. In these preparations practically every vessel was more or less affected by morbid change, and more than a dozen aneurisms, or nodular swellings of the kind described below, were to be observed in many of them. I have also examined several other cases in which a few miliary aneurisms were found either in the membranes or in the brain substance. The conclusion regarding the nature of the process concerned in the development of this vascular lesion which the morbid appearances observed in these cases have led me to adopt, is one entirely opposed to the most commonly accepted theory of Charcot and Bouchard, and essentially in agreement with that of Zenker, Eichler, and J. J. Brown. I think, however, that it is not in the chronic fibroid phases of endarteritis deformans that the explanation of the development of miliary aneurisms is to be found, but in the more acute hyaline degenerative change, which, as has already been contended, may constitute part of the morbid process. This hyaline change, which affects all the tissue-elements composing

the intima of the small arterioles, occurs only locally. It results in the interposition, between the blood-stream and the media, of a layer of comparatively impervious substance, and consequently in the impairment of the nutrition of the muscular fibres, which derive their nourishment from the blood circulating within the vessel. The alteration in the muscular fibres takes the form of granular degeneration. These changes weaken the vessel walls and render them liable to yield before the blood-pressure. This, I maintain, is the typical process of the development of miliary aneurisms. The more complete the degeneration of the muscular coat, the more prone are the vessels to dilate. The state of the arterial pressure must also naturally have an important influence in determining whether dilatation will occur or not. The development of these aneurisms is probably always gradual, giving sufficient time for some reparative tissue-changes to take place in their walls, which, when the aneurisms are fully formed, consist of white fibrous tissue continuous with the adventitia, and often also with a fibrously thickened intima. The muscular coat is always absent (fig. 66).

I have been unable to find any microscopic evidence tending to support the theory of Charcot and Bouchard. Aggregation of leucocytes is no doubt common around miliary aneurisms, but, even if it is inflammatory in character, it is probably a secondary phenomenon indicating nothing as to the essential nature of the morbid process. The very pronounced acute nodular periarteritis which occurs almost constantly in the brain in advanced general paralysis, is not associated in any special way with dilatation of the vessel-lumen, as ought to be the case if Charcot and Bouchard's views were correct. It is true that isolated miliary aneurisms are somewhat common in this form of insanity, but so also are hyaline changes in the intima.

The contention of Eppinger that miliary aneurisms are merely dilatations of the vessels in which all the coats are retained, has not been borne out by the cases that I have examined. In thin sections it could be seen that the muscular coat was always absent.

In association with miliary aneurisms there are generally some local deposits of opaque and deeply-staining hyaline substance in the inner portion of the wall of the small arterioles. They probably result from degeneration of an intima which has been thickened by new fibrous tissue. They form nodular swellings which are apt to be mistaken for aneurisms. The lumen of the vessel is rarely much increased. On the other hand it is frequently completely obliterated. The name "pseudo-aneurism" has been applied to these formations by Kromayer (27), and seems a suitable one, although I am well aware that it has given rise to considerable confusion, owing to the different use of the term "false aneurism" in surgery. The same morbid condition was

previously described and figured by Eichler as a form of aneurism, though he recognised that the swelling might be due solely to thickening of the vessel-wall. The walls of pseudo-aneurisms may in time become entirely replaced by fibrous tissue, in the centre of which a small blood-channel not infrequently remains. Many of the supposed obliterated aneurisms are really these fibroid pseudo-aneurisms. At the same time there is no reason to doubt that clotting of blood occasionally occurs within true miliary aneurisms, leading to their obliteration. Pseudo-aneurisms are exceedingly common in association with multiple miliary aneurisms, often indeed considerably outnumbering them. With the unaided eye, the two conditions are indistinguishable.

When one considers the very large number of miliary aneurisms that often exist in a single case, and the frequency with which they may be found in cases in which there has been no apoplexy, it is evident that their rupture is a comparatively rare occurrence. It probably depends more upon conditions of blood-pressure than upon any independent process of weakening of their walls. This seems to account, as has been contended by Mendel (35), for the frequency with which these aneurisms rupture in the basal ganglia, the arterial pressure being there much greater than in the cortical system of vessels.

The importance of the relation of miliary aneurisms to paralytic insanity, a large proportion of the cases of which are dependent upon an old cerebral hæmorrhage, is obvious, but something further requires to be said about their rôle in senile insanity. In the series of cases of mental disease in which I have made a special study of the condition of the cerebral vessels, there were twenty-five of this form. I found miliary aneurisms in five of these cases, in three of which, as already stated, they were multiple. These figures, though not warranting any important generalisation, at least serve to give some idea of the frequency with which miliary aneurisms occur in this form of insanity. To the rupture of such aneurisms we are bound to attribute most of the old or recent apoplexies, usually small in size, which are so commonly found in the brain in cases of senile insanity after death. Further, the transient attacks of localised paresis from which some of these patients are observed to suffer have been attributed by Clouston (15) and J. J. Brown (7) to the rupture of one of these aneurisms in the motor areas, with the effusion of only a small quantity of blood, which is soon absorbed. Ample confirmation of the accuracy of this view has been furnished by post-mortem examinations on such cases. I think it is probable, however, that some of the hæmorrhages in these cases take place, not from the aneurisms, but from the new capillaries which commonly form around vessels that have been obliterated by the morbid changes in the intima, associated with the development of mili-

ary aneurisms. Another way in which these bodies may probably produce a certain amount of cerebral disturbance, is by pressure upon the surrounding nervous tissues.

CEREBRAL HÆMORRHAGE.

Ordinary cerebral hæmorrhage, or "true sanguineous apoplexy," constitutes the gross lesion in the majority of cases of paralytic insanity. It is also very common in senile insanity, which is so closely allied, both clinically and pathologically, to the former class of mental disease. In the latter, the blood-effusion, at least when of old standing, has not implicated the motor areas to any extent. I have found such hæmorrhages in 11 cases of senile insanity out of 47. In several of these they were multiple. Apart from cases of typical senile insanity, however, the aged insane are certainly very prone to cerebral hæmorrhage. I have had 7 such cases out of 190 post-mortems. In that number of autopsies there were altogether 20 cases in which there was evidence of old or recent cerebral hæmorrhage of the kind under consideration. It would be of much interest to know precisely how these figures compare with statistics of cerebral hæmorrhage in the mentally sound. It is exceedingly difficult, however, to obtain statistics that will bear comparison, owing chiefly to the fact that the mean age of inmates of asylums is much greater than that of general hospital patients. Certainly a far larger number of such cases are met with in the post-mortem rooms of asylums than in those of general hospitals. For example, working in the latter, Bramwell (10) observed 14 cases in 866 examinations. But the mean age of his cases was only 50, while that of mine was 66. The most common cause of hæmorrhage in these cases is, there can be little doubt, rupture of miliary aneurisms of the intra-cerebral arterioles. It is certain, however, that a fairly large proportion of cases have a different origin. This has been especially insisted upon by Löwenfeld (33) in his important work upon spontaneous brain-hæmorrhage. He maintains that the extravasation is very commonly associated with other forms of vascular disease, and attaches also special importance to conditions causing increase of blood-pressure, in determining rupture. Cerebral hæmorrhage, it is known, occasionally follows embolism. Obersteiner (40) states that atheromatous patches in the cerebral arteries may become detached and block vessels further on, and that, as the result of this embolism, their wall ruptures. The well-recognised proclivity to cerebral hæmorrhage in general paralysis has been attributed by Bevan Lewis (30) to weakening of the vessel walls by inflammatory change. Others ascribe it to the presence of miliary aneurisms.

Multiple minute recent blood-extravasations are to be observed

with considerable frequency in microscopic sections of the brain from the insane. Most of such hæmorrhages are capillary ruptures of very small size. When they take place from larger vessels, the blood is often merely poured into the adventitial lymph-space. To this condition the name "dissecting aneurism" has been applied by some authors. The importance of these recent extravasations must, I think, be regarded as very small indeed. They seem to be due largely, as is stated by Gowers (19), to "extreme mechanical congestion such as attends all asphyxial modes of death." It is easy to understand that vessels weakened by disease of any kind, and especially by the molecular changes that tend to occur in the moribund state, must be very prone to rupture under such conditions. Some writers refer to these small hæmorrhages as if they commonly took place from time to time throughout the course of the patient's illness, in certain forms of insanity. The chief evidence that they allege in support of this view is the presence of large quantities of hæmatoidin on the walls of the vessels. But, as has already been maintained, the yellow granules that have been looked upon by many observers as composed of this substance, are for the most part not of this nature at all, but a morbid accumulation of a normal tissue-pigment. They are, therefore, not necessarily evidence of previous hæmorrhage. I think that there can be little doubt that the frequency and importance of capillary hæmorrhages in the brain have been greatly overestimated. At the same time there is satisfactory evidence that such extravasations do occur in some cases. They take place especially from the new capillaries that tend to develop subsequently to the complete or partial obliteration of arterioles by atheromatous changes, but also from original capillaries affected by hyaline or other forms of degenerative change.

EMBOLISM AND THROMBOSIS.

There is probably little of a special character in the relation of these to mental diseases. A certain number of cases of paralytic insanity follow cerebral embolism. Obersteiner and Löwenfeld both draw special attention to embolic plugging of the small cerebral vessels by atheromatous material torn from the intima of the larger arteries. The former believes that it may lead rapidly to rupture of the affected vessels behind the obstruction. The latter states that it results in a local increase of blood-pressure, and a tendency to the formation of miliary aneurisms. Thrombosis is specially liable to occur in arteries affected by severe endarteritis obliterans, but is probably also common in the later stages of other morbid conditions causing narrowing of the lumen of the small cerebral vessels.

ENDARTERITIS OBLITERANS.

This condition, which is described in the text-books of general pathology, is of interest in relation to mental diseases owing to the fact that it is the chief lesion found in the brain in what is known as the vascular form of syphilitic insanity. Cases of this form of mental disease are not very common, and consequently a number of them have formed the subject of papers in the medical journals. The larger vessels supplying the cerebrum, and their branches, are those typically affected. The disease is generally extensive, and developed to a severe degree, so that large tracts of the hemispheres have their blood supply partially or completely cut off. Extensive softenings are thus frequently produced. Some remarkable cases are mentioned by Clouston (15), in which the white matter of the hemispheres had almost exclusively suffered in this way, leaving the grey matter intact. The fatal result in this disease seems frequently to be determined by thrombosis of the affected vessels. This evidently in part accounts for the very extensive character of the softenings often found on post-mortem examinations. I have met with only two typical cases of this form of insanity, in the course of over 300 examinations. In the first, both middle cerebral arteries and many of their branches were greatly thickened, their diminished lumen in some instances containing recent, pale, firm clots. The greater part of the left hemisphere was reduced to a pulpy consistence. Microscopic examination showed typical endarteritis obliterans (fig. 67). The branches of the middle cerebrals throughout the Sylvian fissures were glued together by tissue which had the characters of a caseating gumma. In the second case the arterial disease chiefly affected a large branch of the left middle cerebral artery. This branch was completely occluded, and there was extensive softening, evidently of somewhat old standing, involving the area to which it was distributed. Two small softenings of a similar character were present in the opposite hemisphere. Most of the larger arteries showed nodular thickenings. Microscopic examination revealed in some a typical endarteritis obliterans, in others a dense infiltration of the adventitia with round cells, with or without thickening of the intima. (See references 8, 22, 37, 44 and 46.)

PERIARTERITIS.

In most cases of advanced general paralysis many of the small pial and intra-cerebral arterioles show a localised dense infiltration of their adventitia with leucocytes, which in some instances also extends into the immediately adjoining nervous tissues (fig. 45). Most authorities, including Bevan Lewis and Obersteiner, are agreed

in regarding this condition as inflammatory in character. This view, however, is not adopted by all authorities. For example, Binswanger (54) is of opinion that "these leucocytal crowds are only to be taken as results of long-standing and oft-repeated venous stasis." But so far as is at present known, there is no pathological process excepting inflammation that is attended with so copious a migration of leucocytes from the vessels. It must therefore, I think, be accepted that the condition is a true periarteritis.

This acute periarteritis of general paralysis appears to be pathologically quite distinct from *periarteritis nodosa*, a disease which was first described in 1866 by Kussmaul and Mayer (26), and which is probably of very rare occurrence. In the latter the small arteries of every part of the body are affected, not specially those of the brain.

Apart from cases of advanced general paralysis and syphilitic insanity (fig. 46), distinct leucocyte infiltration of the adventitia of the cerebral arterioles is by no means common. Many of the observers who have expressed an opposite opinion have evidently included appearances that are due merely to proliferation of the connective tissue corpuscles.

GRANULAR DEGENERATION OF THE MUSCULAR COAT.

This morbid change, to which reference has already more than once been made, is exceedingly common in association with atheroma of the small cerebral arterioles. In its earliest stages it is characterised by an opaque, granular and slightly swollen appearance of the muscular fibres, deep staining of them with eosin, and loss of affinity for hæmatoxylin on the part of their nuclei. Some of the granules give a fatty reaction with osmic acid. In the later stages the whole muscular coat is reduced to a more or less continuous, usually shrunken layer of a slightly granular, opaque substance, of a dark red colour in hæmatoxylin and eosin preparations. It may remain in this condition for an indefinite time, or it may entirely disappear. Occasionally it assumes a hyaline aspect.

According to Löwenfeld (33) granular degeneration is a primary morbid change. My own observations oblige me to dissent from this view. It is quite possible that the alteration may be of a primary nature in some instances, but I have never seen it except in conjunction with distinct thickening of the intima. Moreover, when thickening of the intima takes the form of a hyaline layer, the muscular coat constantly shows granular changes. Lastly, a considerable degree of hyaline degeneration of the adventitia may occur without evident interference with the integrity of the muscular fibres. These facts seem to me clearly to point to the conclusion that granular de-

generation of the middle coat is usually secondary to changes in the intima, more especially those of a hyaline nature, which cause interference with the nutrition of the muscular fibres. Its consequences have already been considered in connection with the subject of miliary aneurisms.

COLLOID DEGENERATION.

The somewhat rare condition termed "colloid degeneration of the brain," which specially, though not exclusively, implicates the vessels, has recently been very fully described by Alzheimer (2). It differs from hyaline degeneration both as regards the reaction and origin of the degenerative material. The colloid substance is apparently formed not by degeneration of the tissue-elements, but from precipitation in and around them. It appears as droplets, or as a confluent mass, in and around the walls of arterioles, capillaries and venules, often forming quite a thick sheath. Some of its more important distinctive reactions are as follows. It swells up in weak caustic potash solution and in acids, stains deeply with carmine and with the aniline dye in Weigert's method for fibrin. Hyaline degenerative material, on the other hand, is not readily altered by the action of alkalis or acids, and is stained only faintly by carmine, and not at all by Weigert's method for fibrin. Neither give a waxy reaction.

Alzheimer describes two cases—one of general paralysis and the other of epilepsy—in which this degenerative change extensively affected the vessels of the cerebral cortex. Clouston (15) describes and figures in his text-book a lesion observed in the brain of a case of acute mania by J. J. Brown in 1877, which was without doubt an example of the same form of vascular disease.

CALCIFICATION.

The intra-cerebral vessels appear to be specially prone to a form of calcification that occurs quite independently of atheroma. According to Obersteiner (39 and 40) the change is a very common one. He states that he has frequently found it in the muscular coat even in healthy subjects. When it occurs in the adventitia he thinks it has a more important pathological significance. Most other authorities look upon it as a somewhat rare disease. Very interesting cases have been described by Bramwell (9), Mallory (36) and Hochhaus (24). I have met with two cases in the course of over 300 post-mortems upon asylum patients. It is not certain that this form of arterial disease is more common in the insane than in other persons. Although occurring generally at an advanced age, it is by no means confined to this period of life. In both of my cases the change was limited to the

cerebellum. This appears to be the portion of the encephalon most commonly affected, but the change has also been found to involve extensive areas of the cerebrum. The affected vessels generally project like bristles from the cut surface of the fresh tissue. According to Mallory the infiltration with lime salts is preceded by colloid or hyaline degeneration. The degenerative material forms a basis for the deposit. He states that in the arteries the middle coat is first affected, afterwards the adventitia. The walls of the capillaries and veins are at the same time generally affected. Extensive involvement of the capillaries leads to the formation of "small sand-like deposits and calcareous concretions." Under the microscope the affected vessels appear thickly studded with highly refractile colourless spherules. When they are treated with dilute nitric acid the colloid substance is brought into view. The change, when advanced, leads to extensive occlusion of the affected vessels, and consequent atrophy of the surrounding tissues.

DIFFUSE DILATATION OR ECTASIS.

A condition of slight, diffuse, often irregular dilatation is very common in the cerebral arterioles. It differs essentially from aneurismal dilatation in that all the coats of the vessel remain, though they may show morbid changes. It is sometimes accompanied by tortuosity. It is common in many forms of nervous disease, but most so in general paralysis. Bevan Lewis (30) attributes its occurrence in this disease to weakening of the arterial walls by inflammatory changes. Obersteiner (40) thinks that it is due to a vasomotor paresis affecting individual groups of muscle fibres. Irregular dilatation of the venules and capillaries is also very common in general paralysis, as well as in some other forms of insanity.

ÉTAT CRIBLÉ.

In the normal brain there is no special lymph-space between the walls of the vessels and the nervous tissues (see chapter xi). In certain morbid conditions, however, distinct spaces may be very commonly observed around the larger intra-cerebral vessels. They are often easily recognised with the naked eye, giving rise, when numerous, to a cribriform appearance of the brain-substance on section. The name *état criblé* was applied to this condition by Durand-Fardel (55), who first described it. It affects chiefly the white matter of the cerebrum and the basal ganglia. In the latter situation, however, there are large lymph-spaces in relation to the vessels which produce to a slight degree a very similar appearance in normal conditions. These wide perivascular canals are common in all atrophied brains, and

especially in those of the senile insane. When examined in fresh microscopic sections they show at one side a vessel, the adventitial sheath of which sometimes appears stretched, so as to form an abnormally large adventitial channel. Between this sheath and the brain-tissue there is a much wider space, which often contains a considerable number of yellow pigment granules. These are for the most part adventitial pigment. Less commonly they consist of granular hæmatoidin. Most authorities are agreed in attributing the formation of these perivascular spaces mainly to general atrophic shrinking of the brain-substance.

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DESCRIPTION OF PLATES XIV., XV., XVI. AND XVII.

PLATE XIV.

- Fig. 42. Horizontal view of normal arteriole of human cerebral cortex. Fresh method. ($\times 500$.)
- Fig. 43. Normal minute arteriole of cerebral cortex, devoid of muscular coat. Fresh method. ($\times 500$.)
- Fig. 44. Normal capillaries of human cerebral cortex, showing elongated and rounded nuclei. Fresh method. ($\times 500$.)
- Fig. 45. Horizontal view of cortical arteriole, showing acute periarteritis and increase of adventitial pigment. From a case of general paralysis. Fresh method. ($\times 400$.)
- Fig. 46. Cortical arteriole showing acute periarteritis. From a case of syphilitic insanity. Fresh method. ($\times 400$.)
- Fig. 47. Cortical arteriole showing hyaline fibroid degeneration. From a case of general paralysis. Fresh method. ($\times 500$.)
- Fig. 48. Cortical arteriole showing dark yellow pigmentary deposit and some leucocyte infiltration of its wall. From a case of early general paralysis. Fresh method. ($\times 400$.)
- Fig. 49. Cortical arteriole showing hyaline fibroid degeneration and great increase of adventitial pigment. From a case of acute melancholia. Fresh method ($\times 500$.)
- Fig. 50. Small cortical arteriole showing great increase of adventitial pigment. From a case of epileptic insanity. Fresh method. ($\times 500$.)
- Fig. 51. Cortical capillary, showing small collections of pale yellow pigment at the sides of the rounded or adventitial nuclei. From a case of senile insanity. Fresh method. ($\times 500$.)
- Fig. 52. Horizontal section of small cortical vessel showing leucocytes and yellow pigment granules in adventitial lymph-space. From a case of general paralysis. Bichromate hardening. Section stained with aniline black. ($\times 500$.)
- Fig. 53. Capillary of cerebral cortex showing general thickening, granularity and increase in number of nuclei. From a case of general paralysis. Fresh method. ($\times 500$.)
- Fig. 54. Venule of first layer of cortex showing great thickening from hyaline fibroid degeneration and hypertrophied neuroglia cells in its vicinity. From a case of general paralysis. Fresh method. ($\times 500$.)
- Fig. 55. Small arteriole of first layer of cortex showing two of its capillary branches greatly thickened by hyaline fibroid degeneration. From a case of general paralysis. Fresh method. ($\times 500$.)

PLATE XV.

- Fig. 56. Horizontal view (optical section) of normal arteriole of human cerebral cortex. Hæmatoxylin and eosin. ($\times 400$.)
- Fig. 57. Horizontal section of normal pial arteriole of ox. Hæmatoxylin and eosin. ($\times 400$.)
- Fig. 58. Horizontal view of normal small arteriole (or venule?) of pia-arachnoid and capillaries of first layer of cortex (sheep). Hæmatoxylin and eosin. ($\times 500$.)
- Fig. 59. Horizontal view (optical section) of pial arteriole passing into cerebral cortex (child). Note that the connective tissue fibres of the pia-arachnoid are continuous with those of the adventitia of the cortical vessel, and that the lumen becomes narrowed slightly as the vessel passes into the cortex. Hæmatoxylin and eosin. ($\times 400$.)

PLATE XIV.

Fig 42



Fig 43



Fig 44



Fig 45



Fig 46



Fig 47



Fig 48



Fig 49



Fig 50



Fig 51



Fig 52

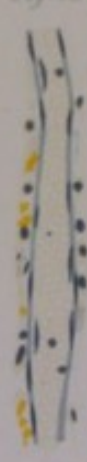


Fig 53



Fig 54

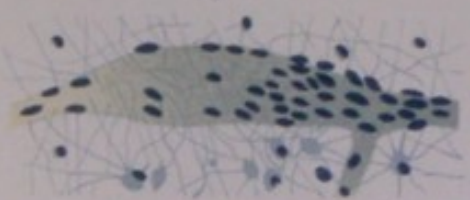


Fig 55

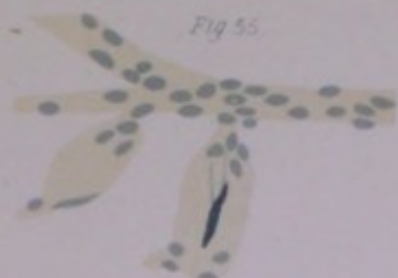




Fig 56



Fig 57



Fig 58



Fig 59

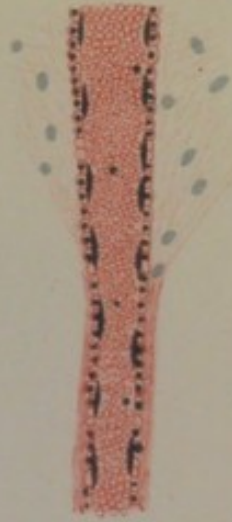


Fig 60



Fig 61



Fig 62



Fig 63



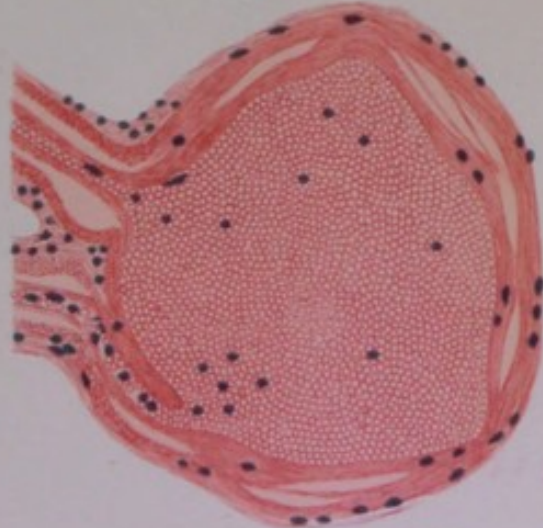
Fig 64



Fig 65



Fig 66



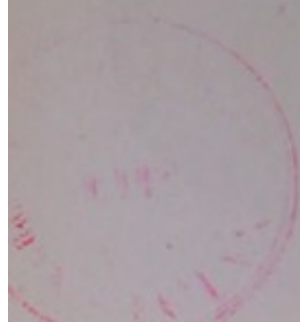


PLATE XVI.

Fig. 57.



Fig. 68

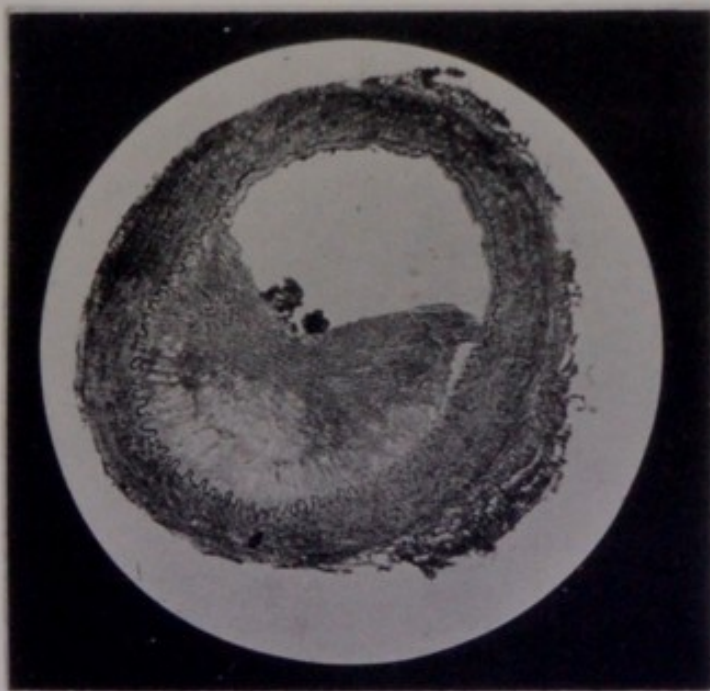




PLATE XVII.

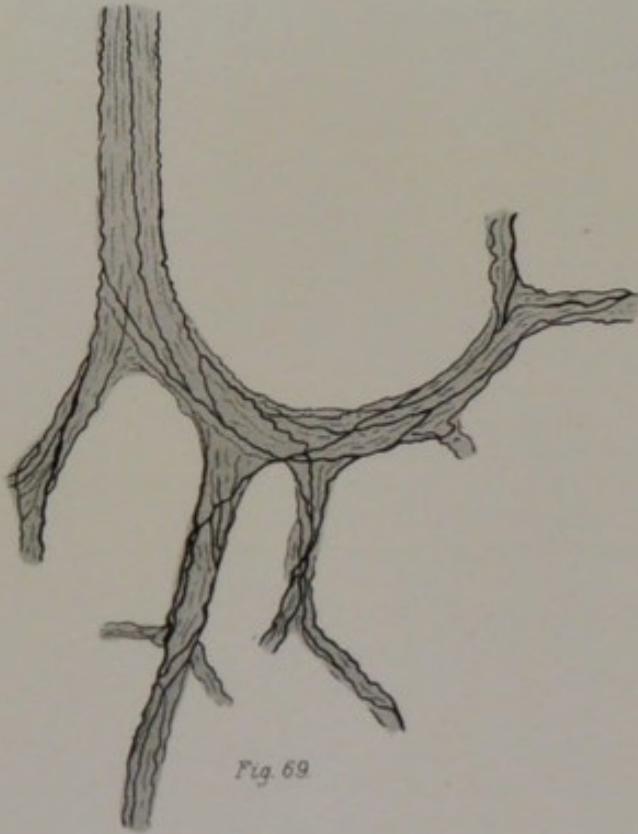


Fig. 69



Fig. 70

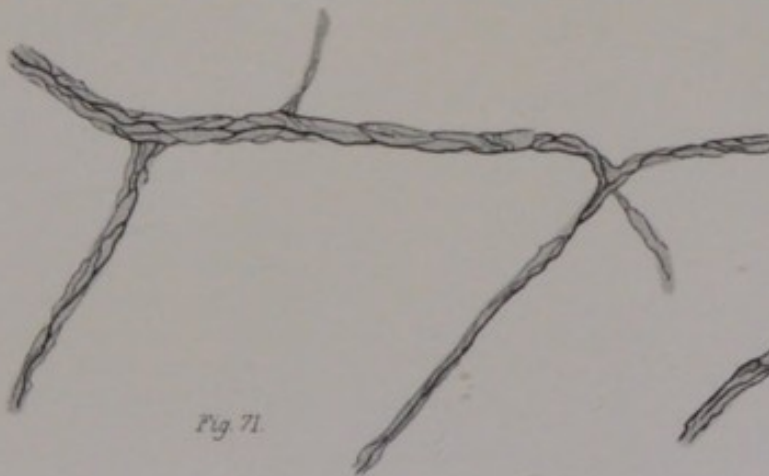


Fig. 71



Fig. 72



Fig. 73



Fig. 74



- Fig. 60. Capillaries of first layer of cortex showing hyaline fibroid thickening. From a case of senile insanity. Hæmatoxylin and eosin. ($\times 500$.)
- Fig. 61. Horizontal section of small venule of pia-arachnoid showing hyaline degeneration. From a case of senile insanity. Hæmatoxylin and eosin. ($\times 500$.)
- Fig. 62. Horizontal section of arteriole of pia-arachnoid showing hyaline change in adventitia, and granular degeneration of the middle coat. From a case of senile insanity. Hæmatoxylin and eosin. ($\times 500$.)
- Fig. 63. Horizontal section of arteriole of pia-arachnoid showing hyaline change affecting both intima and adventitia, and advanced granular degeneration of the middle coat. From a case of senile insanity. Hæmatoxylin and eosin. ($\times 500$.)
- Fig. 64. Horizontal section of arteriole of pia-arachnoid showing great local hyaline thickening of adventitia, granular degeneration and partial disappearance of muscular coat, and separation of endothelium of intima from hyaline material. Such nodular swellings on the arterioles without dilatation of the lumen constitute "pseudo-aneurisms." From a case of senile insanity. Hæmatoxylin and eosin. ($\times 400$.)
- Fig. 65. Horizontal section of arteriole of pia-arachnoid showing degenerative changes similar to those seen in preceding figure, and slight aneurismal dilatation. From a case of senile insanity. Hæmatoxylin and eosin. ($\times 400$.)
- Fig. 66. Section of miliary aneurism of an arteriole of pia-arachnoid showing vessels passing into and out of its cavity. These vessels present fibrous thickening of intima, granular degeneration of muscular coat and a space separating these two layers. Note that the muscular coat is not continued into the wall of the aneurism. From a case of senile insanity. ($\times 400$.)

PLATE XVI.

- Fig. 67. Transverse section of branch of middle cerebral artery from a case of syphilitic insanity, showing endarteritis obliterans. Note the uniform thickening of the intima, and the absence of retrograde changes in the new tissue. From a photograph by W. Forgan. (\times about 50.)
- Fig. 68. Transverse section of branch of middle cerebral artery from a case of senile insanity, showing endarteritis deformans or atheroma. Note the localised thickening of the intima, and the pale area in its outer portion, due to fatty degeneration and calcareous infiltration of the new tissue. From a photograph by W. Forgan. (\times about 50.)

PLATE XVII.

All the drawings were made from platinum preparations. Microscope, Leitz, $\frac{1}{2}$ oil immersion, Ocular No. 3.

- Fig. 69. Arterioles of cerebral cortex of sheep, showing fibres in their walls.
- Fig. 70. Arteriole (or venule?) of white substance of human brain, showing plexus of fine fibres.
- Fig. 71. Capillaries of cerebral cortex of dog, showing fibres in their walls.
- Fig. 72. Two capillaries of human cerebral cortex, showing a fibre passing from one to the other.
- Fig. 73. Two vessels in human cerebral cortex connected by a fibre.
- Fig. 74. Two capillaries of cortex of dog, with very delicate fibre extending from one to the other.

CHAPTER VIII

MORBID CONDITIONS OF THE NEUROGLIA.

(PLATES XVIII., XIX. AND XX.)

THE neuroglia has long been one of the most keenly controversial subjects in the whole field of neuro-histology. There are still the widest differences of opinion among the recognised authorities as to its development, normal structure, functions and behaviour in pathological conditions. Several reasons might be given in explanation of this state of matters, but the chief is unquestionably the great difficulty that has been experienced in devising staining methods capable of revealing its structural features with satisfactory clearness. So great, indeed, has this difficulty been, that a fact of primary importance in regard to the subject has, until quite recently, eluded discovery. This fact, which is brought out by the platinum method, is that the structures hitherto described as the neuroglia, do not consist of one tissue, as has been generally believed, but are composed of at least two kinds of cell-elements, of which the origin, morphology, functions and behaviour in morbid conditions are entirely distinct. Through the whole previous literature of the subject, in which I include three papers of my own (50, 51, and 52), there runs this radical error of recognising only one tissue where there are at least two. Those who have maintained that the neuroglia is developed from the mesoblast as well as from the epiblast have only to a slight extent avoided this error, for their contention has been that the elements derived from these two layers of the blastoderm combine to form one tissue, and not that they preserve an entirely independent existence throughout life, although it is possible that some of the authors referred to may have meant themselves to be understood in the latter sense. Andriezen (2) has, indeed, described separate epiblastic and mesoblastic cell-elements in the adult, to both of which he applies the term "neuroglia," but the distinction he makes is quite a different one from that to be observed in platinum preparations, and can, I think, be shown to be erroneous.

It has been clearly demonstrated by numerous observers that the neuroglia contains elements that are of epiblastic origin. There is evidence so strong as to amount practically to proof that the special

elements differentiated by the platinum method are, on the other hand, of mesoblastic origin. Now if these two tissues are really so essentially different in nature, it is evident that they ought not to be called by the same name, and that in any systematic account of them they should be considered separately. For my own part, I am satisfied that the distinction I have drawn is an accurate one, and I have therefore suggested that the mesoblastic elements should be termed "mesoglia cells," and the term "neuroglia" restricted to the epiblastic elements (54). I have, however, thought it best to consider the two forms together, instead of in separate chapters, preferring to wait until my own studies of the mesoglia cells are more complete before making so wide a departure from the long-established mode of description.

I shall take up *seriatim* the development of these two tissues, their normal histology, functions, reaction to irritants, their rôle in processes of repair, and, lastly, the pathological changes to which they are subject, more especially in insanity.

DEVELOPMENT.

Two different theories are at present held regarding the origin of the neuroglia. According to the one, which has the support of the large majority of authorities on the subject, it is entirely epiblastic; according to the other it is both epiblastic and mesoblastic.

In 1885, Golgi (22) pointed out that at an early stage of development the supporting tissue of the central nervous system, as observed especially in the spinal cord of the chick, consists solely of the epithelial cells lining the neural canal, together with certain processes radiating from them and terminating immediately below the pia mater. He maintained that the neuroglia is developed from these cells, and that it is therefore entirely epiblastic in origin. This view has since been supported and elaborated by numerous other observers, among whom may be specially mentioned—Ramon y Cajal (45), Lenhossék (29), Weigert (66), Schäfer (55), Nansen (36), Kölliker (28), Vignal (64), van Gehuchten (19), Dejerine (11), Eurich (13, 14), Giese (23), Müller (37) and Stewart Paton (42). Several of these observers find confirmation of Golgi's conclusions in the fact that in some of the lower vertebrates the extra-vascular supporting tissues of the brain and cord is, throughout life, represented only by the cells of the ependyma and their processes.

In papers published a few years ago (51, 52), I contended, not on the ground of any observations of my own, but merely on the evidence that had been brought forward by others, that it ought to be regarded as finally settled that the neuroglia (in the generally accepted sense of

the term) is purely epiblastic in origin. Although I cannot now maintain this view, I still think that the evidence up to that time adduced did not warrant any other conclusion.

In 1889-90 His (24, 25) maintained that the stroma, or fundamental part of the interstitial tissue of the central nervous system, is developed from the spongioblasts (derived from the primitive epithelial cells of the central canal), and therefore from the ectoderm, and that on the other hand the cells of Deiters are developed from cell-elements which penetrate from the mesoderm. Shortly afterwards these views were supported by Lachi (31), though in a slightly modified form. In 1893 Andriezen (2) proposed to divide neuroglia cells into "neuroglia fibre cells" and "protoplasmic neuroglia cells," and stated that the former are epiblastic in origin and the latter mesoblastic. More recently the view of the double origin of the neuroglia has been maintained by Valenza (63), Erlitzki (15), Bechterew (4) and Capobianco and Fragnito (7). The work of the last named authors is beyond doubt one of the most important contributions that has yet been made to the controversy. They base their conclusions chiefly upon the results of observations upon the developing chick, but they were able to confirm them in mammals. They found that when vascularisation is just commencing in the embryo of the chick, there is a very active and diffuse penetration of mesoblastic elements into the cord, either along with the penetration of the vessels, or independently thereof. They express surprise that this fact has escaped the notice of previous observers. They obtained evidence that these mesoblastic elements do not perish, but continue to proliferate actively, and penetrate throughout the nervous tissues, both in the grey and white matter. They also traced the origin of the neuroglia from the ectoderm, confirming in regard to this point the descriptions given by Golgi and others. They conclude that "the neuroglia is a tissue of complex constitution, arising from the ectoderm and from the mesoderm, with different and not contemporaneous participation of these two layers." It is further of importance to note here that they regard both of these blastodermic layers as contributing to the formation of the cells of Deiters, or the stellate cells of Golgi.

A year ago, in giving a first account of observations made with the aid of the platinum method, I stated that, in preparations of the dog's brain, I had found throughout the cortex and white matter numerous small branching cells which, in their reaction to this method and in form, were different from the neuroglia cells (53). I hesitated at the time to express a definite opinion as to the exact nature of these cells, but further studies of platinum preparations of various parts of the nervous system from numerous different animals, have served to throw much light upon the

question, and to point very clearly to the conclusion stated in the preceding subsection. As I have recently maintained elsewhere (54), these cellular elements that are picked out by the black reaction in a certain proportion of blocks of nervous tissue treated by this process, are quite different from the neuroglia cells, as these are commonly described. They are mesoblastic elements, whereas the true neuroglia cells are epiblastic in origin. The evidence in support of this view is briefly as follows. In successful preparations the two types of cell differ not only in their reaction to this method, but also in morphological characters. In both of these respects they exhibit the sharpest distinctions without the occurrence of any transition forms. In the elements that are only slightly darkened there can be readily recognised the special characters and distribution of the typical neuroglia cells with their processes or fibres. That these cells are epiblastic in origin does not admit of dispute at the present day. The fact that the other elements are in reaction and form so sharply contrasted is at least strong presumptive evidence that they are of a widely different nature, and therefore mesoblastic in origin. This evidence is strengthened by the fact that in the same preparations other tissues that are known to be of mesoblastic origin tend also to be blackened, more especially the connective tissue fibres and corpuscles in the walls of the vessels. Further, in pathological conditions the behaviour of the two types of cell is totally different, and the changes exhibited by the elements that tend to be blackened are distinctly analogous to those that occur in other tissues known to be mesoblastic. Lastly, the presence of such special mesoblastic elements in the central nervous system coincides with the results of the recent observations of Capobianco and Fragnito (7) upon the histogenesis of the neuroglia.

Upon these grounds I conclude that the structures hitherto described as "the neuroglia," do not consist of a single tissue developed entirely from the epiblast, or of a single tissue to the formation of which both the epiblast and mesoblast contribute, but of two anatomically and physiologically distinct tissues, the one of which is developed from the epiblast and the other from the mesoblast. It is only to the first of these tissues that the term *neuroglia* can be rightly applied, and I shall therefore hereafter use it in this restricted sense (except when stating the views of other writers on the subject, all of whom have employed it in the usual way), and refer to the mesoblastic elements as the *mesoglia*.

This distinction of epiblastic and mesoblastic elements, in the tissues described by others as "the neuroglia," is essentially different from that made by His, and also from that of Andriezen. The

mesoblastic elements of His include all the "Deiters cells," instead of only a certain number of them. Those of Andriezen are stated to be attached to the vessels, and to be the elements which hypertrophy and fibrillate in certain pathological conditions. According to the evidence of the platinum method, these characters belong only to the elements derived from the epiblast.

NORMAL HISTOLOGY.

Literature.—Although a granular ground-substance in which the nerve-cells were embedded was described by Arnold (1) in 1844, the credit of having discovered the neuroglia is now generally given to Virchow (60), whose first paper on the subject was published two years later. The progress of our knowledge of the normal histology of this tissue since that time has been very carefully and exhaustively reviewed by Lenhossék (29) and Weigert (66), to whose works I must refer the reader for a full account of the matter. I shall confine myself to a short statement of the various opinions that have been advanced. They may be classified into four groups.

First, there is the view originally advanced by von Kölliker (27) in 1862, which has since been supported, with various non-essential modifications, by Fromman (17), Deiters (8), Golgi (21), Ramon y Cajal (45), Lenhossék (29), van Gehuchten (19), Woodhead (68), Schäfer (56), Pellizzi (41), and many others. According to the more recent of these authorities, the neuroglia is composed entirely of small cells, provided with very fine, wavy, and only slightly ramified processes, which terminate freely or attach themselves to the walls of the vessels. There are no independent glia-fibres, and no glia-cells without processes.

Secondly, there is the view originally suggested by Boll (3) in 1874, but first clearly advocated in 1883 by Ranvier (43), and more recently strongly supported by Weigert (66) as the result of observations with a new method. According to this view, the neuroglia in its fully developed state is composed of nucleated cells, and of fibres which are chemically distinct and morphologically separate from these cells. Weigert further maintains that the fibres have no vascular or other attachments, and that they do not branch. At the same time he thinks it is possible that there are some neuroglia cells with true protoplasmic processes.

Thirdly, there is the view of Bevan Lewis (33), according to which the neuroglia contains two different kinds of cells—a small element without processes, and a larger element which has a comparatively faintly staining nucleus, and is provided with numerous delicate processes, one or more of which is attached to the wall of a vessel.

This authority further believes in the existence of a structureless or finely molecular basis substance belonging to the neuroglia. Jastrowitz (26), Petrone (40), Popoff (39), and Nissl (35) have also maintained that there are non-ramified as well as ramified neuroglia cells.

Lastly, there is the view of Andriezen (2), who maintains that the neuroglia consists of two different cell-elements, namely, "neuroglia fibre cells" and "protoplasmic neuroglia cells." As already mentioned, he believes that these two forms of cell are developed from different blastodermic layers.

There can be no doubt that the great preponderance of authority rests at the present time with the first of these views. Weigert's theory has, however, many adherents, among whom there may be specially mentioned Dagonet (9) and Eurich (12). It has been criticised by Pellizzi (41), van Gehuchten (20), Spampini (57), Müller (37), myself, and many others.

Pellizzi argues that a chemical differentiation between fibre and protoplasm of the kind displayed in preparations by Weigert's new method, does not suffice to prove that these elements are anatomically separate. He has observed that this fine differentiation is not maintained when these structural elements enlarge in morbid conditions, and he maintains that other methods clearly demonstrate that the fibres are processes of the cell-protoplasm.

Van Gehuchten, while agreeing with Weigert that the protoplasm and fibres have a different chemical constitution, cannot admit that this fact proves that the two are independent of each other. The cellular membrane of most vegetable cells presents a completely different chemical constitution from that of the protoplasmic body, but no one has thought it necessary to contend on this account that the two are independent. On the contrary, all researches have inclined to prove that the membrane is only a product of differentiation of the cellular protoplasm. He also points to the fact of the different affinities for stains presented by different parts of animal cells. The circumstance that the fibres of the neuroglia have a different chemical constitution from the cellular protoplasm is thus not inconsistent with the view that the one represents the cell-body and the other the prolongations of the same cell. He considers that sufficient proof of their mutual dependence is furnished by the results obtained with Golgi's method.

Most of the considerations that I have myself in previous publications urged against the validity of Weigert's conclusions seem to me still to have weight in the controversy. They will be stated presently.

Terrazas (59) distinguishes two types of neuroglia cell—one with long, smooth expansions, which stain easily by the method of Weigert, and the other with granular, feathery appendages, which do not stain

by this method. He thinks it is probable that there are also mixed forms, having some of the characters of each type.

Reinke (49) concludes that the cells of the neuroglia have ramified prolongations, which are rendered visible by Golgi's method, but that the fibres of the neuroglia, which are so clearly displayed by Weigert's method, are morphologically, physically, and chemically different from these prolongations. The fibres are perhaps a product of differentiation of the cells, but in the adult they have become completely independent.

Paladino (38), Marracino (34), Capobianco and Fragnito (7), and Donaggio (10), have specially studied and described the relations of the neuroglia to the nervous elements. Bonne (5) has recently described its mode of connection with the pia-arachnoid.

In 1899 I described certain branching and branchless cellular elements in the brain, which were capable of complete differentiation from the neuroglia by means of the platinum method, and were apparently not nerve-cells (53). I have more recently (54) contended that these special elements are essentially different from the true neuroglia cells, not only in structural features and functions, but also in origin, being developed from the mesoblast, while the true neuroglia cells are developed from the epiblast.

The Neuroglia.—As already indicated, I limit this term to those of the interstitial tissues of the central nervous system that are of epiblastic origin. They are the structures revealed by Weigert's method, while, on the other hand, both they and the mesoglia cells are generally picked out in greater or smaller numbers in preparations by Golgi's method. Both forms are stained by my methyl violet method, which, however, does not clearly reveal the processes of the mesoglia cells. In platinum preparations the neuroglia is either invisible, or only very slightly darkened.

In the adult the neuroglia consists of nucleated cell-bodies and of long, smooth fibres of a chemically different character (figs. 4 and 5). The question around which the greatest amount of controversy has been waged is that of the mutual relation of these two parts. Weigert maintains that they are entirely separate; the majority of other authorities believe that they are essentially connected with each other, forming portions of the same cell-element.

It is certain that the neuroglia fibres are a product of the protoplasm. The whole of the neuroglia must have passed through a purely protoplasmic stage in the course of its development. The fibres are a comparatively late formation. They are elaborated from the protoplasm, of which they may be regarded as a sort of condensation product. In the fully-developed human brain generally only a very small amount of undifferentiated protoplasm remains around the

nuclei of the neuroglia cells. It forms a thin layer, filling up the spaces between the fibres and the nucleus. The study of the neuroglia of the sheep proves that the transformation may, however, go further than this. Many of the neuroglia cells of this animal are entirely devoid of any protoplasm that can be demonstrated. It is probable that in the human subject the protoplasm of many of the neuroglia cells has also become completely differentiated into fibres.

Now the crucial point is, are we to believe with Weigert that the anatomical continuity between the fibres and the remaining undifferentiated protoplasm, or between the fibres and the nucleus, is entirely lost or not? In other words, are the fibres merely leaning against the cell-body, or are these two elements still in essential union with each other? It seems to me that this is a question that can never be definitely decided one way or the other by the mere study of the forms and relations of the elements concerned. A differential staining of tissue-elements lying in contiguity cannot be admitted as proof of their discontinuity. Weigert's case rests essentially upon such evidence, and therefore cannot be allowed to have been proved. Upon such evidence we might, for example, with equal justice maintain that the deeply stained nuclear membrane of the neuroglia cells has no connection with the invisible nuclear matrix. On the other hand, the mere contiguity of two tissue-elements, which can be clearly differentiated by a staining reaction, does not suffice to prove that they are anatomically continuous. Therefore we must seek for evidence of some other kind to decide this question. We require, in fact, evidence that will determine whether fibre and cell are in physiological union or not. I think we have strong affirmative evidence upon this question in the fact that in the fully-developed brain, Golgi's method picks out only an occasional neuroglia cell, along with all the processes radiating from it, to the exclusion, it may be, of all adjacent interlacing fibres radiating from other neuroglia cells. But still more decisive evidence can be obtained from the observation of the changes that take place in the neuroglia in pathological conditions. It may sometimes be observed that certain of the neuroglia cells have undergone marked hypertrophy, while others remain unchanged. Now it is never merely a nucleus and its immediately surrounding protoplasm that become thus enlarged. All the fibres that radiate from the cell undergo hypertrophy simultaneously, often to the entire exclusion of hypertrophy in neighbouring interlacing fibres.

On these grounds I think we are justified in maintaining that the view of the structure of the neuroglia held by Golgi, Lenhossék, and others, is essentially correct, although its advocates had not, previous

to the publication of Weigert's work, fully realised the highly differentiated character of the fibrillar processes.

In advocating his case for the theory of the independence of cell and fibre, Weigert has attached very great importance to the appearance of recurving fibres in the vicinity of the neuroglia nuclei (fig. 4). That the fibres should approach the cell-body, and then curve away from it again without any interruption of their course, appears to him to be convincing proof that the two structures have no connection with each other. While, as already indicated, I cannot admit that such evidence, depending as it does upon a differential staining of contiguous elements, can be accepted as proof of discontinuity, it is nevertheless to be expected that Weigert's opponents should be able to give an explanation of the occurrence of these fibres that is perfectly consistent with their own views. If we keep in mind the two facts that the fibres are a product of the protoplasm, and that any undifferentiated protoplasm that remains is invisible in Weigert's preparations, it is easy, I think, to understand the appearances in question. The arrangement of the fibres corresponds, in a general way, with the original outline of the neuroglia cell in its protoplasmic stage. Therefore we should expect a fibre, as it approaches the nucleus, to divide into two branches, and that these should curve round in opposite directions and join adjacent fibres. Now this is exactly what we find in a great many instances. Indeed, all the fibres radiating from a cell may often be observed to be thus continuous with each other (figs. 5, 6, and 9). This bifurcation of the fibres as they approach the cell, is a phenomenon that appears to have escaped Weigert's notice. It is by no means, however, a constant appearance in his preparations, for one of the branches frequently atrophies; or sometimes one of them is so delicate that it does not retain the stain. The appearance of a single recurving fibre is thus produced. Another reason why this bifurcation of the approaching fibre is not always easy to recognise is, that it occurs frequently at a point at which the original protoplasmic process divided into two delicate branches. Appearances are thus produced which Weigert has interpreted as the crossing of two independent fibres. In many instances at least, this interpretation is, I think, erroneous, the four fibres being really continuous. The space between the nucleus and the fibres may be filled up with undifferentiated protoplasm, which in the angles made by adjacent fibres takes the form of a thin layer. But frequently, owing either to the contraction produced by the hardening agent, to further fibrillar transformation, or to shrinkage from other causes, the protoplasm has disappeared from parts of the intervening space. If we take the view that the fibres are a product of the protoplasm, it will be inaccurate to regard recurving fibres as consisting of two fibres

joined by an envelope of the cell-body, as I did in my first paper upon this subject (50). The whole fibre is really a portion of a protoplasmic envelope of a highly specialised kind.

In a very similar way Weigert has, it seems to me, been misled by his method with regard to the attachment of certain of the fibres to the walls of the vessels. He denies that such an attachment ever occurs. But my methyl violet method shows very clearly that many of the fibres are attached to the walls of a vessel by an expansion which is not cone-shaped, as has been thought, but fan-shaped. The fibre appears to bifurcate at the apex of this triangular expansion, the branches forming two sides of the triangle, the vessel wall the base (fig. 5). One of these branches is generally thinner than the other, and is consequently often not stained in preparations by Weigert's method. The triangular space is filled up with a very thin layer, either of undifferentiated protoplasm, or, more probably, of material of the same kind as the fibre, which remains quite invisible in preparations by Weigert's method, but it is often distinctly shown in those by my method. Thus, all that is seen in the former is generally a single fibre, curving round until it runs for a short distance parallel with the unstained and only imperfectly discernible vessel-wall. The employment of my methyl violet method is by no means essential for the detection of these fallacies. They are evident in many preparations by Weigert's own staining process (fig. 9).

It must, I think, at present be regarded as doubtful whether or not in the fully developed human brain there are any true neuroglia cells of which the protoplasm has undergone no differentiation into fibres. It is now certain that most of the cells of this character are mesoglia cells. In the growing brain, however, there are always large numbers of neuroglia cells of which the prolongations consist only of undifferentiated protoplasm.

It must also be regarded as somewhat doubtful whether or not any of the neuroglia fibres become completely separated from the perinuclear protoplasm, and assume an independent existence like the fibres of ordinary connective tissue. In the present state of our knowledge we cannot entirely deny that such a separation sometimes takes place; but I think that we are in a position to assert positively that the immense majority of neuroglia fibres do not reach an independent stage. It seems very probable that neuroglia fibres are incapable of an independent existence, union with the cell being essential for the continuance of their nutrition.

Authorities are now practically unanimous in their disbelief in the existence of anything of the nature of a transparent or granular ground substance belonging to the neuroglia. Lavdowsky's (32) theory that the fibres are hollow appears to be clearly dis-

proved by Weigert's staining method. Some of the older authorities believed that the processes of neighbouring cells in crossing anastomose with each other, giving rise to a true network of neuroglia. The evidence of modern methods obliges us, I think, to reject this view.

Paladino (38) maintains that the prolongations both of neighbouring and of somewhat distant neuroglia cells are frequently continuous with each other. This view has been supported by Marracino (34), and more recently by Capobianco and Fragnito (7), who insist that the point is one about which there can be no doubt.

Paladino, on the ground of observations made with his own palladium method, has also maintained that the framework which forms the support of the myeline of medullated nerve-fibres is formed of threads that are continuous with the neighbouring neuroglia fibres. He has even been able to observe, especially in the trygon, true neuroglia corpuscles in the interior of the myeline sheath and contiguous to the axis-cylinder. I have previously expressed scepticism as to the accuracy of these views, but they have recently received what I think must be admitted to be very strong support from the observations of Capobianco and Fragnito.

Paladino has further described a reticulum of neuroglia fibres (*ragnatelo nevroglico*) surrounding the nerve-cells. He states that the fibres become extremely fine, and form a network of very delicate threads with complicated meshes, which envelops each nerve-cell and constitutes for it a supporting stroma. This observation is likewise confirmed by Capobianco and Fragnito, who further state that the network envelops not only the cell-body but also its prolongations, and that here and there true neuroglia elements may be observed to take part in its formation. The occurrence of nuclei upon the surface of nerve-cells has frequently been noted by histologists. Some have regarded them as belonging to leucocytes, but according to the most authoritative opinions they represent neuroglia cells. The platinum method proves that, while in many instances the latter view is accurate, a large proportion of these nuclei are those of mesoglia cells.

Donaggio (10), in the course of his studies of the reticulum revealed in the nerve-cells by means of his modification of Ehrlich's methylene blue method, has recently made an observation that is of considerable importance in connection with the subject of the neuroglia. He has been able to demonstrate, more especially with the aid of a slight modification of his method, that some of the fibres of the peripheral portion of this nerve-cell reticulum (which is described in the next chapter) are continuous with the fibres of the surrounding neuroglia. He therefore concludes that some at least of these

peripheral fibres are neuroglia fibres. But he is of opinion that the reticulum he has described is something absolutely different, both as regards configuration and nature, from the *ragnatelo nevroglico* of Paladino.

These finer structural features of the neuroglia are not revealed by Weigert's method, nor by my own methyl violet method, at least so far as I have yet been able to observe. At the same time, in preparations by the latter method there are sometimes appearances which strongly favour the view that some of the neuroglia fibres terminate by breaking up into extremely minute threads. It is probable that the fibres revealed by the method of Donaggio at the periphery of the nerve-cells are of this kind. It seems very probable also that the mode of termination of the neuroglia fibres upon the vessels, connective tissue fibres of the pia-arachnoid and medullated nerve-fibres, is of the same nature.

Bonne (5) has described the termination of the processes of the neuroglia, upon the pia-arachnoid in the form of expansions or plates which are joined to each other after the manner of epithelium. It is to be noted that his observations were made upon material from newly-born kittens. I am of opinion that the structural feature he describes, though persistent in the lower vertebrates, is in the mammalia merely a developmental one of which there is little trace remaining in the adult.

Van Gehuchten (20) and some other authors have, I think, laid undue emphasis on the ependymal cells as a constituent of the supporting tissue of the central nervous system. The important relation of these cells to the neuroglia at an early stage of development has already been referred to. But in the adult they would appear to be little more than an epithelial lining of the ventricles. The processes that extend from them into the deeper tissues are few in number, and probably very short. Their value as a supporting framework must be so slight that for all practical purposes we may leave it out of account. It seems unnecessary, therefore, to complicate the description of the neuroglia in the way that these authors have done, by regarding the ependymal cells as one of the constituents of the supporting tissues of the cerebro-spinal axis.

To sum up, I would describe the neuroglia (in the restricted sense in which I suggest the term should be used) of the fully developed human brain as consisting essentially of special, highly branched cells, which vary greatly in size, and in the number and arrangement of their processes (figs. 1 to 7). Their nuclei are oval or rounded in form, have a prominent nuclear membrane, and chromatic filaments distributed evenly throughout the nuclear matrix. Their protoplasm, originally large in amount, has become in greater part differentiated into a denser substance, which forms fine fibres. In some instances it would appear

to be entirely so differentiated. But the fibres remain in anatomical and physiological union with the cell-body. They do not end in the cell-body, but, passing over it, are continued beyond it. As they pass out from its vicinity, two (sometimes more) of them frequently join to form a single fibre. This, almost immediately beyond the point of junction, occasionally divides into two. At a greater distance from the cell-body the fibres seldom branch. Neuroglia fibres are not hollow tubes, but are solid in structure. They are probably smooth, but we cannot at present assert this absolutely, owing to their somewhat rough aspect in some preparations by Golgi's method. They are straight or gently curved. They differ greatly in length, and considerably in size, but individual fibres remain of about the same thickness throughout their course. Many of them are attached to the adventitia of the vessels either directly, or by means of fan-shaped expansions. At the surface of the brain they are in a similar way attached to the connective tissue fibres of the pia-arachnoid, with which they also slightly interlace. There is now strong evidence to show that they are also in some way connected both with the nerve-cells and medullated nerve-fibres, probably by very fine terminal ramifications. It is uncertain whether or not any of the fibres terminate freely. It cannot yet be excluded that there remain some neuroglia cells the protoplasm of which has not undergone any differentiation into fibres, but the vast majority of the cells hitherto supposed to be of this nature are really mesoglia elements. On the other hand, it is possible that some fibres become entirely separated from the cells, and assume an independent existence, but there are strong grounds for believing that this does not occur. It certainly does not take place to any great extent.

I think it is worth advancing as a theory that the fact of the great differences in the size of the neuroglia cells is in some way related to the circumstance that, like most other cell-elements, they have only a limited existence, and require to be slowly renewed. In the brain of the fully grown, healthy sheep there is strong evidence that some of the neuroglia cells are proliferating. It may be regarded, I think, as certain that the neuroglia cell only lives for a limited number of years, and that, therefore, a slow process of regeneration must be continually going on. This being so, there must be a cycle in the life-history of a neuroglia cell, and it is conceivable that cells of different sizes represent different stages in this cycle.

The neuroglia is most abundant in the white matter of the brain (fig. 8), in the first layer of the cortex, below the epithelium of the ventricles, and around the larger vessels. The largest and most richly branched cells occur also in these situations, but more especially immediately below the pia-arachnoid and epithelium of the ventricles, where their fibres form a delicate felt-work. This felt-work can

frequently be recognised in aniline black fresh sections of the normal human brain, and must not be mistaken for sclerosis (fig. 11). It becomes more distinct as age advances. The direction in which the fibres radiate depends entirely upon the arrangement of the adjacent tissues to which the fibres have to accommodate themselves; and there seems, therefore, to be no justification for making this feature a ground for classification of neuroglia cells, as some authors have done. Immediately subjacent to the pia-arachnoid, the fibres naturally either run parallel with the membrane, or stream down into the cortex. Around the larger vessels, they must have a corresponding arrangement. In general they radiate from the cell-body in all directions.

It should perhaps be mentioned that Lenhossék and many other German writers classify neuroglia cells into those with long processes, and those with short processes (*langstrahler* and *kurtzstrahler*). I think that such classifications are to be avoided, as they are apt to give rise to an erroneous impression that they imply a difference of an essential kind.

The Mesoglia.—The mesoglia cells occur, like the neuroglia cells, throughout the central nervous system, and are probably about equally numerous. They are specially revealed by the platinum method which tends to pick them out in black, while leaving the neuroglia either invisible, or only very faintly darkened. (See chapter ii.)

Although both may be regarded as consisting of branching cells, the two tissues present morphological characters that are absolutely distinct. The mesoglia cells have processes which are composed of the same substance as the cell-body, and which are generally markedly dendritic. Moreover, they have no connections with the vessels or other structures. Their typical appearance in platinum preparations of the brain of the dog, in which animal I have so far chiefly studied them, is represented in figs. 20, 21 and 23. The nucleus may be visible, or it may be obscured by the black deposit. It varies in size within about the same limits as the nucleus of the neuroglia cells. Very occasionally two nuclei may be seen in one cell (fig. 22). The perinuclear protoplasm varies considerably in amount, but, especially in the richly branched cells, is generally somewhat scanty. When not obscured by excess of black deposit, it has a very characteristic granular appearance, which, there is reason to believe, corresponds to some structural feature. Extending from the cell-body in various directions there are commonly from three to six delicate processes, which branch dichotomously, sometimes dividing three or four times. These processes diminish gradually in thickness towards their free extremities. They generally exhibit little varicose swellings in their course. They are never very long, seldom extending further from the cell-body than to a distance equal to about ten times its diameter. They appear to have no special relation to any of the other tissues.

Not infrequently they may be observed to lie in close proximity to a nerve-cell, and to extend some of their processes alongside it (fig. 23), or to rest upon the adventitia of a vessel, but there is no reason to believe that these occasional relationships are anything more than accidental. In general the mesoglia cells are evenly distributed throughout the tissues, but they are more abundant in the grey matter than in the white. They are comparatively scanty in the outermost layer of the cortex. While the great majority of them are richly branched, some are only slightly so, and a few may be recognised which have no processes at all. The identity of these last with the others is clearly proved by their similar reaction to the platinum method.

In platinum preparations of the sheep's brain, the mesoglia cells have essentially the same characters as those just described, but the cell-body is generally larger, and the processes shorter and less numerous than in the dog (fig. 25). Cells without branches are more abundant.

In the human brain the branchless, or only very slightly branched mesoglia cells seem to predominate (fig. 27), but richly branched cells may frequently be observed (fig. 26). The protoplasm has generally a very granular appearance.

FUNCTIONS.

The Neuroglia.—There are, I think, only two functions that this tissue has, as yet, been clearly proved to subserve.

1. The neuroglia gives mechanical support to the neighbouring tissues, especially to the nerve-cells and their prolongations. The attachment of the neuroglia fibres to the capillaries and larger vessels, which probably occurs to a much greater extent than has generally been believed, is essentially related to this function. The great internal supporting framework of the brain is obviously the network of vessels that permeates it. The finer supporting framework is the neuroglia. The neuroglia fibres are guy ropes for the capillaries, and at the same time supports for the nerve-cells and their prolongations.

2. The neuroglia is the tissue of repair in the brain. In this respect it corresponds exactly to the white fibrous tissue in other parts of the body.

I believe that authorities are pretty generally agreed regarding these two functions of the neuroglia. Of the additional functions that have been attributed to it, some, I think, are uncertain, others are erroneous.

Ramon y Cajal (47, 48) has strongly advocated the theory, originally advanced by P. Ramon, that the neuroglia serves to isolate the fibres of the nerve-cells, and so to prevent their contact with adjacent fibres. He has even gone so far as to maintain that the processes of the neuroglia cells undergo contraction and expansion, and that the former state permits of contact taking place between the

processes of different nerve-cells, while the latter causes interruption of such contact. These views have been opposed by Weigert, van Gehuchten (20), and many others. According to the last named writer, they have been abandoned by Cajal himself. It seems to me that it must be recognised that it is in some degree true that the neuroglia-fibres serve to separate the nerve-fibres from each other, and so to prevent their contact and consequent transmission of impulses, but they can do so only passively. The view that they can perform this function in an active sense appears inconsistent with their structural characters.

Ramon y Cajal (46) has also maintained that the neuroglia-cells, in virtue of their contractility and attachment to the capillary walls, are able to cause expansion of these vessels and local congestion in association with psychical activity.

Golgi, Clouston, and others have suggested that the neuroglia-cells fulfil a nutritive function in relation to the nerve-cells.

The theory of Bevan Lewis (33) that certain of the neuroglia-cells constitute the distal expansion of a lymphatic system, serving to drain the intervacular areas, is, I think, quite untenable. Solid fibres cannot perform any such function, and, moreover, provision of this kind for drainage of the intercapillary areas appears superfluous, as it is certain that for this purpose there exists an efficient arrangement of the usual kind, or at least differing only slightly from that in other tissues. Nor can we, I think, accept Bevan Lewis's theory that hypertrophied neuroglia cells act as phagocytes. This theory has found little or no support among other authorities. I think it is based on a misinterpretation of microscopic appearances, and on a misconception of the meaning of neuroglia hypertrophy.

The Mesoglia.—Regarding the functions of the mesoglia I can, as yet, say little more than that they are essentially different from those of the neuroglia. It is obvious that the mesoglia cells cannot serve in any important measure as a supporting tissue, for they are not attached to the vessels, and there is conclusive evidence that they do not take an active part in the formative processes of repair in the central nervous system. Their rôle seems to correspond up to a certain point to that of endothelial cells or connective tissue corpuscles in ordinary fibrous tissues. Like these they are capable of taking up foreign particles from the surrounding fluids and altering them, in other words, of acting as phagocytes, but unlike them they present no evidence of having the power of forming fibrils.

REACTION TO IRRITANTS; RÔLE IN PROCESSES OF REPAIR.

Our knowledge of the reaction of the neuroglia to irritants is, as yet, far from being so precise as it is desirable that it should be. The

experimental work of Friedmann (16), Goodall (18), and some others, though of much value, has by no means served to solve all the problems connected with the subject. Further careful research along similar lines is still required before we can be quite certain as to the true interpretation of many of the proliferative phenomena that occur in the brain in disease. As far as we understand them at present, the effects of the application to the neuroglia of an irritant of a suitable kind and intensity, are as follows:—The cells, along with their fibrillar processes, swell up often to several times their usual dimensions, displaying at the same time a greatly increased affinity for various stains. Goodall found this condition established to a marked degree after twenty-eight hours. This great hypertrophy of the neuroglia cell is merely the first stage in the process of its proliferation. Several observers have noted that this takes place by the indirect method. Friedmann observed karyokinetic figures in the nuclei of the neuroglia on the third day after the application of irritants, but it seems probable that the cells may begin to divide at a much earlier period than this. The daughter cells increase in size, and in their turn may divide into two. New processes, probably at first dendritic in form, are thrown out from the protoplasm. They tend to attach themselves to neighbouring vessels. Some time after the irritant ceases to act, the proliferated cells begin to diminish in size. This change, which is a very slow one, is accompanied by partial differentiation of the protoplasm into fibres. After some weeks, all the proliferated cells have again assumed normal dimensions. The area involved is now one of sclerosis. This in the case of the central nervous system implies increase in the number of neuroglia cells and of their fibrillar prolongations, which are usually less delicate than in the normal tissue.

Colella (6) and Capobianco and Fragnito (7) have described the multiplication of neuroglia cells by gemmation. It is not quite clear whether or not they regard this process as one that excludes mitotic division. The appearances they describe are common in the brain of general paralytics, and arise, I believe, from the circumstance that, after mitotic division of the nucleus, one of the portions is often, though not always, pushed to a considerable distance from the other, and from the centre of radiation of the fibrils, by elongation of the intervening protoplasm.

Eurich (12) considers that neuroglia sclerosis occurs only by proliferation of neuroglia cells that have parted with their fibrillar processes, and that new branching cells are thus formed which attach themselves to the vessel-walls. This theory, though very plausible, is not, according to my observation, in harmony with the phenomena that may be observed in various irritative conditions in the brain.

The neuroglia cell and its fibrillar processes appear always to behave as one tissue-element in pathological conditions.

In simple processes of repair in the central nervous system, as after the occurrence of a small hæmorrhage or of the degeneration of nerve-fibres, phenomena of essentially the same kind as those that may be observed to follow the action of an irritant take place in the adjoining neuroglia. In other words, it undergoes hyperplasia and replaces the tissue that has been destroyed. In the case of large destructive lesions, this only occurs, however, at the periphery, the centre developing into a cyst.

A noteworthy feature of neuroglia sclerosis is that it is accompanied by little or no contraction of the area involved. The great importance of this is obvious. If repair had taken place in the brain by means of the formation of ordinary granulation tissue, it would have been associated in its later stages with much contraction, which would inevitably have implicated a wide area of surrounding nervous tissue, with the most disastrous consequences.

The Mesoglia.—Under conditions of irritation mesoglia cells appear to lose their branching character, and to assume the aspect of small granular cells. They probably undergo proliferation, but as yet I have no preparations that prove this very clearly. In processes of repair, while, as I have stated, they take no formative part, they certainly act as phagocytes. It is to be noted, however, that they do not appear to do so to the exclusion of the leucocytes. This corresponds to what occurs in connective tissues, where under similar conditions, both leucocytes and endothelial cells take up foreign particles into their interior.

HYPERTROPHY AND HYPERPLASIA OF THE NEUROGLIA IN DISEASE.

It has long been recognised that these hypertrophic and sclerotic changes are specially common in the brains of the chronic insane. It is well known also that they occur in the neighbourhood of gross lesions, such as softenings, localised centres of inflammation, and tumours, and that they accompany degeneration of the nerve-fibres in chronic diseases of the spinal cord. In any case in which they can be proved to be the result of the action of an irritant, we are warranted in regarding them as inflammatory in character. But as changes, which as far as we know are of exactly the same kind, may occur purely as a physiological process of repair, we are not justified in regarding neuroglia hypertrophy and sclerosis as in themselves proof of inflammatory action.

A considerable degree of neuroglia hypertrophy may occur and remain as a chronic condition without proliferation taking place to any great extent. This condition is one that is specially common in insanity.

The layer of neuroglia which lies immediately subjacent to the soft membranes is very frequently affected by sclerosis in the brains of the insane. A broad band of dense and coarse subpial felting is thus developed, in place of the narrow felt-work of delicate fibres normally existing in this position (fig. 11). Favourable microscopic preparations of such morbid subpial felting furnish strong evidence that the fibres composing it are all processes of cells and never independent threads. The condition is an almost constant one in advanced general paralysis (fig. 12), senile insanity (fig. 13), and alcoholic dementia. It is generally accompanied by hypertrophy and hyperplasia of the neuroglia throughout the rest of the outermost layer of the cortex. As to its causation, little of a definite character can probably yet be said. Sclerosis occurs with equal frequency, in the same classes of cases, in the dense layer of neuroglia which lies immediately subjacent to the epithelium of the ventricles. But here the tissue-proliferation tends specially to affect numerous small areas. The surface of the ventricles consequently assumes a granular aspect. It seems now to be pretty clearly established that these "granulations of the ependyma," as they are frequently termed, are entirely composed of proliferated neuroglia, and that the surface epithelium does not contribute to their formation. This is the view of their structure maintained by Pellizzi (41), and the results of my own observations are entirely in accord with it.

When hypertrophy and hyperplasia of the neuroglia are due to the action of an irritant which does not seriously affect the nerve-tissues, it is clear that they must in themselves do injury to these tissues by encroaching upon the space which they normally occupy. On the other hand, when they are simply the expression of a reparative process, following loss of the nervous elements, they are merely secondary pathological changes. We are scarcely yet in a position to say to what extent these neuroglia changes, as they occur in insanity, are in this sense primary, and to what extent they are merely secondary. They are always, however, a most important index of the amount of degeneration affecting the nervous elements. For example, it can be shown that when they are developed to a marked degree in the outermost layer of the cortex, the delicate medullated nerve-fibres normally present in this situation have entirely disappeared. At the same time, some writers have, I think, gone too far in their conclusions regarding this matter, more especially in respect of their contention that nerve-cells destroyed by degenerative change are always replaced by neuroglia. Destruction of nerve-cells is frequently accompanied by well-marked hyperplasia of the adjacent neuroglia, but there are very strong grounds for believing that in such instances both are the result of the action

of a common irritant. There is considerable evidence to show that loss of nerve-cells is not necessarily accompanied by such hyperplasia. Lugaro (30) found that after section of the sciatic the loss of substance due to destruction of the cells of the anterior horn is not compensated for by proliferation of neuroglia, but by shrinkage of the grey horn. Equally weighty evidence is supplied by the fact that in cases of secondary dementia in which a large proportion of the cortical nerve-cells have entirely disappeared, there is often little or no cortical sclerosis.

It is a remarkable and important fact that the neuroglia is capable of thriving under abnormal nutritive conditions which quickly result in death of the nervous tissues. Thus, if a cerebral capillary is rendered impervious by hyaline change, the adjoining nerve-elements die, but the neuroglia hypertrophies and proliferates.

PIGMENTARY DEGENERATION OF THE NEUROGLIA.

This change consists in the accumulation, in and around the protoplasm of the neuroglia cells, of small homogeneous globules of a yellow tint (fig. 19). It is most commonly seen in its extreme degrees, in the outermost layer of the cortex, in senile insanity (fig. 13). Sometimes the globules are so numerous that they almost completely obscure the body of the cell. There is little difficulty in recognising that they are not colloid bodies. Bevan Lewis has figured them, and has stated that they are fatty in character. They are, however, insoluble in ether, and are not blackened by the prolonged action of osmic acid. Whatever their chemical nature may be, I think there is strong evidence for believing that they are developed within the protoplasm of the neuroglia cells, from which they are thrown out as they accumulate. They are composed of some very insoluble substance, which the leucocytes appear to be unable to carry away. They are specially the product of chronically hypertrophied neuroglia cells, and may be seen wherever these occur. They are by no means confined to the outermost layer of the cortex.

OTHER DEGENERATIVE CHANGES AFFECTING THE NEUROGLIA.

A peculiar swollen, blurred condition of the cell-body of otherwise normal or slightly hypertrophied neuroglia cells, may occasionally be seen in fresh sections. I think it can be shown that this is not always a mere post-mortem change, but that it may be a true pathological condition, the nature of which, however, is still obscure.

In methyl violet preparations some of the cell-bodies and fibres of the neuroglia may occasionally be observed to have a granular and dis-integrated appearance. I have only found this condition as a wide-

spread and well-marked change in one case; but I am inclined to believe that it is nevertheless somewhat common in its slighter degrees. The case referred to was one of very rapid general paralysis. In various parts of the cerebral cortex and white matter, large numbers of the neuroglia cell-bodies and fibres, while to a certain extent preserving their form, were reduced to minute, deeply staining granules. There is satisfactory proof that this change also is not necessarily one due to post-mortem disintegration. It corresponds very closely to an alteration observed by Sacerdotti and Ottolenghi (58) in experimental uræmia.

MORBID CHANGES AFFECTING THE NEUROGLIA IN INSANITY.

My conclusions on this subject are based mainly upon the study of fresh sections of the cerebrum from three hundred consecutive cases of insanity examined at the Royal Edinburgh Asylum, and of thirty-one cases of other diseases from general hospitals.

I confess that the results of the comparison of these two series have come as a considerable surprise to me. I was scarcely prepared, at the outset of the investigation, to find that the cerebral neuroglia of the chronic insane differs in so marked a manner from that of the mentally sound as my statistics show. It may be objected that the series from the mentally sound is too small to form a fair comparison with that from the insane. This objection would certainly have weight if the differences between the cases in the two series were only slight; but they are so pronounced, that it is practically impossible that the continuation of the hospital series (the cases included in which are already fairly representative) to any length could modify in an important manner the general conclusions which the comparison has already seemed to warrant.

In compiling my statistics, I adopted the plan of dividing hypertrophy and hyperplasia of the neuroglia into three degrees—slight, moderate, and marked. Some such classification as this was rendered necessary by the nature of the changes under investigation; and I am certain that its adoption, though open to objection, has enabled me to arrive at more precise conclusions than I could otherwise have framed.

The study of the hospital series brought out very clearly the facts that a slight degree of subpial felting in fresh sections is a perfectly normal appearance, and that it increases somewhat with age. A moderate degree of subpial felting, which I would regard as distinctly a morbid condition, along with a similar degree of neuroglia overgrowth throughout the outermost zone of the cortex, was present in three cases. One of these was, on inquiry, ascertained to have been virtually a case of senile insanity which could have been certified, while another was a case of chorea in an adult. The former showed

also numerous small areas of sclerosis in the cortex and white matter, such as are common in senile insanity. In only two other cases were single minute areas of sclerosis observed. Three cases showed a slight prominence of the neuroglia cells in the white matter. In no instance was there any general hypertrophy of the neuroglia in the cortex. Slight degrees of pigmentation of the neuroglia were common, both in the outermost layer of the cortex and in the white matter.

The statistics compiled from the examination of the Asylum series of three hundred consecutive cases, bring out a most striking contrast to this Hospital series. This contrast remains as great, if the comparison of the latter is made with only an equal number of consecutive cases from any part of the former series. There was a marked degree of subpial felting in 11 per cent. of cases, a moderate degree in 35 per cent., giving a total of 46 per cent. of cases with morbid subpial felting. There was a marked degree of neuroglia overgrowth throughout the first layer of the cortex in 15 per cent. of cases, a moderate degree in 28 per cent., and a slight degree in 40 per cent., the morbid condition thus being present altogether in 83 per cent. of cases. The occurrence of proliferative changes in the neuroglia throughout the cortex, exclusive of the outermost layer, was almost confined to cases of general paralysis. Only six cases of other forms of mental disease presented the condition, which in each instance was very slight. There was a slight degree of overgrowth of the neuroglia in the white matter of the brain in 22 per cent. of cases, a moderate degree in 22 per cent., and a marked degree in 7 per cent., or 51 per cent. in all. There were localised areas of sclerosis in thirty-six cases, or 12 per cent. These included all forms of sclerosed patches, from large nodules in cases of epilepsy to minute spots only recognisable with the aid of the microscope, and also the neuroglia proliferation associated with localised atrophies, old hæmorrhagic and embolic softenings, tumours, tubercular nodules, and gummata.

In the face of these statistics, it is scarcely possible to maintain, as some have done, that the brains of the insane present no demonstrable structural changes that are in any way special. In the morbid changes affecting the neuroglia alone, we have abundant evidence of the existence of a special condition of widespread damage to the cortical nerve-cells and their processes in chronic insanity.

General Paralysis.—The great neuroglia hypertrophy and proliferation—involving the whole of the cortex as well as the white matter—regarded by many authorities as typical of this disease in its advanced stage, I have only found in about one-third of such cases, of which I have examined sixty-four. A much less marked degree of these morbid changes was present in the large majority of the cases. They were, further, often confined to the outermost layer of the cortex

and the white matter. When the nerve-cell layers of the cortex were involved, large areas usually remained unaffected. Several patients who clinically were beyond any doubt advanced general paralytics, showed no pronounced neuroglia change at all. In three additional early cases the neuroglia was either normal, or only very slightly hypertrophied in the outermost layer of the cortex and in the white matter. These observations lead me to support the views of those who have already maintained that hypertrophy and hyperplasia of the neuroglia are secondary and non-essential tissue-changes in general paralysis.

Senile insanity.—In senile insanity there is almost constantly a pronounced degree of hypertrophy and hyperplasia of the neuroglia in the outermost layer of the cortex, along with a more or less thick band of subpial felting. In more than half of the cases there is general neuroglia hypertrophy in the white matter. It is, however, usually slight in degree. In the cortex, subjacent to the outermost layer, hypertrophy and sclerosis almost never occur as general conditions, but they are common in connection with atrophic softenings, which may be extensive or quite microscopic in size. Such areas are also common in the white matter. The hypertrophied cells, especially in the outermost layer of the cortex, always show pigmentation, which is frequently developed to an extreme degree.

Chronic alcoholic insanity.—The neuroglia changes here closely resemble those in senile insanity. Pigmentation is usually comparatively slight. The limitation of a marked degree of hypertrophy to the outermost and the deepest layers of the cortex is much more common in this form of insanity than in any other, but the condition can be demonstrated in only a minority of cases. A similarly limited distribution of hypertrophy not infrequently occurs in general paralysis and in senile insanity, and therefore the condition would seem not to be so special to alcoholic insanity as has been believed. Areas of atrophic softening in the cortex, or in the white matter, with their associated neuroglia hypertrophy and sclerosis, are common, but much less so than in senile insanity.

Chronic epileptic insanity.—A very dense and broad layer of subpial felting is present in the majority of cases. This fact has been noted by many observers. I think that the change is clearly a secondary one, and that it has no essential connection with epilepsy. In a certain proportion of cases the condition does not occur. A slight degree of hypertrophy and sclerosis is present throughout the first layer of the cortex and in the white matter in the majority of cases. These changes, however, are in no sense special to epilepsy. Their occurrence is the rule in all cases of insanity of long standing. In only one case out of thirteen did I find sclerosis of the cornu

Ammonis, but the condition was merely part of a somewhat marked degree of general sclerosis throughout the white matter of the brain. There were extensive areas of dense sclerosis in the cerebrum in five cases. Without going into the difficult questions of the pathology of these areas and their relation to epilepsy, I would merely state that observation proves that, while such lesions very commonly occur in cases of congenital epileptic idiocy and imbecility, they are by no means an essential factor in the pathology of these conditions, being frequently entirely absent; and that, on the other hand, they may be present in cases of acquired epilepsy in which there was no prior condition of congenital imbecility.

Cases of acute insanity, as a rule, show no very distinct morbid changes in the neuroglia.

MORBID CHANGES AFFECTING THE MESOGLIA CELLS.

My information upon this subject is as yet very limited, for it is only recently that I have endeavoured to apply the platinum method to the study of pathological changes. Two or three interesting facts have, however, emerged, some of which have already been mentioned.

It is certain that the pathological changes that occur in the mesoglia cells are of quite a different order from those that affect the neuroglia. They present a close resemblance to those that occur in the connective tissue-corpuseles or endothelial cells of the pia-arachnoid and dura mater.

In irritative conditions, such as general paralysis, they probably tend to undergo proliferation, but in the only two cases of the kind I have yet examined by the platinum method the evidence of it was not distinct. It is more certain that they lose their branching character and become simple, granular cells. The two morbid changes that I have been definitely able to trace in these elements are their development into the well known granular corpuscles in association with local destructive processes in the nervous tissues, and their degeneration into "amyloid bodies."

In the first of these changes the mesoglia cells exhibit their phagocytic functions. There are the strongest reasons for believing, however, that they only contribute to the formation of the granular corpuscles, many of these being leucocytes. Nissl (35) has recently maintained that granular corpuscles are merely neuroglia cells devoid of their processes, and charged with fatty and other granular matter. He does not, however, recognise the two-fold character of the tissues composing "the neuroglia," and therefore must be regarded as including the epiblastic elements in the cells which undergo the alteration in question. In regard to this point I think he is in error.

"Amyloid bodies" have long been described as occurring in the central nervous system in various chronic morbid conditions. The question of their origin has given rise to much dispute. It is probable that several different degenerative products are included in the structures generally referred to by the term, but the typical "amyloid body" is, I believe, a mesoglia cell which has undergone a change analogous to the hyaline degeneration that so commonly affects the endothelial cells of the pia-arachnoid.

"MILIARY SCLEROSIS."

Some reference to this subject is probably required in this chapter. I shall only very briefly state the views that my own observations have led me to form upon it. In the course of the study of over three hundred morbid brains, I have never met with a pathological condition corresponding to that which has been described as "miliary sclerosis," and I venture to maintain—as others have already done—that the appearances described under this name have to a large extent been misinterpreted, and that there is no such disease. In the first place, we must separate off from "miliary sclerosis" all cases of disseminated sclerosis, which is a disease of youth and middle age and somewhat rare in occurrence, while "miliary sclerosis" has been described as an "all-important feature in the white medullated strands of the cerebral convolutions in chronic alcoholism, and especially in senile atrophy of the brain." Now, in these forms of mental disease, small sclerosed areas undoubtedly occur with some frequency both in the cortex and in the white matter. But they differ considerably in appearance from "miliary sclerosis," and they never occur in the multiple fashion that has been stated to be typical of this disease. At the same time, multiple areas, having appearances identical with or closely resembling those described as characteristic of "miliary sclerosis," are common, in my experience, both in fresh and hardened brain-sections, but I think that in the great majority of instances they are not morbid areas at all. My belief with regard to the matter is that, while some of the areas described as "miliary sclerosis" have been genuine atrophic areas with neuroglia sclerosis, the great majority of them are to be explained chiefly in the following ways:—(a) In hardened preparations some of them are produced by post-mortem change (more especially post-mortem evolution of gas), others result from the action of alcohol on imperfectly fixed myeline, and others from too prolonged immersion of blocks of tissue in gum solutions; and (b) in fresh sections some of them are due to post-mortem change; some result from the formation of minute air bubbles in the sections before or during the process of staining; and lastly, some are produced by

the falling out of small vessels, the tissues in the immediate vicinity of which, in cases of senile insanity, commonly show a degree of sclerosis.

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DESCRIPTION OF PLATES XVIII, XIX. AND XX.

- Fig. 1. Large neuroglia cell attached to vessel-wall. From the white matter of brain of sheep. Cox's method ; mercurial deposit blackened by Lugaro's method. ($\times 500$.) Most of the processes show no branching. This is the typical form of the fully-developed neuroglia cell.
- Fig. 2. Neuroglia cell showing dendritic branching and mossiness of its processes. From the white matter of brain of sheep. Cox's method ; sublimate deposit blackened by Mirto's method. ($\times 500$.) This form is common in growing brains. It is to be regarded as a neuroglia cell that has not yet reached full development.

- Fig. 3. Large neuroglia cell from white matter of brain of sheep. Aniline black fresh method (Bevan Lewis). ($\times 500$.) Note the attachment of three of the processes to the vessel-wall by small sucker-like expansions.
- Fig. 4. Copy of fig. 1A in plate i. of Weigert's monograph (66). Neuroglia nucleus and fibres (human) stained by his own method. Weigert maintains that the fibres have no connection with the cell-body, and no vascular attachments.
- Fig. 5. Large neuroglia cell from the white matter of brain of sheep. Author's methyl violet method. Formalin hardening. ($\times 500$.) Note the relations of fibres and undifferentiated protoplasm, and also the mode of attachment of the vascular process to the vessel-wall.
- Fig. 6. Types of neuroglia cell in brain of sheep. Author's methyl violet method. Sublimite fixation. ($\times 500$.) The vascular attachments are not shown in this and the succeeding figure.
- (a) Large cell with pale nucleus and abundant protoplasm. Note the relations of the fibres to each other, and to the protoplasm. It is to be understood that, although here represented in one plane, the continuity of the fibres of such cells can only be recognised under the microscope by focussing at various levels.
 - (b) Large cell showing only pale nucleus and fibres. The protoplasm has probably become entirely differentiated into fibres.
 - (c) Cell similar to *a*, but with small dark nucleus.
 - (d) Small cell with dark nucleus, and fine fibres radiating from it, but without visible protoplasm.
 - (e) Small cell with dark nucleus and protoplasm, but without visible fibres. Probably a mesoglia cell.
 - (f) Cell similar to *e*, but without visible protoplasm. Probably also a mesoglia cell.
- Fig. 7. Types of large neuroglia cells in normal human brain. Author's methyl violet method. Bichromate and formol hardening. ($\times 500$.)
- (a) Cell with abundant perinuclear protoplasm, and processes which do not appear to be differentiated from it. This form is not very common.
 - (b) Cell with distinct differentiation of fibres from protoplasm. The interval between the fibres and the nucleus is generally only partially filled by protoplasm. It is probable that this condition is, in part at least, the result of shrinkage from the action of the hardening fluid.
 - (c) Cell with nucleus and radiating fibres, but no visible protoplasm.
- Fig. 8. White matter of normal human brain in preparation by author's methyl violet method. Bichromate and formol hardening. ($\times 500$.) The stained fibres here belong entirely to the neuroglia.
- Fig. 9. A large neuroglia cell in normal human brain stained by Weigert's method, showing complete continuity of fibres, and the interval between the nucleus and the fibres filled up with faintly stained protoplasm. ($\times 600$.) It is only rarely that the protoplasm is stained in preparations by Weigert's method. Such continuity of the fibres can, however, very frequently be traced by focussing at various levels. It is shown here in one plane, merely for the purposes of illustration.
- Fig. 10. Hypertrophied neuroglia cell from the outermost layer of the cortex, in a case of senile insanity. Weigert's method. ($\times 500$.) In preparations by this method, the enlarged protoplasm of such cells often stains of a yellow colour, while the fibres are thickened and easily traced. Note how the latter tend to bifurcate as they near the cell-body. Each branch may generally be followed into an adjacent fibre. In some hypertrophied cells these

branches have disappeared, and the fibre ends abruptly at the protoplasm, or merges gradually with it. Note that the nucleus of the cell is dividing.

- Fig. 11. Outermost layer of normal cerebral cortex (human). Aniline black fresh method. ($\times 300$.) The pale oval nuclei belong to the endothelium of the capillaries. The dark rounded nuclei are mostly those of neuroglia cells. The neuroglia fibres are unstained, with the exception of some near the outer edge, where they form a special layer, in which many of them are less delicate than in the deeper parts. The pia-arachnoid is not shown.
- Fig. 12. Outermost layer of cerebral cortex from a case of advanced general paralysis, showing great hypertrophy of neuroglia, and thickening of the vessel-walls. Aniline black fresh method. ($\times 300$.)
- Fig. 13. Outermost layer of cerebral cortex from a case of senile insanity, showing a moderate degree of hypertrophy and hyperplasia of the neuroglia, subpial felting (containing some colloid bodies), and thickening of vessels. The neuroglia cells are pigmented. Aniline black fresh method. ($\times 300$.)
- Fig. 14. Outermost layer of cerebral cortex from a case of epileptic insanity, showing slight hypertrophy of neuroglia, together with very marked subpial felting. Aniline black fresh method. ($\times 300$.)
- Fig. 15. Two greatly hypertrophied neuroglia cells from the tissues adjoining a small secondary carcinomatous nodule in the cerebrum. Aniline black fresh method. ($\times 500$.) Tumours, localised centres of inflammation, and recent softenings are generally surrounded by a broad zone of neuroglia cells of this kind. They are swollen to several times their normal size, and it can be recognised that many of them are dividing. Note the dendritic branching of the processes.
- Fig. 16. Greatly hypertrophied neuroglia cells, surrounding an arteriole in the deepest layer of the cortex, in a case of advanced general paralysis. Aniline black fresh method. ($\times 500$.) The arteriole shows periarteritis. The nerve-cells have for the most part disappeared. Those that remain show advanced pigmentary degeneration.
- Fig. 17. Cerebral cortex from a case of advanced general paralysis, showing hypertrophy and proliferation of neuroglia cells. Author's methyl violet method. Sublimate fixation. ($\times 500$.) Observe that some of the neuroglia cells show two nuclei. Note also the mode of attachment of the thick vascular processes to the vessel-wall. The nerve-cells have entirely disappeared.
- Fig. 18. Sclerosed area in the subcortical white matter from the brain of a case of epileptic insanity. Author's methyl violet method. Sublimate fixation. ($\times 500$.) Compare with fig. 8. The neuroglia cells are increased in number, and their fibres are less delicate than normal.
- Fig. 19. Pigmented neuroglia cells from the outermost layer of the cortex, in a case of senile insanity. Aniline black fresh method. ($\times 500$.) The pigment may be in the form of globules (as here), or of small granules.
- Fig. 20. Three mesoglia cells of cerebral cortex of dog. Platinum method. ($\times 800$.)
- Fig. 21. Mesoglia cell of cerebral cortex of dog, showing nucleus. Platinum method. ($\times 800$.)
- Fig. 22. Mesoglia cell of cerebral cortex of dog, showing two nuclei. Platinum method. ($\times 800$.)
- Fig. 23. Mesoglia cell of cerebral cortex, lying upon a nerve-cell of which only the nucleus is visible (dog). Platinum method. ($\times 800$.)

PLATE XVIII.

Fig. 1.

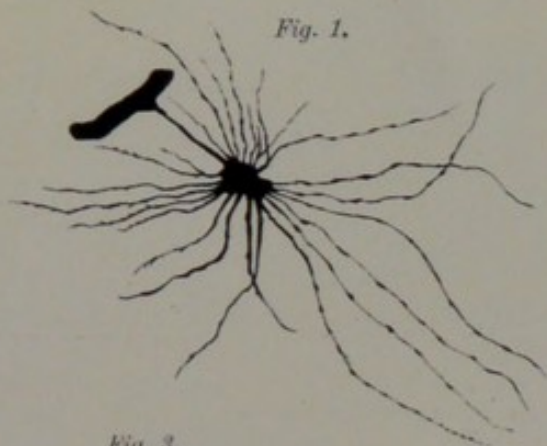


Fig. 2.

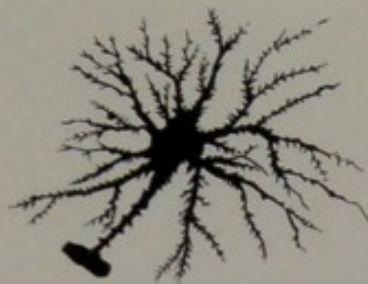


Fig. 3.



Fig. 4.



Fig. 5.

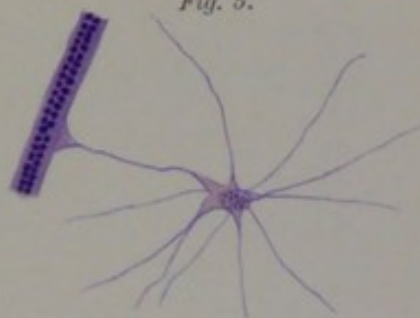
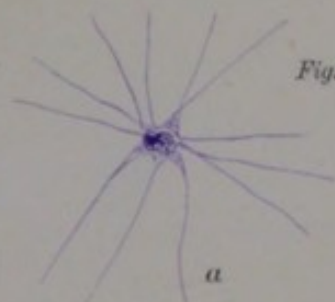


Fig. 6.



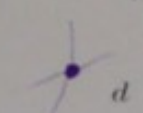
a



b



c



d

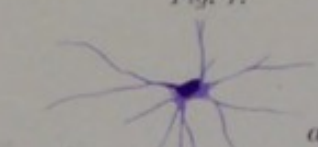


e



f

Fig. 7.



a



b



c

Fig. 8.

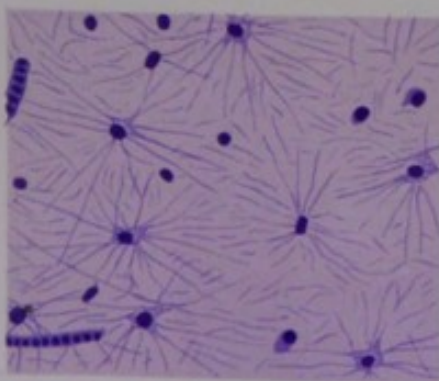


Fig. 9.



Fig. 10.





PLATE XIX.

Fig. 11.

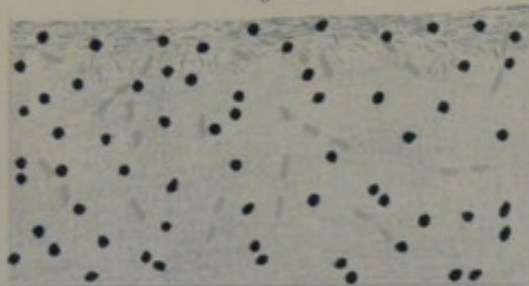


Fig. 12.



Fig. 13.

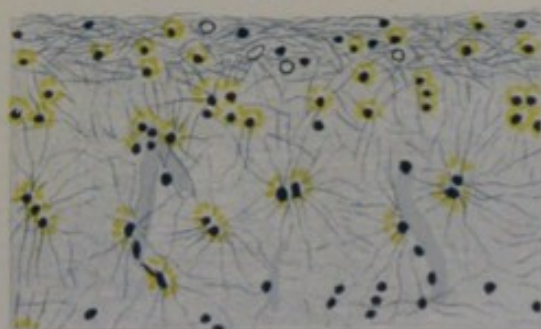


Fig. 14.

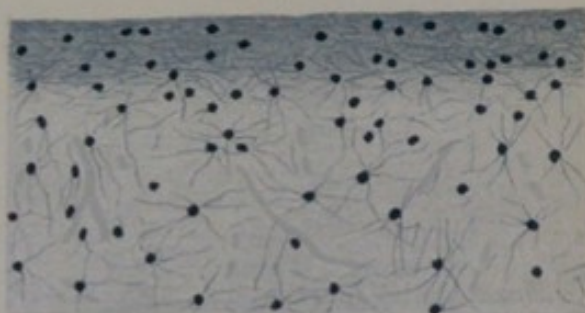


Fig. 15.

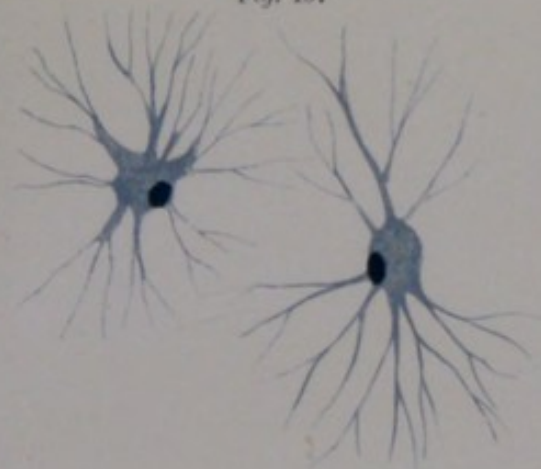


Fig. 16.

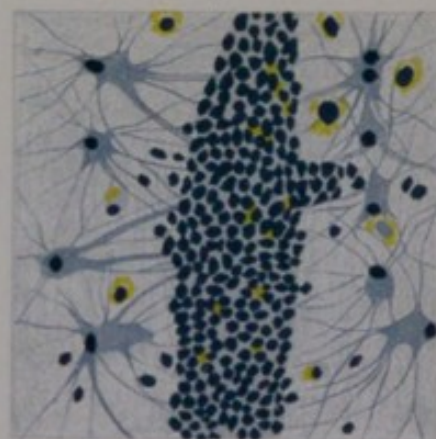


Fig. 17.

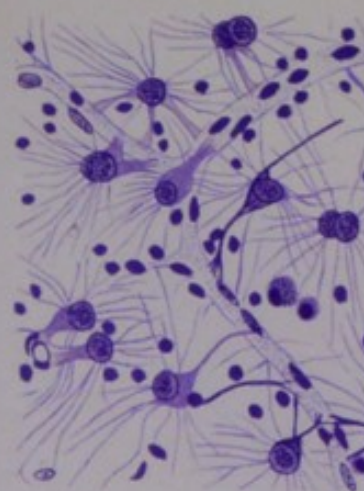


Fig. 18.

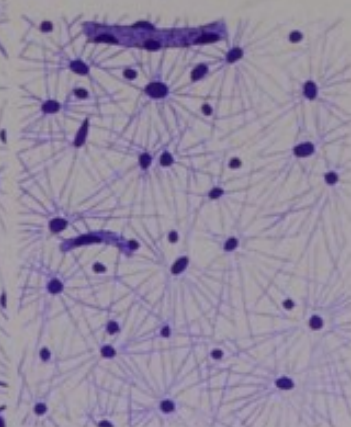


Fig. 19.

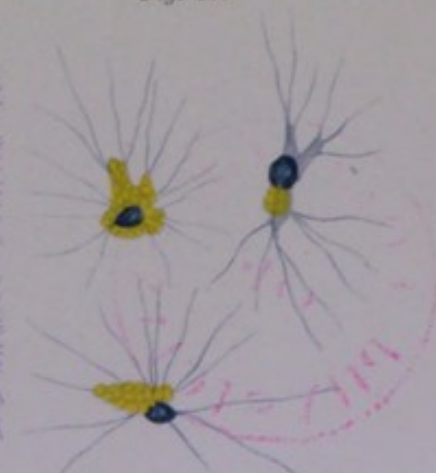




PLATE XX.



Fig. 20.

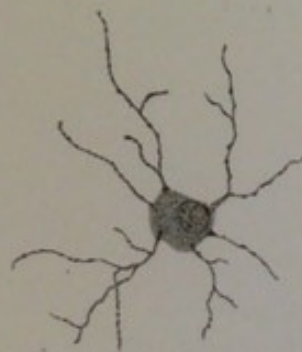
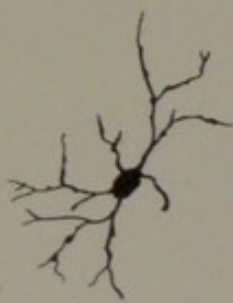


Fig. 21.



Fig. 22.



Fig. 23.



Fig. 24.



Fig. 25.

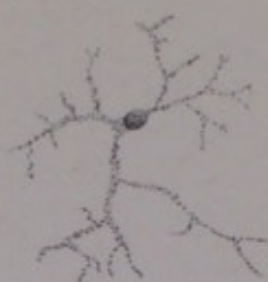


Fig. 26.

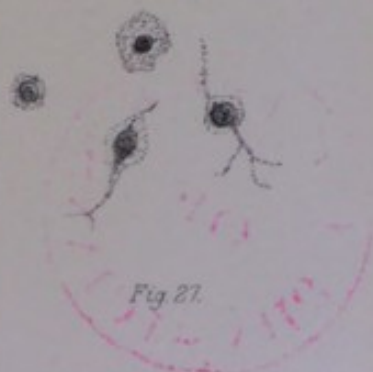


Fig. 27.



- Fig. 24. Three mesoglia cells of cerebral cortex of dog, one of which is branchless and the others only slightly branched. Platinum method. ($\times 800$.)
- Fig. 25. Mesoglia cells of corpora quadrigemina of sheep. Platinum method. ($\times 800$.)
- Fig. 26. Branching mesoglia cell of human cerebral cortex. Platinum method. ($\times 800$.)
- Fig. 27. Branchless or only slightly branched mesoglia cells of human cerebral cortex. Platinum method. ($\times 800$.)

CHAPTER IX

MORBID CONDITIONS OF THE NERVE-CELLS.

(PLATES XXI. TO XXIX.)

THE nerve-cells (using the term in its widest sense) being the special tissue-elements upon the functional activity of which depend all nervous phenomena, whether motor, sensory, or psychical, it is clear that in this chapter we have to do with the subject of primary importance in the pathology of mental diseases. All other morbid tissue-changes that in any way affect the mental operations, do so simply in consequence of the injurious influence they exert upon those nerve-cells of the cerebral cortex that specially subserve the psychical or associative functions.

Our present knowledge of the anatomy, physiology, and pathology of the nerve-cells is almost entirely the growth of the last twenty years, and chiefly of the last ten. During the latter period there has been manifested in this special field of scientific inquiry, a most extraordinary activity of research, through which an enormous number of new and important facts have been discovered. Nevertheless, the subject is yet far from having been completely elucidated. That division of it that specially concerns us here, the pathology of the nerve-cells in relation to mental diseases, is naturally still the most obscure, because it is in itself by far the most difficult to investigate, and moreover can only be illuminated by light reflected from the other divisions. Hence we must bring to bear upon it all that is known regarding the normal anatomy, physiology, and experimental pathology of nerve-cells in general. Recognising this fact, I have thought it necessary to enter somewhat fully into these subjects here, and all the more so in view of the very numerous additions that have lately been made to our knowledge of them. For the many details that are unavoidably omitted here, I would refer the reader to such works as the third edition of van Gehuchten's *Le Système Nerveux de l'Homme*, and Barker's *The Nervous System and its Constituent Neurones*, as well as to a recent critical digest of my own upon the normal and pathological histology of the nerve-cell (263).

1. NORMAL STRUCTURE OF THE NERVE-CELL.

(1) Terminology.

The term *neuron* is now in general use to denote the whole nerve-cell, including its processes. The suggestion of Schäfer (265) that it should be employed for the axis-cylinder process has not been adopted. Kölliker (119) has objected to Waldeyer's use of the word *neuron* upon etymological grounds, and has advocated instead the terms *nervenbäumchen*, *neurodendron*, or *neurodendridion*, which, however, have been very little employed by others. Schäfer proposed that the term *nerve-cell* should be used in the same sense as *neuron* at present is, and in the writings of most authorities this signification is now generally given to it.

Taking the motor-cell of the anterior horn of the spinal cord as the type, we may enumerate the various constituent parts of the nerve-cell as follows: The nucleus and nucleolus; the Nissl-bodies; the achromatic substance, composing the greater portion of the cell-body, the protoplasmic processes with their gemmulæ and the axis-cylinder process with its collaterals and terminal arborisations; the pigment; and lastly, the pericellular and endocellular networks of Golgi and others. For some of these constituents of the nerve-cell a large number of different terms have been employed by recent writers. The Nissl-bodies have been referred to as the *visible, formed, or stainable part of the protoplasm* (Nissl), the *chromatic substance* (Marinesco, Lugaro, and others), the *chromophile part of the cytoplasm* (Levi and others), the *chromatophile elements* (Lugaro, Marinesco, van Gehuchten, and others), the *chromophilic particles* (Berkley), the *basophile constituent* (Eve), the *tigroid substance* (Lenhossék), the *collagenous substance* (van Gieson), etc. The employment of the term *chromatic*, which has been very general, has led many into the belief that the Nissl-bodies are regarded as composed of chromatin. Some writers have indeed maintained this view, but it has clearly been proved to be erroneous. *Chromophile* (*part, substance, or elements*) is the term that is probably least open to objection, and it is one that has recently been largely used. It has, however, been employed by Nissl in a different sense, namely, to denote that condition of the nerve-cell which is characterised by abnormally deep staining with his method (a condition which is now generally regarded as due to the action of the fixing agent), and by Flesch to designate nerve-cells (such as the small, dark cells of the spinal ganglia) that have a very strong affinity for basic dyes, in contradistinction to those that have not this character, which he termed *chromophobe* cells. These early uses of the word have now, however, been practically abandoned. *Basophile*

constituent must be rejected, because, as Nissl and Levi have shown, this substance has only relative basophile properties.

There is, unfortunately, considerable confusion regarding the terminology of that portion of the nerve-cell which is not coloured by Nissl's staining process, arising chiefly from the difference of opinion that has existed as to its essential structure. The term *achromatic substance* is that which has undoubtedly been most largely employed. Many writers now use the expression *fundamental substance* synonymously with it. Nissl (211) used the terms *invisible*, *not formed* and *unstainable* substance upon grounds that are now known to be erroneous. In 1896, Marinesco (169) applied the term *trophoplasm* to the achromatic part, believing that this part presides over the nutrition of the neuron. The chromatic part he called the *kinetoplasm*. Lugaro (128) has pointed out certain objections to these terms. Marinesco in a later paper (178) gives a fuller exposition of his use of them. Recognising with many other authorities that the achromatic part of the protoplasm is composed of two different elements, he divides it into—(a) *the fundamental achromatic substance* and (b) *the organised fibrillar achromatic substance*. He therefore, it will be seen, limits the meaning of the term *fundamental substance*. He now restricts the term *trophoplasm* to this non-organised portion and calls the fibrillar substance the *spongioplasm*.

The protoplasmic processes are also called the *dendrites*, *dendrons* and *dendritic processes*. The gemmulae of the protoplasmic processes have been variously referred to as the *spines*, *thorns*, *spinous processes*, *lateral buds*, *pyriform processes*, etc. Synonymously with *axis-cylinder process* the terms *nervous process*, *nervous prolongation*, *neurite*, *neuraxon* and *axon* have frequently been employed. Kölliker made certain distinctions in the use of these terms which have not been generally observed by others. He restricted the terms *nerve-fibre process*, *neuraxon* and *axon* to those processes that become axis-cylinders of medullated fibres, and the terms *nervous process* and *neuropodion* to those that run a short course and do not become true nerve-fibres. The term *neuroplasm* was given by Kölliker to the homogeneous interfibrillar substance of the axis-cylinder of nerve-fibres. It has been applied by Benda (12), Nissl (214) and Bühler (15) to certain elements that they distinguish in the cell-body, which, however, are not strictly identical.

The term *neuropilema* or *neuropil* was applied by His to the dense trellis-work of fine fibrils which occurs in the nerve-centres. Its use has lately been revived in the discussion of the special views of Apáthy and Bethe regarding the constitution of the nervous system.

Foster (82) has proposed that the cell-body should be called the *perikaryon*, and that the connection of one nerve-cell with another, by

means of a terminal arborisation applied to the cell-body or to the dendrites, should be termed a *synapsis*.

(2) *The Achromatic or Achromophile part of the Protoplasm.*

No question regarding the structure of the nerve-cells has been more keenly discussed than that of the essential nature of the framework of their protoplasm. Although histologists are still far from being in entire agreement on the subject, the great weight of authoritative opinion undoubtedly now supports the reticulo-fibrillar view first advanced by Flemming (75) in 1882, and since maintained and further elaborated by himself (76, 77), Lugaro (125, etc.), Marinesco (173, 174 and 176), Giuseppe Levi (147, 149 and 152) and numerous others. According to this view the cellular prolongations and that portion of the cell-body which is colourless in Nissl-preparations, contain numerous, delicate, smooth fibrils, which for the most part unite with each other to form a network in the latter, and course independently in the former (figs. 3, 4 and 14). There is still, however, much difference of opinion as to the exact relation of the fibrils to each other. Some observers maintain that they anastomose only in the cell-body, while others believe that they also do so in the prolongations. Bethe holds the extreme view that the fibrils are entirely independent of each other throughout the cell. These differences of opinion probably arise, partly from the differences in the histological technique employed by the various observers, and partly from the fact that the arrangement of the fibrils varies to a considerable extent in individual nerve-cells and especially in different kinds of nerve-cells.

This organised fibrillar portion of the protoplasm (the *spongioplasm* of Marinesco) is embedded in a non-organised, probably fluid substance (the *trophoplasm* of Marinesco). These two together constitute the achromatic or achromophile portion of the protoplasm.

The evidence in support of the existence of fibrils consists especially in the direct observation of them with the aid of numerous different staining processes. The iron hæmatoxylin method of Heidenhain and Delafield's hæmatoxylin stain were chiefly used in the earlier studies upon this structural feature of the nerve-cell (Flemming, Lugaro, etc.). Within the last two or three years, however, several elective staining methods have been devised. Among the more important are those of Becker, Bethe, Apáthy and Donaggio. Under certain conditions which as yet I do not fully understand, the platinum method also serves to give remarkably clear pictures of these fibrils, picking them out in black on a faintly yellow, grey or almost clear ground. It is impossible to believe that the pictures of fibrils

presented by these different histological processes are fallacious, and therefore it must be allowed that, for the larger nerve-cells at least, the fibrillar doctrine has been proved. Future investigations, aided by further improvements in technique, will gradually define the various arrangements that the fibrils present in nerve-cells of the same and of different kinds. The view that the achromatic substance is entirely unorganised, or that it has a honeycomb, foam or continuous closely reticular structure, must be attributed to the employment of a technique that does not serve to show the fibrils, which, as is well known, are quite invisible in specimens prepared by the methods most commonly used in the examination of the nerve-cells.

The general arrangement of the fibrils, as for example in the pyramidal cells of the cerebral cortex, appears to be as follows. In the terminal branches of the dendrites they consist of only one, two, or three extremely delicate threads. Nearer the cell-body they are thicker and vary in number in accordance with the size of the prolongation. In the apical process at a little distance from the cell-body, they number from forty to one hundred, or even more. As they pass into the cell-body the larger proportion of them go to form a close reticulum in the neighbourhood of the nucleus, the deep or perinuclear reticulum. In the superficial part of the cell-body the reticular character is less distinct, and many of the threads appear to course independently. Fibrils may occasionally be observed which pass from one dendrite to another, without, as far as can be made out, having any connection with the perinuclear reticulum. The fibrils of the axis-cylinder process, which are more closely set than those of the dendrites, arise chiefly from the perinuclear reticulum, but at the same time some of them are derived from the superficial portion of the cell-body.

Most authorities believe that the fibrils take origin in or near the gemmulæ of the protoplasmic processes, but Apáthy, Bethe, Nissl and some others maintain that they arise from an inter-cellular common elementary network (*elementargittar*).

The non-organised achromatic substance, or trophoplasm, contains certain special elements, namely, the fuchsinophile granules of Giuseppe Levi (147). This observer has shown that these granules, which are exceedingly minute, are considerably increased in numbers during functional activity of the cell. They display a special affinity for the red dye in preparations stained by Galeotti's acid fuchsine and methyl green method after certain modes of fixation.

The gemmulæ of the protoplasmic prolongations.—In preparations by Golgi's method the protoplasmic prolongations of the nerve-cells are generally studded with numerous, minute short processes, consisting typically of an extremely delicate stalk and a slight terminal enlarge-

ment (fig. 28). Some observers have maintained that these appendages are simply artificial products of the Golgi method. This view is, however, untenable, for gemmulæ of typical form have been demonstrated by certain modifications of the vital methylene blue method and are also present in some platinum preparations. It has also been maintained that they are post-mortem products and do not represent any structural feature of the living cell. This view seems to be rendered inadmissible by the fact that Lugaro (139) has been able to observe the gemmulæ in the cortex of dogs, the cerebral tissues of which had been instantaneously fixed by intra-vascular injection of Cox's fluid during life. Hill (208, 210) thinks that "the thorns" are organic structures which are not shown in their entirety by the chrome silver method, and that the typical form of a rod with a dot at the end is due to a post-mortem change in the tissue. He describes the numerous variations in form which they present. He believes that they are really the ends of unstainable nerve-filaments surrounded by a film of staining cell-plasm. He has observed that in the cells of Purkinje in the skate they are replaced by long striæ streaming away from the protoplasmic process on either side. According also to the special views of the structure of the nervous system maintained by Apáthy and Bethe, the evidence of terminations presented by Golgi preparations is fallacious, the primitive fibrils being continued beyond the gemmulæ.

It is scarcely now open to doubt, I think, that the gemmulæ are genuine structural features of the protoplasmic prolongations, but it may be questioned if the pyriform condition represents their natural form. It seems to me very probable that in the living state these appendages are somewhat longer than they generally appear in Golgi preparations, and filiform throughout.

The Spiral Vortices of Levi.—In 1895, Lenhossék (156) described in the cells of the spinal ganglia of the frog, a figure to which he applied the term *centrosome and sphere*, and which he demonstrated especially in iron hæmatoxylin preparations. He found that in certain cells the nucleus is eccentric, and that on the side to which the greater part of the protoplasm is placed there is a concentric arrangement of the protoplasm. The central point of this figure, the *centrosome*, is somewhat granular, and surrounding it there is the more homogeneous *sphere*. At this period, Lenhossék denied the existence of fibrils in the body of the nerve-cell. Dehler (61) shortly afterwards confirmed Lenhossék's observation, and similar figures were described by Bühler (14) in *lucertola*, by J. Schaffer (268) in *petromyzon*, and by Lewis (164) and Maclure (191) in the nerve-cells of invertebrates.

In 1897, Levi (149), in the course of his comparative researches, observed in the protoplasm of the cells of the spinal ganglia of the toad the occurrence of a spiral vortex (fig. 5) composed of converging

fibrils, and having a distant resemblance to the centrosome and sphere described by Lenhossék in the frog. He observed similar figures in the frog and in *zamenis*, but they were less distinct. He states that he is satisfied that what Lenhossék regarded as a homogeneous sphere is really composed of a vortex of fibrils, and that his centrosome is a transverse section of the axis of this vortex. He therefore maintains that one cannot give to this figure the significance either of a centrosome or a sphere, more especially since he has been able to trace the fibrils of the vortex into direct relationship with the origin of the axis-cylinder. This, he says, consists badly with the meaning that is commonly given to the term *centrosome*, i.e., a formation which, at least at a certain period of ontogenetic development, takes an active part in the reproduction of the cell. In his paper upon karyokinesis in the nerve-cell, Levi (150) maintained the same view regarding the nature of this so-called centrosome and sphere. He could see no reason for doubting that the centrosome of the somatochrôme cells, like that of the *kernzellen* (in the case of which he has proved the point) resides in the nucleolus. Bühler (15), in his work on the nerve-cell, devotes a chapter to the subject of the concentric figure described by Lenhossék, and fully confirms Levi's statements regarding it. He also gives a description of another structure which he was the first to observe in the nerve-cell (14), namely, the "centrierte system" of Heidenhain. "It is a system of organic rays with central corpuscles and microsomes." It is placed between the nucleus and the inferior pole of the cell, but resides in the proximity of the inferior margin of the nucleus. Often it is double, and always lies on the principal axis of the cell, or in immediate proximity to it. Its presence in the cells of the toad and frog is constant. Szczawinska (271) has recognised in the nerve-cells of the skate, figures similar to those described by Levi and Bühler. Levi (152), in a more recent paper upon the changes in nerve-cells during hibernation, gives a very minute description of the vortices as they occur in the toad, and compares his description with that of Bühler, which differs in certain points of detail. He now recognises that it is only during hibernation that a clear view of these formations can be obtained, as at other times they are obscured by the chromophile elements.

Up to the present these spiral vortices have, I believe, been observed in the higher vertebrates only very occasionally. They are chiefly interesting on account of the explanation they furnish of the supposed centrosome and sphere.

(3) *The Chromophile part of the Protoplasm.*

The body and the initial portion of the protoplasmic prolongations of the larger nerve-cells, in tissues fixed by means of such reagents as

corrosive sublimate, alcohol or formalin, and suitably stained with certain dyes, present numerous deeply coloured particles which contrast in a striking manner with a colourless ground-substance. These particles, on account of having been first minutely described by Nissl (206, 207 and 208), are still commonly termed the "Nissl-bodies." A detailed account of the more important observations recorded up till the end of the year 1898, regarding this chromophile part of the protoplasm, will be found in the critical digest already referred to (263).

In the large nerve-cells of the anterior horn of the mammalian spinal cord (fig. 1) and cerebral cortex (figs. 15 and 22) stained with thionin, toluidin blue or methyl violet, the chromophile bodies, when examined with a medium power, appear as rounded, oval, wedge-shaped, spindle-shaped or irregular particles, which in general may be described as arranged concentrically around the nucleus, and parallel to the adjacent edge of the cell towards the periphery of the perikaryon and in the initial portion of the prolongations. The elongated forms occur chiefly in the last-named situation. The cone of origin of the axis-cylinder process is always devoid of chromophile granules. In other nerve-cells the form and arrangement of the Nissl-bodies often differ considerably from those just described. In the spinal ganglia of the dog, for example, Lugaro (130, 131 and 140) has described five types of nerve-cell, in each of which these elements present characteristic appearances (fig. 2).

Comparatively little importance is, however, now attached to the form of the chromophile particles, for it is generally recognised that it depends upon the arrangement of the achromatic reticulum, and has practically no other significance. Lugaro (125) first pointed out this fact in 1896. He contended that the chromatic part of the protoplasm represents an inter-fibrillar mass, and that preparations by Nissl's method therefore give only a negative, as it were, of the true structural configuration of the nerve-cell. It is now also recognised by the great majority of authorities that the chromophile part of the cytoplasm, as we see it in properly fixed and stained preparations, is composed ultimately of minute granules, and that the bodies consist of local aggregations of these granules.

Much controversy has taken place as to the form in which the chromophile part of the cytoplasm exists in the living cell. Held (105, 106) maintains that the Nissl-bodies do not exist as such in the living state, and that their formation depends upon the acid reaction assumed by the grey substance after death, or upon precipitation determined by the fixing fluid. Although this view has received a considerable amount of support, it is not shared by the great majority of authorities at the present day. The most generally accepted opinion appears to be that the Nissl-bodies occur in the living cell as

masses of a homogeneous albuminoid substance, localised as they appear in microscopic preparations, and that their granular character is artificially produced by the fixing agent. It is to be noted, however, that Donaggio (58), from certain appearances to be observed in preparations by his modification of the vital methylene blue method, deduces that the chromophile substance, in its unaltered form and arrangement, consists of minute granules which uniformly incrust the achromatic reticulum in the cell-body and initial portion of the large protoplasmic prolongations (fig. 7). Van Gehuchten (94) has also likened the chromophile substance to an incrustation upon the achromatic reticulum, but his description applies to the cell-stained after fixation.

Chemical physiologists seem now to be agreed in regarding the chromophile substance of the nerve-cell as consisting of nuclealbumin.

(4) *The Physiological Pigment.*

In perfectly normal conditions certain of the cortical and other nerve-cells in the human adult contain a small collection of colourless, yellow or brown granules, generally situated in proximity to the nucleus. It is now recognised that the term "pigment," which has long been applied to these granules, is scarcely an accurate one, but so far nobody seems to have been able to suggest a better.

As the subject of this pigment has until somewhat lately been very imperfectly understood, and as it has considerable importance in relation both to the physiology and the pathology of the nerve-cell, it may be useful to notice here its recent literature in some detail.

Schäfer (265) has maintained that the presence of pigment is not a sign of decadence, but rather one of activity. Pilcz (233) has distinguished two kinds of nerve-cell pigment, which are different as regards their development, and react differently to staining reagents. One is pale yellow, and occurs in the cells of the cerebral cortex, basal ganglia, cord, and spinal and sympathetic ganglia. The other is dark brown, and is present in the cells of the locus cœruleus, substantia nigra of Sæmmering and nucleus of the vagus. These two kinds of pigment are not different forms of the same substance, but are of an entirely distinct nature. The yellow pigment is blackened by osmic acid, the brown is not. Neither of them is hæmatogenous. He has studied the period in development at which these pigments make their appearance. The brown pigment first appears in the cells of the locus cœruleus at the twelfth month. In general it appears at an early period of life, and ceases to increase after a few years. On the other hand, the yellow pigment is first seen (in the spinal ganglia) about the sixth year, and continues to increase throughout life. In the lower animals this pigment is much less abundant than in man.

It is never found in the cells of Purkinje. Hutchison (111) found that an amount of pigment, far in excess of the ideal standard, was present in nearly 50 per cent. of presumably healthy human brains. Rosin (257) found that the yellow pigment in the nerve-cells of the human cord is blackened by osmic acid, but that this reaction does not occur if the preparations are first treated with ether. He therefore thinks that it is partly of a fatty nature. Colucci (43) states that chemical reactions prove that the yellow globules in nerve-cells are not fat. They may, however, undergo a fatty metamorphosis, and then a black reaction is obtained with osmic acid. He regards them as a manifestation of cellular metabolism. It has not been proved that they are true pigment granules, such as those in the cells of the locus niger, etc. Marinesco (178*a*) believes that the yellow substance in the nerve-cells arises from a transformation of the chromatophile particles, and that it is allied to fat. He notes that it stains with basic fuchsine, with hæmatoxylin in Weigert's method, and with osmic acid. Lord (154) holds that the pigment of the nerve-cell results from fatty degeneration of the Nissl-bodies. Obreja and Tatuses (224) consider that it is fatty or, more correctly speaking, myelinic in character, and that it forms a store of nutritive material which is utilised during the activity of the nerve-cell. In two papers more recent than that referred to above, Marinesco (182, 184) records some further observations and conclusions upon this subject. He states that the pigment does not generally appear in the giant-cells of the cortex until about the twentieth year, but occurs earlier in some of those of the cord and spinal ganglia. It continues gradually to increase in amount with advancing age. He believes that it is derived chiefly from the chromatophile elements (in the transformation of which he describes three successive phases), but probably also from the amorphous fundamental substance. Among the granules of which it is composed he distinguishes three different varieties, viz., (*a*) those that are not coloured by any staining agent; (*b*) erythrophile granules, or those that are stained by erythrosin in preparations by Romanowski's method; and (*c*) cyanophile granules, or those that are coloured green or blue by this staining process. He maintains that the pigment is an indication that the nerve-cell has reached its full development and passed into the stage of involution; it only appears when the cell commences to lose its vitality and functional energy; its formation is in a measure proportionate to the weakness of the organic resistance of the cell.

Most of the small nerve-cells, as well as the cells of Purkinje, appear to be devoid of pigment throughout life. On the other hand, many of the cells of the column of Clarke in normal conditions contain a large central mass of generally colourless granular material,

which occupies the greater portion of the cell-body, and which is apparently identical with the paler varieties of the pigment of other nerve-cells.

(5) *Nucleus and Nucleolus.*

The knowledge that we at present possess regarding the normal structure of the nucleus and nucleolus of the nerve-cell, we owe chiefly to the very able researches of Giuseppe Levi. Previous to his taking the matter up, the study of this portion of the nerve-cell had been comparatively neglected, and all descriptions of it that had been given were more or less inaccurate and incomplete. The publication of his first paper on the subject in 1896 may justly be said to mark one of the important epochs in the history of the progress of our knowledge of nerve-cell anatomy. I enter somewhat fully into the matter here, as I believe that nuclear changes are destined in the future to occupy an important place in descriptions of pathological conditions affecting nerve-cells.

Flemming (75), in his early paper upon the cells of the spinal ganglia, expressed the belief that both the nuclear membrane and nucleolus are rich in chromatin. In 1893, Nissl (208) described a nuclear membrane, a reticular framework, from one to three nucleoli and also accessory nucleoli. In the same year, Rosin (256), basing his conclusions upon results obtained with Biondi's stain, maintained that the nucleus and nucleolus are neutrophile. In 1894, Nissl (209) distinguished in the nucleolus a delicate external layer, which stained deeply, and a central colourless part. In 1895, Lenhossék (155) described a very delicate nuclear membrane and a faintly-staining nuclear reticulum. In the nucleolus he distinguished a group of from three to five punctiform, strongly colourable endo-nucleoli. Dehler (61) noted at the periphery of the nucleolus a deeply-staining zone. Roncoroni (258) described in the nuclei of some of the pyramidal cells of the cerebral cortex, the occurrence of a sharp line, coloured deep blue in methylene blue and eosin preparations, and extending sometimes from one pole of the nucleus to the other. He thought that this line was probably composed of chromatin. Lugaro (126) maintained that Roncoroni's line is nothing more than a fold of the nuclear membrane, due to shrinking of the nucleus, generally from alcohol hardening, and that staining reactions prove that it is not composed of chromatin. Roncoroni (259) defended his original opinion against the criticisms of Lugaro, who, in turn, replied with further arguments in support of his contentions (127). There can be little doubt that Lugaro's view of this matter is the correct one.

In 1896, Ramon y Cajal (245), from studies with the method of Nissl, concluded that the nucleus of the nerve-cell undergoes,

along with its differentiation, a process of simplification, consisting in a progressive concentration of all the nuclein in one or two spherical nucleoli, and that it is probable that nerve-cells with the nuclein thus concentrated have lost the power of proliferation. He believed that in the large cells the nuclear contents were devoid of nuclein, but that, on the other hand, the nucleolus was formed entirely of nuclein, which, however, was modified in the central portion by long mitotic repose. Levi (146) published his first paper upon this subject contemporaneously with the preceding. He pointed out that Rosin's conclusion that the nucleus and nucleolus of the nerve-cell are neutrophile is in contradiction to established views regarding the structure of nuclei in general, since it is now believed that the chromatin (or nuclein) of the nucleus has affinities for the basic aniline dyes, the nucleolus for the acid. He considers that Rosin used Biondi's stain in too concentrated solution, and therefore obtained reactions which were largely artificial. It is now known that for elective coloration, dilute solutions which stain slowly and progressively are always to be preferred. He has himself employed this progressive method of coloration with Biondi's stain (after sublimate fixation), and has obtained results entirely different from those of Rosin. He finds that in the somatochrome cells all the different elements—including the Nissl-bodies and the achromatic part of the protoplasm, the nuclear membrane and nuclear granules or network—take the acid stain (acid fuchsine and orange G), excepting from two to four particles adherent to the nucleolus, which take the basic stain (methyl green) (fig. 6). The large globular nucleolus (or nucleoli, as there are occasionally two), apart from these particles, is very strongly acidophile. The basophile particles vary considerably in form and volume. They may have the aspect of semilunar bands or of spherical masses, or may assume any intermediate form. He has never seen them detached from the nucleolus, nor has he seen other basophile particles among the contents of the nucleus. He describes the special features of the basophile particles in the somatochrome cells of different regions. In the anterior horn of the spinal cord, for example, they are constantly semilunar, delicate and elongated, so that often they embrace the voluminous nucleolus in a green ring. He also describes the somewhat different characters presented by the nuclei of the two varieties of karyochrome nerve-cells, but this subject is more fully dealt with in a later paper (149). He has never seen in his preparations the endo-nucleoli to which Lenhossék refers. The accessory nucleoli that have been described evidently correspond to the acidophile granules, some of which in lower vertebrates are little inferior in volume to the nucleolus. They differ, however, from the

latter in never being surrounded by basophile particles. He maintains that the basophile particles are composed of nuclein (chromatin), and that they constitute the whole of this substance present in the somatochrome nerve-cells. In the course of his observations upon the fuchsinophile granules of the nerve-cell, he observed (147) that the basophile particles of the nucleoli of the cells of the spinal ganglia are rounded in form in the resting condition and elongated in that of fatigue. This change he attributes to the enlargement of the nucleolus which occurs in activity and physiological fatigue of the cell, according to the observations of Mann, Lugaro and others. In his comparative researches upon nerve-cells, of which he published his account in 1897, Levi (149) included the study of the characters of the nuclei. He confirms his previous description, more particularly as regards what he terms the "centralisation of the nuclein in the somatochrome cells." He has found that the nuclei of this class of nerve-cells have essentially the same structural features in all the animals he has studied, but describes the various slight differences observed. He regards the nuclear membrane as a true membrane and not merely a part of the nuclear stroma, as in neuroglia cells. In mammals the nuclear network, or *linin reticulum*, is very loose and faintly colourable. While the centralisation of the nuclein is complete in the somatochrome cells of mammals, in all the lower vertebrates, although the greater part of the nuclein is centralised, there is a certain quantity of it diffused throughout the nucleus. The nuclei of the *kernzellen* have a delicate, acidophile membrane. Their nucleoli present many variations. They are very small, generally irregular in outline and always composed of two substances, nuclein and one or two acidophile particles. Centralisation of the nuclein is, as a rule, only partial. In the granules of the cerebellum, etc., it is doubtful if the nuclear membrane is always acidophile. Acidophile substance is always present in the nucleus, but it is very scanty. Chromatin is, on the other hand, abundant. The nuclei of the neuroglia cells have a membrane composed of chromatin and a dense reticulum of the same substance. There is, however, no precise differential criterion by which it is possible to distinguish them from those of the granules.

Van Gehuchten (94) refers to Levi's observations, and gives a description of the nucleus essentially in agreement with his view, except as regards the nucleolus, which he seems to regard as composed entirely of chromatin. Lenhossék (158) confirms Levi's statement that the nuclear reticulum is always acidophile. He doubts, however, if the basophile particles in the nucleolus are a constant morphological feature, and thinks that their basophile character is only relative. As will be seen, he altered this opinion

shortly afterwards. Prenant (234) describes the occurrence of crystalloid rods in the nuclei of the nerve-cells of the sympathetic ganglia of the hedgehog. They are straight or curved, generally long and intensely coloured.

In 1898, Bühler (15) distinguished in the nucleus of the nerve-cell an acidophile chromatin and a basophile one; the first (oxychromatin) is much more abundant than the second; the nucleolus is composed of a substance very nearly allied to basi-chromatin but not identical with it. He did not refer to the special disposition of the nuclein described by Levi. Heimann (112) states that the nucleolus presents a resistance to stains similar to that exhibited by bacterial spores. He regards the nuclear reticulum as basophile (113). Lenhossék (159) considers that the terms acidophile and basophile should not be used in too absolute a sense with regard to the staining reactions of the constituents of the nucleus and nucleolus. He regards it as settled that the nuclear reticulum of nerve-cells has only a very faint affinity for basic dyes, and that on the other hand it colours intensely with acid dyes. With regard to the nucleolus he now accepts the views of Levi.

Timofeew (280) states that the nuclei of the nerve-cells of birds have two nucleoli, one of which has the characters described by Levi, while the other is entirely acidophile.

In his latest paper on the subject of the nucleus, Levi (151) reviews the recent observations recorded by other authorities, and defends his opinions against certain criticisms that have been offered. He refers to the fact that his statement that the nuclear membrane of the large nerve-cells is always acidophile in reaction has been confirmed by Lenhossék (159), Ramon y Cajal (245) and van Gehuchten (94). He especially criticises the conclusions of Bühler (15), which differ essentially from his own. He maintains his statement that the basophile character of the nucleolar particles is absolute, and disputes the opinion of Ramon y Cajal (245) that the whole of the nucleolus is composed of chromatin, insisting on the acidophile character of the central portion.

Levi's contention that the nuclear membrane, reticulum and granules are acidophile structures, receives confirmation from the way in which they react to the platinum method. Along with the connective tissue fibres of the vessels, the acidophile character of which is indisputable, they are the first elements to be darkened by the platinum deposit. The nucleolus is generally pale, but is dark in some preparations. On the other hand, the particles attached to the nucleolus never present any special attraction for the platinum. That the reaction of these particles is basophile and differs in this respect from all the other constituent elements of the nucleus, I have also been able to

satisfy myself from the examination of some specimens of the human brain which were kindly sent to me by Dr David Orr, and which were prepared by him in accordance with Levi's technique.

(6) *The Pericellular Reticula of Golgi and others.*

Several different observers, working in most instances with modifications of Golgi's method, or of the vital methylene blue method, have described a reticular investment upon the nerve-cells. There is, however, a wide divergence of opinion among them as to the form it presents, its relations to the subjacent cell and to the surrounding tissue-elements, and its physiological significance.

In 1882, Golgi, from observations with his own method, was led to express the opinion that it is probable that the nerve-cells possess an investment of the nature of neurokeratin. In 1893, he spoke more decidedly regarding the existence of such an investment, and invoked it as an argument against the theory of transmission of the nervous current by contiguity (88). In 1895, Lugaro (123) described a similar appearance of the cells in the dentate nucleus of the cerebellum, stating that in silver preparations these cells appear as if invested by a brown shell, which is homogeneous and riddled with holes. In 1897, Martinotti (187) described a fine peripheral reticulum which he had succeeded in demonstrating by Golgi's silver method especially upon the nerve-cells of the spinal cord of pups. He thought that it was composed of neurokeratin, and that it probably had an isolating function. In the following year, Golgi (90) published a paper in which he gives a further and very minute description of this pericellular investment, as observed in sections prepared by modifications of his silver method. He states that it is a very delicate structure formed of a substance clearly differentiated from the cell-body (fig. 8). It sometimes appears as a reticulum, sometimes as a continuous homogeneous stratum, or as closely applied squames. Not rarely it presents striations which might be interpreted as fibres crossing over the cell-body. Most frequently it has a finely reticulated structure, with round, uniform, regular meshes. It forms a cuirass which clothes not only the cellular body but also the protoplasmic prolongations, along which it may be followed even to the subdivisions of the second and third order. Upon these, however, it loses its reticular aspect and becomes a uniform stratum. The cellular substance, including the prolongations, remains colourless and transparent. The investment is seen in its most characteristic form upon the cells of the spinal-cord, nuclei of the medulla, dentate nucleus of the cerebellum, etc., but it may be observed upon all varieties of nerve-cell, even the smallest. The cells of Purkinje show it generally as a continuous investment or

composed of fine little squames. In the cells of the cerebral convolutions it is commonly uniform and continuous, although the reticular form may also be observed in some.

Shortly after the appearance of this paper, Lugaro (138) published a reply to it, necessitated by certain references to his observations and views. He explained that he had not given to the structure in question the value of an integral part of the nerve-cell, but only that of an interstitial substance. More recent observations had still more fully convinced him of the correctness of this view. The aspect of a cellular investment was only obtained when the cells were at a short distance from each other. Where they were crowded together the apparent investment tended to become confluent, so that there was produced that picture which Cajal had described and compared to the aspect of a honeycomb. He could not affirm with certainty what was the nature of the part that coloured, but he was inclined to regard it as an interstitial liquid.

Martinotti (188) has recently given an account of the results of further studies upon this supposed reticulum, carried out with the aid of certain special modifications of Golgi's silver method, which serve to darken the nerve-cells only at their periphery. In preparations by these methods the nerve-cells and their protoplasmic prolongations, even to the smallest ramifications, appear as if enveloped in a delicate, almost homogeneous membrane, consisting for the most part of fibrils, which run nearly parallel, and which sometimes cross and anastomose. This investment is specially well seen in the nerve-cells of the anterior and lateral horns of the spinal cord. The fibrils vary very much in thickness. They are generally straight, but may be tortuous. Occasionally they are continuous with a portion of the substance of the cell which gives the same reaction and has the same homogeneous appearance. On the inner aspect of the investment there are occasionally to be seen fibrils which dip into the unstained portion of the nerve-cell. This reticulum is absent from the axis-cylinder process. He still regards it as a neurokeratin investment, serving to isolate the cell-body and protoplasmic prolongations.

Reference has already been made to the reticular figure observed by Donaggio (55-58) in preparations by his own modification of the vital methylene blue method. This reticulum, which pervades the whole cell-body and at least the initial portion of the prolongations, was first described by him in 1896, and has since formed the subject of three additional communications. He now identifies it with the achromatic reticulum of the nerve-cell. Quite recently (59), by means of a modification of his method, he has been able to obtain preparations in which the peripheral portion is especially coloured, and concludes that it corresponds to the peripheral network of Golgi as well as to the

reticula lately described by Nissl (220), Ramon y Cajal (254), and Semi Meyer (198, 199). Nissl made his observations upon preparations by Bethe's method, Ramon y Cajal and Semi Meyer employed adaptations of the vital methylene blue method. Somewhat similar figures have also been described by Aldren Turner and William Hunter (289) in preparations by the latter process, and by Held (107) in Golgi preparations. Bethe (22*a*) has studied the peripheral reticulum in preparations by his own method, and describes in considerable detail its various special characters in different categories of nerve-cells. He has been unable to demonstrate it on the cells of the spinal ganglia. He regards it as something apart from the cytoplasm, and thinks that it probably represents the termination of axis-cylinder processes. He believes that while it is thus continuous externally with axis-cylinder processes of other cells, internally it establishes connections with the fibrils of the cytoplasm by numerous processes which dip down from the nodes.

Golgi and Martinotti regard this pericellular reticulum as having an isolating function. Nissl and Bethe maintain that it consists of nerve-fibrils, continuous with the fibrillar network which they believe to occur throughout the grey substance. Held, Semi Meyer, and Aldren Turner and Hunter believe that the reticula that they have observed are terminations of the axis-cylinders of other nerve-cells. Ramon y Cajal (254) maintains that the pericellular reticulum is merely the more superficial and coarser part of the spongionoplasm to which the coloration is sometimes limited in preparations by Ehrlich's method. It belongs to the cell, and has no connection with the nervous filaments that surround it. He regards the figures described by Golgi as produced by coloration of the interstitial cement, of the superficial part of the network, or, in certain instances, of pericellular nests. In any case, there is no reason to consider the superficial network as either an isolating investment or as a pericellular plexus (143).

Lugaro (140) is inclined to doubt the existence of anything of the nature of a true cellular membrane, and thinks that the cell is probably limited by fibres that are coarser than those situated more deeply. Donaggio (59, 60) agrees with Cajal except as regards the absence of peripheral connections. From the first he has observed that the fibres of the reticulum are continuous with those in the vicinity of the cell. On the evidence furnished by his new preparations, he now maintains that the peripheral portion of this reticulum is not merely a portion of the chromatic reticulum of the cell, but is in part at least neuroglial in nature, and he opposes the contention of Nissl and others that it consists of nerve-fibrils continuous with those of an interstitial nervous network.

It is clear that the subject of these pericellular reticula is one requiring further elucidation. At the same time, upon various grounds, I am strongly inclined to regard the view of Donaggio as essentially accurate, and as offering a sufficient explanation of Nissl's alleged observation of the direct passage of nerve-fibrils into the cell-body from its vicinity. The nerve-fibre terminations figured by Aldren Turner and Hunter have little or no resemblance to the reticula described by Donaggio, and may quite well be co-existent structures. Indeed the existence of such nerve-fibre terminations upon the nerve-cell bodies has long been regarded as an established fact. The exact forms assumed by the terminal organs, and the categories of cells upon which they occur, are the points regarding which further information has been needed, and the paper of Aldren Turner and Hunter is, I think, a valuable contribution to their elucidation. On the other hand, the figures described by Semi Meyer have a close resemblance to those of Donaggio and of Golgi. If the structures are identical, the individual interpretation of their anatomical relations and functional significance is in each case inconsistent with that given by the two other observers.

(7) *The Endocellular Reticulum of Golgi. Lymph Canaliculi of the Nerve-cell Protoplasm.*

In 1898, Golgi (90) described a new structural feature, revealed by modifications of his silver method, within certain nerve-cells (fig. 9). In the first of two publications dealing with the subject, he states that the structure in question consists of a delicate and beautiful reticulum hidden within the cell-body. It has a characteristic aspect on account of which, if the reaction happens to be partial, even little fragments of it can be recognised. It is best examined in mounting media of a lower refractive index than Canada balsam, such as glycerine. It consists of threads of irregular thickness, often somewhat tortuous, which freely anastomose with each other. Between its peripheral limits and the surface of the cell, there remains a zone of clear cell-protoplasm. While externally the reticulum is sharply limited, towards its inner aspect, around the nucleus, the threads dip down to different levels. Some of those derived from the peripheral plane present short offshoots which terminate as delicate pyriform swellings. Similar swellings may occur in the course of the threads, more especially at the nodal points. The reticular body has, in relation to the whole cell, a definite orientation, which, however, presents certain differences in the various categories of cells. In the cells of Purkinje (in which alone up to this time he had made an extensive study of it) the reticulum tends to assume the form of a

pear, with the narrow end directed towards the molecular stratum, in correspondence with the point of exit of the large protoplasmic prolongation, in which the various threads run together into one, two, or three terminal threads.

In his second paper (91) he states that he believes that this internal reticulum occurs in all the principal categories of nerve-cells, and gives a minute description of it as it appears in those of the spinal ganglia of the dog. Its characters here are very similar to those already described in the cells of Purkinje, but, at the same time, they present characteristic differences. It has a globose form, adapting itself (as in other situations) to that of the cell, and it has no special orientation. The reticular constitution is less distinct, giving place to what is rather an irregular filamentous apparatus, complexly convoluted, the threads of which it is difficult to trace. There is undoubtedly, however, the structure of a network. With advancing age, the reticular character seems to become more pronounced. Some of the threads are very fine and of regular thickness, others, in the same cell, may present a succession of dilatations and constrictions. They may give off some lateral processes which may terminate after a short course in rounded or oval swellings. There is generally a clear zone around the nucleus, but occasional threads appear to terminate in contact with it. He believes that this reticulum is something absolutely different from the Nissl-bodies and primitive fibrils described by others.

In a later communication (92) he gives an account of an investigation upon the differences presented by this endocellular reticulum of the spinal ganglion cells at various periods of life. He finds that the apparatus is well developed in the bovine foetus of from two to three months. At this period it presents itself only towards one side of the cell, while the nucleus is often placed towards the opposite side. It consists of short filaments disposed in various directions, rather than of a distinct network. The reticular character gradually becomes more pronounced. In the newly-born animal many of the figures are similar to those of the adult, but some still have the foetal characters. In a horse of twenty years the reticulum showed certain special features which he regards as pertaining to senility. It was placed towards the periphery of the cell, and arranged in more or less distinctly defined conical, globose lobes with their apices directed towards the perinuclear zone.

Veratti (297) has described similar figures in the nerve-cells of the sympathetic ganglia.

In my recent critical digest upon the normal and pathological histology of the nerve-cells (263), in giving an account of the observations of Donaggio upon his nerve-cell reticulum, I make a

statement from which some may have inferred that this author considers that the deep portion of his reticulum is identical with the endocellular reticulum of Golgi. Dr Donaggio has kindly directed my attention to the point, and I take this opportunity of correcting as far as possible any false impression that I may have given. He certainly did not endeavour to identify any portion of his reticulum with the endocellular reticulum of Golgi; on the contrary, he expressly states (57) that between the reticulum observed by him in the interior of the cell and the internal reticular apparatus described by Golgi, there are differences so profound that no comparison of the two structures is possible ("*un raffronto non ha ragione d'essere*").

Considerable light has recently been thrown upon the question of the nature of this remarkable structure. Holmgren (116, 116a) has observed in the interior of various nerve-cells of all classes of vertebrates, glomerular or reticular figures which he regards as lymphatic canaliculi. They are revealed owing to the fact that they remain colourless in preparations by certain staining methods. He describes them as having special walls and as continuous with similar minute extra-cellular channels. He thinks that they correspond to the endocellular reticular apparatus of Golgi. Studnicka (274), from independent observations, confirms the fact of the existence of these lymphatic canaliculi in the nerve-cells, but he does not consider that they have special walls, and maintains that they simply open upon the surface of the protoplasm. Nelis (204) has described somewhat similar figures, which, however, are sometimes situated at the periphery of the cells, instead of in the perinuclear zone. They give the cell a very characteristic appearance, to which he has applied the name *état spirémateux*. He is inclined to regard them as normal constituents of the cell. He excludes that they are the same structures as the reticular figures of Golgi. Lugaro, however, in a review of the paper, points out that they correspond to the figures described by Holmgren and Studnicka, and maintains that the hypothesis that they are identical with the endocellular reticulum of Golgi cannot be altogether rejected.

Bethe (22b) has also been able to observe these canaliculi in preparations by his own method. He considers that they have not a true membrane in their walls, that they have no connection with the blood-vessels, and that they are not identical with the endocellular reticulum of Golgi.

In a paper which has just come to hand as this chapter is about to go to press, Donaggio (305) gives an account of some observations of his own upon this subject, carried out with the aid of a modification of his methylene blue method. Except as regards certain details, he

confirms the conclusions of Holmgren and Studnicka. The most important new fact that he has observed is that the nucleus is surrounded by a narrow space communicating with two or three of the canaliculi. This perinuclear space is crossed by delicate threads which are attached to the nucleus, and which, as maintained by him in 1896, belong to the reticulum of the cytoplasm. He refers to the views of Adamkiewicz (306, 307) regarding the existence of an internal vascular apparatus in the nerve-cell. This authority, on the ground of observations made with the aid of injection of the vessels, has long maintained that in the spinal ganglia (and also in other parts of the nervous system) delicate vessels, derived from the arterial capillaries, transport the liquid part of the blood to the nerve-cells. One of these vessels, on reaching a cell, dilates and envelops it like a glove. A similar efferent vessel carries the fluid back to an arterial capillary. There is also another minute vessel which takes origin "in that empty space which goes by the name of the nucleus," and carries waste materials into the venous circulation. Holmgren supports Adamkiewicz's views, except as regards the existence of the central vein. He endeavours to explain the seeming injection of a channel of this nature obtained by Adamkiewicz, by supposing that the coloured fluid passed along a canaliculus, ruptured its walls, and then flowed around the nucleus. Donaggio suggests that the appearance is rather to be explained by the passage of the injection into his perinuclear space. He regards the existence of endocellular vessels as merely a hypothesis, and maintains that it is not yet possible to say if the canaliculi really represent lymphatic paths.

Colucci (308) directs attention to the fact that in 1897 he described a perinuclear halo as present in many forms of nerve-cell (43, 44). He did not attribute to it any special importance as an apparatus concerned with the nutrition of the cell, but is now inclined to regard Donaggio's view as probably correct, although not yet satisfactorily proved.

(8) *Morphological Classification of Nerve-cells.*

Nerve-cells have long been classified in accordance with their external form as *unipolar*, *bipolar*, and *multipolar*. Those of the last class are by far the most numerous.

In recent years attempts have been made to find the basis for a scientific classification in the various special features of their internal structure, but so far without much success.

In 1894, Nissl (211) maintained that the various arrangements presented by the chromatic substance in the protoplasm of the nerve-cells of the central nervous system, permits of the distinction of different types of cell. In the following year (213) he developed this idea

further, and gave an elaborate classification of nerve-cells according to their morphology. He divided them into:—

- (a) Cytochrome nerve-cells, or granules.
- (b) Karyochrome nerve-cells, or nuclear cells.
- (c) Somatochrome nerve-cells or cell-body cells.

The cytochrome nerve-cells are small elements which present only a nucleus, the protoplasm being indistinguishable (in preparations by Nissl's method). The nerve-cells of the granular layer of the cerebellum are an example of this class.

The karyochrome nerve-cells differ from the preceding only in the larger size of their nucleus. Examples are seen in the cells of the *substantia gelatinosa* of Rolando.

The somatochrome nerve-cells have a cell-body which completely surrounds the nucleus, has a distinct outline and contains a stainable substance.

Virtually, there are only two classes—the somatochrome and the karyochrome—the cytochrome cells being merely a variety of the latter.

Nissl divides the somatochrome cells into four groups, each of which again he divides into various types. The four groups are as follows:—

1. *Arkyochrome nerve-cells*.—The colourable constituent is arranged in the form of a network.
2. *Stichochrome nerve-cells*.—The colourable constituent is arranged in the form of parallel bands (motor cells, etc.)
3. *Arkyostichochrome nerve-cells*.—The arrangement of a network and of parallel bands is combined. (Cells of Purkinje, etc.).
4. *Gryochrome nerve-cells*.—The colourable constituent consists of small granules.

It is scarcely necessary to enter into the further details of this classification here. It has been much criticised, and little of it except its broad distinction of somatochrome and karyochrome nerve-cells is now in general use.

Van Gehuchten (93) thinks that the distinction between karyochrome and cytochrome cells is not justified, and that the division of somatochrome cells into different groups according to the special disposition of the chromatic substance has as yet only an exceedingly limited value. Colucci (42) considers that the view of the nerve-cells obtained by Nissl's method is too one-sided to allow of a classification being based upon it. Levi (149) is of opinion that nerve-cells have as yet been too little studied to permit of a morphological classification of them. In his description of the results of his comparative researches, he retains the classification of Nissl merely for convenience, stating at the same time that the criteria of his distinctions are different from those of Nissl. Marinesco (174) has justly remarked that a rational

classification of nerve-cells ought not to neglect either of the organised elements of the cytoplasm. A classification having for its basis the chromophile elements alone is incomplete. Goldscheider and Flatau (103), on the other hand, think that Nissl's classification is not yet sufficiently valued.

(9) *Mode of Connection of Nerve-cells.*

According to the neuron theory, which during recent years has been very generally regarded as an established doctrine, every nerve-cell is anatomically separate from other nerve-cells; when impulses pass from one nerve-cell to another, they do so only by way of prolongations of the first which terminate merely in contiguity with the prolongations or the body of the second.

The structural characters of the terminations of nerve-fibres upon the bodies of nerve-cells have lately been studied by several observers, including Semi Meyer (198, 199), Auerbach (3, 4, 5), Held (107), and Aldren Turner and Hunter (289). In most instances these endings seem to take the form of a fibrillar reticulum more or less completely investing the cell-body, but the various descriptions that have been given of their morphological details are as yet little in harmony with each other.

The neuron theory has always had its opponents, and recently it has been severely attacked from many sides. The anatomical evidence that has been brought against it, consists chiefly of the alleged demonstration of various forms of continuity between one nerve-cell and another. The occurrence of anastomoses between the nerve-cells of the retina has been asserted by some authorities and denied by others. Numerous observations have been recorded of the occurrence of twin cells, and of cells with lobes united to a central portion by means of fibrillar bridges. Capobianco and Fragnito (46) have lately maintained that direct connection of nerve-cells by their protoplasmic prolongations is a common histological feature, although one that does not readily admit of demonstration. Golgi still maintains his theory of the existence of a diffuse network formed by the branches of adjacent axis-cylinder processes. Vassale and Donaggio (299) have observed, in preparations by a modification of Golgi's silver method, appearances suggesting the existence of anastomoses between the gemmulæ of the protoplasmic processes of one nerve-cell and the fine ramifications of the axis-cylinder processes of other nerve-cells. Alexander Hill (108), from his studies with the chrome silver method, has been led to conclude that it is at least possible that the thorns of the protoplasmic processes of the cells of Purkinje contain the ends of the axis-cylinder processes of the granules. Held (106) believes that

he has observed in the adult a true concrescence, a relation of continuity and not simply one of contiguity, between the terminations of a branch of an axis-cylinder process, on the one hand, and the cell-body or protoplasmic process of another cell, on the other. He does not himself regard this observation as antagonistic to the neuron theory, but it is certain that many others have done so since the publication of his paper.

In 1897, Apáthy (6) published his important monograph upon the conducting element of the nervous system and its relations to the cells, which may here be referred to a little more in detail than has already been done. His investigations were made chiefly upon leeches and earth-worms, but he maintains that he has been able to confirm his main conclusions in observations upon certain vertebrates. He distinguishes between ganglion cells and nerve-cells. The existence of the latter as cells is for the most part only temporary, as the greater number of them early differentiate into neurofibrils. These he regards as the conducting elements and the true anatomical units in the nervous system. Each neurofibril, or *primitivfibrille*, may pursue an uninterrupted course through several ganglion cells. It is composed of numerous elementary fibrils (*elementarfibrillen*) through which, both within the ganglion cells and outside of them, numerous anastomoses are formed with other neurofibrils. The continuous intercellular reticulum that is thus formed he terms the *elementargittar*. Bethe (17, 19, 20, 22a) has carried out similar investigations in crustaceans and vertebrates, and is satisfied that he has been able to prove the existence of the intercellular reticulum described by Apáthy, but denies that there is an intracellular reticulum, excepting in the cells of the spinal ganglia.

It will be seen that these conclusions of Apáthy and Bethe are diametrically opposed to the anatomical conception upon which the neuron theory is based.

(10) *Nerve-cells of the Cerebral Cortex.*

I must refer the reader to the recent text-books upon the anatomy of the nervous system for an account of the vast array of facts that are now known regarding the forms, arrangements and connections of the nerve-cells of the cerebral cortex. It may, however, be of service briefly to enumerate here its typical layers. They are variously described. I state them as recently given by Lugaro (144), from without inwards:—

1. The plexiform layer.
2. The layer of the small pyramids.
3. The layer of the large pyramids.

4. The layer of the granules.
5. The layer of the deep pyramids.
6. The layer of the spindle-shaped and polymorphous cells.

II. PHYSIOLOGY OF THE NERVE-CELL.

(1) *The Neuron Theory.*

According to the neuron theory, every nerve-cell with its protoplasmic processes, axis-cylinder process and collaterals, is an anatomical unit, structurally independent of other nerve-cells; the nerve-wave passes from one cell to another by way of contiguous terminal arborisations of axis-cylinder processes and protoplasmic processes or nerve-cell bodies, never by anastomosing branches; neither the network of Gerlach, formed by anastomoses of protoplasmic processes of adjacent cells, nor the diffuse network of Golgi, formed by the branches of adjacent axis-cylinder processes, has any real existence.

For nearly a decade this theory of the constitution of the nervous system has been accepted by the great majority of neurologists, although certainly not by all. From the first it was opposed by Golgi, and recently (90, 91) he has signified his continued belief in the existence of his diffuse network. During the last three or four years, the case against the neuron theory has undoubtedly been greatly strengthened by the numerous recorded observations of various forms of direct connection between nerve-cells. Of these observations by far the most important are those of Apáthy and Bethe. The others need scarcely detain us here; they fall into two categories, namely, those that do not materially affect the neuron theory, and those that are of an isolated and unconfirmed nature.

It must be admitted, I think, that Apáthy (6) has established the fact that nerve-fibrils pass uninterruptedly from cell to cell in certain invertebrate animals. His previous high reputation as an able and accurate observer in similar fields, almost precludes any suspicion that he has been misled, as less experienced workers so frequently are, by fallacious appearances due to the technique employed. But when we pass from his purely anatomical observations to the generalisations that he bases upon them, it is scarcely possible to allow that he speaks with the same authority, and it is in the latter rather than in the former that the neuron theory is seriously assailed.

Bethe (17, 19, 20) considers that he has obtained histological evidence sufficient to prove the existence of intercellular continuity of the neurofibrils through a diffuse network in vertebrate animals, as well as in certain invertebrates. He believes that the fibrils do not anastomose with each other except in this diffuse network, and maintains that the cell-bodies have therefore only a trophic function, and

that it is in the diffuse network that the important functional activities take place. As will presently be seen, however, the grounds of these inductions are such as to render them open to very effective criticism.

Bethe has also endeavoured to disprove the neuron theory by means of a physiological experiment. In *carcinus maenas* he separated from their fibrils all the ganglion cells supplying the second antenna, and found that he was still able to induce reflex movements of flexion and extension in the organ. He thinks that this result can only be explained on the view that the sensory and motor fibrils form a continuous network outside the ganglion cells.

Against the attack that has been made upon it by Apáthy, Bethe and Nissl (220), the neuron theory has been defended by Lenhossék, Lugaro, van Gehuchten and Barker, as well as by numerous other eminent neuro-histologists.

Lenhossék (160), whose article is a critical review of one of Bethe's recent papers, can find in the discoveries of this observer, as also in those of Apáthy, nothing that really contradicts the neuron theory. He notes that Bethe admits that he has not been able to demonstrate direct connections between the finest fibrils of one neuron and those of another in *carcinus maenas*. He does not regard the results of the experiments upon this animal as furnishing proof of the existence of such connections. The cellular prolongations contain protoplasm identical with that of the cell-body, and it is therefore quite conceivable that the impulses which occasioned the reflex movements were transmitted from sensory fibres to contiguous motor fibres. Apáthy's conception of the central neuropil as a true diffuse elementary network has not, he thinks, been conclusively demonstrated; it at least requires confirmation.

Lugaro (142, 144) has made two exceedingly able contributions to the controversy. Only the more recent of them needs be noticed in detail here. It is contained in his brilliant address on the recent progress of the anatomy of the nervous system in relation to psychology and psychiatry, delivered to the tenth Congress of Italian Alienists, which was held at Naples in the autumn of 1899. In the first place, he maintains that the demonstration of the non-existence of intracellular reticula would not touch the fundamental part of the neuron theory. At the same time, he points out the weakness of the evidence that Bethe has brought forward in support of his conclusion that the fibrils do not anastomose within the nerve-cells of vertebrates. The occurrence of Y-shaped divisions (which Bethe admits) is a sufficient fact to render it impossible to exclude absolutely the existence of anastomoses. Moreover, other workers have clearly observed such anastomoses, more especially in the cells of the spinal ganglia. (Bethe (22a) now admits the existence of a true

network in these cells.) In the second place, he maintains that if proof were forthcoming that the cellular body is only a trophic centre, and that the nervous actions occur at the intercellular connections, the neuron theory would not be injured thereby. He further contends that even the denial of free terminations, and the demonstration of the existence of a continuous intercellular reticulum, would not deprive the neuron theory of its value in so far as it affirms embryological and trophic autonomy; and up to a certain point even physiologically it would scarcely be altered, for there is little difference between transmission by contact and transmission by uninterrupted and homogeneous continuity of fibrillar ties. The demonstration of a fixed interstitial reticulum would be fatal only to hypotheses such as that of the variability of the nervous connections. But the reticulum of Bethe is far from having yet been demonstrated. Its existence is only a supposition. Bethe admits that he has not yet been able to establish the direct connection of fibrils of two different neurons. He bases his position especially on the fact that in his preparations he has never observed free terminations, and that the fibrils can always be followed to one of the surfaces of the section. The weakness of this induction is perfectly apparent when we reflect that the method of staining employed by Bethe is one that necessitates the use of extremely thin sections. In such preparations it is very difficult, if not indeed impossible, to judge accurately of the continuity or contiguity of single fibrillar elements, and of their free termination or artificial interruption. It is a singular fact, says Lugaro, and one that merits being drawn attention to, that Bethe, while admitting that he has not observed either direct connections or free terminations, ends by maintaining the occurrence of the first and denying that of the second. With regard to Apáthy's observations, he remarks that the demonstration that this authority has given of undoubted anastomoses between the nerve-cells of peripheral and (with greater rarity) central organs of some invertebrates, does not permit of general inductions. Such anastomoses may represent an arrangement compatible with relatively simple and constant functions, but incompatible with those that are more complex and variable. He thinks it is possible that in phylogenetic evolution the anatomical relations between neuron and neuron are differentiated in two opposite directions; in the one direction the nervous system, endeavouring to perfect invariable (and also unconscious) reflex functions, has found advantage in the fusion of the independent embryological neuron individuality; in another direction, endeavouring to perfect the capacity of associating in a variable manner the most different combinations of stimuli, it has found advantage in the conservation of

the anatomical independence of the nerve-units and in the development of the active and plastic power of modifying connections by simple contiguity. It is at least very improbable that in the cerebral cortex of the mammalia there occur, between the nervous elements, relations entirely identical with those that are to be observed in the walls of the intestine or ganglionic cord of the worm. A fixed reticulum permits of our imagining the mechanism of a reflex, but not that of a variable associative process, or of a new acquisition of intelligence. He further maintains that Bethe and Nissl have not taken into account the many positive arguments that go to support the neuron theory. For them the laws of the orientation of the axis-cylinders, the laws of their development and of their degeneration, have no weight; they reduce the whole question to one of the existence of free terminations. They regard these free terminations as nothing more than an appearance due to the interruption of the reaction of Golgi. But, if this were really so, the reaction would not circumscribe itself within certain constant limits, marked by special morphological features, such as the spinous appendages, which vary in aspect and number in every single category of elements, and which even modify in correspondence with functional state. This shows that the interruption is not accidental, but a sign of a morphological limit. He cannot admit the accuracy of the assertion that Golgi's method does not stain the fibrils. He recognises the high importance of the observations of Apáthy and Bethe, but maintains that they have not yet overthrown the various principles that constitute the theory of the neuron, among others, that of the existence of free terminations in virtue of which each neuron appears independent. One of the advantages of this theory is precisely that it brings the nervous system into line with the cellular doctrine. The hasty conclusions of Bethe and Nissl can only be regarded as of the nature of a backward step.

Van Gehuchten (97) thinks that the neuron theory has not been affected by any of the attacks that have been made upon it. He doubts if the intercellular fibrils described by Apáthy are nervous elements at all, and considers that we should await the results of researches by other observers with the same methods before judging of the value of Apáthy's conclusions. He maintains that Bethe's affirmation that in all animals there is an elementary network through which continuity is established between the different nervous elements, is nothing more than a hypothesis.

Barker (23) admits the great value of Apáthy's observations, but is sceptical about the accuracy of his deductions and hypotheses.

It seems to me that Lugaro's hypothesis that intercellular continuity of neurofibrils is compatible with the comparatively elementary

nervous functions of some of the lower invertebrates, but not with the complex operations of the nervous system of animals higher in the zoological scale, is one of great importance in this controversy. It would explain the exact value to be attached to Apáthy's discoveries, and would permit of the retention of the neuron theory, altered only in respect of its being qualified by an exception of great scientific interest, but of no practical importance. A similar explanation of Apáthy's observations has been suggested by van Gieson (99a). If, however, Bethe's elementary network can be proved to exist in vertebrate animals, the neuron theory must fall; no attempt to explain its consistency with such an anatomical arrangement would ensure its continued general acceptance. But Bethe has not yet proved the existence of this network. His view is nothing more than a hypothesis, the evidence in support of which is absolutely insignificant when set beside the great mass of accumulated evidence against it. I think that the present position of the controversy justifies the conclusion that no discovery that has yet been made really weakens the case for the neuron theory.

(2) *Functions of the Achromatic Part of the Protoplasm.*

The great majority of authorities are agreed that the fibrillar portion of the achromatic substance subserves the function of conduction of the nervous wave. Cajal (252), Lenhossék, and some others, however, consider that we are not warranted in attributing the performance of this function to the fibrils alone. The non-organised portion of the achromatic substance is believed by Marinesco to be the seat of intense chemical phenomena, and of such importance for the nervous element as to be appropriately designated the *trophoplasm*. That this substance is the seat of important metabolic changes is amply confirmed by other observers, more especially by Giuseppe Levi from his study of the fuchsinophile granules.

(3) *Functions of the Chromophile Elements of the Protoplasm.*

According to van Gehuchten, Nissl, Lugaro, Lenhossék, Cajal, and many others, the chromophile substance of the protoplasm is "a material of reserve destined to serve for the nutrition of the nervous elements." Marinesco (169, 174, 183) further believes that "it serves to augment the difference of potential of the centrifugal nerve-wave."

Lugaro (137) expressly states that he believes that the chromatic substance has an important and indispensable part in the functional metabolism of the nerve-cell. Bevan Lewis (165), in stating that "Lugaro regards Nissl's granules, so far as function is concerned, as

having a passive rôle," has unwittingly misrepresented the view of the Italian neurologist, whose use of the term "passive" in this connection has reference not to function, but to the morphological relationship of the chromatic substance to the achromatic fibrils (Lugaro, 125, 137).

The contention of Goldscheider and Flatau (102), that the Nissl-bodies have no vital importance for the nerve-cell, has been fully answered by Lugaro (137) and Marinesco (181).

The histological evidence that the chromatic substance is utilised during functional activity of the nerve-cell (as maintained by Mann in 1894) was for long of a somewhat unsatisfactory kind, but recent observations have placed the matter beyond question (see page 226).

(4) *Functions of the Protoplasmic Prolongations.*

There are two opposing views at present held with regard to the function of the protoplasmic prolongations. Firstly, there is that of Golgi, according to which they have a merely nutritive function without subserving that of nervous conduction; and secondly, there is that supported by the large majority of other authorities, according to which this portion of the neuron is essentially related to nervous conduction.

Several observers, on the ground of alleged observation of varicosity of the protoplasmic processes advancing centripetally in certain morbid conditions, have maintained that these processes must have a nutritive function. The fallacious character of such evidence has been repeatedly pointed out by Lugaro.

(5) *The Law of Dynamic Polarisation.*

The enunciation of this law has very commonly been attributed to Ramon y Cajal (240), but van Gehuchten (93) has maintained, evidently upon good grounds, that it was really he who was the first to advance it. According to this law or theory (which has been very widely accepted), as originally stated, the nervous current is cellulipetal in the protoplasmic processes and cellulifugal in the axis-cylinder process; in other words, the dendrites are the organs of reception of the nervous impulse, the axon is the organ of its distribution and application. In order to obviate certain objections to this theory, and to permit especially of its being applied to the case of the cells of the spinal ganglia, both Ramon y Cajal (251) and van Gehuchten (93) have proposed to alter slightly its formula. The former thinks that there may be a direct passage of the nervous current from a dendrite to an axon arising from it, and that we should therefore speak of the

nerve-current as *axipetal* (instead of *cellulipetal*) in the dendrites, and *dendrifu*gal (instead of *cellulifugal*) in the axis-cylinder process. Van Gehuchten regards the large protoplasmic processes and the cell-body as forming together the true cellular body, and believes that the conduction is here indifferent, occurring in any direction. Tanzi (279) thinks that Cajal's new theory is unnecessary, and is inclined to admit the correctness of van Gehuchten's view, but insists more upon the fact of the fibrillar structure of the prolongations, and therefore of the possibility of conduction in them in both directions. He points out that Cajal's imagined correction of the law of dynamic polarisation does not remove its essential defect, which consists in the necessity of considering as gigantic dendrites the peripheral sensory fibres coming off from the cells of the spinal ganglia, although they are medullated and do not differ in any respect from the nervous prolongations. Lugaro (133) considers that neither of the new interpretations is necessary, since the fibrillar structure of the prolongations admits of a double conduction and of the separate existence of dendrite and axon in a common trunk, such as that given off by the cells of the spinal ganglia. Striking confirmation of this opinion of Lugaro's has been furnished by the results of some more recent investigations carried out by van Gehuchten (96, 97). He found that under the action of nicotine, which has been shown by Langley to destroy conduction in the body of the nerve-cell, there was obstruction of the afferent impulses which pass by way of the posterior roots of the spinal nerves. From this experiment, which he repeated several times with the same results, van Gehuchten concludes that an impulse carried by a peripheral nerve only reaches the cord after having passed through cells in the spinal ganglia.

(6) *Functions of the Cell-body.*

The cell-body, in virtue of the fact that it contains the nucleus, is clearly the trophic centre for the whole cell-element. That this is so is fully borne out by experimental evidence. But there seem to be the strongest reasons for believing that the cell-body has also other special functions to perform, although there are some authorities who would limit its rôle to that just stated. According to the law of dynamic polarisation, the nervous wave is received by the terminations of the dendrites, carried to the cell-body, and thence to the axon. Now, the best authorities on the subject believe that this nerve-wave, arriving at the cell-body, is there essentially modified and reinforced before being discharged by way of the axon. This is the teaching of the two Continental neurologists who have given most attention to the question, and who, from the vast range of their experimental observa-

tions, have the best title to be heard upon it. I refer, of course, to Marinesco and Lugaro.

According to Marinesco's theory of the function of the chromatophile elements, in the cell-body the nerve-wave has its potential energy largely increased in virtue of the chemical changes which occur in these elements. He says (174), "It is owing in part to the modifications which the chromatophile elements impress upon the nervous wave that the nerve-cell becomes a source of energy. . . . The mechanical conception of nervous phenomena which I have just formulated in this work is in harmony with many physiological and pathological phenomena. In fact physiology teaches us that the nerve-cell is a source of energy, and this energy, according to my view, is due at least in large part to the modifications which the chromatophile elements impress on the nervous wave which traverses the cell." In several other papers he defends the same opinion, maintaining that in the body of the nerve-cell there takes place a liberation of force which serves to augment the nerve-current as it traverses the cell. Lugaro's views upon this subject have also been often and clearly expressed. I need quote only one passage:—"From facts regarding the structure of the cell-body it is seen that this is not a simple conductor but a modifier of the nervous wave, whence the necessity of the afferent current traversing it in every case before passing in a modified form to the efferent prolongation" (134).

Gowers (100) has recently taught that the cell-body does not generate nerve-force, and that the fibrils "can merely conduct through the cell-body as they do elsewhere in their course." This view is also maintained by Bethe and some others. It is advanced mainly as a corollary to the conclusion that the fibrils pass through the cell-body without communicating with each other. But, as we have seen, the great weight of authoritative opinion at the present day is against this conclusion and in favour of the existence of a perinuclear reticulum, out of which there arise most, although it may be not all, of the fibrils of the axis-cylinder process.

(7) *Structural Changes accompanying Modifications of Functional State.*

A long series of very careful experimental observations has been conducted during the last ten or eleven years with a view to the elucidation of this question. I have endeavoured to give an account of what is of chief importance in the results of these researches in my recent critical digest upon the histology of the nerve-cell (263). For a time the conclusions of the different workers were greatly at variance with each other, but the more recent observations of Pergens (230, 231), Pognat (236), Pick (235), Luxenburg (161, 162), Pellizzi (228,

229), and Guerrini (104) have made it possible to understand pretty clearly, at least the main essential facts.

The two special functional conditions to which definite structural changes may now be said to have been proved to correspond, are (1) normal activity, and (2) exhaustion of energy or fatigue.

During normal activity the chromophile substance is utilised by the cell and slowly diminishes in quantity. At the same time the fuchsinophile granules of Levi increase considerably in numbers. The nucleolus undergoes an increase in volume, and the particles of chromatin adherent to it consequently tend to become more elongated. During rest the chromophile substance gradually accumulates again, the fuchsinophile granules diminish in numbers and the nucleolus assumes a smaller volume.

When the energy of the cell is exhausted by prolonged or excessive activity, the cell-body and the nucleus are distinctly diminished in volume; the chromophile substance of the cytoplasm is small in amount, and appears diffusely granular, instead of forming local aggregations.

(8) *Physiological Regressive Changes.*

Granting that senility may be regarded as a physiological condition, there are certain nerve-cell changes constantly associated with it which we may perhaps correctly designate by the above title. Hodge (114) studied these changes in man and in the bee, and observed not only alterations in the nucleus and pigmentation and vacuolation of the protoplasm, but also a complete disappearance of a large percentage of the cells. Pognat (237), who supports the views of Hodge, has observed in the spinal ganglia of aged animals nerve-cells profoundly altered, and invaded by leucocytes. Dr David Orr (264) and I have described the changes observed in the cortical nerve-cells in a case of apparently uncomplicated senility in a woman aged 90. Most of the cells showed a large collection of yellow pigment in their interior, often replacing the greater part of the protoplasm. A large proportion of these cells appeared in other respects perfectly healthy, showing very clearly marked and abundant Nissl-bodies in the remaining protoplasm, and a normal number of processes (fig. 19). Very many of them, however, showed further changes of a disintegrative character, consisting in progressive atrophy of the protoplasmic processes, shrinkage of the cell-body and loss of its angular form, dissolution of the Nissl-bodies and loss of their affinity for basic dyes, and disintegration of the nucleus (fig. 20). In many instances there were left only a few stained granules representing the remains of the nucleus and Nissl-bodies, accompanied generally, but by no means always, by some scattered granules of yellow pigment.

Marinesco (184), in his recent paper upon the evolution and involution of the nerve-cells, records a series of very interesting observations upon the special characters presented by various categories of nerve-cells from intra-uterine life until extreme old age. He thinks it is certain that the nerve-cells decrease in size in normal senility. They also exhibit certain very distinct structural changes, which are seen in their most typical form in the large pyramidal cells of the cortex, and in the root-cells of the cord. The chromatophile elements diminish in volume, especially in the perinuclear region; they also diminish in number and tend to become rounded instead of angular. At the same time many of the cells contain a collection of pigment granules, the formation of which, as already stated, he regards as generally associated with the process of involution of the cell. These changes do not affect all the cells in an equal degree. Cells having an almost normal appearance may be observed alongside others in an advanced stage of involution.

It seems very probable that these regressive changes, which are typically seen in senility, occur to a slight extent throughout life, increasing as age advances. There seems at least at present to be no other hypothesis that will explain the presence of the occasional disintegrating cell that may be found in even the healthiest brain obtained under the most favourable conditions. Luzenberger (163) observed in the cerebral cortex of the guinea-pig, cells of this nature in very limited numbers, surrounded by quite normal cells. He concluded that their occurrence could not be accounted for by defects of *technique*, and that it could only be explained by supposing that in normal conditions a certain number of cells are in a regressive phase which ends in complete destruction. He described this "involution of normal life" as consisting in the homogeneous rarification of the cell with destruction of the nucleus. Dr David Orr (264) and I, on the ground of observations of our own, have supported Luzenberger's hypothesis, and insisted upon its practical importance. It would seem that even in the healthiest nerve-cell community there are some sickly individuals,—cells which from some cause, hereditary or acquired, have become unable to maintain a normal correspondence with their environment.

(9) *The alleged Amœboidism and Plasticity of the Nerve-cell.*

A large number of observers, chiefly belonging to the French and Belgian schools, have maintained, partly from experimental evidence, partly upon purely theoretical grounds, that the protoplasmic prolongations of nerve-cells exhibit functional contractility. They maintain that contraction of them occurs in fatigue of the nerve-cells, and that

it is also capable of explaining sleep, hysteria, and many other cerebral phenomena. Lugaro (139), on the basis of a series of entirely new experiments, denies that the processes of nerve-cells contract to any important extent in different functional states, and maintains that only the gemmulæ undergo movements of retraction and expansion, and that not retraction of these processes, but general expansion of them, is characteristic of sleep. His experimental results, obtained with the aid of a much superior technique, certainly go far to prove that the histological evidence of contraction of the protoplasmic processes obtained by other observers is entirely fallacious. Further evidence in support of this view has recently been obtained by Weil and Frank (303), who, from the results of a series of observations specially undertaken to test the point, have been led to conclude that the varicosities, which so many writers have considered as indicative of neuron retraction, "are to be regarded as artefacts of the Golgi method." They found that in preparations by the slow method there was as a rule an almost absolute freedom from varicosities, while the same material, treated by the rapid methods and by the method of Cox, generally showed them in considerable numbers.

In connection with this subject, it should be mentioned that in making preparations by the fresh method of Turner (291), a beautiful demonstration of the remarkable elasticity of the nerve-cells may be obtained. But it is, of course, impossible to affirm that this elasticity postulates anything as to their functional plasticity.

(10) *Lugaro's Theory of the Functional Contractility of the Gemmulæ.*

While Lugaro (139) denies the amœboidism and plasticity of the nerve-cells in the sense maintained by Rabl-Rückhard (260), Lépine, Duval, Van Gieson (99a), and others, he believes, as above indicated, that the gemmulæ are capable of rapid movements of retraction and expansion which have an important functional significance. He thinks that during sleep there is general expansion of these processes, implying multiplication of contacts and wide diffusion, and consequent weakening of stimuli. In conditions of fatigue their contractility is greatly diminished; after rest the capacity to contract is fully restored. During psychical activity the gemmulæ undergo continuous movements of retraction and expansion, whereby contacts with the terminations of the axis-cylinder processes of other cells are broken and made. He believes that a nerve-cell on receiving a stimulus must, while elaborating it, retract all its drawbridges in order to prevent the access of other stimuli. Such modifications of the gemmulæ must occur in a very large number of neurons in correspondence with every elementary state of consciousness, but they do not last longer than the said act of

consciousness, the gemmulæ quickly reassuming their condition of expansion and readiness to receive new impressions.

(11) *Lugaro's Hypothesis regarding the Distinctive Functional Values of the Intra-neuronic and Inter-neuronic Elaborations.*

In the course of the address which he delivered last year to the tenth Congress of Italian Alienists, Lugaro (144) enunciated the hypothesis that two distinct elaborations of external impressions occur in the nervous centres, one inter-neuronic, at the terminations of the afferent fibres, and the other intra-neuronic, between the wave conveyed by the dendrites and the dynamical processes that develop in the interior of the cell-body; and that the first corresponds to the phenomena of consciousness or perception (*fenomeni di conoscenza*), the second to the affective states.

It is apparent that a hypothesis of this nature, if supported by facts that furnish strong presumptive evidence in its favour, must be one of the highest importance in relation to the pathology of insanity. No person who will take the trouble to look carefully into the published communication will venture to doubt that Lugaro has brought forward such evidence. It is impossible, however, to convey in brief form an adequate impression of the grounds of this hypothesis, which is led up to by fourteen pages of the printed communication, and afterwards defended in nearly as many more. I shall, therefore, not attempt to present here the full case that Lugaro makes out in support of it, but merely endeavour to give some indication of the line of argument he adopts.

He gives reasons for believing that an afferent nervous wave, having reached the termination of the afferent fibre, modifies the physico-chemical state of the termination, and provokes in consequence a physico-chemical modification throughout a certain area in its neighbourhood, and that this modification in its turn acts by physico-chemical stimulation on the parts of the other neurons with which the termination is in intimate relation of contiguity, but not necessarily of contact. The fact that the nervous current undergoes a retardation when it passes through the grey substance—that is to say, from neuron to neuron, proves that in these passages there is not a simple transmission by contact, but a true transformation of energy. He shows how this physico-chemical theory of the transmission of the nervous wave would explain certain morphological features of some of the inter-neuronic connections which otherwise have no significance. His hypothesis of the diversity of the seat of the perceptive and affective phenomena is suggested to him chiefly by consideration of the tendency to stability on the part of the per-

ceptive acts on the one hand, and the variability of the affective colouring of the more simple sensations and perceptions on the other. He illustrates the fact of this difference more especially as it is manifested in the operations of the olfactory organ, pointing out how the affective colouring of a particular impression received by it varies in different species of animal and, within certain limits, in individuals of the same species, and even in the same individual, according to the functional state of the digestive organs and the desire for food, whereas from the objective side the odour is in all conditions recognised as identical. The inter-neuronic actions tend to be constant, and therefore to them he attributes the elaboration that gives a constant result. The more variable elaborations he refers to the cellular body, which has been shown by experimental observation to be that part of the neuron that is most susceptible to the influence of abnormal nutritional conditions, and especially to the action of toxines. He further illustrates how the sensory impressions have their affective colouring varied by the dynamical state and nutrition of the neurons, while their objective significance does not vary. He sums up the thesis that he has been defending, as follows:—The external impressions arrive at the peri-cellular and peri-dendritic arborisations, and there assume relations corresponding to the objective relations: whence the perceptive act. The product elaborated and received by the dendrites reaches the cell-body in which a new effect is produced, a subjective modification in accordance with its state of nutrition and specific constitution: whence the affective act. According to the character that the process of intra-cellular elaboration assumes, one has finally various forms of discharge from the cellular body by way of the axon.

For information upon all that relates to the physiology of groups of neurons, as distinguished from that of the individual cell, including the important hypothesis of Flechsig regarding the existence of associative centres, I must refer the reader to the recent text-books upon the anatomy and physiology of the nervous system, in most of which these matters are now fully explained.

III. EXPERIMENTAL PATHOLOGY OF THE NERVE-CELL.

During the last ten years a very large number of investigations have been made upon the reaction of nerve-cells to various simple pathological conditions experimentally produced. As the result of these investigations a great amount of light has been thrown upon the meaning of certain abnormal appearances to be observed in the nerve-cells of the human subject, which otherwise must for long have

remained almost completely obscure. In this subsection I shall endeavour to give a short account of the more important facts that have been ascertained.

(1) *Changes following Section of the Prolongations.*

The first observers to investigate this subject with the aid of suitable histological methods—that is to say, with those that reveal the chromophile elements of the cytoplasm—were Nissl (206) and Onuf (225), but our present knowledge of it we undoubtedly owe chiefly to the labours of Marinesco, Lugaro, and van Gehuchten, and in a less degree to those of R. A. Fleming (79, 80, 81), Colenbrander (49), Marina (189), Bunzl-Federn (24), D. Mirto (192), Warrington (300), W. H. Cox (50), Foà (84), and Ballet and Faure (28).

There is still considerable difference of opinion as to the exact changes that occur, the course they follow, and the conditions that specially influence them. It is now evident, however, that these differences have in large part arisen owing to the fact that the reaction of the nerve-cells varies considerably in accordance with certain conditions, such as the nature of the lesion (section, excision or evulsion), its distance from the centre, the special neurons injured (spinal or cranial, motor or sensory), and the species of animal experimented upon. The typical changes will perhaps be best understood from some of the descriptions that have been given by Marinesco, Lugaro, and van Gehuchten.

In 1896, Marinesco (169) distinguished two phases in the series of changes that affect the fibres of the central end of a cut nerve and their cells of origin. In the first, the central end of the nerve remains intact, while in the cell there is produced a *réaction à distance*, characterised by more or less complete dissolution of the chromatic elements of the protoplasm, a morbid change which he here designated *chromatolysis*; in the second, there is disintegration of the trophoplasm (a term which at this time he applied to the whole of the achromatic part of the cell) and changes in the central end of the cut nerve. The first is the degeneration of Nissl; the second is the degeneration of Hayem and Forel. These changes differ from Wallerian degeneration, which has its seat in the peripheral end of the cut nerve. In a later paper (174, 175), he distinguishes three phases in the changes that occur in the nerve-cell after section of its axis-cylinder—the reactive, the degenerative and the reparative. The time of the onset of the reactive phase varies considerably in accordance with certain conditions. After section of the hypoglossal in the rabbit, it could be observed in from two to three days; in the dog only after four or five

days. He gives a description of the reparative phase as observed in the hypoglossal nucleus of the rabbit after section of the nerve. It may be clearly observed in some cells by the twenty-fourth day, when reunion of the ends of the cut nerve commences to take place. The cells undergoing repair are increased in volume, and stain deeply, owing to the density and large volume of the newly-formed chromatophile elements. After forty-six days a greater number of cells have undergone repair. There are now no cells in the reactive phase, but there are still many pale degenerated cells. After seventy-three days the density of the chromatic substance, and the volume of the cells undergoing repair, are still further increased. After ninety days the cells have attained their maximum of hypertrophy. After this they diminish in volume, and in an animal killed after 111 days the hypoglossal nuclei of the two sides are indistinguishable from each other. The rapidity of the repair depends chiefly upon two factors—the age of the animal (being more rapid in young animals) and the union of the two cut ends of the nerve. If union does not take place the number of cells that degenerate and disappear is increased.

Lugaro (128) describes the changes that occur in the large cells of the anterior horn of the spinal cord after section of the sciatic nerve as follows:—In the first phase of alteration (reactive phase), one observes disintegration of the chromatic part, starting from the origin of the axis-cylinder; the cell otherwise preserves its normal form and the nucleus its position (fig. 10). With hæmatoxylin staining it can be seen that the achromatic part, in the prolongations and in the cell-body, perfectly preserves its delicate striation, which, indeed, is often rendered more evident by the disintegration of the chromatophile particles. In the more advanced stage (degenerative phase), the chromatolysis extends to the greater part of the cell-body, and the nucleus is distinctly displaced (fig. 11). The chromatolysis advances gradually to the protoplasmic processes. In hæmatoxylin preparations the delicate striation has now disappeared from those parts of the cell-body that are most altered, and from the protoplasmic prolongations involved in the degenerative process. When the degenerative phase is at its height, the chromatic part appears powdery, and the striation is completely lost. From an examination of the same tissues by Golgi's method, he concluded that it is only with the initiation of the destruction of the cell (degenerative phase) that alterations become recognisable with this method.

From similar experiments upon the nerve-cells of the spinal ganglia he ascertained the important fact, which has since been fully confirmed, that although these cells undergo very marked changes, of the kind just described, after injury to the peripheral branch of their prolongation, they are not morphologically affected by section of their central branch

(130). He explains this difference by supposing that the sensory element resents specially the suppression of external stimuli, the motor element the suppression of the discharge of the energy which it elaborates.

Van Gehuchten (94) has described two stages in the alterations that occur in the cells of the spinal cord, firstly that of the breaking down of the chromatic particles, and secondly that of their restitution. The first stage is characterised by rapidly spreading destruction of the chromatic elements from the centre to the periphery, increase in the volume of the cell and displacement of the nucleus. It begins about forty hours after section of the nerve, quickly attacks simultaneously all the nerve-cells connected therewith, and lasts from fifteen to twenty days. The stage of restitution then begins, in which the chromatic elements slowly form again, and the cells exhibit a pycnomorphous condition. His conclusions differ in an important respect from those of Marinesco and Lugaro, for he maintains that the changes observed are due merely to a simple disturbance of the cell which affects exclusively the chromatic substance. In effect he asserts that the occurrence of the degenerative phase has not been proved. He believes that destruction of cells is very slight, and to be attributed when it occurs to loss of the nucleus owing to exaggerated displacement from swelling of the cell. He states that in the cells of the spinal ganglia, on the other hand, reorganisation of the cell does not occur, but complete degeneration and destruction of it. He attributes this difference between the behaviour of the sensory cell and that of the motor cell to the fact that the former is deprived of the trophic influence exercised by its physiological excitement, while the latter is not.

A controversy on this subject has recently been carried on between van Gehuchten (95) and Marinesco, the former, in opposition to the latter, maintaining, among other points, that section of a motor spinal nerve is not constantly followed by chromatolysis in the cells of origin (especially in the rabbit), that repair of the cellular lesion takes place whether the cut ends of the nerve unite or not, and that degeneration of the cells of the human cord in correspondence with the loss of a limb is due to some other cause than merely the lesion of the nerves. Marinesco (185), on the ground of his own experimental observations, defends his previous conclusions upon these points.

It has now been fully established through the observations of Monakow, Dotto and Pusateri (67), Ceni (38), Ballet and Faure (28), and Marinesco (182), that the giant and large pyramidal nerve-cells of the cerebral cortex likewise undergo degeneration of the secondary type, proceeding in many instances to complete destruction of the element, after injury to their axis-cylinder prolongations.

(2) *Changes produced by various Poisons (including Bacterial Toxines).*

The earliest observations upon the effects of poisons upon nerve-cells, carried out with the aid of suitable staining methods, appear to have been those of Nissl (207) with lead and arsenic, of which an account was published in 1892. Since that time the alterations produced by almost innumerable different toxic agents, including those generated by various pathogenic micro-organisms, have been most minutely described by a very large number of observers.

The characters of the lesions differ very widely in accordance with the toxic agent employed, but in practically every instance the first alteration has been, as in the case of the lesion resulting from section of the prolongations, a disintegrative change in the chromophile elements (figs. 12 and 13). This chromatolysis begins in most instances at the periphery of the cell, but with some poisons it is diffuse from the first. Among the other changes that commonly occur are disintegration of the achromatic part, vacuolation, displacement of the nucleus, and, in advanced stages, atrophy and varicosity of the protoplasmic processes. If the action of the poison is prolonged and sufficiently intense, large numbers of the cells may undergo complete disintegration.

An account of the literature of this subject up to the end of 1898 will be found in my recent critical digest (263). The laws that appear to govern the action of toxines upon nerve-cells are considered under the General Pathology of the Nerve-Cell (p. 253).

(3) *Changes produced by other Experimental Lesions.*

The morbid changes that affect the nerve-cells in conditions of inanition, pyrexia, uræmia, anæmia, and insomnia, have also been the subject of a large amount of experimental investigation. They are of great practical importance, as they tend to complicate the pathological picture in cases of nervous disease in the human subject, and therefore require to be recognised and discounted before conclusions of any value can be formed regarding the relation of morbid appearances in the nerve-cells to the special clinical symptoms.

Inanition.—The changes in the nerve-cells in this condition have been studied by A. Monti (194, 195), Pernice and Scagliosi (227), K. Schaffer (267), Lugaro and Chiozzi (145), Ganfini (99), Daddi (64), and Müller and Manicatide (190).

Monti, using the method of Golgi, observed varicose atrophy of the protoplasmic prolongations. Pernice and Scagliosi observed in fowls deprived of water alone complete disappearance of the chromatic substance and vacuolation, with Golgi's method deformity of the cell-

bodies and fragmentation of the dendrites. K. Schaffer observed in the nerve-cells of the cord in rabbits chromatolysis, vacuolation, and the homogeneous change of Sarbò in the nucleus. The lesions were specially severe in animals deprived of water as well as of food. Lugaro and Chiozzi, from observations upon dogs and rabbits killed after various periods of starvation, concluded that the nervous elements remain for a long time intact, or only show slight alterations in the chromatic substance. These alterations are, however, aggravated during the few days preceding death. The achromatic substance and the nucleus may also become involved. Varicose atrophy of the protoplasmic prolongations is always slight, and is not preceded by loss of the spinous processes. They think that the lesions observed are not an expression of atrophy of the nervous elements, but that they are the result of a true auto-intoxication, which becomes rapidly aggravated in the last days of life, through simultaneous alterations in the structure of the various viscera. Ganfini found in the rabbit chromatolytic changes in the cells of the cord, but not in those of the cerebral cortex. Daddi has studied the subject in dogs, and obtained results corresponding very closely to those of Lugaro and Chiozzi. He thinks, however, that the changes depend upon general denutrition, and not upon auto-intoxication.

Experimental Elevation of Temperature.—Goldscheider and Flatau (101, 102, 103) studied the influence of the elevation of the body-temperature in rabbits (by placing them in a thermostat) upon the nerve-cells of the spinal cord. They found that marked changes occurred as soon as the temperature of the animals was raised to 43° C. (109.5° F.). In preparations by Nissl's method the Nissl-bodies had almost completely disappeared. The cell-body was swollen, homogeneous and stained bright blue. It contained some minute granules, and presented also the appearance of a thread-network. The dendrites were pale blue and swollen, somewhat varicose and shadow-like. The nucleus was also more or less altered. Temperatures of from 41.7° to 42° C. (107-108° F.), if maintained for about three hours, produced similar but less distinct changes. The cells returned to normal in from two to three days. Lugaro (137) studied these pyrexia-changes throughout the nervous system in the rabbit and dog. Summing up the results of his observations he states that the nerve-cells of animals of which the temperature has exceeded 43° present the following characters (fig. 14):—Profound disintegration, very marked dissolution of the chromatic part; integrity of the achromatic part, the reticulo-fibrillar structure of which is often rendered more evident than in the normal state; integrity of the external form and of the morphological characters of the protoplasmic and nervous prolongations; integrity of the nuclear membrane and reticulum, diminu-

tion of the colourability (with thionin) of the acidophile portion of the nucleolus, and slight modifications of form in its chromatin particles. A feature of the morbid change is that (unlike chromatolysis from most other causes) it is diffused throughout all the cells in an almost equal degree. Moxter (201), in experiments upon the effects of the local application of heat after trephining of the cord in rabbits, found that with temperatures between 40.5° and 41.5° changes occurred in the nerve-cells of the anterior horns only after twenty-two and a-half hours. Marinesco (181), who has also made an experimental enquiry into this subject, thinks that the alterations resulting from artificial elevation of temperature may be divided into three groups, according to the height and duration of the abnormal temperature. The first type of alteration results from the action of a maximum of heat (reaching about 47°) and a minimum of its duration (forty minutes), and consists in a dissolution of the chromatic substance only at the periphery of the cell. The second results from the action of a less degree of heat (the temperature of the animal varying during the experiment from 43° to 45°), extending over a considerably longer time, and consists essentially in those lesions described by the previous observers, except that the chromatophile elements are not always completely dissolved. The third results from the action of a temperature of about 44° for several hours, and consists of a still more severe lesion. The cell stains very deeply, has an opaque appearance, and has lost all trace of chromatophile elements. There has in this instance probably been a coagulation of the protoplasm, a lesion which is equivalent to the death of the cell. Ewing (71) records some experiments upon rabbits, which he states bear out completely the conclusions of Goldscheider and Flatau regarding the structural changes produced.

The bearing of these experimental observations upon the study of nerve-cell changes in the human subject, has been incidentally alluded to by several writers, including those mentioned above, but the point is one that seems still to require careful investigation. It is obvious that in the human subject the action of the elevated temperature must in the great majority of instances be complicated by that of toxines generated in the course, and more especially towards the termination, of the particular disease with which the pyrexia is associated. In other words, pyrexia-changes in the nerve-cells of the human subject must as a rule be combined with chromatolysis of toxic origin, and therefore probably manifest themselves at considerably lower temperatures than those required in experimental observations.

Experimental Uremia.—Acquisto and Pusateri (7), in dogs which died as the result of ligature of the ureters, found varicose atrophy affecting specially the pyramidal cells of the cerebral cortex, and

various phases of chromatolysis, often very advanced, in the cells of the cerebral cortex and spinal cord. Sacerdotti and Ottolenghi (273), after ligature of the ureters, or nephrectomy, in dogs and rabbits, found changes in the nerve-cells essentially the same as those described by the preceding observers.

Experimental Anæmia.—Sarbo (275) found that one hour after ligature of the abdominal aorta, the nerve-cells of the spinal cord showed disintegration of the chromatic substance of the cell-body and "homogeneous swelling" of the nucleus. Marinesco (169) observed peripheral chromatolysis of the nerve-cells of the cord five to six hours after ligature of the abdominal aorta. The nucleus remained central. In a later paper (170*a*) he described these changes more fully. In advanced stages he found the nucleus altered. The achromatic network of the protoplasm was disintegrated and replaced by vacuoles and even cavities. In another paper (174) he regards the morbid changes as essentially the result of œdema of the nerve-cell. Ballet and Dutil (25) observed changes very similar to those described by Marinesco. They found that commencing dissolution of the chromatophile elements could be recognised after the abdominal aorta had been compressed for only a few minutes. In advanced stages they often found the nucleus eccentric in position. Soukhanoff (276), using the method of Golgi, observed varicose atrophy of the protoplasmic prolongations of the cortical nerve-cells after ligature of both carotids. A valuable detailed *résumé* of the results of previously recorded observations upon the effects of experimental anæmia, will be found in a recent paper by Righetti (261), who has himself made a highly important contribution to our knowledge of the subject. He concludes that changes in the nerve-cells of the lumbo-sacral cord consecutive to temporary compression (half to one hour) of the abdominal aorta manifest themselves early (within six hours). The predominant type of alteration of the chromatic substance, characteristic of the early phase of the lesion, is a diffuse chromatolysis. The nucleus and nucleolus may also undergo early alteration, which, however, up to a certain point, is compatible with subsequent restoration of the cell to normal. This, when it is possible, takes place rapidly (in forty-eight hours). When its functional activity is permanently abolished, the cell undergoes rapid disintegration, which is undoubtedly hastened by re-establishment of the blood-circulation. The alterations that follow permanent ligature are comparatively slow in developing. They are characterised by progressive shrinking of the cell, and by modifications in the staining reactions of its various parts. There is no true chromatolysis.

Insomnia.—Daddi (63), in experimental insomnia in dogs, found especially in the cortical nerve-cells more or less advanced chromato-

lysis, swelling of the cell-body, and vacuolation of the protoplasm. The method of Golgi revealed varicose atrophy of the protoplasmic prolongations and disintegration of the cell-body. The nucleus also presented marked structural changes, and in many instances was displaced to the periphery of the protoplasm. Agostini (1) independently carried out similar experiments and observed practically the same morbid changes.

(4) *Proliferative Capacity of the Nerve-cell.*

This question, which is one of considerable physiological and pathological importance, was for a long time a subject of dispute. It has, however, been recently most thoroughly worked out by Giuseppe Levi, thanks to whom it now rests upon a satisfactory scientific basis. Most of the previous observations upon which were founded assertions of the capacity of the nerve-cell to proliferate, are necessarily of doubtful accuracy, since the histological methods employed did not permit of a distinction being clearly made between nerve-cells and neuroglia-cells. It was not until Levi had analysed the constitution of the resting nuclei by means of staining with Biondi's reagent that trustworthy criteria for such a distinction were provided.

Friedmann (74), Caporaso (51), Vitzou (296), and Tedeschi (281) maintain that they have observed the regeneration of nerve-cells; Friedmann (74), Sanarelli (278), and Tedeschi (281) believe that they have observed karyokinetic figures in nerve-cells either during repair or irritation. Marinesco (166), Sanarelli (278), Tirelli (282), and Monti and Fieschi (197) have been unable to obtain evidence that the nerve-cell is capable of regenerating.

Golgi (89) observed karyokinetic changes in the nerve-cells in experimental rabies, but thought that they represented rather a regressive process of karyolysis than a true karyokinesis. Valenza (295) was unable to observe any evidence of karyokinesis in the nerve-cells of the electric lobe of the triton after stimulation or cauterisation. In 1895 Stroebe (270) published a review of the literature of this subject.

In 1896, Levi (148), after the publication of his first paper upon the normal structure of the nucleus, briefly related some observations made with Biondi's staining upon healing aseptic wounds of the cerebral cortex of the guinea-pig. Among the abundant karyokinetic figures found especially in the healthy tissue surrounding a wound, many were in nuclei which could be proved to be those of nerve-cells from their staining reactions, as well as from other evidence. A complete account of his researches upon this subject was published in 1898 (150). In this more recent paper he states that the object he specially set before

him in his researches was to study the process of karyokinesis in nerve-cells, admitting that it occurs, and to observe what deviations from the normal it presents. The methods of observation employed were those already indicated, but experiments were made upon the spinal cord as well as upon the cortex. He states the criteria which served him for the distinction of the nerve-cell nuclei from those of neuroglia and other cells. He found that the process of karyokinesis in the nerve-cells has, in its early phases, certain special features dependent upon the peculiar structure of the nucleus. It is doubtful if it would serve any purpose to endeavour to describe this process here. Anyone who desires to understand the matter must necessarily consult the original paper, and follow the description of the process with the aid of the beautiful coloured plates by which it is illustrated. Levi has only been able to observe karyokinesis in the medium-sized and small pyramidal cells of the cortex of the guinea pig. He could not find it in very highly differentiated nerve-cells, such as the large cells of the cord and brain. Although he has never observed complete division of a nerve-cell, he is inclined, from the advanced stages of karyokinesis that he has observed, to think that it can occur. It is probable, however, that such multiplication of nerve-cells is simply a reaction to the stimulus that has affected them, and that it does not lead to a stable regeneration. In favour of this view is the fact, noted by several observers, that the proliferation of the nerve-cells is most active from the second to the fifth day, afterwards diminishing gradually and ceasing about the twentieth day. He thinks that very highly differentiated nerve-cells, when affected by a stimulus, undergo degeneration instead of attempting to multiply. Their reproductive capacity has become lost in favour of that of fulfilling their special function. The index of this loss of reproductive capacity is probably the paucity of nuclein, which, as has been seen, diminishes with the higher differentiation of the cells.

(5) *Post-mortem Changes in Nerve-cells.*

This subject, the importance of a thorough knowledge of which to the neuro-pathologist must be obvious, has recently been studied experimentally by several observers. Tirelli (285), in his lengthy work upon the chronology of the death of the elements of the nervous system, which is chiefly of medico-legal interest, states that nine hours after death there can be observed a diffusion of the chromatic substance into the achromatic part of the protoplasm. The cell-body then assumes a finely granular aspect throughout. According to Colucci (43), the chief alterations are a diffuse granular disintegration of all the cell-elements excepting the nucleolus, pale and turbid staining with methyl-

ene blue, loss of affinity for this stain in tracts of the prolongations, rupture of the protoplasm in various directions in many cells, etc. Neppi (205) studied the cadaveric alterations in the cells of the anterior horn of the spinal cord of the dog, using sublimate fixation and thionin staining. He could not find distinct changes until forty-eight hours after death. They consisted chiefly in dissolution of the chromophile substance (the particles of which first showed badly defined outlines and then diminished affinity for the stain) and diffuse coloration of the nucleus. The nucleolus was only affected at a very late period. The cells tended to shrink and not to swell as in chromatolysis. Barbacci and Campacci (29) have made a very elaborate series of observations upon rabbits killed by bleeding and afterwards kept at a uniform temperature of 22° C. After various periods they examined different portions of the central nervous organs by the methods of Nissl (sublimate-thionin modification), Cox and Marchi. Their description of the changes observed is full of minute details of which it is impossible to give an accurate epitome. They state that the first alteration as a rule consists in the progressive paling of the chromatic particles. These next generally break up into fine granules which become smaller and smaller, giving the protoplasm a characteristic powdery look; sometimes, on the other hand, there is a fusion of the particles into irregular masses. Later the protoplasm assumes a pale, finely granular appearance, and tends to lose its regular outline. The nucleus undergoes a dropsical change, which leads to its rupture and shrinkage. It then appears as an irregular homogeneous mass which stains deeply. The nucleolus only at a very late stage becomes pale, irregular in form and displaced. In preparations by Cox's method there is detachment of the gemmulæ, erosion and breaking across of the protoplasmic processes and cell-bodies. Later the whole element assumes a very characteristic powdery aspect. Giulio Levi (153) has also carried out a very careful investigation into this subject upon rabbits, using the sublimate-thionin method. His results differ from those of the preceding observers, chiefly in regard to one point. He describes an initial hyperchromic phase, or a condition of abnormally deep staining of the chromatic elements which precedes that of pallor and fragmentation. França (85) has obtained in guinea-pigs results which are essentially in agreement with those of previous observers. Tirelli (286) has recently made a comparative study of the appearances of cadaveric and pathological changes in the brain of the rabbit with the aid of the rapid silver method. His results are not at all in accord with those obtained by Barbacci and Campacci with Cox's method, to which, however, he does not refer. He finds that even somewhat advanced putrefaction does not deprive the nerve-cells of their charac-

teristic aspect in silver preparations. An excellent account of these cadaveric changes has been given by Ewing, both in his preliminary communication (70) and in his comprehensive monograph upon ganglion cells (71). In his first paper he especially notes deep diffuse staining of the nucleus at an early stage, shrinkage of it and of the nucleolus in advanced stages; granular subdivision of the chromophilic bodies and reticulum, without actual loss of chromatic substance, which gives to the cell-body a characteristic, uniformly granular appearance. In his more recent work he deals with the subject still more fully, and describes some experimental observations upon the rabbit. In addition to the above changes he mentions the occurrence of vacuoles in the protoplasm which he believes to be one of the most constant of *post-mortem* products.

IV. TYPES OF MORBID CHANGE AFFECTING THE NERVE-CELL.

It is necessary to distinguish clearly between special diseases of the nerve-cell, and mere types of morbid change that may be observed to affect it. Changes such as chromatolysis, vacuolation, and pigmentary degeneration, cannot be regarded as diseases of the nerve-cell, but only as types of morbid alteration occurring in several forms of disease. At present the only definite diseases of the nerve-cell that are known are primary degeneration (in which, however, future research will, without doubt, enable us to recognise various distinct forms) and secondary degeneration.

(1) *Chromatolysis.*

The term "chromatolysis," introduced by Marinesco (169), implies, strictly speaking, merely disintegration of the chromatic particles of the protoplasm—breaking up of the aggregations of granules that form the Nissl-bodies and gradual disappearance of the individual granules, accompanied in transition stages by their diminished affinity for basic dyes (figs. 23 to 27). But it has been frequently used in a wider and more general sense, namely, to indicate the whole series of changes in the constituent elements of the cell, of which dissolution of the chromatic particles is merely the first that is recognisable. Its employment in this wider sense can only lead to confusion, and ought to be abandoned. In its narrower and literal sense, on the other hand, the term is now an almost indispensable one for descriptive purposes. Van Gehuchten and some others prefer the term "chromolysis."

The various causes of chromatolysis have already been indicated. It accompanies primary and secondary degeneration in almost all their forms. Moreover it occurs as a physiological condition in fatigue of the nerve-cell. As far as can be determined by microscopical examina-

tion, the chromophile part of the cytoplasm is the most sensitive constituent of the nerve-cell under abnormal nutritional conditions.

The exact mechanism of the production of chromatolysis in pathological states is little understood. Probably in certain instances there is especially an increased consumption of the chromophile material, in others especially an arrest of its formation.

Chromatolysis has been observed in the human subject in a very large number of different morbid conditions. Indeed it is now known that it occurs in some degree in a proportion of the nerve-cells of almost every individual dying a natural death. Even in non-nervous diseases it is very commonly an extensive and well-marked morbid change in the cells of the cerebral cortex, spinal cord, &c. In such cases it is to be attributed to the action of toxic substances generated in the course of the particular disease, to pyrexia, terminal auto-intoxication, or local vascular lesions. At the same time, abundant evidence has now been accumulated of the special incidence of chromatolysis in various forms of nervous disease. But in these cases it is generally accompanied by other morbid alterations in the cells, which at once give to the pathological picture a much graver aspect.

Marinesco (186) has applied the term "achromatosis" to a change which consists essentially in an extreme degree of chromatolysis—complete disappearance of the chromophile elements of the cytoplasm (fig. 18). In preparations stained with polychrome blue, the cytoplasm appears pale or absolutely colourless, resembling dull glass. He has observed this condition of achromatosis in the cells of the anterior root after evulsion of spinal nerves (179), and in those of the cerebral cortex in diabetes insipidus, leprosy, pellagra, etc. It corresponds morphologically to the extreme degree of the lesion observed to attend experimental elevation of temperature.

(2) *Achromatolysis or Plasmolysis.*

These terms have been applied by Marinesco (174) to one of three different morbid changes which have been recognised, by him and others, to occur in the constituent elements of the achromatic part of the cytoplasm, either simultaneously with, or consecutive to, chromatolysis in the narrower sense. He describes it as consisting of a molecular disintegration of the achromatic substance. It is to be observed that he does not restrict the term to disintegration of the formed or fibrillar portion of this substance. Loss of the primitive fibrils and their replacement by powdery granules is, however, practically the only visible alteration in achromatolysis. It was Lugaro (128) who first described this alteration, and he has since given several minute descriptions of it as observed in various experimental lesions.

(3) *Coagulation of the Achromatic Substance.*

This is the second lesion of this part of the cytoplasm distinguished by Marinesco (174). He describes it as consisting in the coagulation, and probably the chemical transformation, of the achromatic substance into a colourless mass of vitreous aspect. It is most typically seen in the cells of the spinal cord after ligature of the abdominal aorta.

(4) *Intense Colourability of the Achromatic Substance.*

This is the third morbid change distinguished by Marinesco (174) in this substance. It is displayed especially in preparations by Nissl's method and its modifications, and has been noted by several observers, more especially in poisoning by arsenic and antimony, and in Landry's paralysis.

(5) *Partial or Superficial Coagulation with Corpuscular Formation.*

Under this designation Marinesco (186) has recently described a morbid change of the nerve-cell which would seem to partake of the characters of both of the immediately preceding types. He observed it in the large and medium pyramidal cells of the cerebral cortex in six cases of acute encephalitis. The cytoplasm colours intensely with polychrome blue. The cellular contour is irregular, and in its concavities there are numerous rounded and deeply-stained granules, which he thinks are not artificially produced, and are not micrococci. He believes that they result from a process of peripheral destruction of the cytoplasm, dependent upon the necrosis of coagulation.

(6) *Pigmentary or Yellow-globular Degeneration.*

Neurologists in this country have been made familiar with the subject of pigmentary degeneration of nerve-cells (figs. 19, 20, 21 and 27), more especially through the writings of Bevan Lewis. On the Continent comparatively little importance had been attached to this transformation until somewhat recently, when important papers by Colucci (43) and Marinesco (184) directed general attention to it. The nerve-cell pigment in normal conditions has already been considered in another subsection (p. 202), which should be read in connection with what is stated here.

Pilcz (233), in his important work on nerve-cell pigment, states that the pale yellow variety continues to increase with age in the human subject. This statement is confirmed by many other observers. Hutchison (111) does not accept Bevan Lewis's statement that the accumulation of pigment is "invariably a witness to bygone func-

tional hyper-activity." He has found such accumulation to be the rule rather than the exception in the human brain. He believes that pigment is specially increased in renal disease, and that it is not more abundant in the insane than in the mentally sound. Colucci (43) objects to the term "pigmentary degeneration" on the ground that it is not proved that the globules are true pigment granules, and that it is probable that they are really a product of metabolism in the cell. He advocates the employment of the term "yellow-globular degeneration." He thinks that all the elements at the spot are probably involved in the transformation, as every trace of the original structure disappears. He describes the appearances that the globules present in normal and pathological conditions. The criterion of degeneration is especially their appearance in portions of the cell that are not normally provided with them, as at the base of the protoplasmic prolongations and in the peripheral zone. Occasionally the nucleus becomes affected. The yellow globules undergo various transformations, the most common being fatty and pigmentary degeneration. In the latter they may become quite black. He thinks that yellow-globular degeneration is most marked in slow dementias, such as epileptic dementia and general paralysis. Lugaro (131), in experimental lead poisoning in the dog, observed in the cells of the spinal ganglia and cerebral cortex the occurrence of yellow pigment granules, which are normally wanting in these elements in this animal. Adolf Meyer (200) has described the various manifestations of pigmentary degeneration in the giant cells of the para-central lobule. Cristiani (41), Turner (292), and Lord (154) have published papers in which pigmentary changes are described as observed in the brains of the insane. Bevan Lewis (165), in the second edition of his important text-book, has recently given a very full account of his views regarding "pigmentary or fuscous degeneration." He still maintains that excessive pigmentation is a witness to bygone functional hyper-activity. He considers that the "fuscous state" is not truly a degeneration of the cell-protoplasm, although it may be accompanied by it, or be its immediate cause. He gives a minute description of the various phases of excessive pigmentation, which he divides into three stages or periods, namely, those of over-activity, diminished activity, and absorption. Epileptic insanity and general paralysis are the forms of mental disease in which he has found the nerve-cells most prone to this morbid change. Marinesco (182, 184) regards pigmentary degeneration as primarily a manifestation of the senile involution of the nerve-cell, and not a phenomenon of an absolutely pathological nature. But while, as a rule, the quantity increases with age, it is especially in chronic pathological processes that the pigment attains

its maximum development. He describes this pathological transformation as it occurs in the large pyramidal cells of the cerebral cortex, consecutive to lesions of the internal capsule. In advanced stages there is in the interior of the protoplasm a mass (varying considerably in size in different instances) of the so-called pigment of the nerve-cell; the protoplasmic prolongations are more or less atrophied, as also the axis-cylinder process, the cone of origin of which is indistinct. The nucleus is displaced and reduced in volume. Its membrane is irregular. The nucleolus is sometimes pale, sometimes deeply stained. W. K. Hunter (115) has recently described a case of gastric tetany in a woman aged 41, in which there was an extreme condition of pigmentation of the nerve-cells in the pons, medulla, and cord. He traces the formation of the pigment from the chromophile bodies. He considers that in this case, in which the illness was only of a few days' duration, the extreme pigmentation was "to all intents and purposes just another form of chromatolysis, by means of which the cell becomes a pigmented cell in place of a 'ghost-cell.'"

For my own part I have never seen any evidence that seemed to me to support the view of Bevan Lewis that pigmentary change in nerve-cells is to be attributed to "bygone functional hyper-activity," or that his "first stage"—characterised especially by deep staining of the cell-body in aniline black preparations—is entitled to be regarded as any part of the pathological process. With Marinesco I would regard the condition as primarily an evidence of the senile involution of the nerve-cell, or of its loss of vitality and functional energy. In various chronic morbid states of nutrition, such as those attending atheromatous and hyaline degeneration of the cerebral vessels, this physiological involutive process becomes greatly intensified and assumes a pathological significance. In some of its manifestations, however, pigmentary change cannot be regarded as of this involutive nature, but must be recognised as simply a type of pathological alteration to which the nerve-cell is subject. The case recorded by W. K. Hunter is, I think, of great value on account of the clear proof it furnishes of the fact that this alteration may develop rapidly as well as slowly. It throws much light upon some forms of nerve-cell pigmentation that may be observed in the insane, and must henceforth serve to alter the common conception of this condition as necessarily one of a chronic nature. Regarding the origin of the pigment globules, I think it may be provisionally accepted that it is chiefly from the chromophile elements. Little seems to have been yet ascertained as to the extent to which the globules may be reabsorbed.

The fact of chief importance in the chronic forms of this morbid alteration is not the accumulation of an abnormal quantity of yellow

granules, but the associated destruction of the spongioplasm and trophoplasm. That these are destroyed at the seat of the granular accumulation is clearly proved by platinum preparations. But whether this destruction precedes or follows the development of the pigment, I am as yet unable to say.

(7) *Fatty Degeneration.*

The possibility of the occurrence of fatty degeneration in nerve-cells, as in other cell-elements, seems now to be satisfactorily demonstrated, although at one time it was denied. Elkins and Middlemass (72) observed the change in an extreme form, affecting both protoplasm and nucleus, in a case of phosphorus poisoning. It seems certain that vacuolation in some of its manifestations depends upon the formation of fatty globules; it has been noted also that in pigmentary degeneration the yellow globules are capable of undergoing a fatty metamorphosis. Lugaro (131) and others have observed fat granules in nerve-cells affected by chromatolysis.

(8) *Vacuolation.*

Vacuolation of nerve-cells has recently been the subject of special papers by Campbell (52) and Skae (272), and it has also been considered somewhat fully by Colucci (43), van Gehuchten and Buck (98), Bevan Lewis (165), and Ewing (71). Its occurrence has further been incidentally described by Daddi (62) in passive congestion, by Piccinino (238) in a case of Landry's paralysis, by Ceni (40) in experimental acute septic meningitis, by Corrado (47, 48) and Fish (83) in death by electricity, by Marinesco (177) in paraplegia, by Berger (30) and Anglade (9) in general paralysis, by Soukhanoff (277) in arsenic poisoning, by Köster (120) in carbon bi-sulphide poisoning, and by Sarbò (275), Marinesco (170a), and Righetti (261) after ligature of the abdominal aorta, and by many others.

It would serve little purpose to give an outline of the views expressed regarding vacuolation in each of these publications, for it is the fact that no satisfactory investigation upon this morbid change has yet been recorded. The truth of this contention is fully recognised by van Gehuchten and Buck, who, after reviewing the literature of vacuolation and stating practically all that is definitely known about it, conclude that further research is required on the subject before precise statements can be made regarding it.

The important facts that have been established may be summed up in a few words. Vacuolation may affect either the nucleus or the

protoplasm, or both; it consists in the formation in the cell-substance of one or more, small or large, non-colourable globules which are probably most commonly of a fluid character, although the observations of Corrado demonstrate the possibility of their sometimes being vacuoles in the stricter sense of the term; when fluid in character, they may almost certainly be composed of essentially different substances in different instances. They are undoubtedly composed of fatty matter in certain instances, but the assertion that they are, as a rule, of this nature has not been satisfactorily proved, and is probably erroneous. The various causes that determine their formation, the processes of their development, the associated changes in the chromatic and achromatic substances of the protoplasm and in the various constituents of the nucleus, and their pathological significance have yet to be determined.

(9) *Invasion by Bacteria.*

While it is certain that bacteria exert their morbid influence upon nerve-cells practically only by means of the easily diffusible toxins that they generate, the observation of the occurrence of these organisms within the cell-body is one of considerable interest and importance. Such observations have recently been made by Nissl (218), Piccinino (238), and Babes (31). Piccinino found a diplococcus in the acutely degenerated nerve-cells of the spinal cord in a case of Landry's paralysis, while Babes observed the specific organisms in nerve-cells in plague, leprosy and other infective diseases.

(10) *Varicose Atrophy.*

This term has been applied to certain morbid appearances sometimes to be observed in the nerve-cells in preparations by Golgi's method and its modifications. It consists in the presence of irregular swellings or varicosities in the course of the protoplasmic prolongations, partial or complete disappearance of these prolongations and shrinkage and deformity of the cell-bodies (fig. 29). It is certain that such abnormal appearances in Golgi-preparations may be the result of genuine pathological changes in the form of the cell; but it is equally certain that many of its slighter manifestations, more especially varicosities, may be, and in many published descriptions have been, of a purely artificial character. It is to be borne in mind that the presence of varicosities on the protoplasmic prolongations is normal in the fœtus. Loss of the gemmulæ has sometimes been referred to as a distinct morbid alteration, but it can scarcely be separated from varicose atrophy. The subject is one of considerable importance, and therefore I give a somewhat detailed account of its literature.

In 1893, Colella (45) described the occurrence of varicose changes in the nerve-cells in general paralysis. In 1894, Golgi (89) described similar alterations in experimental rabies. They resembled those that he had described in chorea in 1874. Ceni (36) found them in secondary degeneration of the cord, Andriezen (8) in alcoholic insanity, Klippel and Azoulay (11) in general paralysis and melancholia. The last-named authors stated that the alteration began as an abrasion of the gemmulæ, or as an agglutination of them, and that it spread gradually from the periphery of the protoplasmic prolongations towards the cell-body.

In 1895, Berkley (32) described changes, similar to those just mentioned, in chronic alcoholic poisoning in rabbits. In another paper (33) he recorded the observation of the loss of a large number of the gemmulæ in secondary dementia. Ceni (37) described varicose atrophy in the cells of the cerebellum after lesions of the cord, Tirelli (283) in the cerebrum of general paralytics, and of epileptics dying in *status epilepticus*, Pernice and Scagliosi (226) in diphtheritic infection, Monti (193) in experimental embolism, and (194) in inanition.

In 1896, Demoor (68) described the production of varicosities upon the protoplasmic processes by the action of morphia, chloral and chloroform, as well as by that of prolonged electrical stimulation, and their disappearance on the return of the elements to normal conditions. Berkley (34) gave a further account of the varicose changes in the cortical nerve-cells of rabbits subjected to chronic alcoholic poisoning, describing especially a distinct diminution in the size of the cells, a shrinkage of the vast majority of them, swellings of the dendritic processes with disappearance of the gemmulæ, and roughening of the stronger processes and to a less extent of the cell-bodies. At the same time, he drew attention to certain "normal inequalities or varicosities in the construction of the dendrons." In another paper (35) he described the changes produced by experimental acute alcoholic poisoning as revealed by his modification of Golgi's silver method, mentioning especially irregular tumefaction of the protoplasmic processes, and considerable loss of the lateral buds, with or without such tumefaction. Dotto (65) described varicose atrophy in chronic poisoning by perchloride of mercury, and (66) by quinine and ergotinine; Ceni (38) in the cells of the cerebral cortex after section of the spinal cord in dogs, and (39) in diphtheritic poisoning (chiefly experimental). Lugaro (128) drew attention to the difficulties that surround the employment of Golgi's method in pathology. He stated that alterations simulating varicose atrophy were readily produced by defects of fixation, such as commonly resulted from the use of bichromate of potassium, either alone or with osmic acid. He recommended the use of Cox's solution, even with which, however, the pieces should not

exceed 6 mm. in thickness. He attributed to such imperfect fixation the results obtained by Demoor, whose experiments he had repeated with totally negative results. All these reservations, however, did not prevent the acceptance of varicose atrophy as a real anatomical alteration, as it had been observed in experimental material examined with the most rigorous technique. Its exact value could not yet be established. It could be excluded, however, that it expressed a simple disturbance of the nutrition of the element, or an initial alteration. It probably represented a final destructive process which revealed itself first in the most delicate parts. Ramon y Cajal (247) also drew attention to the production of these varicose changes by defective methods of examination. Acquisto and Pusateri (7) observed varicose atrophy of many of the cells of the cerebral cortex in acute experimental uræmia.

In 1897, Sacerdotti and Ottolenghi (273) confirmed the immediately preceding observation. Dotto and Pusateri (67), from a study of the cortex in a case of cerebral hæmorrhage, supported the opinion of Lugaro that varicose atrophy represents not an early, but a late phase of alteration in the nerve-cell. Lugaro (131), in his investigations of the changes in poisoning by arsenic and lead, obtained further important evidence in support of this conclusion. He found that even when there were distinct cytological alterations, the external form of the nerve-cell, as revealed by Cox's method, might appear quite intact. When alterations did appear they affected specially the cell-body and large protoplasmic trunks, and notwithstanding their presence the fine branches and the gemmule might be preserved. He expressed himself as more than ever doubtful of the pathological value of swellings in the form of a rosary, preceded by loss of the spines and invading the protoplasmic prolongations progressively. He had been able to prove that such varicosities could be produced in enormous numbers by the employment of fixatives that are not very energetic and of too thick pieces of tissue. Further, he believed that mechanical maltreatment of the pieces, and their subjection to the action of the air, could produce similar modifications. In support of the latter contention, he referred to the fact that Ramon y Cajal (247, 248) had been able to demonstrate that the numerous varicosities which appear in preparations by the Ehrlich-Dogiel method in all prolongations of the nerve-cells, are due to the altering action of the air. Lugaro added that sometimes in normal preparations treated with all possible precautions, there were to be observed prolongations with the characters of the so-called varicose atrophy, which must have been affected by some cause of alteration that had escaped notice. Lugaro and Chiozzi (145), in their observations upon the changes resulting from inanition, found that varicosity occurred only at a very late stage of the cellular alteration,

and that it was not preceded by disappearance of the spinous appendages.

In 1898, Monti (196) described, in the nerve-cells of animals subjected to inanition, varicose atrophy proceeding regularly from the extremity of the dendrites towards the cell-body. He maintained that the dendrites are the first to undergo alteration in inanition, and that there exists a perfect correspondence between this alteration and chromatolysis, both of which are to be observed in disturbance of the nutrition of the nerve-cell. This paper elicited from Lugaro (136) a very vigorous criticism, which, however, was not directed solely against the views just mentioned. He maintained that the appearances described were nothing more than artificial products depending upon errors of technique. In his observations upon experimental pyrexia (137), he found that the extreme chromatolysis thereby produced is not accompanied by any alterations of the protoplasmic prolongations in Cox-preparations. Batty Tuke (288) accepts as demonstrated the loss of the gemmulæ of the dendrons under the action of disease (in cases of chronic insanity). Peters (282) concludes that the gemmulæ are diminished in correspondence with the degree of intellectual decadence in the insane. Wright (301) describes varicose changes in the cortical nerve-cells in accidental and experimental poisoning by potassium bromide. Soukhanoff (276) describes gross changes in the form of the protoplasmic prolongations in experimental cerebral anæmia, and Corrado (47, 48) in death by electricity. Dr David Orr (264) and I, following essentially the technique advocated by Lugaro, have observed in the human brain in various pathological conditions occasional varicose changes corresponding to those recognised as genuine by that authority. Demoor (68, 69), Stefanowska (269), Querton (239), Manouelian (202) and Odier (223), have described varicosities of the protoplasmic processes, with or without disappearance of the gemmulæ, as evidence of contraction in various functional modifications of the nerve-cells. On the other hand, Azoulay (10) has been unable to obtain such evidence, and Lugaro (139), by injection of the vessels of the living brain with Cox's fluid, has also obtained results contrary to the conclusions of these observers.

Weil and Frank (303) have recently made a series of experimental observations (see page 228), from the results of which they conclude that varicosities must be regarded as artefacts of the Golgi method.

(11) *Varicose Hypertrophy of the Axis-cylinder Process.*

This is another morbid appearance that may not infrequently be observed in preparations by Golgi's method. It consists, as the name that has been given to it implies, in globular, fusiform or irregular

swelling in the course of the axis-cylinder process (fig. 30). It was first recognised by Golgi in 1874, in chorea, and afterwards in rabies (89). Colella (45) believes that it is sometimes a primary change in general paralysis. In 1896, Lugaro (128) expressed the opinion that it was improbable that the condition could be separated from lesions of the cell-body, but at the same time seemed to doubt if it was a genuine pathological alteration at all. Numerous incidental references to these varicosities are also made in other papers, but the subject seems to be one that still requires to be placed upon a sound scientific basis. Dr Orr (264) and I have described and figured a more gross change in the axis-cylinder processes in the human brain in various pathological conditions, and have expressed the opinion that simple swellings in the form of a rosary are not necessarily pathological alterations at all.

(12) *Displacement of the Nucleus.*

In advanced stages of either primary or secondary degeneration, the nucleus tends to become displaced or dislocated to the periphery of the protoplasm. It may come to project beyond the surface of the cell, and occasionally, according to some authorities, may even be completely extruded. This displacement probably depends upon the fact that the achromatic reticulum, which normally holds the nucleus in its generally central position, has been destroyed.

(13) *Homogeneous Degeneration of the Nucleus.*

In 1895, Sarbò (275) described in the cells of the spinal cord affected by chromatolysis after ligature of the abdominal aorta, a peculiar change affecting the nucleus, and characterised by a homogeneous aspect, deep staining with methylene blue, and atrophy. He designated it *acute Homogenisierung mit atrophie*. This expression cannot be rendered literally in English, but probably it is sufficiently represented by "homogeneous degeneration." Many writers, in describing similar appearances of the nucleus in various morbid conditions, identify them with this change described by Sarbò. Among these writers may be mentioned Colucci (44), Donaggio (56), Marin-esco (186), and Lugaro (132), the last of whom briefly indicates the parts that the acidophile and basophile constituents of the nucleus appear to play in the morbid alteration.

(14) *Loss of Nerve-Cells.*

Death and total disappearance is the fate of a certain percentage of nerve-cells affected by acute primary lesions. Whether or not the

same result occurs in secondary lesions is a matter of dispute. Chronic forms of degeneration, such as that which occurs in senility, must also, it is evident, result in the loss of large numbers of nerve-cells. Dr Orr and I (264) have found that in many cases of secondary dementia it can be satisfactorily demonstrated that about 50 per cent. of the cortical nerve-cells have entirely disappeared.

The question of the manner in which the dead nerve-cells are removed is one that has given rise to some dispute. Marinesco (174) thinks that proliferated neuroglia cells, conjointly with leucocytes, act as destroyers of degenerated nerve-cells. Bevan Lewis (165) believes that certain large cell-elements of the neuroglia are the all-important elements in this connection. Turner (290) describes leucocytes as attacking, destroying and removing nerve-cells in the cerebrum in senile insanity and other morbid conditions. Pognat (237) has described the invasion and removal of degenerating nerve-cells by leucocytes in senility, an occurrence which he attributes to the diminished resisting power of the nervous elements. Nissl (215), in his paper upon general paralysis, maintains that the nuclei to be observed upon the degenerating nerve-cells are only those of neuroglia cells, and that leucocytes are never to be observed in this position. Lugaro (141) supports Nissl's view from his own observations. He states that he has searched in vain for leucocytes in the cortex of paralytics, and in that of the rabbit in meningo-encephalitis; neuroglia-cells are to be observed grouped about the pyramidal nerve-cells in the healthy state; their nuclei are sometimes so planted on the nerve-cell as to simulate a lymphoid element in the act of penetrating it. According to my own observations, the mesoglia cells are the special phagocytes of the central nervous system.

(15) *Granular Changes.*

Bevan Lewis (165) describes "granular disintegration of nerve-cells" as if it were a special disease, characterised by a definite series of structural alterations. I shall merely say here that I entirely dissent from this teaching, and pass on to note briefly the various conditions under which granular appearances may be observed in the cytoplasm of the nerve-cells.

In the first place it is to be remarked that the normal nerve-cell, as observed in preparations by many different histological methods, has an aspect which may accurately be termed "granular." The chromophile elements are often termed "the Nissl-granules," and the achromatic substance as observed with the aid of various useful processes of staining has a distinctly granular appearance.

In various structural alterations of the nerve-cell, the aspect of the protoplasm in preparations by Nissl's method and its modifications, as

well as by certain others, is also more or less markedly granular. The granules may be fine or large, numerous or scanty, localised or scattered diffusely throughout the cell, deeply stained or colourless. Such appearances occur especially in various forms of chromatolysis, in achromatolysis, in early stages of *post-mortem* alteration, in fatty degeneration, in some forms of vacuolation, and in yellow-globular or pigmentary degeneration, in which condition, it is to be borne in mind, the granules are not always distinctly coloured.

V. GENERAL PATHOLOGY OF THE NERVE-CELL.

The morbid alterations to which the nerve-cell is subject may be divided into two great classes, namely, primary lesions and secondary lesions. The former result from the direct action of a toxine, the latter follow injury to the nervous prolongation. Marinesco (169, 172, 174), who has specially insisted on the necessity of this distinction, maintains that these two forms of nerve-cell degeneration present different morphological characters. He states that in secondary degeneration the nerve-cell always comports itself in a uniform manner. The alteration begins by disintegration of the chromatic substance in the neighbourhood of the cone of origin of the axis-cylinder process, and gradually extends to the greater part of the cell-body. At an advanced stage the nucleus is often displaced to the periphery. The cell may undergo repair, or it may atrophy and disappear. In primary degeneration, on the other hand, the alterations are specially characterised by their variable multiplicity and by their gravity. The chromatolysis may be partial or complete, peripheral, perinuclear or diffuse, etc. The achromatic substance and the nucleus tend to be involved, and repair is then impossible.

Most of those who have since written upon the subject are in agreement with Marinesco in regard to the necessity and importance of this distinction, but some observers have been unable to see any essential difference in the morphological characters of the two kinds of lesion, and have questioned the validity of the pathological classification. It is doubtless true that primary and secondary lesions cannot always be distinguished under the microscope, even in their early stages. But it seems probable that, as histological methods are improved, sharper morphological differences will become recognisable. In any case, upon general grounds the pathological distinction will remain perfectly valid. Its practical importance probably few will question.

The alterations caused by elevation of temperature, inanition, anæmia and insomnia may probably be correctly classed as primary lesions, since they depend either upon the direct action of toxines, or upon an equivalent interference with the nutrition of the cell.

Primary degeneration of nerve-cells may be acute or chronic. Its acute forms, the characters of which vary with the toxine and with the intensity of its action, may commonly be observed in the human subject in cases of acute disease of a distinctly toxic nature, such as pneumonia, delirium tremens, exophthalmic goitre, etc. Its chronic forms are equally common, and have a special importance in relation to mental diseases; they are typically seen in the cerebral cortex in cases of general paralysis and senile insanity.

Secondary degeneration, on the other hand, runs a definite course, though one that is influenced very greatly by various concomitant circumstances. It may be likened to a specific fever, which may be mild or severe, short or prolonged, and end in recovery or in death of the subject. We cannot divide it into acute and chronic forms. The lesion occurs typically in the cells of the anterior horns of the spinal cord in peripheral neuritis, and in the giant cells of the cerebral cortex after hæmorrhage into the internal capsule.

A special form of secondary degeneration is that which, in certain instances, appears to affect a neuron in consequence of cessation of the functional impulses that are normally transmitted to it by another neuron, owing to degeneration of the latter. Some of the evidence that has been brought forward in support of the occurrence of degeneration from this cause may be noticed here. Jelgersma (117) and Klippel (121) have described the occurrence of such "degeneration by transmission." Marinesco (167, 170) maintains that trophism is a reflex action propagated from one neuron to another, and that continued functional excitation is indispensable to trophic activity in the nerve-cell. He points to examples of what he terms "secondary neural atrophy" of nerve-cells in the human subject, as the result of degeneration of the cells from which they normally receive stimuli. K. Schaffer (266) has attributed the degeneration of the cells of the anterior horn of the spinal cord in amyotrophic tabes to degeneration of the collaterals of the posterior roots, and the consequent loss of the stimuli normally received from them. He has also observed degeneration of these cells in cases of hemiplegia from cerebral lesions. Van Gehuchten (94) attaches great importance to the trophic influence that one nerve-cell exercises over another. He records some experimental observations which go to show that after section of the sensory nerves the histological alterations do not confine themselves to the first neurons, but affect also the second which are in connection with them. He thinks that this degenerative process may pass on to neurons of the third order, and even be transmitted to the motor neurons.

There is, however, at least one abnormal condition of the nerve-cell which, since it is not, strictly speaking, a morbid *alteration*, cannot be regarded as either a primary or a secondary lesion, namely, its de-

velopmental arrest. Various degrees of this condition can undoubtedly be recognised in the cerebral cortex in a considerable number of cases of idiocy and congenital imbecility.

Lugaro (144) has recently summarised the position of our knowledge of the effects of different toxic agents upon the nerve-cells, and as no pronouncement of greater authoritative weight could be made on the subject at the present day, I reproduce his statement here. He says :—

“The study of subacute intoxications has shown us that, while the primary lesions of the nerve-cells have common features, there are not wanting in them particular characters by which we can more or less completely distinguish one intoxication from another. We can in general establish the facts that the various elements of the nervous system of an organism react for the most part in various ways to the same agent; that the picture of the cellular modifications varies within certain limits in one species and another; that the capacity of reacting diversely to different agents is not equal in all the cellular types, and that therefore some present little diversity of modification; that, taking into account collectively the type, distribution, and intensity of the lesions produced, we can recognise in every subacute poisoning a constant and special physiognomy.

“The alterations that result from chronic intoxications present, according to Nissl, a remarkable uniformity both as a whole and individually. This fact, I believe, may be explained by the circumstance that the toxic action is complicated by auto-toxic actions resulting from secondary disturbances of metabolism, and from alterations of the other viscera that reciprocally exercise an influence on the brain. These secondary disturbances, relatively uniform, must tend to mask the primary action, cancelling the original diversity of the picture produced by the various agents. But in any case the gravity of the lesions, their elective distribution, and the rapidity of their establishment, stand in direct relation to the toxic agent and to its energy of action.

“The action of general and local infections on the nervous system has a very great analogy to that of the acute, sub-acute and chronic intoxications, according to the case. This we can easily understand, if we consider the greater importance of the indirect and general action exercised by the micro-organisms through their toxins in comparison with their direct and local action.”

A fact of the utmost importance in connection with this subject, and one in support of which there is the most convincing evidence, is that the nerve-cells of some individuals are much more liable to be injuriously affected than those of others by a given toxic agent. Moreover, cells of the same category in one individual vary within considerable limits in their power of resistance to a toxic agent, some remaining structurally unaffected, others undergoing a more or less

marked degree of chromatolysis, and others succumbing, just as when a storm sweeps over a forest some of the trees successfully withstand it, others suffer damage from which they can more or less completely recover, while others again are uprooted. These special reactive qualities of the nerve-cells appear to depend essentially upon inheritance.

In 1896, Lugaro (128) formulated an important generalisation with regard to the respective significance of lesions of the chromatic and achromatic parts of the cytoplasm. He maintained that alterations of the chromatic part do not represent more than a reaction of the cell to a disturbing force and are reparable, while, on the other hand, alterations of the achromatic part are to be regarded as degenerative and irreparable. This view, which had been foreshadowed by Marinesco (169), has since been very generally accepted as essentially accurate.

Goldscheider and Flatau (101, 102, 103), from their observations upon the occurrence of chromatolysis in experimental pyrexia and in malonnitril poisoning, were led to maintain that chromatolysis has little significance as a pathological change. An animal with its motor cells thus markedly altered was still able to perform all kinetic functions. Therefore, they argued, the Nissl-bodies can have no great importance either for the vitality or for the functional activity of the nerve-cell. Lugaro (137) states that he cannot accept these opinions in their entirety. According to his own observations, although the motor functions may be preserved apparently intact in experimental pyrexia, with the progress of the alterations there is a motor weakening. The chromatic part fulfils its functions through its chemical, not through its morphological, structure. Its quantitative and structural integrity is not essential for motor function, yet its progressive dissolution causes progressive weakening of that function. The morphological conditions necessary to function consist in the structure of the achromatic part and in the connections between the various nervous elements, determined by the disposition of the cellular arborisations. While these morphological conditions are preserved, the possibility of functional activity is also preserved, but its intensity depends upon the quantity of the chromatic substance existing in the cell. This substance has, without doubt, an important and indispensable part in the functional metabolism of the element, Marinesco (181) has supported Lugaro's opinion in this matter, and has expressed himself even more emphatically with regard to the importance of the chromatophile elements for the vitality and functional activity of the cell.

Lugaro's more recent views upon the pathological significance of lesions of the chromatic and achromatic parts of the cell are also of

much interest and of great practical importance. The following is a continuation of the passage already quoted:—

“From the complex of the studies that have been made, we may also form criteria of the reparability of the lesions. We now know that the lesions of the chromatic part are the first to appear, in all cases in which the harmful action does not act suddenly and with such energy as to paralyse function; that they are in every case reparable even when very grave, provided that the other parts of the cell have not suffered serious damage. It is very doubtful if lesions of the achromatic part can be repaired, more especially since they very often appear contemporaneously with lesions of the nucleus, the integrity of which is indispensable for the conservation of the cell.

“Of great importance is the question if the functional disturbances ought to be considered as an expression, pure and simple, of the lesions revealed by the method of Nissl, that is to say, of those that concern the chromatic part of the cell. The results of experimental researches tell us clearly that an exact and constant relation there is not; that function can be disturbed without there being any apparent lesion of the chromatic part, which on the other hand may be altered, even gravely, without our being able to discover any evident functional disturbance.

“In acute poisonings, especially by substances which exhibit rapid diffusion and action, such as ether and chloroform, when there is already an imposing symptomatological picture, or when the toxic action has even determined death, one cannot recognise any apparent modifications in the chromatic part of the nerve-cells. Modifications are, on the other hand, very evident in the subacute poisonings, even before functional disturbances have appeared. The lesions of the chromatic part consequent upon elevation of temperature (*ipertermia*), and upon temporary compression of the abdominal aorta, persist for some time after their cause has ceased to act and after the functional disturbances have disappeared.

“This shows without doubt that the functional activity of the cell can continue even when the chromatic part is injured, and that this part does not possess structural arrangements necessary for the fulfilment of its function, which depends therefore upon chemical composition, and not upon morphological disposition. If to this we add the fact that the chromatic part is rapidly affected every time that metabolism is disturbed, locally or generally, and that it diminishes in quantity in consequence of protracted functional activity, we can hardly doubt that the chromatic part plays a very important rôle in the functional metabolism of the nervous element, and that therefore its alterations are a direct index of a nutritive alteration. In other words, they are not exactly proportional to the functional disturbance: within certain limits of structural alteration function can remain intact, and will not exhibit disturbance with certainty except in cases of grave alteration, when the nutritive alteration is also grave. On the other hand, function will be entirely suppressed when the structural dispositions of the achromatic

part, which seem more strictly related to the nervous conduction, are altered, or when they are suddenly affected by energetic chemical action.

"Still the alterations of the chromatic part can show us what is the seat of action of the hurtful cause, since it is natural that functional disturbances should be connected with disturbances of function of those elements that are affected in their nutrition, rather than of others that remain entirely intact. It is to be borne in mind, on the other hand, that with the protraction of the hurtful action the nutritive disturbance is aggravated, that the lesion becomes more profound and even irreparable, and that thus also the fibrillar mechanism may become involved, which lesion immediately translates itself into functional disturbance."

It is possible, and seems indeed very probable, that purely local degenerative changes in the branches of the dendrites and in the collaterals of the axis-cylinder processes are of considerable importance in nerve-cell pathology. But, as yet, histological investigations have failed to demonstrate conclusively the occurrence of such alterations apart from general lesions of the cell-element. Atrophy and varicosity of the protoplasmic prolongations and local absence of gemmulæ, which many observers have correlated with important clinical phenomena, have been proved to occur quite independently of such phenomena. Moreover, experimental observations have shown that distinct degenerative changes may be recognisable in the cell-body, while in preparations of the same material by the method of Golgi the protoplasmic prolongations are perfectly normal in appearance; and that in conditions of slowly progressive general atrophy of the nerve-cells, the alterations do not advance from the periphery, as has been inferred by some from the appearances they have found in the human brain, but simultaneously affect the whole element.

Regarding alterations affecting some of the finer structural features of the nerve-cell, such as the endocellular reticulum of Golgi and the pericellular nerve-endings, which probably also have considerable pathological importance, nothing has as yet been ascertained. Nor does any systematic research appear to have yet been made upon the pathological alterations of the nucleus in the light of modern conceptions of its normal structure.

VI. SPECIAL PATHOLOGY OF THE NERVE-CELLS IN RELATION TO MENTAL DISEASES.

The difficulties that confront the investigator when he seeks to determine the exact nerve-cell changes that form the physical basis of disorders of the mental faculties, are certainly unsurpassed by those that are to be met with in any other portion of the wide field of modern pathological science. They are in part inherent to the subject

itself, and in part depend upon the conditions under which such researches are necessarily carried out.

The inherent difficulties may be readily appreciated. The neurons are, as we have seen, tissue-elements of extraordinary complexity and considerable variety of structure; the myriads of them that go to constitute the human organ of mind are arranged upon a definite and invariable and, at the same time, exceedingly intricate plan. The means by which these general facts can now be recognised have themselves had to be discovered and gradually developed; as yet they are far from perfect or adequate for the demonstration of every structural detail, even supposing it were possible to survey rapidly the whole cerebral field with their aid. Consequently, our knowledge of the normal structure, arrangements, and mutual relations of the cerebral neurons is still far from complete; indeed, it is certain that the important facts still to be discovered greatly exceed in number those that have so far been ascertained. Although we have now a considerable amount of trustworthy information with regard to the special functions of the various groups of neurons in the central nervous system, endless important questions of cerebral physiology are still entirely obscure, whilst as to the exact nature and seat of the various physico-chemical processes upon which the different manifestations of neuron-activity depend, we have as yet but a number of theories of various degrees of credibility.

The progress of any department of pathology is necessarily limited by that of the corresponding departments of anatomy and physiology. Hence the investigation of the nerve-cell changes upon which the various disorders of the nervous system depend is hampered by an incomplete knowledge of the normal structure, special functions and mode of action of the elements concerned. But, even within the limits within which anatomy and physiology already assist it, nerve-cell pathology has its own exceptional difficulties in the number and complexity of the problems that it presents. Many of these problems have been solved in recent years entirely through the magnificent series of analytical experimental researches that have been carried out chiefly by continental workers—among whom Lugaro and Marin-escio may justly be singled out as those to whom neurological science in this connection owes the largest debt—but still a very large number of them remain unsolved. If the problems presented by the general and experimental pathology of the nerve-cells are numerous and complex, those that we have to face specially in connection with mental diseases are, in the nature of things, still more so.

The difficulties that depend upon the conditions under which studies upon the nerve-cells of the insane are necessarily carried out, are not quite so obvious; indeed, most of the early investigators

in this field almost entirely failed to appreciate them, and were consequently led into all sorts of erroneous conclusions. The nature of the difficulties referred to will perhaps be best understood from a comparison of the conditions under which the human brain is examined with those that attend the carrying out of researches in experimental pathology. In the latter case the desired pathological state is produced in a previously healthy animal, which at any stage of the disease may be rapidly killed under chloroform, or in other suitable way, and at once dissected, the organs which it is intended to examine being immediately placed in fixing solution; in such investigations there is generally obtained an uncomplicated picture of the tissue-alterations that characterise the disease. In the former case, on the other hand, the conditions are very different. In typical instances the patient dies at an advanced stage of the particular form of mental disease from which he suffered; the immediate cause of death is some intercurrent disorder of the thoracic or abdominal organs; a post-mortem examination is made from twenty-four to forty-eight hours after death. Under such conditions there are numerous grave disadvantages at which an investigator is placed who desires to ascertain the precise nerve-cell changes upon which the disorder of the patient's mental functions depended. In the first place, the changes that were present some days before death were those characterising an advanced stage of the pathological process; consequently, the primary and more essential changes are obscured by numerous secondary ones. Further, the intercurrent disease that determined the patient's death must have been associated with various forms of auto-intoxication, and may also have been attended by elevation of temperature. Experimental researches have shown that these morbid conditions are readily capable of producing marked alterations in the cortical nerve-cells. But even apart from distinct intercurrent disease and elevation of temperature, almost all natural modes of death are attended with some degree of auto-intoxication, and they not infrequently reproduce states more or less closely resembling experimental inanition and anæmia. Hence we might expect it to be quite exceptional to find perfectly healthy nerve-cells in the tissues from the human subject, and that this is indeed so is abundantly confirmed by the results of observation upon a series of brains from the post-mortem theatre of a general hospital. But pathologists have to contend with still another very serious cause of nerve-cell alteration, to which human nervous tissues are almost inevitably exposed—namely, post-mortem decomposition, which undoubtedly becomes appreciable under the microscope within a few hours after death, and at ordinary temperatures is always far advanced within twenty-four hours.

It must be evident that the difficulties that beset the investigator in this field are very serious and apt to be discouraging. Indeed there are some alienists of high reputation who are inclined to regard the task of ascertaining the exact nerve-cell changes related to mental disorders as a hopeless one. But it is a notable fact that those who best understand the nature and magnitude of the difficulties to be faced are the most confident that they are not insuperable. Year by year large additions are being made to our knowledge of the anatomy and physiology of the nervous system, and thereby the task of the pathologist up to a certain point is gradually being made easier and clearer. Experimental pathology has now accurately defined, as far as is possible in the light of present knowledge of normal structure and function, the reaction of the nerve-cells to various simple pathological conditions, and has thus enabled us to rightly understand the significance of various morbid appearances in the nerve-cells of the human brain; at the same time it has enabled us to recognise, and in some measure to discount, those changes that tend to be superadded to the true pathological picture during the last few days of life and after death. In every department of knowledge bearing upon the pathology of the nerve-cell most remarkable advances are now continually being made. Each fresh discovery is leading on to others, and there seems every prospect that this rapid progress will continue indefinitely. Under such circumstances the difficulty of the task before us and the inadequacy of the present means to the end in view, need not discourage us. The study of the cortical nerve-cells in the insane has not yet had time to advance nearly so far as the recent large additions to our knowledge of the structure, physiology and experimental pathology of the nerve-cells clearly permits; and it may safely be predicted that the latter will long continue to keep considerably in advance of the former. Hence we may look forward with confidence to continued progress which must inevitably result in the gradual elucidation of the pathology of mental disorders.

The trustworthy facts with regard to the special nerve-cell changes that occur in mental diseases that have so far been ascertained are not very numerous. They may conveniently be considered in three categories:—(1) The occurrence of special types of nerve-cell change peculiar to individual forms of mental disease, (2) the occurrence of primary and secondary degeneration in an essentially diffuse and specially severe form, (3) the local occurrence of these degenerative changes.

In the writings of the earlier investigators, and even in some of those of the present day, there is discernible a distinct attempt to discover special types of nerve-cell alteration which would constitute the essential pathological anatomy of the individual forms of insanity. Thus it might be imagined that acute mania, acute melancholia, stupor,

etc., each depends upon a special type of nerve-cell lesion. While it cannot be excluded that future research may reveal some changes of this special kind, there are strong reasons for believing that it will not succeed in doing so, or at least that any such special changes will consist merely in the unusual prominence of some not uncommon feature in the ordinary types of nerve-cell degeneration. Up to the present, as far as I am aware, there is no well authenticated instance of the observation of a special nerve-cell lesion in any form of insanity. Recent experimental researches distinctly point to the conclusion that the different forms of mental disease depend not upon different forms of nerve-cell change, but upon the nature and intensity of the toxic or other condition causing the lesion, the localisation of the morbid action and the special reactive qualities of the individual nervous system.

The occurrence of either primary or secondary degeneration in a more or less diffuse and specially severe form in certain varieties of insanity, is now a thoroughly established fact. One of the most striking examples of this kind is to be found in cases of acute mania and acute melancholia dying in the course of the disease. In such cases from twenty-five to fifty per cent of the cortical nerve cells show distinctly marked degeneration of the primary type. This percentage is much in excess of that which is generally to be found in persons succumbing, for example, simply to pneumonia, or exhaustion from any wasting disease, such as phthisis. Moreover, as Dr Orr (264) and I have contended, the difference is not merely one of the percentage of the cells affected, but also of the *intensity* of the degenerative changes that are present. The affection is essentially diffuse in character, although some areas are much more seriously involved than others. There is in many instances abundant proof that very many of the nerve-cells have entirely disappeared. In cases of secondary dementia following attacks of acute mania the number of the cortical nerve-cells is often diminished by nearly one-half.

In senile insanity also there is a slow degeneration of the cerebral nerve-cells, which, provisionally at least, may be looked upon as for the most part of the primary form. In a typical case its severity is far in excess of that of the similar changes that are associated with normal senile involution. The nerve-cell lesions are essentially diffuse in their distribution, but at the same time their local incidence largely determines the special individual features of different cases. In advanced cases a large percentage of the cells has disappeared. Very commonly there is complete destruction of the nerve-cells throughout considerable areas, owing to involvement in local softenings. In general paralysis there is also a diffuse degenerative change in the cortical nerve-cells, chiefly of a primary type. The process is a much more acute one than that in senile insanity, and the number of cells severely

affected is generally greater. In advanced cases extensive areas may be almost entirely depleted of nerve-cells. In choreic insanity there are extensive, more or less acute degenerative changes in the cortical nerve-cells, also of a far more severe character than those that occur from simple terminal auto-intoxications. In chronic alcoholic insanity there is very considerable loss of cortical nerve-cells, while a large proportion of those that remain show degenerative changes either of a primary or of a secondary character. A closely related type of case in which the secondary form of degeneration is specially prominent is that of which the pathological anatomy has lately been described by Ballet and Faure (27, 28, 86, 87). In 1898, these authors gave an account of two cases of alcoholic peripheral neuritis associated with mental confusion (polyneuritic psychosis), in which they found advanced degenerative changes in the large pyramidal and giant cells of the cerebral cortex. These changes had the characters of secondary lesions. More recently Faure (86, 87) has described four additional cases which were clinically of the same or of a closely allied kind; they were all examples of "primary mental confusion." In each there were degenerative changes in the large pyramidal and giant cells of the cortex, similar to those found in the first two cases described by Ballet and himself. He could not ascertain with certainty that the small nerve-cells of the cortex were similarly affected. He maintains that these changes were probably the result of injury to the fibres of projection, and supports this contention by reference to the results of the experimental observations carried out by Ballet and himself, as well as by others (see page 233). He points out the analogy that the condition presents to the changes in the cells of the anterior horns of the spinal cord in peripheral neuritis, and maintains that this disease, polyneuritic psychosis and a certain type of mental confusion are probably to be placed in the same pathological group, as they would all seem to represent the reaction of the neurons to slow injury from internal poisons, acting specially upon their fibres of projection. It may be assumed that in the two latter conditions these degenerative changes are not limited to secondary lesions of the giant and large pyramidal nerve-cells, but that the toxins which injure the axons of these motor neurons at the same time produce primary lesions in these and other cortical nerve-cells, just as in peripheral neuritis there are generally primary as well as secondary lesions to be observed in the cells of the anterior cornua. John Turner (294) has recently described a series of seven cases of a form of dementia in which nerve-cell degeneration of this secondary type extensively affected the pyramidal and giant cells of the cerebral cortex. At least some of them correspond clinically to the cases described by Ballet and Faure. Hamilton Wright and Orange (302) have also described nerve-cell lesions of similar type

and localisation in a case of alcoholic dementia and symmetrical polyneuritis.

I think that a little caution is required in the interpretation of the significance of lesions of secondary type in the giant cells of the cerebral cortex. Their occurrence is by no means limited to cases of the confusional and demented form described above. They are very common in other forms of mental disease, such as senile insanity and general paralysis.

With regard to the influence of the special localisation of nerve-cell lesions upon the production of insanity very little can yet be said to be known. It is certain, however, that in future investigations into the pathology of mental diseases, studies upon this subject must take an important place, although as yet the anatomical and physiological foundations for them can hardly be said to have been securely laid.

The recently enunciated hypotheses of Lugaro permit of certain provisional inductions as to the condition of the neurons in certain psychopathic states. As this authority has had occasion to remark, so long as these hypotheses are regarded as such, and not mistaken for facts, they may serve a useful purpose.

Thus in accordance with the theory of the functional contractility of the gemmulæ, we may conceive of the insomnia of mental diseases as dependent upon an irritable condition of the neurons in consequence of which these appendages of the protoplasmic processes are unable, even in states of fatigue, to assume their position of rest, that is, general expansion, but continue to contract in response to the slightest stimulus, expanding again when this has passed. On the other hand we may conceive of stupor as dependent upon an abnormal condition of the neurons in consequence of which the contractility of the gemmulæ is more or less completely abolished.

The theory of the distinctive functional values of the intra-neuronic and inter-neuronic elaborations also suggests some interesting inductions. In considering the bearing of this hypothesis upon problems in pathology it is, I think, important to have clearly in mind that an inter-neuronic elaboration may be suppressed by interruption of the conducting fibrils at any point in their course in one or other of the two neurons concerned, and not merely by some abnormal condition of the intervening lymph. The former is probably by far the more common cause of such suppression in mental disease. The latter would appear to be the essential factor in chloroform anæsthesia, and allied conditions. We may probably exclude any state of continued general contraction of the gemmulæ from the possible, or at least the common, causes of suppression of the inter-neuronic discharge, for contraction of these appendages would seem to be essentially associated

with their functional activity; it is the response to a stimulus received, and is of short duration; the position of rest is that of expansion.

Upon this hypothesis we may conceive of states of simple mania and melancholia as dependent upon abnormal metabolism within the substance of the nerve-cell, and understand how they are compatible with unimpaired action of some of the purely intellectual faculties, the integrity of which is dependent upon the maintenance of certain mutual relations of groups of neurons. We may picture a momentary amnesia as implying a temporary failure of a particular inter-neuronic discharge, profound dementia as dependent upon the fact that the majority of the special inter-neuronic connections that education had slowly developed and perfected have suffered destruction, owing to the death of one or both of the neurons concerned with each. Between these two degrees of failure of mental action we may conceive of endless varieties, dependent upon the number and the special functional rôle of the neurons involved. In a general way we may regard a delusion, or at least some forms of delusion, as the result of suppression of certain inter-neuronic elaborations included in those that are collectively required to form a particular association. In consequence of this suppression of one or more of its usual factors, the association is rendered imperfect, the mental picture is distorted, one part of it is lost to view and another attains undue prominence, just as a little flaw in an otherwise faultless window pane is capable of making us see valleys and hills in a landscape in which there are none. The suppression of the inter-neuronic discharge being purely of local incidence, it may be inferred that it does not depend upon any abnormal condition of the intervening lymph, but upon some alteration in the fibrils of the neurons concerned. Such alterations commonly imply involvement of the whole cell-element and a lesion of considerable severity. It is known that for every nerve-cell that suffers to this extent from any toxic condition, there are generally several others that suffer in a smaller measure. From these considerations we may perceive at least one reason why delusions are generally accompanied by either excitement or depression. It is further to be observed that the suppression of the inter-neuronic discharge is not necessarily permanent; it may result merely from fatigue of an element of which the structural and functional integrity is already impaired, or from a degenerative process which may be arrested on withdrawal of its toxic cause.

MORBID CONDITIONS OF THE MEDULLATED NERVE-FIBRES OF THE BRAIN IN MENTAL DISEASES.

The degenerative changes that affect the medullated nerve-fibres are, like those of the nerve-cells, either of a primary or secondary

nature. Primary degeneration is caused by the direct action of a toxine upon the fibre; secondary degeneration follows a local lesion of the fibre, or degeneration of the nerve-cell from which it takes origin, and extends in the direction of nervous conduction. The anatomical differences presented by these two forms of nerve-fibre lesion have been described by Adamkiewicz, Vassale, and others. According to Vassale (298), secondary degeneration is characterised by a grave destructive process which affects both the medullated sheath and the axis-cylinder, quickly leading to disappearance of the whole fibre. On the other hand, in primary degeneration (or "systematic atrophy," as he prefers to call it) there is generally a comparatively very slow progressive atrophy, with gradual disappearance of the myeline sheath and persistence of the axis-cylinder, often for a long time. Secondary degeneration in its early stages, before the complete disappearance of the medullated sheath, is revealed by the method of Marchi, which blackens the disintegrating myeline; in its later phases, when the fibres have entirely disappeared, it is revealed by those histological methods that determine the presence or absence of myeline, such as the Weigert-Pal method. On the other hand, primary degeneration is not revealed at any stage by the method of Marchi; Vassale recommends for its study especially the carmalum stain of Mayer, nigrosin, and azolitmine. With these stains the degenerated axis-cylinders appear swollen, varicose, and granular, and not very sharply distinguished from the atrophied and diffusely coloured myeline sheath.

The observations that have as yet been made upon the morbid alterations that affect the medullated nerve-fibres of the brain in cases of mental disease, are in most instances somewhat limited in their scope. They concern chiefly the fact of the presence or absence of secondary degeneration; some attempts have been made to determine the localisation of such degeneration in different forms of mental disease, but the conclusions arrived at by the different investigators are little in harmony with each other.

Extensive degenerative changes, partly at least of a secondary nature, affect the cortical nerve-fibres in general paralysis. Such changes also occur, but generally to a much less extent, in several other forms of mental disease, more especially senile and alcoholic insanity. So far as they are of secondary origin, they may be regarded as chiefly dependent upon the nerve-cell lesions that we have seen to occur in the same forms of mental disease. Areas of degenerative change, corresponding to atrophic and sclerotic foci, are very common in senile insanity, general paralysis, and epileptic insanity.

This subject of the relation of nerve-fibre lesions to insanity un-

questionably presents a very wide and important field for research. The incidence of primary degeneration appears still to require investigation. The mere fact of the occurrence of primary or secondary degeneration is, however, of comparatively little importance; the really important point to be determined is its *localisation*.

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DESCRIPTION OF PLATES XXI. TO XXIX.

PLATES XXI. TO XXVI.

The figures in these plates are photographic reproductions of illustrations accompanying recent papers by other authors. They are described on the plates.

PLATE XXVII.

Large pyramidal nerve-cells of human cerebral cortex. Methyl violet method. Sublimate fixation. ($\times 800$.)

Fig. 15. Normal nerve-cell, showing the chromophile elements of the protoplasm and the cone of origin of the axis-cylinder process.

Fig. 16. Nerve-cell altered by post-mortem change. The nucleus is stained deeply and diffusely; the chromophile bodies are partially disintegrated, and the particles show a tendency to form local aggregations.

Fig. 17. Nerve-cell from a case upon which the post-mortem examination was made

three days after death. The nucleus stains deeply and diffusely, and shows slight vacuolation; the chromophile elements of the protoplasm have almost entirely disappeared.

- Fig. 18. Nerve-cell showing type of morbid change that is produced by experimental pyrexia. The chromophile elements of the protoplasm have entirely disappeared, and the fibrils are abnormally prominent. The nucleus is stained deeply and diffusely, probably owing to post-mortem change.
- Fig. 19. Nerve-cell of cortex of a woman aged 90, who died from uncomplicated senility. It shows a large collection of pigment in the protoplasm and displacement of the nucleus. The chromophile elements are normal, in so far as they are not replaced by pigment.
- Fig. 20. Three nerve-cells from the same case as preceding fig.; *a*, cell showing very large collection of yellow pigment in protoplasm, loss of processes, pallor of remaining chromophile elements and deep, diffuse staining of the nucleus; *b* and *c*, cells showing advanced disintegration of nucleus and protoplasm.
- Fig. 21. Three cortical nerve-cells from a case of advanced general paralysis, showing slow degenerative changes of primary type; *a*, cell with large pigmentary accumulation in the protoplasm and pallor and slight disintegration of the chromophile bodies; *b*, advanced chromatolysis; *c*, advanced chromatolysis, loss of processes and commencing disintegration of the nucleus.

PLATE XXVIII.

This plate is intended to illustrate the morbid changes that occur in the cortical nerve-cells in cases of acute insanity. Sublimite fixation. Methyl violet method. ($\times 900$.)

- Fig. 22. Two normal, large pyramidal nerve-cells of human cerebral cortex for purposes of comparison.
- Fig. 23. Two adjacent nerve-cells from a case of acute delirious mania. Both show central chromatolysis. In the one to the left the nucleus has undergone disintegration.
- Fig. 24. Two adjacent nerve-cells from a case of acute mania. Both show advanced degeneration of primary type. The appearance of the cell to the left closely resembles that which may be produced by post-mortem change, but it may be excluded that the chromatolysis was due to this cause, as similar alterations were to be observed only occasionally, instead of being general throughout the cortex. Note the disintegration of the nucleus of the cell to the right.
- Fig. 25. Two adjacent nerve-cells from a case of acute melancholia. Both show advanced degeneration of primary type.
- Fig. 26. Group of four nerve-cells from a case of acute mania, showing advanced degenerative changes. Note the disintegration of the nucleus in three of the cells.
- Fig. 27. Two adjacent nerve-cells from a case of acute mania. Note the deep diffuse staining of the protoplasm in the cell to the right. The more advanced stage of the change is represented in the cell to the left, the nucleus of which is disintegrating. This type of alteration, which was very general in this case, may frequently be observed in its slighter degrees in the cortical nerve-cells. Its exact significance is doubtful. Observe also the pale yellow pigment at the bases of the cells.

PLATE XXI.

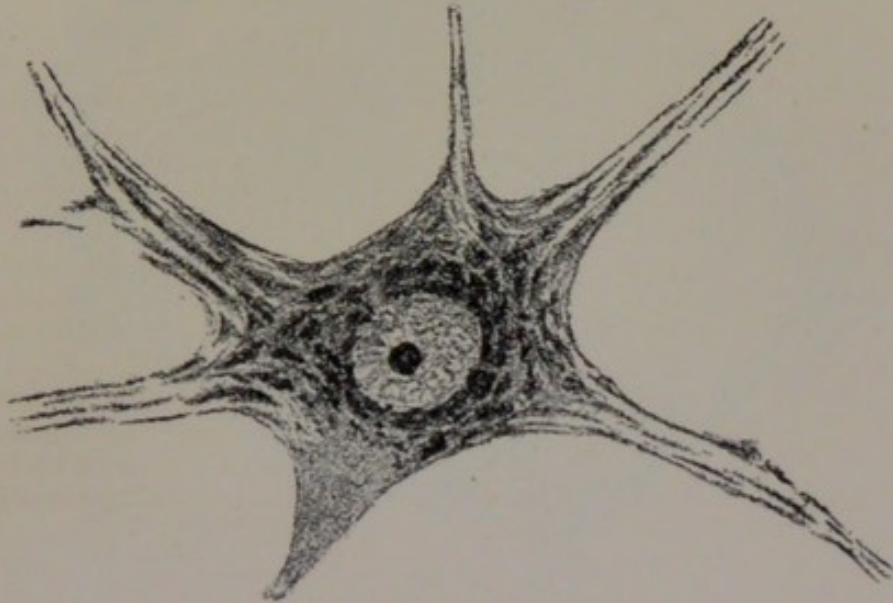


Fig. 1.

Cell of anterior horn of spinal cord of normal rabbit. Sublimate.
Thionin. Lugaro (137).

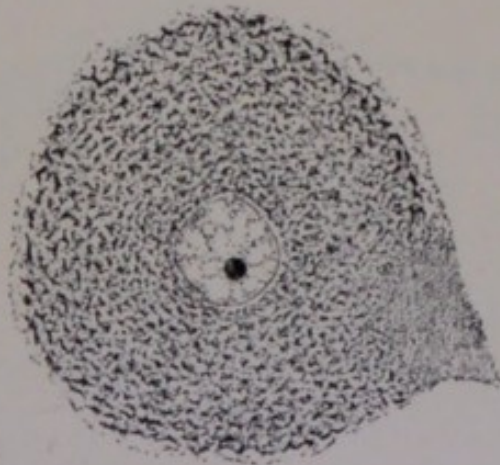


Fig. 2.

Cell of spinal ganglion of normal dog. Lugaro's first type. Sublimate.
Thionin. Lugaro (130).



PLATE XXII.

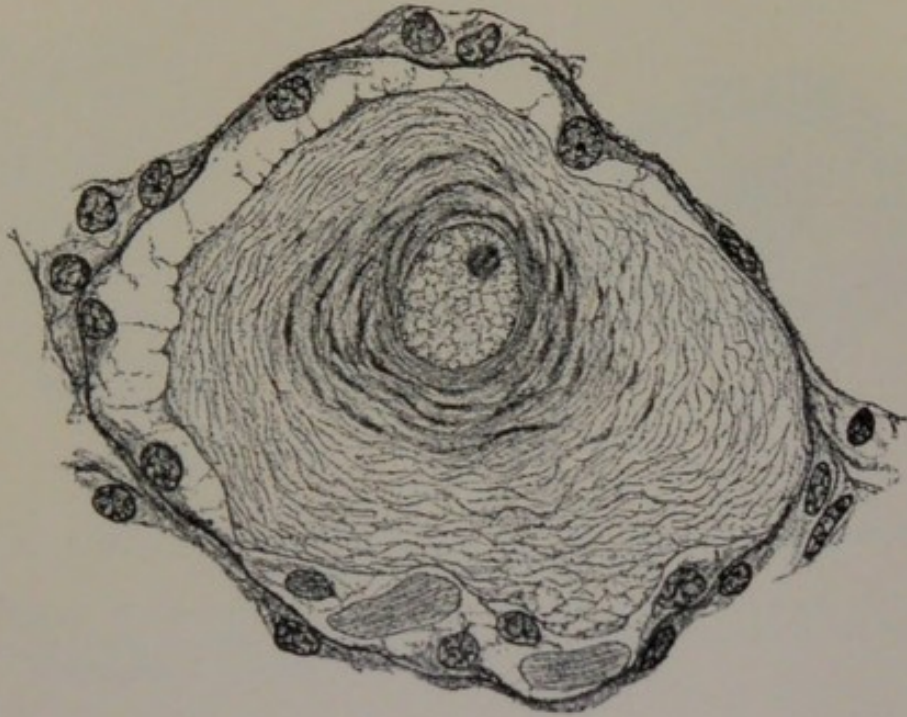


Fig. 3.

Cell of spinal ganglion of dog poisoned with arsenic, showing concentric arrangement of chromatic particles and fibrils. Section in the plane of the course of the fibrils. Owing to peripheral chromatolysis the fibrils are distinctly visible. Sublimate. Delafield's hæmatoxylin. Lugaro (140).

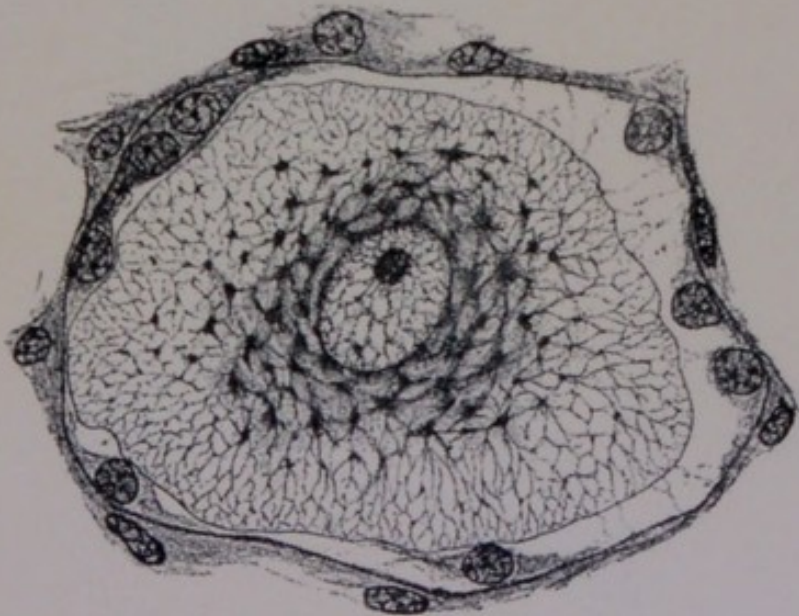


Fig. 4.

Same as Fig. 3, except that the section is in a plane perpendicular to those in which the concentric fibrils run. Lugaro (140).



PLATE XXIII.

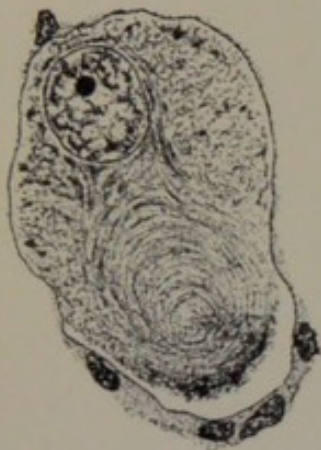


Fig. 5.

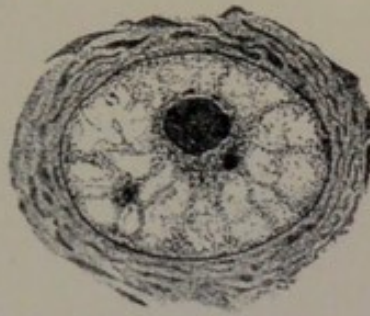


Fig. 6.

- (5) Cell of spinal ganglion of *Bufo vulgaris*. Winter. Shows the spiral vortex in oblique section. Giuseppe Levi (152).
- (6) Nucleus of nerve-cell of anterior horn of spinal cord of guinea-pig, showing basophile particles attached to the nucleolus. The original is in colour, Ehrlich-Biondi staining. Giuseppe Levi (149).

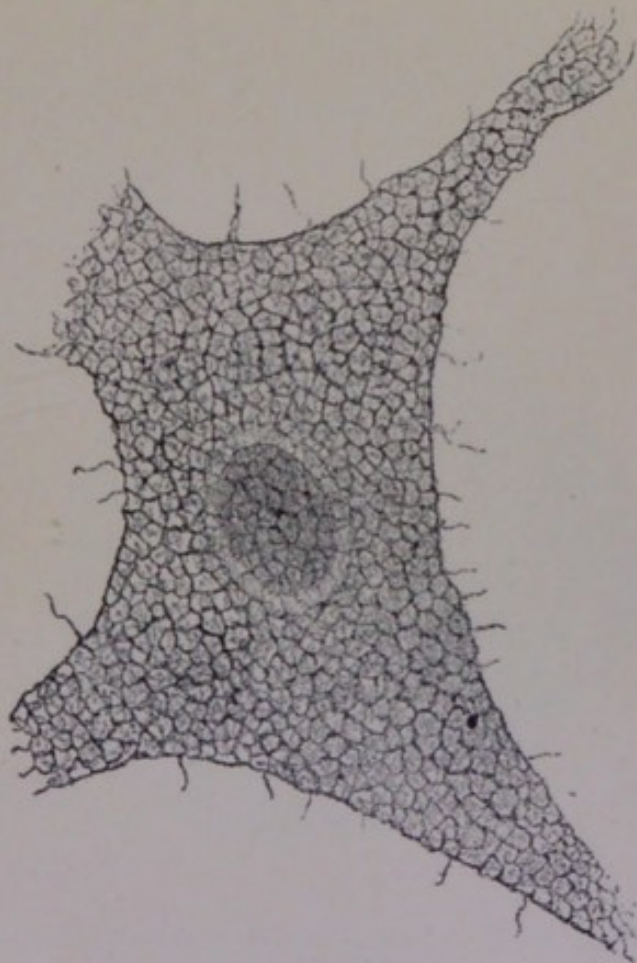


Fig. 7.

Nerve-cell of anterior horn of spinal cord of dog, showing reticulum. The original is in colour. Donaggio's methylene blue method. Donaggio (58).



PLATE XXIV.

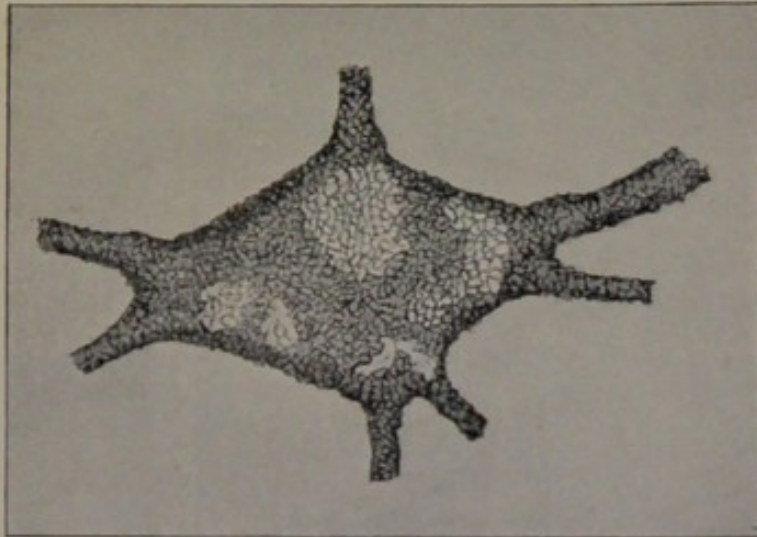


Fig. 8.

Nerve-cell with reticular investment. Cell of anterior horn of spinal cord of cat.
Golgi (90).

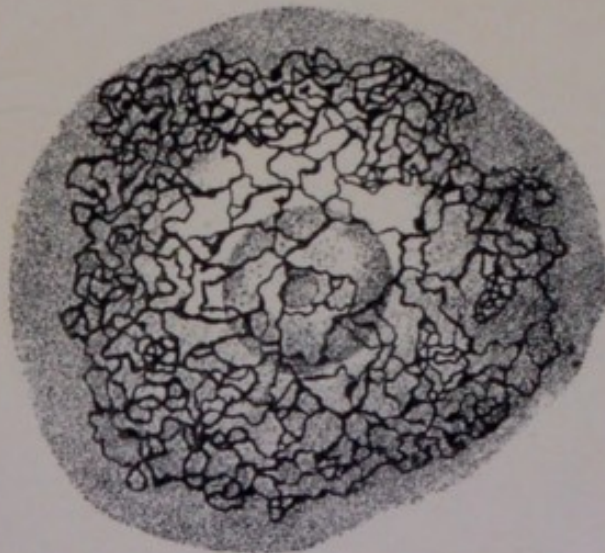


Fig. 9.

Spinal nerve-cell with internal reticular apparatus. From a ganglion of adult dog.
Golgi (91).



PLATE XXV.

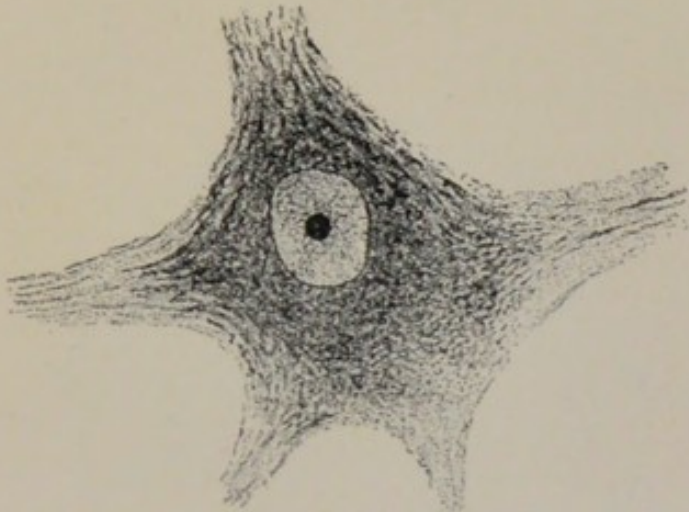


Fig. 10.

Nerve-cell of anterior horn of spinal cord of guinea-pig. Incipient chromatolysis from section of nervous prolongation. Reactive phase. Sublimate. Thionin. Compare with Fig. 1. Lugaro (128).

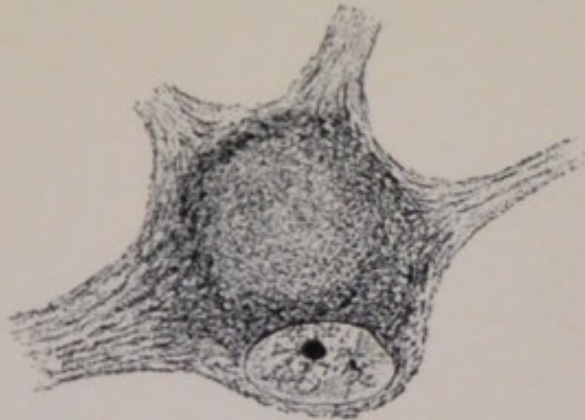


Fig. 11.

Nerve-cell of anterior horn of spinal cord of guinea-pig after section of the nervous prolongation. Initiation of the degenerative phase. Sublimate. Thionin. Lugaro (128).

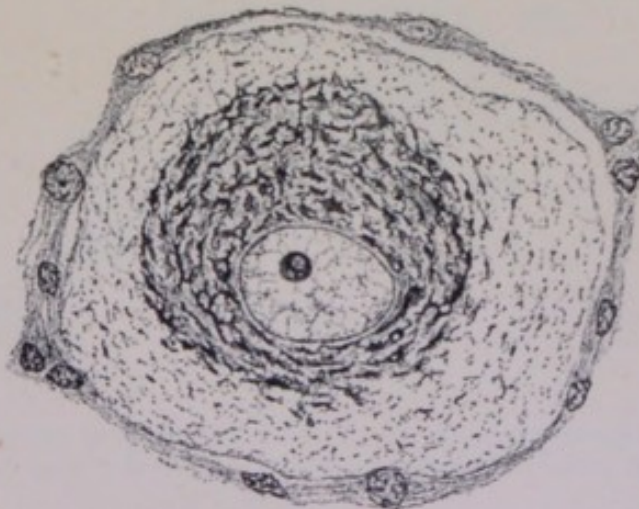


Fig. 12.

Cell of spinal ganglion (dog) showing peripheral chromatolysis. Poisoning with arsenic. Sublimate. Thionin. Lugaro (131).



PLATE XXVI.



Fig. 13.

Cell of spinal ganglion (dog) with advanced diffuse chromatolysis. Severe poisoning with lead. Sublimate. Thionin. Lugaro (131).

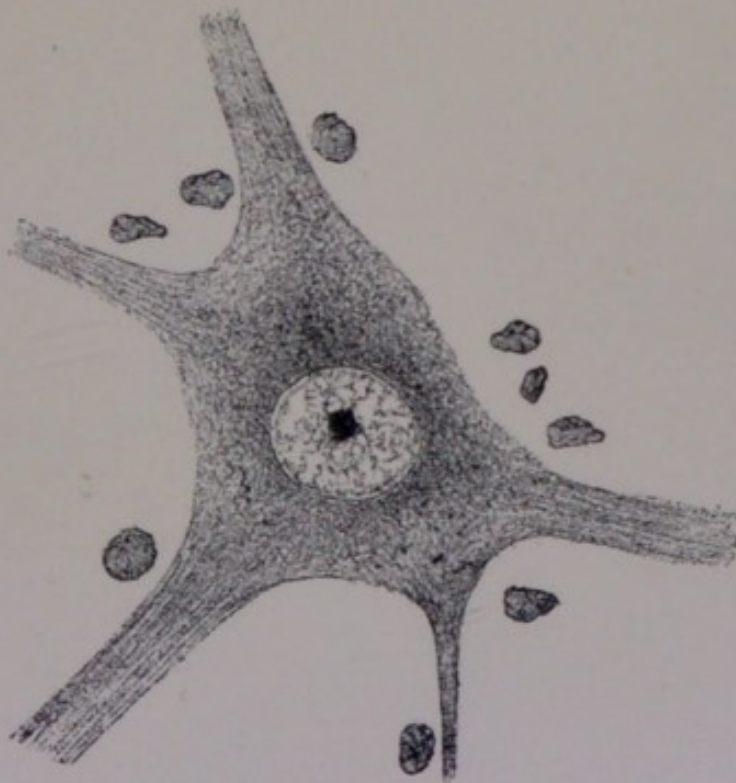


Fig. 14.

Cell of anterior horn of spinal cord of rabbit. Experimental elevation of temperature. Compare with Fig. 1. Sublimate. Thionin. Lugaro (137).



PLATE XXVII.

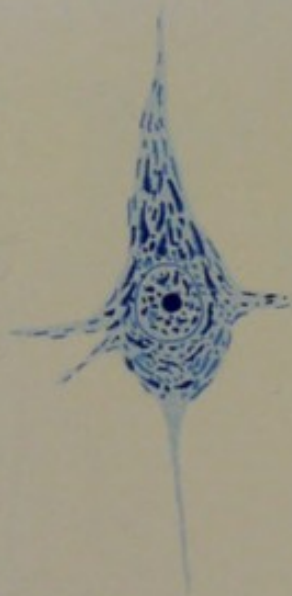


Fig. 15.

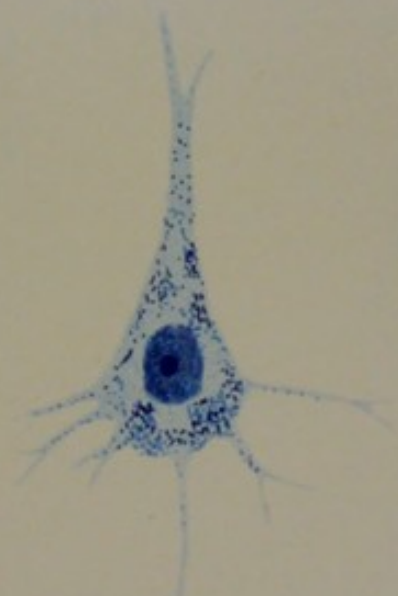


Fig. 16.

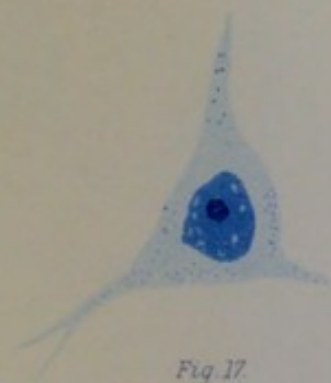


Fig. 17.

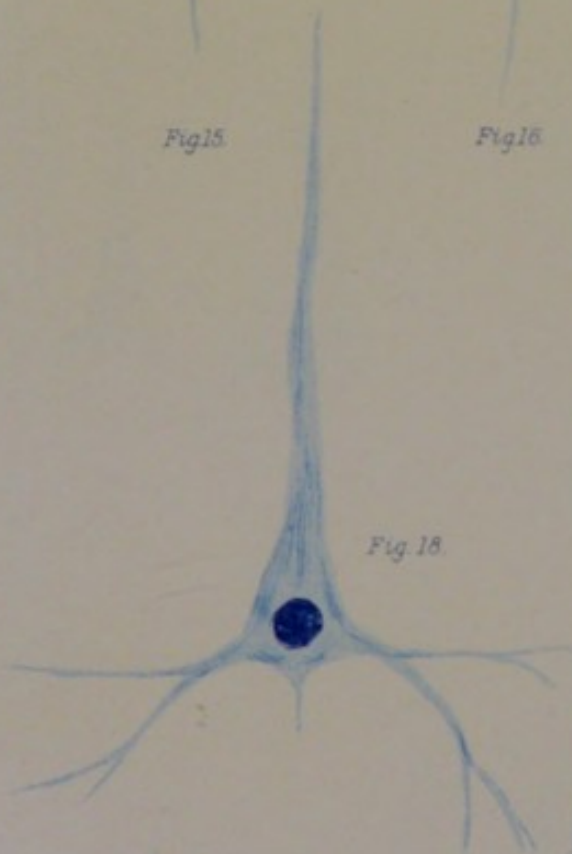


Fig. 18.

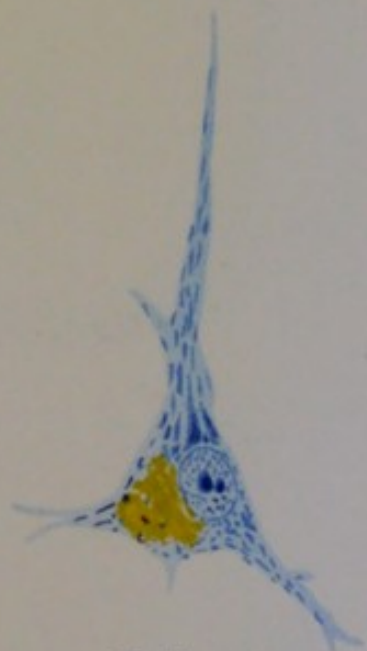
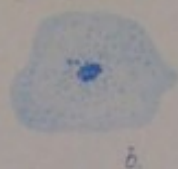


Fig. 19.



a.



b.

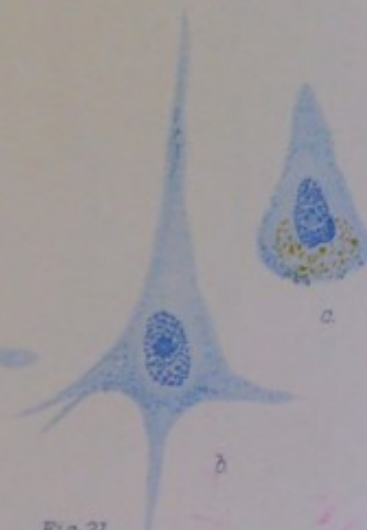


c.

Fig. 20.



a.



b.

Fig. 21.



PLATE XXVIII.

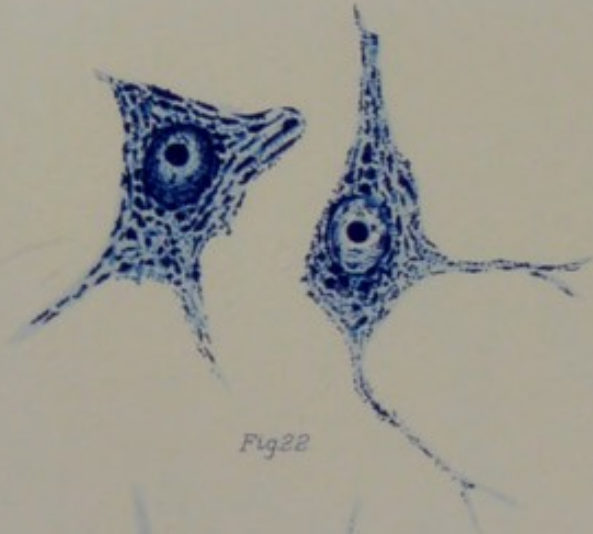


Fig 22

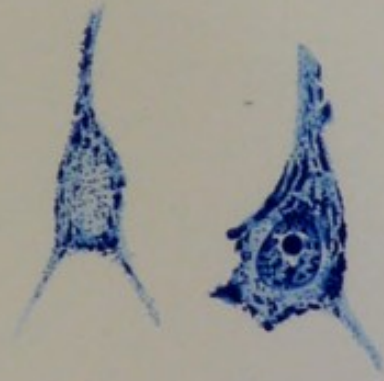


Fig 23

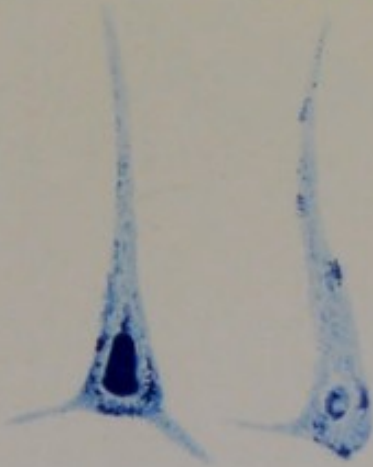


Fig 24

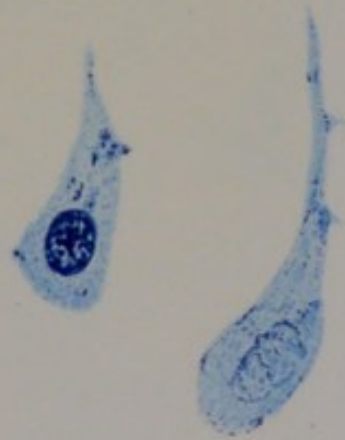


Fig 25

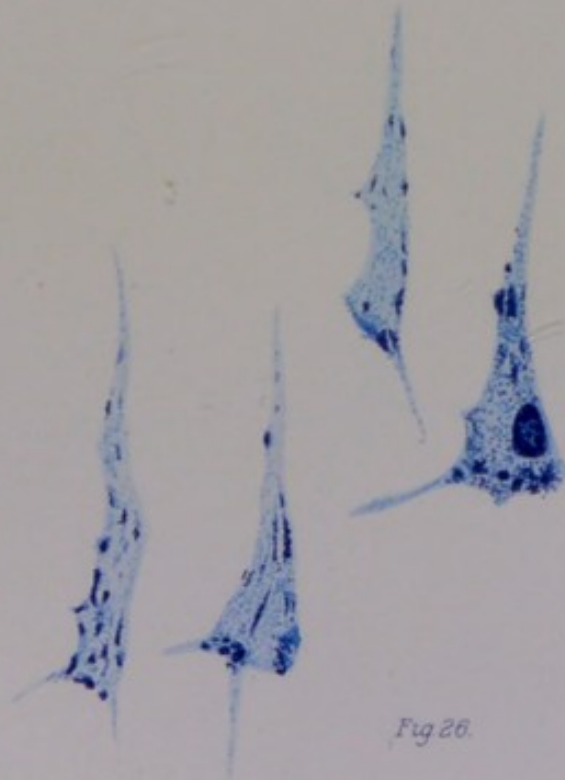


Fig 26



Fig 27



PLATE XXIX.

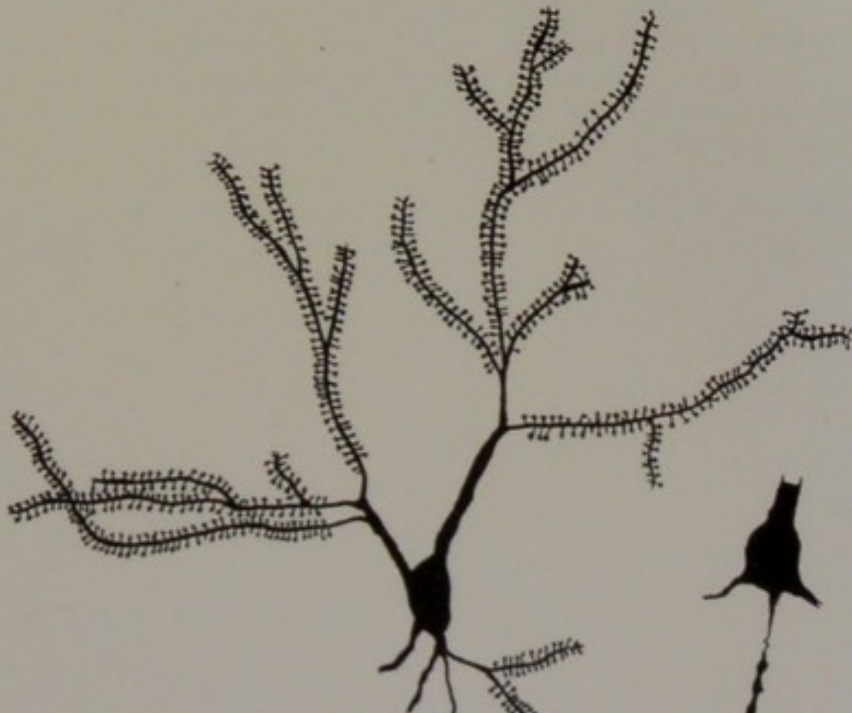


Fig. 28.

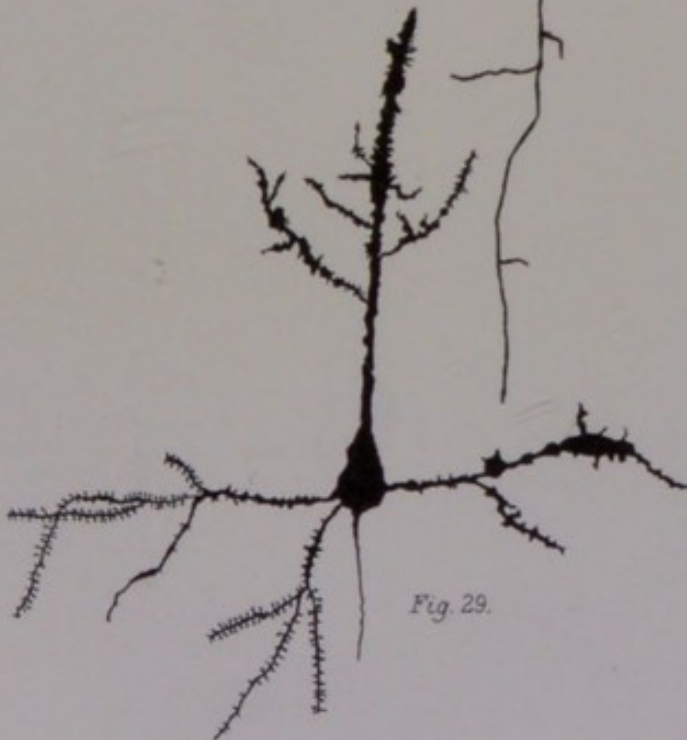


Fig. 29.



Fig. 30.



PLATE XXIX.

Nerve-cells of cerebral cortex prepared by the Cox-Mirto method. ($\times 500$).

- Fig. 28. Nerve-cell of cerebral cortex of healthy dog, showing protoplasmic processes with gemmulae, axis-cylinder process and collaterals.
- Fig. 29. Pyramidal nerve-cell of cerebral cortex from a case of chronic tuberculosis of kidneys and bladder, showing varicose atrophy of protoplasmic processes.
- Fig. 30. Axis-cylinder process of cortical nerve-cell from a case of exophthalmic goitre, showing varicose hypertrophy.

CHAPTER X

MORBID VARIATIONS IN THE PHYSICAL PROPERTIES OF THE BRAIN.

WEIGHT.

THE average weight of the normal human brain may be regarded as about 49 oz., or 1389 grammes, in the male, and 44 oz., or 1247 grammes, in the female. It is, however, very variously stated by different observers.

The weight of the brain of different individuals of normal intellectual powers varies within wide limits. In adults, there is a range of nearly 1000 grammes. Although persons who have been of good education, or have possessed special intellectual acuteness, are found, as a rule, to have a brain of at least average, and often considerably over-average weight, there does not appear to be any very direct relationship between brain-weight and mental power. Brain-weight is influenced to an important extent by sex, age and race. The difference in the two sexes, the extent of which is fairly indicated by the above figures, appears not to be dependent merely upon difference of height or of body-weight. The statistics of Meynert and Crichton Browne prove it to represent a fundamental sexual distinction. Brain-weight reaches its maximum between the ages of twenty and thirty, and remains constant until about fifty, when it begins to decrease.

Several unusually heavy brains have been described. Some of them have belonged to individuals who were mentally sound, others to idiots and imbeciles. Middlemass (25) has described one weighing $65\frac{1}{4}$ oz. (1850 grammes), from an idiot who died at the age of seventy. In this case, on microscopic examination, the organ was found to present the alterations characteristic of the condition known as "hypertrophy of the brain," which consists essentially of a diffuse overgrowth of the neuroglia, chiefly in the white matter. Obersteiner (26) examined a brain which was calculated to weigh 2028 grammes; it was from a man, aged fifty-eight, of good intellectual endowments. Walsem (33) has recently published an account of a brain which he claims to be the heaviest yet described; it was that of an epileptic idiot, twenty-two years of age, and weighed 2850 grammes. Microscopic examination revealed indistinctness of the layers of the cortex and paucity of nerve-

cells, but no alteration in the neuroglia. Most of the heavy brains of idiots and imbeciles appear, however, as in the case described by Middlemass, to be associated with a diffuse overgrowth of this tissue.

It is generally agreed that the average weight of the brain is less in the insane than in the sane. Dr Middlemass (24) and I, in 315 cases examined by ourselves at Morningside Asylum, found it to be 1353 grammes ($47\frac{3}{4}$ oz.) in males, and 1226 grammes ($43\frac{1}{4}$ oz.) in females. The results arrived at by some other observers are shown in the following table:—

	M.	F.	Country.		M.	F.	Country.
Bergmann, .	1372	1272	Hanover.	Boyd, .	1305	1206	England
Bartels, .	1392	1255	Do.	Clapham, .	1356	1230	Do.
Koster, .	1405	1259	Westphalia.	Crichton			
Tigges, .	1362	1244	Mecklenburg.	Browne, .	1335	1198	Do.
Meynert, .	1296	1170	Austria.	Parchappe, .	1368	1206	France.
				Amadei, .	1403	1198	Italy.

The average weight of the brain in different forms of insanity, as ascertained by various observers, is shown in the following table:—

	Bartels.		Clapham.		Tigges.		Amadei.		Jensen.		Middlemass and Robertson.	
	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.
General Paralysis, .	1353	1185	1302	1134	1284	1185	1300	1075	1314	1144	1322	1161
Senile Insanity, .	1359	1200	1348	1205	—	—	—	—	1381	1197	1324	1236
Epilepsy, .	1421	1231	1391	1217	1345	1267	1296	1185	1373	1255	1371	1192
Secondary Dementia, .	1408	1263	1356	1234	1401	1240	1342	1225	1370	1228	1374	1225
Mania, .	1423	1286	1441	1278	1430	1251	1404	1226	1344	1269	1478	1236
Melancholia, .	1437	1284			1392	1294	1395	1213	1353	1287	1368	1283
Idiocy, .	1335	1194	1201	1078	1262	1164	1297	1114	1390	1076	—	—

The most marked decrease in weight occurs in general paralysis. In idiopathic epilepsy the brain is as a rule well developed and often above average weight; on the other hand, in cases of idiocy and imbecility, due to defective development or gross organic disease of the brain, and associated with epilepsy, the weight is much below the average. In idiocy and imbecility, apart from epilepsy, while the brain is generally small, in some instances, as already indicated, it is much above average size and weight.

The statistics of various observers appear to prove that the smaller average weight of the brains of the insane as compared with those of the mentally sound, is dependent upon the cerebral hemispheres alone.

It is well known that in normal conditions the cerebral hemispheres

are rarely of equal weight; most of those who have studied the point are agreed in stating that the right is generally the heavier. Rey (28) found an average difference of 1.2 grammes in favour of the right hemisphere in men, and of .55 grammes in women. In cases of insanity this inequality of the two hemispheres is also a distinct feature, especially, it is said, in epilepsy, general paralysis and idiocy, but there seems reason to doubt if it is commonly much more pronounced than in the mentally sound.

Many details regarding this subject that are here omitted will be found in the paper of Dr Middlemass and myself, already referred to.

SPECIFIC GRAVITY.

The specific gravity of different parts of the normal and morbid brain has been studied by a large number of observers, the names of some of whom will be found in the Bibliography appended to this chapter.

It has been clearly proved that the specific gravity of the white matter is normally slightly higher than that of the grey matter. The following are some of the figures given by the different observers:—

	Grey Matter.	White Matter.
Sankey . . .	1.0346	1.0412
Thudichum . . .	1.032	1.041
Morselli . . .	1.0335	1.0435
Baistrocchi . . .	1.0206	1.0273
Agostini . . .	1.033	1.040

The specific gravity of the grey matter of the individual convolutions has been found to present slight differences. According to Agostini (34), the frontal convolutions have the lowest, and the occipital the highest. The specific gravity has also been observed to vary to some extent with age. Sankey (41) states that it gradually increases up to 30 and then diminishes slightly.

Very elaborate investigations have been made into the alterations in the specific gravity of the brain associated with insanity, but the results obtained can scarcely be said to have much practical value. At most the variations are only extremely slight, and it has been found that the mode of death and the amount of blood in the cerebral vessels, as well as other conditions, affect the results in an important measure. Only some of the main conclusions, regarding which there is something like unanimity among the different observers, need be indicated here. It should be said that by far the most careful and complete observations upon this subject are unquestionably those of Agostini (34, 35).

In melancholia and simple mania there is little or no deviation from the normal. In acute delirium the specific gravity, especially of the grey matter, is much elevated in all the cerebral convolutions. In general paralysis, if death occurs in the terminal period of the disease, the specific gravity of both grey and white matter is much diminished; on the other hand, if death takes place before this period from a congestive attack, the specific gravity of the grey matter is found to be increased, while that of the white substance is below normal. In alcoholic dementia it is above the average in both grey and white matter. In epileptic insanity it is always increased in the grey substance, especially in the Rolandic regions. In secondary dementia it is generally above normal.

ELASTICITY.

The various tissues of which the brain is composed have a remarkable degree of elasticity. The subject derives its importance chiefly from its bearing upon questions regarding the physiology and pathology of the cerebral circulation, and the pathological increase of intracranial pressure, and is therefore dealt with in the next chapter.

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CHAPTER XI

MORBID CONDITIONS OF THE INTRACRANIAL LYMPHATIC SYSTEM AND CEREBRAL CIRCULATION; PATHOLOGICAL INCREASE OF INTRACRANIAL PRESSURE.

THESE three subjects are so intimately connected with each other that it is convenient to consider them together. Before dealing with them it will be necessary to enter at considerable length into the physiological arrangements of which they constitute disturbances. I take the lymphatic system first, because I believe that an accurate knowledge of its normal features is essential to a correct conception of some of the most important points regarding the cerebral circulation and intracranial pressure.

To essay the discussion of questions of intracranial physics is to enter the field of acute polemics. For more than a century they have formed the subject of keen debate among a very large number of scientists, and even at the present day no two authorities seem to be able to form the same conclusions upon them. The reason for this state of matters is not far to seek. Beyond any doubt the problems that meet the neurologist when he endeavours to grapple with this subject are among the most difficult and complicated that he has to face in the whole range of his special field. The various factors that have to be taken into account are exceedingly numerous, and their individual importance is often difficult of accurate appreciation. Moreover, certain of them are not on the surface, and have consequently often been altogether overlooked. But it is certain that it is only by taking into account all the factors that bear upon this subject, and correctly appreciating their individual importance, that we can hope to attain to a full and accurate knowledge and something approaching unanimity of opinion regarding it.

I make no claim to having succeeded in taking such a complete view of the subject here. All that I have to offer is merely a statement of the conclusions that it seems to me we are at present most fully warranted in adopting, and of the grounds upon which these conclusions are based.

PHYSIOLOGY OF THE INTRACRANIAL LYMPHATIC SYSTEM.

Although the brain does not possess lymphatic vessels strictly corresponding to those found in most other organs and tissues of the body, it contains lymph-spaces and channels of a special kind which subserve the same functions and which are no less important for the nutrition of its tissue-elements. The radicles of this special lymphatic system are the inter-capillary spaces. The fluid which passes from the blood, through the walls of a cerebral capillary, enters at once into what is really a large lymph-space, which for descriptive purposes, since we study the minute structure of the brain in thin microscopic sections, it is convenient to speak of as bounded by the vessels. In these spaces, which it is obvious are merely segments of one which permeates the whole brain, lie the nerve-cells and their processes and the glia-cells, not closely packed together, but so disposed as to be everywhere bathed by the lymph from which they have to select the nutritive materials that they require. The platinum method demonstrates that there is nothing of the nature of a special lymph-channel between the walls of the arterioles, capillaries, and venules on the one hand, and the nerve-tissues and neuroglia on the other. Nor is there any special lymph-space around the bodies of the nerve-cells. Appearances suggesting its existence are merely artificially produced by certain hardening reagents which cause severe shrinkage of the tissues. In the natural state innumerable delicate neuroglia-fibres are attached to the adventitia of the arterioles, capillaries and venules, and the nerve-cell processes, which compose the greater portion of the nerve-substance, come also into close proximity with the vessel-walls. The lymph, after passing out of the capillaries and permeating the interstices of the intervacular tissue-elements, finds its way into the adventitial lymph-channels of the arterioles and venules, which have already been described in chapter vii. Along these channels it flows to the surface of the brain, where it is poured into the arachnoid spaces. Probably some lymph passes directly into these spaces from the inter-capillary lymph-spaces near the surface of the brain, through the very open mesh-work of the connective tissue fibres of the pia-arachnoid. The existence of an epicerebral space—that is to say, a lymph-space lying between the brain substance and the pia-arachnoid—must, I think, be entirely denied. From the arachnoid spaces the lymph passes out of the intracranial cavity into the venous system by numerous different paths. Leonard Hill (37) lays special stress upon the fact of its passage through channels in the walls of the venous sinuses. Most other writers on the subject describe it as escaping chiefly along the channels in the sheaths of the cranial and spinal nerves, and through the Pacchionian villi into the superior longitudinal sinus. More important than any of

these paths are, I think, the perivascular canals of the dura mater (see chapter v.). It can be demonstrated that fluid can pass through the uninjured pia-arachnoid as readily as through a piece of filter paper. I find, further, that coloured fluids will percolate through a piece of human dura mater from within outwards in from five to ten minutes. From this it may be justly inferred that in the living state the passage is a very free one. Strong evidence in support of this belief was shown to me last year by the late Dr George Elder. He found that coloured injections into the subdural space of a recently killed animal very quickly passed through the dura into the veins both of this membrane and of the skull. On microscopic examination of the dura he was able to observe the injection mass in many of the perivascular canals, which therefore appear to discharge into the dural and cranial veins, as has already been maintained by Obersteiner.

The cerebro-spinal fluid is probably chiefly derived from the capillaries of the nervous substance. It is the lymph of the brain. The importance of the choroid plexuses as a source of this fluid has, I think, been much over-estimated. As strong arguments can be adduced in favour of the view that these organs absorb cerebro-spinal fluid, as in support of the opinion that they secrete it. The truth probably is that they subserve both functions. In any case it is certain that the fluid in the lateral ventricles is derived to an important extent from the capillaries of the surrounding nervous tissues.

D'Abundo (19, 20) and, more recently, Guillain (67) have endeavoured to study the lymphatic paths in the central nervous system with the aid of injection of Chinese ink. These researches have served to establish certain facts regarding the direction of the flow of the lymph, but they have not revealed any new point as to the precise nature of the paths.

The rate at which the cerebro-spinal fluid is produced probably depends upon several different circumstances. It seems to be still an unsettled point among physiologists whether lymph is secreted by the endothelial cells of the capillaries, as Heidenhain maintained, or merely filters through the vessel-walls. The question, however, is scarcely one that is of much moment in connection with this subject. The important fact that seems certain is that the rate of production of cerebro-spinal fluid depends chiefly upon the relation between the pressure in the capillaries and that of the fluid in the cerebral lymph-spaces. It will increase with any increase in the difference between the former pressure and the latter, and if the two should become equalised, it will probably cease altogether. It is specially to be observed that the rate of secretion does not depend upon the blood-pressure, the variations of which may be rapidly followed by similar

variations in the pressure of the cerebro-spinal fluid, without any increase or diminution of the difference between the two being maintained. Among other conditions which may influence the rate of production are the quality of the blood, the degree of distension of capillaries and morbid alterations in the vessel-walls.

The rate of absorption of the cerebro-spinal fluid depends chiefly on the difference between its pressure and that of the blood in the dural and cranial venous channels, into which the fluid is discharged. As will be explained in considering the physiology of the cerebral circulation, this venous pressure varies in an important manner with the respirations. During expiration it is probably equal to that of the cerebro-spinal fluid (or to the intracranial pressure), and if so the outflow of this fluid will cease. During inspiration, on the other hand, the dural venous pressure falls considerably below the intracranial pressure, and therefore an outflow of cerebro-spinal fluid will then take place. It will thus be seen that a certain quantity of this fluid tends to be aspirated from the cranial cavity with each inspiration. Adamkiewicz (2) has especially insisted upon the importance of this rhythmical action in preventing stagnation of the cerebro-spinal fluid. Another condition upon which the rate of absorption must depend is the patency of the channels by way of which the fluid is conveyed from the cranial cavity.

Opinions differ considerably as to the amount of cerebro-spinal fluid present in physiological conditions. Recent observations seem to prove that it is much less than used to be supposed. Leonard Hill (37) states that in the course of his experimental observations he has never been able to find such injection of the cisternæ and ventricles as Key and Retzius have figured. He believes that the living brain, with its circulating blood, almost entirely fills the cranium, and that the fluid that moistens the surface is little more in amount than the synovial fluid in a joint. At the same time he recognises that certain inequalities of the brain surface must be rounded off by small collections of fluid. There can, I think, be little doubt that we gain a false impression regarding the normal quantity of cerebro-spinal fluid from observations made at post-mortem examinations, whether upon the human subject or upon lower animals. Owing to the special elasticity of the cerebral vessels, including the capillaries, cessation of the circulation is immediately followed by contraction of them, and by a certain diminution in the size of the brain. Coincident with these changes there must be an equal transudation of fluid from the vessels. Hence the cerebro-spinal fluid undergoes a considerable increase immediately after death. Probably during life the intracranial subdural space has only a potential existence, containing merely the fluid that is passing across it, while the arachnoid spaces are distended only in

the sulci, and the walls of the lateral ventricles are almost in apposition. Most of the fluid will then be contained in the lymph-spaces of the brain itself. There is, however, reason to believe that the total amount of cerebro-spinal fluid varies considerably in accordance with different states of the cerebral circulation. As will be maintained further on, the amount of blood in the brain is capable of variation very much as in other organs, and inversely with it will vary the amount of cerebro-spinal fluid. It is to be borne in mind that there is always a considerable quantity of fluid in the arachnoid spaces of the spinal cord.

There is also still considerable difference of opinion as to the amount of cerebro-spinal fluid that is normally secreted in a given time. For my own part I am inclined to think that the lymphatic system of the brain is functionally much more active than is at present commonly supposed. It is impossible to believe that the elaborate and efficient anatomical arrangements that we have seen to exist for the carrying away of the cerebro-spinal fluid, can be related to a physiological process of merely secondary importance. Moreover, the provision of a continuous fresh supply of lymph seems to be essential for the nutrition of the nervous elements, even although, as in other organs, the exchange of nutritive materials and waste products of metabolism between the blood and the lymph, takes place largely by processes of diffusion and osmosis.

For what is known regarding the chemical composition of the cerebro-spinal fluid, we are chiefly indebted to the investigations of Halliburton (39) and E. Cavazzani (13). The opportunities of obtaining the fluid in the fresh state from the human subject in sufficient quantity for purposes of analysis are very rare, but Thomson, Hill and Halliburton (61) have recently published a very full report upon its characters in a case in which it dripped continuously from the nose.

In appearance the cerebro-spinal fluid is clear, colourless or faintly yellow. Its specific gravity generally ranges between 1005 and 1010. It is practically devoid of cellular elements. It is faintly alkaline in reaction during life, but quickly becomes acid after death. John Turner (60) has recently made a series of observations from which it would appear that the reaction varies according to the indicator used. Thus he found that it was always acid to phenolphthalein, amphoteric to litmus, and alkaline to methyl orange. The solid constituents amount to about 1 per cent., and chiefly consist of salts. The proteids are exceedingly scanty, seldom exceeding .1 per cent. They consist almost entirely of globulin. Serum albumin, fibrinogen and fibrin ferment are absent. Consequently cerebro-spinal fluid does not clot like ordinary lymph. It further contains a substance which reduces Fehling's solution. Nawratski (53) has stated that this

reducing substance is dextrose. Halliburton and other authorities, however, maintain that it is pyrocatechin, or a substance closely allied to it, and that dextrose is absent. Mya (47) states that the fluid contains traces of dextrose, but that there is also another reducing agent present. Cavazzani (13), in experiments upon dogs, observed that cerebro-spinal fluid collected in the morning was more alkaline, and contained more solid residue, than fluid collected in the evening. Thomson, Hill and Halliburton (61) state that similar experiments, carried out upon their case already referred to, confirm this observation.

PHYSIOLOGY OF THE CEREBRAL CIRCULATION.

In order that we may be in a position to understand this very difficult and complicated subject aright, it is essential to have clearly in mind certain anatomical and physiological facts that bear upon it in an important manner. Most of these facts have already been the subject of discussion in this and preceding chapters, so that they need here be alluded to only somewhat briefly. There is, firstly, to be borne in mind the double source of the blood supply for the brain, by the two internal carotid arteries on the one hand, and the two vertebrals on the other, and the free anastomosis that these four vessels form with one another through the basilar artery and the circle of Willis. While at the base of the brain some small arterioles directly penetrate the nervous substance, by far the larger portion of the blood is carried to it by vessels which first pursue a longer or shorter course in the pia-arachnoid, in which they ramify freely. These arterioles have well developed muscular coats. Small branches, none of which have more than a single layer of muscular fibres in their middle coat, dip into the brain at right angles to the surface of the convolutions. It is specially to be observed that in the pia-arachnoid there are no anastomoses between arterioles and venules, and that there are no capillaries. There is thus no possibility of short-cutting of the blood-stream. All the blood carried by the cerebral arteries, with the exception of that supplying the choroid plexuses, must pass through the nervous tissues before being discharged by way of the veins. While the intra-cerebral arterioles do not anastomose, the capillaries into which they divide form freely communicating networks. But by far the most important feature in the structure of these intra-cerebral vessels in relation to the physiology of the cerebral circulation is the remarkable development, and the highly elastic character, of their adventitia, which invests not only the arterioles and venules, but also the capillaries. The venules return the blood to the pia-arachnoid, where they unite to form larger vessels which discharge into the venous sinuses of the dura mater. These venous sinuses do not possess valves, nor can the oblique

direction of the entrance of the pial veins into them be regarded as having the effect of such (Symington). There are also to be borne in mind the special lymphatic arrangements of the brain and its membranes, which have just been described. Lastly, there is the circumstance that the walls of the cranial cavity are, at least after infancy, of a rigid, unyielding character, in consequence of which, it is said, the cranial contents are not subjected to the action of atmospheric pressure. It has been disputed whether or not the spinal cavity ought also to be regarded as practically closed. Upon this point it seems to me that the arguments brought forward by Elder (25) are valid, and I agree with his conclusion that the physical conditions subsisting in the two cavities are much the same.

It would occupy too much space here to give a systematic account of the various views that have been advanced, and of the experimental observations that have been made, by the numerous writers who have endeavoured to elucidate the physiology of the cerebral circulation. I must refer the reader who desires to know the complete history of the long controversy that has been waged to the works especially of Leonard Hill (37) and Elder (25, 26), and to the original papers enumerated in the Bibliography at the end of this chapter. I shall only shortly indicate some of the more important views that have been advanced.

In 1783, *Monro secundus* enunciated the doctrine that the quantity of blood in the cranium is practically invariable, except under certain pathological conditions in which it is partly replaced by effusions. He stated the matter himself thus: "For being enclosed in a case of bone, the blood must be continually flowing out of the veins that room may be given to the blood which is entering by the arteries. For, as the substance of the brain, like that of the other solids of our body, is nearly incompressible, the quantity of blood within the head must be the same, or nearly the same, at all times, whether in health or disease, in life, or after death, those cases only excepted in which water or other matter is effused or secreted from the blood vessels; for in these a quantity of blood equal in bulk to the effused matter will be pressed out of the cranium." Some years later this teaching was supported by Kellie (44) on the ground of experimental and pathological observations, and was afterwards generally referred to as "The *Monro-Kellie doctrine*." In 1842, Magendie (52) advanced another view which, until a few years ago, was very generally regarded as in accord with fact, and as superseding the older teaching of *Monro* and Kellie. He maintained that, when the cerebral arteries become distended, room is made within the cranium for the increased quantity of blood by a flow of cerebro-spinal fluid into the spinal cavity, and that conversely, when the arteries contract, a corresponding amount of

cerebro-spinal fluid returns to the cranium. Four years later the *Monro-Kellie* doctrine was also combated by Burrows (11), who repeated Kellie's experiment. He admitted that the whole contents of the cranium—the brain, the blood and the serum—must be at all times nearly a constant quantity, but maintained that the serous fluid, which he recognised as being present in the substance of the brain as well as in the ventricles and membranes, could vary in amount and so allow of an increase or diminution in the quantity of blood. Very numerous observers have since endeavoured to obtain conclusive experimental evidence as to the truth or error of these two opposing views, but the results have in many respects still been contradictory. The whole subject of the physiology and pathology of the intracranial circulation has recently been most carefully investigated by Leonard Hill (37), who in making some of his earlier observations was assisted by Bayliss (6). Of Hill's work it may safely be said that it is the most complete and important that has yet been carried out in this field. He has beyond question advanced our knowledge of intracranial physics a very long way beyond the point that it had previously reached, and he has swept away, once and for all, numerous errors, some of which had received considerable credence as established facts of physiology. In this country his experimental results and conclusions have been very widely accepted as accurate and decisive. Nevertheless, bearing in mind the great difficulty and complexity of many of the problems that demand answer, one can scarcely be surprised if there are some who find it impossible to agree with certain parts of his teaching. Thus Elder (25), on the ground of experimental observations of his own, while agreeing with most of Hill's conclusions, differs from them upon several points. For my own part I am obliged to take the view that Hill has been led into error by omitting to take into consideration certain essential factors bearing on the questions at issue, and that some of his main conclusions are untenable.

Hill's investigations, which were carried out chiefly upon dogs, aimed at elucidating all that is of practical importance regarding the physical conditions of the cranio-vertebral contents. They embraced the subjects of the pulsations of the brain, the cerebro-spinal fluid, the cerebral circulation, the influence of the force of gravity on the circulation of the blood, cerebral anæmia and cerebral compression. In the course of his experiments he made simultaneous records of (*a*) the arterial pressure in the central end of the carotid; (*b*) the general venous pressure in the right auricle; (*c*) the cerebral venous pressure in the torcular Herophili, and (*d*) the cerebro-spinal fluid pressure, taken by trephining the atlas and screwing a tube into the hole, and connecting this with a manometer; or the intracranial pressure, taken by means of the cerebral pressure-gauge.

These experiments, along with similar observations conducted by others, have served to establish certain important facts regarding the pulsations within the closed cranium which it is necessary to mention at this stage. The arterial pulsation is transmitted to the cerebro-spinal fluid and to the cerebral and cranial veins. There is also a respiratory pulsation which affects especially the blood in the veins and the cerebro-spinal fluid; this pressure-wave rises with expiration and falls with inspiration.

Hill summarises his conclusions in the section on the cerebral circulation as follows:—

“(1) No evidence has been found of the existence of cerebral vaso-motor nerves, either by means of stimulation of the vaso-motor centre, or central end of the spinal cord after division of the cord in the upper dorsal region, or by stimulation of the stellate ganglia, and, that is to say, the whole sympathetic supply to the carotid and vertebral arteries.

“(2) Evidence is not forthcoming of the existence of any local vaso-motor mechanism.

“(3) In every experimental condition the cerebral circulation passively follows the changes in the general arterial and venous pressures. The intracranial or cerebral venous pressure varies directly and absolutely with general venous pressure, but only proportionately with general arterial pressure.

“(4) The intracranial pressure is in all physiological conditions the same as the cerebral venous pressure.

“(5) The volume of the blood in the brain is in all physiological conditions but slightly variable.

“(6) There is no compensatory mechanism by which the intracranial pressure is kept constant. The intracranial pressure or cerebral tension, which in all physiological conditions is circulatory in origin, may vary with the circulatory pressure from zero to 50 mm. Hg. The functions of the brain matter continue in this varying condition of pressure.

“(7) In all physiological conditions a rise of arterial pressure accelerates the flow of blood through the brain and a fall slackens it. The cerebral circulation is controlled by the vaso-motor centre acting on the splanchnic area.

“(8) There is no evidence of the causation of cerebral anæmia by spasm of the cerebral arterioles.

“(9) Arterial hyperæmia of the brain produces no experimental results of importance. Cerebral venous congestion, on the other hand, is of great pathological significance.”

It will be seen that Hill here concludes in favour of the Monro-Kellie doctrine, or the theory that “the quantity of blood within the

head must be the same, or nearly the same, at all times." His grounds for agreeing with this doctrine are very clearly stated in another passage: "When the arterial pressure rises, the expansion of cerebral volume can take place only to a certain limited amount. For as soon as all the cerebro-spinal fluid has been driven out from the cranium the brain is everywhere in contact with the rigid wall of the skull. The cerebro-spinal fluid in the cranium of the living animal is insignificant in amount. Any further expansion of the arteries and capillaries can now only take place by an equivalent compression of the veins, for the semi-fluid brain matter is incompressible. The reservoirs of blood in the veins will therefore be so far constricted until the cerebral venous pressure again becomes equal to the intracranial pressure; that is, to the pressure of the brain against the veins. Then the whole circulatory system of the brain will have assimilated itself to a scheme of rigid tubes."

I believe that it is the case that at the present day, in this country at least, Hill's investigations are pretty generally regarded as having closed the discussion upon this particular question of the variability of the quantity of blood within the cranium. To most people who have examined them, his experimental data and his manner of reasoning from them are alike unassailable. Thus J. B. Bradbury (12), in his Croonian Lectures, has lately stated that, "In view of Leonard Hill's researches, it seems absolutely necessary to recognise the Monro-Kellie doctrine (the incompressibility of the brain and constant volume of the cerebral contents) in dealing with the causal factors of sleep." From the context in which this sentence stands, it is clear that by "cerebral contents" the writer means only the blood in the cerebral vessels. Numerous other high authorities could be named who have similarly accepted Hill's teaching upon this question.

Notwithstanding this very general acceptance of Hill's teaching, I feel obliged to maintain that the Monro-Kellie doctrine is erroneous, and that the quantity of blood in the brain is capable of varying to an important extent, though not precisely as in other organs. I think that Hill has been led into false conclusions upon this question, firstly by failing to take into account the variability of the quantity of fluid in the lymph-spaces of the brain, and secondly, by accepting as an axiom what can be shown to be really one of the most transparent of fallacies, namely, the doctrine of the incompressibility of the brain.

According to Hill's view, the expansion of the cerebral volume that tends to occur when arterial pressure rises, is limited to an amount corresponding to the quantity of cerebro-spinal fluid that can be driven out from the subdural and subarachnoid spaces. This fluid is "insignificant in amount," and therefore, he argues, the extra

quantity of blood that can be accommodated must be correspondingly insignificant. "Any further expansion of the arteries and capillaries can now only take place by an equivalent compression of veins, for the semi-fluid brain-matter is incompressible." On the contrary, I maintain that a further expansion of the arterioles and capillaries can take place, without corresponding diminution of the amount of blood in the veins, by displacement of fluid from the lymph-spaces of the cerebral substance and approximation of the tissue elements; and that, conversely, when the arterial pressure falls again, the walls of the arterioles and capillaries contract (in virtue of their special elasticity), the amount of blood in the brain diminishes and the fluid in the cerebral lymph-spaces becomes correspondingly increased. The conditions which regulate this ebb and flow of lymph, in correspondence with variations in the volume of blood within the cranium, will be more fully considered presently.

This theory that the amount of fluid in the interstices of the cerebral tissue-elements is capable of undergoing important variations in order to compensate for alterations in the quantity of blood in the vessels, may still appear to some to be rendered entirely inadmissible by the circumstance that the brain substance is incompressible—a fact which, it is asserted, has been proved experimentally. In reply to such an objection, it is to be submitted that the physical property that the above view requires on the part of the tissue-elements of the brain, is not compressibility, but elasticity—the power of returning to the form from which, within certain limits, they are bent, extended, pressed or distorted. This doctrine of the incompressibility of the brain, upon which Hill largely bases some of his chief conclusions, will not bear examination. It rests upon the common fallacy of making a generalisation of a particular fact. Let it be admitted that the individual tissue-elements composing the brain-substance are incompressible, although it must be said that to obtain proof or disproof upon this point is a practical impossibility. It does not, however, follow that a block of brain substance is incompressible, for the interstices of the incompressible, but elastic, tissue-elements are everywhere filled with fluid, of which a large proportion can be readily driven out. Therefore the block of brain substance is capable of occupying a smaller space, and this is the physical property of compressibility. Of course if, in conducting an experiment of this kind, we prevent the escape of the lymph, the brain substance does become as "incompressible as water," precisely because water is virtually incompressible. But in physiological conditions there is no such obstruction to outflow of lymph, which on the contrary can occur with great rapidity whenever the necessary pressure conditions are established. Of the elasticity of the individual elements which compose

the brain, there is abundant proof. If the nerve-cells are watched under the microscope while pressure is being exerted upon the cover glass in the course of making a preparation by Turner's fresh method, it will be seen that they readily elongate, and that on withdrawal of the pressure, provided it has not been excessive, they return to their original shape. Similarly in making preparations by Kronthal's method for the cerebral vessels, it can be observed that the capillaries possess this same property in a very high degree. In like manner it can be demonstrated that the neuroglia and medullated nerve fibres are tissues possessing a considerable degree of elasticity. When we further bear in mind that the expansion of the cerebral arterioles and capillaries under the action of the blood-pressure, is limited by their highly developed elastic coats, it must be evident that it is erroneous to invoke the incompressibility of the tissue-elements of the brain as a factor in the physics of the intracranial circulation in physiological conditions.

While the *Monro-Kellie* doctrine of the practical invariability of the quantity of blood within the cranium must be rejected, the theory of *Magendie*, according to which such variations are rendered possible by ebb and flow of cerebro-spinal fluid between the cranial and spinal cavities, must also, I think, be dismissed as untenable. The supposition upon which it is based has, it seems to me, been clearly disproved by the observations of *Elder* (25) upon the movements of the cerebro-spinal fluid, as evidenced by the rate of diffusion of granules of Prussian blue introduced into it. On the ground of these experiments *Elder* concludes that "there is no flow of cerebro-spinal fluid from the spinal cavity to the intracranial cavity, either with respiratory movements or with arterial pulsation, as has usually been supposed."

The only view that appears to me to be consistent with the now known facts bearing upon the question, is that variations in the quantity of blood in the cranial cavity are rendered possible within considerable limits, by inverse variations in the quantity of cerebro-spinal fluid, contained not only in the pia-arachnoid, but also in the lymph-spaces of the brain itself. This view is essentially in accord with the doctrine of *Burrows*, as well as with the conclusion of *Elder* that "in rises of pressure lasting some time there may be alterations of the quantity of blood inside the cavities, resulting from alteration in the rate of secretion or absorption of cerebro-spinal fluid." It is evident that the rapidity with which such variations in the quantity of blood can occur, must be restricted on the one hand by the rapidity with which the cerebro-spinal fluid can escape from within the cranium, and on the other by the rate at which it can be poured out from the cerebral capillaries. Our knowledge about these points is as yet not very definite. But it may be freely admitted that such compensatory

variations in the quantity of cerebro-spinal fluid, cannot occur with that rapidity which we know may sometimes characterise alterations in the arterial blood-pressure. Therefore a sudden increase in the volume of blood in the cerebral arterioles must be rendered possible, in the first instance, by displacement of a corresponding amount of blood from the veins. This is in accord with the evidence of some of Hill's experiments. But such displacement of blood from the veins will only be maintained for the time required for the escape of a volume of cerebro-spinal fluid, equivalent to that of the venous blood displaced. That this is so will perhaps appear more clearly if we consider *seriatim* the changes that probably affect the vessels and the cerebro-spinal fluid, along with each rise or fall in the blood-pressure within the cerebral arterioles. Before doing so, however, it is necessary that we should understand what are the normal comparative fluid pressures in the arterioles, capillaries, veins and cerebral lymph-spaces. I think that in regard to this matter, there is satisfactory evidence in support of the following statements, although they do not exactly accord with what is at present generally taught. There is a gradual and continuous fall of pressure as the blood passes along the intra-cerebral arterioles, capillaries, intra-cerebral venules and pial veins. The pressure in the cerebral capillaries is much higher than that which such vessels are commonly required to sustain in other organs. That this is so is sufficiently proved by the fact that they are provided with special elastic coats. The pressure in these capillaries must be considerably higher than that in the venous sinuses of the dura. The cerebro-spinal fluid pressure (*i.e.* that of the intra-cerebral lymph) approximates to that of the blood in the dural sinuses, and in physiological conditions cannot remain appreciably higher for any length of time; it is lower than the pressure in the intra-cerebral and pial venous channels.

For the present any possible vaso-motor action upon the arterioles may be left out of account, as in any case it is not an essential factor in the production of the changes about to be considered. Let it be granted simply that the arterioles dilate and contract in accordance with the height of the blood-pressure. It is likewise unnecessary to complicate the problem by taking into account the modifying effect of coincident changes in the venous pressure.

To begin with, let us suppose the intracranial vessels and lymph-spaces to be in average conditions as regards distension and hydrostatic pressure of their contents. If now the arterial pressure is suddenly raised, the arterioles immediately endeavour to dilate. In this effort they are resisted by the cerebro-spinal fluid which fills all the tissue-interstices, and consequently its tension is increased throughout the cranial cavity. This increased tension of the cerebro-spinal fluid is

felt by the veins, and if it should rise above that of the blood within them, their walls will to a certain extent be compressed.

The pial veins will be affected first, as the pressure in them is lower than that in the intra-cerebral venules. There is, however, no sufficient reason for believing that the pial veins can be closed by a sudden rise in the cerebro-spinal fluid pressure. The wide extent of the venous channels over which the compression must be distributed, the relative capacity of the arterioles and venules, and the fact that the tension in the veins is raised by such compression, render such an occurrence practically impossible. Room has now been made for the increased quantity of blood in the arterioles by the expulsion of a corresponding quantity from the veins. But such an effect can only be of short duration for the difference between the pressure of the cerebro-spinal fluid and that of the blood in the dural and cranial veins has been increased, and consequently there is an acceleration of the outflow of cerebro-spinal fluid not only from the pia-arachnoid, as Hill describes, but also from the lymph-spaces of the brain. The intra-cranial pressure therefore again approximates to the dural venous pressure, and the pial veins are no longer compressed. The space required by the increased amount of blood in the arteries and capillaries has now been provided for by an equivalent diminution in the amount of cerebro-spinal fluid. The acceleration of the outflow of lymph will not be immediately balanced by a corresponding acceleration of the outflow from the capillaries, for the increased tension of the fluid tells as much against the latter as it favours the former. Not until the tension of the lymph has closely approximated to that within the dural sinuses will the inflow again equal the outflow. In the new conditions now established the arterioles and capillaries, and it may be also the veins, are more fully distended with blood, the rate of the flow through them is accelerated, and the production and absorption of lymph are both increased, but the quantity of lymph within the cranial cavity is diminished.

If now the arterial pressure should suddenly fall, the arterioles and capillaries will tend to diminish in size in virtue of the elasticity of their walls. The immediate effect must be to lower the pressure of the cerebro-spinal fluid. This is probably followed by distension of the thin-walled pial and intra-cerebral veins. Thus the decrease in the amount of blood in the arterioles and capillaries is balanced by an increase of that in the pial veins. But this state of matters will only be very temporary. In consequence of the lowering of the pressure of the cerebro-spinal fluid, the absorption of this fluid will be diminished or even arrested, and its production will be accelerated. Therefore it accumulates, and the interstices of the tissue-elements are distended until its tension again corresponds to that within the dural sinuses.

The veins return to their normal condition. The blood within the cranium is now diminished in amount, and its rate of flow is decreased. The production and absorption of lymph take place more slowly, but the one is exactly balanced by the other. If the fall of arterial pressure takes place gradually instead of suddenly, the temporary distension of the veins will not occur.

It is important to understand clearly by what means the distension of the cerebral vessels is limited under conditions of high intravascular pressure. Hill virtually asserts that it is by the rigid cranial walls and the incompressible brain substance. This view is, I am convinced, quite untenable. The essential agent in the limitation of vascular distension can only be the vessel wall itself. It is assisted by the fluid pressure of the surrounding lymph, but not to any important extent by the nervous tissues. In arterioles, capillaries, and venules, the strength of the wall corresponds to the amount of pressure it is required to withstand in physiological conditions.

Geigel (32) has contended that dilatation of the arterioles of the brain, by increasing the intracranial pressure, must compress the capillaries and thus cause anæmia of the brain, not hyperæmia; and, conversely, that constriction of the arterioles, by decreasing the intracranial pressure, results in hyperæmia, not anæmia. Grashey (33) has advanced a slightly different view, maintaining that high arterial pressure is attended with compression of the cerebral veins and consequent obstruction of the capillary circulation. Such doctrines depend upon an erroneous conception of the lymphatic arrangements of the brain and of the laws that regulate intracranial pressure. That they are false has been clearly proved from the experimental side by Bayliss and Hill. These observers have satisfactorily shown that in all physiological conditions a rise of arterial pressure accelerates the flow of blood through the brain, and that a fall slackens it, and that the general intracranial pressure does not depend directly upon the tension of the cerebral arteries, but follows the venous pressure.

Regulation of the Blood-Supply of the Brain.—In order to avoid the unnecessary complication of the difficult problems that have been under consideration, I have thus far left out of account the whole question of the general and local regulation of the cerebral blood-supply. Unfortunately we are here still in a region of unsettled controversy and of much uncertainty. It is still disputed whether or not the cerebral circulation is in any degree under the direct control of the general vaso-motor centre. Much discussion has also taken place regarding the possibility of the existence of a local regulating mechanism depending upon chemical changes in the cerebro-spinal fluid, and it has further been suggested that there may be a special

cerebral vaso-motor mechanism independent of the general vaso-motor centre.

Anatomists have long taught that nerve-fibres from the cervical sympathetic are distributed to the cerebral vessels, and that they are vaso-motor in function. Somewhat recently the existence of such fibres has been conclusively demonstrated in the walls of the pial arterioles, but there is as yet no proof that they also occur in those of the arterioles within the nervous substance. While the anatomical evidence in support of the existence of a cerebral vaso-motor mechanism is thus still incomplete, the physiological evidence is of an even less decisive character. The various observers who have endeavoured to settle the question by direct experiment have arrived at the most diverse conclusions.

Among the earlier of these observers, Ackermann and Nothnagel believed that they had obtained more or less distinct evidence of constriction of the cerebral arterioles on the stimulation of the cervical sympathetic, while Riegel and Jolly, and Gaertner and Wagner (36) obtained entirely negative results. Schultz came to the conclusion that the cervical sympathetic only exceptionally contains vaso-motor fibres. Schultén found that stimulation of this nerve greatly lowered intracranial pressure; Cramer could observe no oscillations of pressure in the jugular vein from such stimulation. In more recent times the question has been very carefully investigated by Hürthle, Roy and Sherrington, Cavazzani, and Bayliss and Hill.

Hürthle (40) endeavoured to obtain evidence of contraction of the cerebral vessels by studying the changes of pressure in the circle of Willis, by means of a manometer placed in the peripheral end of a divided carotid artery. At the same time he registered the general arterial pressure, and in some experiments also the pressure in the jugular vein. His investigations, which were carried out upon rabbits, cats, and dogs, under morphia, led him to conclude that the pressure in the circle of Willis is not modified on the section of the cervical sympathetic; that, on the other hand, stimulation of the sympathetic on the side on which the canula is placed in the carotid, constantly results in elevation of this pressure, often without the general arterial pressure being modified, or with only slight increase of it; and that stimulation of the sympathetic of the opposite side does not give rise to any distinct modification of pressure in the circle, owing probably to a certain independence of its two sides.

Roy and Sherrington (56) used the plethysmographic method of Mosso after trephining. They concluded that the blood-supply of the brain varies directly with the blood-pressure in the systemic arteries, and that there is no evidence in favour of the existence of vaso-motor nerves for the brain either in the cervical sympathetic, spinal cord or medulla.

E. Cavazzani (14), whose experimental work upon this subject is, I venture to think, the most important that has yet been done, used chiefly the method employed by Hürthle, but with certain material alterations which he considered were required to render it perfectly trustworthy. He especially avoided the use of morphia, as he had reason to believe that the powerful action of this drug on the central nervous system rendered it difficult to obtain clear and decisive results. The observations were made upon fourteen rabbits and five dogs. The latter were curarised. He did not register the general venous pressure, probably because it appeared from the experiments of Hürthle that there was no object in doing so.

He found that on section of the cervical sympathetic on the normal side, *i.e.*, on the side opposite to that on which the canula was fixed in the carotid, there was always a slight elevation of the pressure in the circle of Willis, which, however, was transitory. Section of the nerve on the other, or hypohæmic side, always resulted in a more distinct elevation of the pressure lasting some seconds. The elevation was never permanent; it was determined rapidly and disappeared somewhat more slowly. In two cases there was a fall of the pressure. Electrical stimulation of the sympathetic also gave different results according as it was carried out on the normal or on the hypohæmic side. Stimulation on the hypohæmic side constantly produced a well-marked elevation of pressure in the circle of Willis, and this elevation was independent of any increase of the general arterial pressure. It was obtained alike by excitement of the sympathetic of the rabbit and of the vago-sympathetic of the dog. It manifested itself the moment the stimulus was applied, and gradually rose to its full height in the course of some seconds. If now the stimulation was continued the sphygmographic tracing formed a slightly undulating plateau. This was prolonged for a few seconds after suspension of the stimulation. Then the pressure slowly returned to its normal level. These phenomena were repeated as often as the stimulus was applied, and had always the same characters. On stimulation of the sympathetic on the normal side he obtained quite an opposite result. There was immediately a rapid and well marked fall of the pressure, which was independent of any fall in the general arterial pressure. It was more marked upon stimulation of the isolated sympathetic than upon stimulation of the vago-sympathetic, and therefore was seen better in the rabbit than in the dog. It had the same duration as the stimulus, immediately on the withdrawal of which the manometric line began to rise and, after two or three slight undulations, rested at the normal level. These phenomena were also constant. If now the carotid artery that had been left in the normal state was ligatured, the pressure in the circle of Willis fell to a certain level. Stimulation of

the sympathetic of this same side a few seconds after the closure of the artery had been effected, caused the pressure in the peripheral end of the opposite carotid to fall greatly. On the other hand stimulation of the sympathetic on the hypohæmic side produced increase of pressure. If after the lapse of some little time the stimulation of the other sympathetic was repeated, there was no longer a diminution in the pressure, but an increase which was the more marked the longer the time between the closure of the vessel and the application of the stimulus. These results were also constant. In two animals he carried out similar experiments with the method of artificial circulation, and found that the results were perfectly in accord with those of the graphic method.

On the ground of these observations he concluded that the cervical sympathetic contains both vaso-constrictor and vaso-dilator nerves for the brain. The vaso-constrictor fibres are the more excitable and the more easily exhausted; they are active while the conditions of the circulation are normal. The natural stimulus of the vaso-dilator fibres is anæmia. He explained the fall of pressure in the carotid of the opposite side on stimulation of the sympathetic of the normal side, as the consequence of constriction of the branches of the latter side. This explanation seemed to be in conformity with the facts that the fall was more marked in rabbits than in dogs, in correspondence with the comparatively poor development of the collateral paths in the former, and that the sphygmographic lines of closure of the carotid, and of stimulation of the sympathetic on the normal side were almost equal. The fact that when the carotid on the normal side was closed, the sympathetic of this side still responded to stimulation by a fall of pressure in the peripheral stump of the other carotid, implied that it innervates not only the carotid branches, but also all the afferent vessels of the circle of Willis.

He summed up his conclusions as follows:—(a) The cervical sympathetic system contributes to the innervation of the cerebral vessels. (b) There are vaso-motor and vaso-dilator fibres; the first are directly excitable by electrical stimulation, the second by this in union with the stimulus of anæmia. (c) The vaso-motor action of the sympathetic on the vessels of the brain is not displayed in ordinary conditions; but it is energetic, even so as to resemble cramp of the vessels, during mechanical and electrical stimulation. (d) The excitement of the vaso-dilator fibres is due to anaemia. He did not consider that the vaso-constrictor activity of the sympathetic was constant and tonic, but that it was exercised in consequence of irritation. In physiological conditions the cerebral circulation was rather regulated by some intrinsic vaso-motor mechanism, such as had been described by Roy and Sherrington.

Bayliss and Hill (6, 37) carried out a very complete investigation upon this subject, in the course of which they stimulated the whole sympathetic supply of the carotid and vertebrals. In these experiments the cerebral venous pressure (taken in the torcular Herophili) served as the indicator of any alteration in the cerebral circulation. At the same time note was taken of the variations in the general arterial pressure, and in the general venous pressure. They found that the cerebral venous pressure passively followed the slightest changes in the general arterial and general venous pressures. They could obtain no evidence whatever of any independent change pointing to the existence of any cerebral vaso-motor nerves. Hill (37) mentions that Cavazzani found evidence of both constrictor and dilator fibres for the brain in the cervical sympathetic, but includes him among those workers whose methods "are valueless in deciding such a question." It must be said that the force of this criticism scarcely appears from anything that Hill states in his book. The alleged grounds of objection would seem to be that Cavazzani did not register either the general venous pressure or the cerebral venous pressure. But a careful consideration of the results recorded will, I think, serve to satisfy most people that many of them at least could not have been produced by any change in the general venous pressure; and it may fairly be contended that the pressure of the blood in the circle of Willis, which Hill did not register, is a more delicate indicator of alterations in the calibre of the cerebral arteries, than the venous pressure in the torcular Herophili can possibly be. Moreover, it seems not at all improbable that the accuracy of Hill's experiments was impaired by his employment of anæsthetics, more especially of morphia, which Cavazzani expressly, and for this very reason, avoided.

Roy and Sherrington (56) believed that they had demonstrated that the intra-venous injection of a small dose of an acid, results in general expansion of the cerebral vessels, and that on the other hand the injection of alkalies induces contraction of these vessels. They observed also that brain extract administered in the same way produced expansion of the brain. From these and their other experimental observations that have already been referred to, they concluded that the cerebral circulation is regulated by three factors, namely, (*a*) the general arterial pressure, (*b*) the general venous pressure, and (*c*) the presence or absence of the chemical products of cerebral metabolism in the lymph that bathes the walls of the arterioles of the brain. In the last of these factors they believed that the brain possessed an intrinsic mechanism by which its vascular supply could be varied locally, in correspondence with local variation of functional activity. As already indicated, Cavazzani supports these views, but maintains also that, when ordinary physiological conditions are exceeded, a

vaso-constrictor and vaso-dilator mechanism may be brought into action.

Hill denies the existence of any kind of direct vaso-motor mechanism for the regulation of the cerebral blood-supply. He maintains that "the cerebral circulation passively follows every change in the general circulation," and that it is controlled indirectly by the vaso-motor centre acting on the splanchnic area. "Anæmia of the central nervous system excites the vaso-motor centre, and if the splanchnic vessels constrict the blood pressure rises, and more blood is driven through the brain. . . . At the moment that excitation from the outside world demands cerebral response, the splanchnic area constricts, and more blood is driven through the brain." In his most recent work upon this subject (38), he admits that the nerve-fibres demonstrated in the pial arterioles may be vaso-motor in function, but thinks that they are of very little importance, and that "their power must be insignificant since in every experimental condition the cerebral circulation passively follows the changes in the aortic and vena cava pressures."

Somewhat recently, Spina (57, 58) has described the results of a series of experimental observations, from which he concludes that the cerebral arteries are under the influence of a vaso-constrictor centre situated in the medulla oblongata and spinal cord, and extending as far down as the level of the third cervical vertebra. He thinks, however, that the amount of blood in the cerebral vessels is dependent on the general arterial pressure, and that only when the dilatation of the arteries reaches a certain point the vaso-constrictors are brought into action in order to prevent excessive expansion.

A very suggestive contribution, and one that I am strongly inclined to think may yet prove highly important, has lately been made to this question of the control of the cerebral circulation by Acquisto and Pusateri (5). As has already been mentioned (chapter v.), they have made a minute study of the nerves of the dura mater, and have shown that these comprise not only vaso-motor fibres for the meningeal arteries, but also very abundant sensory fibres, some of the branches of which, it is specially to be noted here, they have observed to terminate in little club-shaped swellings near the endothelium of the inner surface. They state that they are inclined to regard the dura mater as a true sensory surface, and enunciate the hypothesis that variations in the pressure of the cerebro-spinal fluid stimulate the nerves of the dura in such a way as to provoke vaso-motor phenomena, which, by modifying the conditions of the cerebral circulation, serve to regulate the production of the said fluid. D'Abundo (21), who has also made a special study of these nerves, supports this hypothesis. I cannot agree with these authors that a reflex

mechanism of this kind could be efficient if it received its stimulus from the pressure of the cerebro-spinal fluid alone, for this pressure, although momentarily influenced by sudden variations in the arterial pressure, does not in general vary with it, but with the venous pressure. Their observations, however, suggest another agency by which such a vaso-motor mechanism might very well be set in action, viz., the pressure of the surface of the brain upon the dura mater. It is, I think, quite conceivable that when the general arterial pressure is suddenly increased, and a larger amount of blood is driven into the brain, the rush of blood is in some measure controlled by a constriction of the cerebral arteries which is induced reflexly by undue pressure of the surface of the expanded cerebral hemispheres upon the sensory nerves of the dura mater. The action of such a mechanism would allow the cerebro-spinal fluid to pass out of the cranial cavity at a lower pressure than would otherwise be made to bear upon it, while room was being made for an increased amount of blood, and thus any danger that may exist of constriction of the veins would be entirely obviated. If such a mechanism exists it probably also serves to check an excessive flow of blood to the brain under the action of gravity. According to Hill (37) "the important duty of compensating for the simple hydrostatic effects of gravity in changes of position" is entirely fulfilled by the splanchnic vaso-motor mechanism. It is obvious that this mechanism may serve to counteract a tendency to cerebral anaemia when the erect attitude is resumed after rest in the horizontal position. But it cannot in the same degree act in an opposite direction, that is to say, to check excessive hyperaemia of the brain when the head is placed at a lower level than the body. But this function might quite well be fulfilled by such a dural reflex mechanism as I have suggested may be capable of being brought into action.

When all the facts bearing upon the question are taken into consideration, I think it must be admitted that there are the strongest reasons for believing that the mechanism by which the cerebral blood-supply is regulated is not nearly so simple as Hill would have us believe it to be. Much patient observation will yet require to be carried out before all its parts have been thoroughly examined and their individual actions precisely determined.

Condition of the Cerebral Circulation in different Physiological States of the Brain.—Very numerous investigations have been made upon the special vascular conditions accompanying sleep, mental activity, painful and pleasurable excitement, etc., and have led to the establishment of several important facts, although there is still some want of agreement among the different observers regarding certain points.

With regard to sleep there is a large amount of experimental

evidence in favour of the view that it is accompanied by intracranial arterial anæmia and venous congestion. These conditions, according to Hill (38), are results of the state of the general circulation; the arterial anæmia follows diminished action of the heart, lowering of the arterial pressure, and determination of the blood to the limbs; the venous congestion is to be attributed to the horizontal position, shallowness of the respirations, and cessation of muscular movements.

There are now on record many direct observations by Mosso (48), Tuke (62), and others, of the onset of arterial hyperæmia of the surface of the brain coincident with psychical activity. Hill attributes this hyperæmia entirely to constriction of the vessels of the splanchnic area "at the moment that excitation from the outside world demands cerebral response." Thus the general arterial pressure is raised and "more blood is driven through the brain."

De Sarlo and Bernardini (24), in a series of observations upon a man who had a defect in the skull, the result of injury, found that all emotions, whether pleasurable or painful, caused increase of cerebral volume and enlargement of the individual pulsations of the brain. Hill (37), on the other hand, states that "each pleasurable emotion raises the general blood-pressure and increases the blood-flow through the brain, and each painful emotion brings about the opposite result." This conclusion is, however, contrary to the results obtained by several other observers with the aid of the sphygmograph and sphygmometer. Maurice Craig (64), W. R. Dawson (65), and others, have found that the general arterial pressure is characteristically high in conditions of mental depression, and low in those of mental pleasure and excitement.

NORMAL INTRACRANIAL PRESSURE.

It was contended by Fick that the intracranial pressure is equal to the intra-arterial pressure, minus the resistance opposed to it by the tension of the arterial walls. This dictum, which has had a large amount of favour especially among German writers, can, I think, be shown to be inaccurate. A consideration of the existent anatomical arrangements and physical conditions that bear upon the question, points to the conclusion that the intracranial pressure is controlled by the venous pressure and not by the arterial, and that this is so is sufficiently confirmed from the experimental side by the investigations of Bayliss and Hill (6, 37). I do not think, however, that we are justified in accepting the whole of the teaching of these two authorities upon the subject of the normal intracranial pressure. They have again been misled by their belief in the doctrine of the incompressibility of the brain. Hill (37) distinguishes between the intracranial tension, or pressure, and the cerebro-spinal fluid pressure. By the former he

means "the pressure which the surface of the brain is exerting against the walls of the cranium." The latter he registered by a manometer connected with a trephine opening in the atlas vertebra. He believes that there is experimental proof "that the cerebro-spinal fluid within the cranium is not sufficient in amount to allow complete expansion of the brain, and that the brain becomes actually pressed against the cranial wall and its tension not fully recorded by that of the cerebro-spinal fluid." But he has here, as in discussing the physics of the cerebral circulation, left out of account the displaceable lymph in the substance of the brain; and, moreover, he does not seem to have given due weight to the compensating action of the veins. When, owing to the arterial pressure being suddenly raised, the brain expands and tends to press against the cranial wall, there must at once be a very marked increase in the tension of the intra-cerebral lymph. The immediate effect of this will be the displacement of a certain amount of blood from the pial, and it may be also from the intra-cerebral veins. But when such partial compression of the veins has taken place the tension of the lymph does not fall exactly to its former level. As has already been contended, it remains above its normal relation to the pressure in the venous sinuses. Therefore, the fluid drains rapidly away from the cranial cavity until its pressure is again adjusted to that in the venous sinuses, while simultaneously the pial veins return to their normal state of distension. We thus see that there are at least two compensating mechanisms—the one of which acts immediately, the other somewhat slowly—which serve to prevent undue expansion of the brain when an increased volume of blood is suddenly driven into its arteries. It may safely be asserted that such pressure of the brain against the cranial walls as would from time to time occur if Hill's hypothesis were correct, is incompatible with normal cerebral activity. These compensatory mechanisms—assisted, it may be, by a dural reflex mechanism of the kind it has been suggested may exist—are doubtless more than sufficient for all demands within physiological limits. Matters must be so adjusted within the cranium that the greatest possible physiological distension of the blood-vessels is reached long before the intra-cerebral lymph-spaces are completely emptied. In other words, the brain in average conditions contains a quantity of expressible lymph considerably greater than the additional amount of blood that the vessels are capable of containing when distended to their extreme physiological limits. In the special vascular and lymphatic arrangements of the brain there is to be recognised a highly efficient mechanism for the protection of the delicate nerve-tissues from injurious pressure from within—that is, from the blood-pressure—just as the rigid skull serves to protect them from injurious pressure from without. In physiological conditions the true intracranial pressure is simply the

hydrostatic pressure of the cerebro-spinal fluid, within the brain substance as well as external to it. The pressure exerted by the brain against the rigid cranial walls is a different matter, and Hill is, I think, in error in designating it "the intracranial pressure." That this is so will be apparent if we consider that there must be times when the pressure exerted by a portion of the upper surface of a cerebral hemisphere against the cranial wall is *nil*, although at the same time the cerebro-spinal fluid pressure is normal.

The normal hydrostatic pressure of the cerebro-spinal fluid—that is to say, the intracranial pressure—varies within considerable limits, in accordance with the wide variations in the general venous pressure to which it is continually endeavouring to conform. This pressure, being exerted equally in all directions, within the brain as well as at its surface, does not injure the nerve-tissues.

The question of the pressure exerted by different portions of the brain's surface against the cranial walls is one of very special difficulty, which perhaps had best be left to the expert physicist to decide. The problem is complicated by the facts that the brain lies in a somewhat closely-fitting, rigid case, which virtually shuts it off from the influence of atmospheric pressure; that it is permeated and surrounded by fluid; that this fluid has only a slightly lower specific gravity than the nervous tissues, and is under a certain degree of tension, which varies within considerable limits; and that the volume of the brain and that of the total extra-vascular fluid are subject to inverse variations of moderate range.

MORBID CONDITIONS OF THE INTRACRANIAL LYMPHATIC SYSTEM.

Obstruction of Lymph-channels.—To Batty Tuke (62) is due the credit of having been the first observer to recognise the great importance of obstruction of the intracranial lymphatic paths as an element in the pathological process in some forms of insanity. That such obstruction has all the importance that this authority has claimed for it, I am fully convinced from my own observations. Indeed, I think that it has an even greater significance than he attributed to it. There is as yet no evidence that it is ever a primary factor in the causation of mental disease, but as a secondary factor, aggravating the original morbid process in the brain, and retarding or preventing its arrest, it has, I believe, an influence of the most potent kind.

In preceding chapters (v., vi. and vii.) I have already fully described the morbid changes in consequence of which this obstruction is brought about. The whole course of the lymphatic paths, from the commencement of the adventitial lymph-channels to the entrance of the perivascular canals of the dura mater into the veins, is liable to

involvement, but the most serious obstruction undoubtedly occurs in the dura mater.

As has already been contended, the chief cause of the proliferative and degenerative changes that result in this obstruction to the outflow of cerebro-spinal fluid is an abnormal condition of the fluid itself, in consequence of which it is no longer suitable for the healthy nutrition of the tissues which form the walls of the lymph-channels. This abnormal condition of the cerebro-spinal fluid in its turn is the result especially of a morbid metabolism in the cerebral tissues, but may also be owing to a morbid condition of the blood from which the fluid is derived.

Obstruction of the intracranial lymphatic paths occurs in its most severe form in general paralysis. In advanced stages of this disease it is invariably a very well marked condition. It also constantly occurs to a more or less pronounced degree in senile insanity, alcoholic insanity and choreic insanity. It is likewise an important morbid condition in most cases of acute insanity, although the tissue-changes producing it have here some special characters. Probably no form of organic brain disease is entirely exempt from it.

The slighter degrees of obstruction probably cause little or no disturbance of the cerebral functions, for the other channels that remain patent may still be able to convey the cerebro-spinal fluid away as rapidly as is required. But immediately the obliterated channels become so numerous that the free escape of cerebro-spinal fluid is interfered with, the brain must suffer. There are practically three different situations in which obstruction of the lymphatic paths may occur, namely, in the adventitial lymph-channels of the intra-cerebral vessels, in the arachnoid spaces and in the perivascular canals of the dura. Within the brain the local obstruction of the lymph-channels in the adventitia of one vessel is probably very readily compensated for, on account of the readiness with which the lymph can find its way through the tissue-spaces to a neighbouring channel. It is only when many adventitial lymph-channels are obstructed that the outflow of the fluid is seriously retarded. The pia-arachnoid is, in the normal condition, so readily permeable by fluids that it is probable that a very considerable degree of thickening may occur before the transudation of the lymph is impeded to any harmful extent. It is, as has already been stated, in the dura mater that the most severe obstruction to the outflow of the cerebro-spinal fluid commonly occurs. The channels in the sheaths of the cranial nerves, being subjected to the same morbid influences, are doubtless affected in the same way. The Pacchionian granulations suffer with the pia-arachnoid, and there is conclusive evidence that their functional activity is impaired in direct proportion to their enlargement.

The obstruction of the perivascular canals of the dura is harmful in proportion to its extent. When it is nearly complete, as it would appear to be in all cases of advanced general paralysis and in many of senile insanity, the normal mechanism by which variations in the amount of blood sent to the brain are compensated for must be very seriously disorganised, and therefore the brain will tend to be subjected to those pressure disturbances which, as I have already endeavoured to show, this compensating mechanism serves to obviate. But this severe degree of obstruction of the lymphatic channels has another and still more serious consequence. The cerebro-spinal fluid instead of being constantly renewed, becomes more or less stagnant. The more nearly stagnation is reached the more largely does the removal of products of metabolism come to depend upon processes of diffusion through the capillary walls. Hence the lymph becomes charged with effete products and a chronic condition of cerebral auto-intoxication is brought about. It is to be observed that such auto-intoxication from retention of the cerebral lymph when once established probably tends to be aggravated and confirmed, for the toxicity of the fluid has been thereby increased, and the walls of the lymph-channels in the dura that have remained open will be bathed by a still more irritant lymph, and further endothelial proliferation and degeneration will tend to occur.

The importance of this obstruction of the lymphatic channels in some of the chief clinical types of insanity may, I think, be fairly accurately gauged. Thus, taking first general paralysis, it may be affirmed that, independently of any other grounds upon which this disease is to be considered as incurable, the very extensive obstruction of the perivascular canals of the dura, which probably is established even before the end of the second stage, is of itself sufficient to determine that the patient's condition must go from bad to worse. In this connection it may here be remarked that much light would probably be thrown upon the pathology of general paralysis if it could be ascertained by experiment (1) what cerebral tissue-changes are produced by complete or partial obstruction of the lymphatic paths of the dura when gradually produced, and (2) how long such obstruction is compatible with life.

In cases of senile insanity the obstruction of the lymphatic channels in the dura mater is rarely so widespread as in general paralytics. It is, however, sufficiently well marked to justify the belief that its effects must be such as to greatly aggravate the morbid tissue-changes that occur in the brain. There is histological evidence to show that in some cases there is an almost complete blocking of the dural canals, and it is a noteworthy fact that it is exactly in such instances that the tissue-changes in the brain are almost indistinguish-

able from those of the third stage of general paralysis. In cases of acute insanity a certain degree of obstruction of the dural lymph-channels unquestionably occurs. But the proliferative changes are of an acute, diffuse nature, rather than of the chronic and local type commonly to be observed in other forms of mental disease. The amount of obstruction caused by these acute changes must vary greatly in different instances. As a rule, it does not seem to be very great. Nevertheless it is probable that in many cases it has an important influence in aggravating the disease, and even in determining a fatal issue. If the proliferative changes in the endothelium of their walls has only been slight and of short duration, the perivascular canals are doubtless readily opened up again upon the cessation of the irritation.

Alterations in the Composition of the Cerebro-spinal Fluid.—

Although the observations that have yet been made upon the subject do not appear to be very numerous, it is now a sufficiently well-established fact that in those forms of insanity in which very profound tissue-changes constantly occur in the brain, such as general paralysis and senile insanity, the cerebro-spinal fluid is loaded with abnormal constituents, or contains normal constituents in abnormal quantity. So far as is at present known, such alterations in the composition of the cerebro-spinal fluid, except in cases in which they are dependent upon an abnormal state of the blood, are the result of the tissue-changes and not their cause, although, as has just been maintained, they may, when once established, react upon the cerebral tissues and aggravate the morbid processes already at work.

The abnormal constituents in the cerebro-spinal fluid may have at least three different sources; they may be derived from the blood, they may be products of abnormal metabolic changes in the cerebral tissues, or they may be the result of disintegration of the cerebral tissues. They are probably derived from the blood in several different forms of mental disease, among which there is specially to be mentioned that group of cases of mania which, as seems now to be proved, is determined by gastro-intestinal auto-intoxication. Organic changes in the nerve-cells and other cerebral tissues are doubtless always accompanied by the formation of abnormal products of metabolism, which, in so far as they are soluble, are discharged into the surrounding lymph. Lastly, disintegrative changes in these tissues, such as occur especially in general paralysis, senile and alcoholic insanity, and the acute insanities, must result in the formation of various abnormal substances, which likewise are discharged into the lymph. The products of these disintegrative changes have recently formed the subject of careful investigation by Mott (51) and Halliburton. According to these authorities, when the nervous tissues undergo degeneration, protagon or lecithin breaks up into cholin, glycero-phosphoric acid, and stearic acid. They have shown

that cholin may be obtained from the cerebro-spinal fluid after death, and that it exists in the blood and cerebro-spinal fluid of general paralytics. At the same time, the cerebro-spinal fluid contains an excess of nucleo-proteid. Mott states that he has found that the cellular proliferation and leucocyte accumulation within the lymphatic sheaths of the vessels of the brain are always most marked where the cellular degeneration is most profound and recent, and believes that it is possible that this inflammation is due to irritation produced by the products of degeneration.

Occasionally it may be observed that, quite apart from the recent occurrence of subdural hæmorrhages, the cerebro-spinal fluid coagulates shortly after it has been collected. This, of course, indicates the presence of entirely abnormal constituents.

Gonzales and Verga (35) found that the specific gravity of the cerebro-spinal fluid tended to be considerably increased in cases of insanity. They further observed that albumin was always very scanty, and that the reaction of the fluid was always alkaline.

Variations in the quantity of Cerebro-spinal Fluid.—In most forms of insanity the amount of cerebro-spinal fluid that can be collected at autopsy is considerably in excess of that commonly obtainable in other cases. According to Gonzales and Verga (35) it is, however, abnormally scanty in epileptics. I think it may be affirmed that an excess of cerebro-spinal fluid is generally compensatory for brain-atrophy, and that it only rarely has any other significance. When the amount is very considerable it may often be observed that it has not collected merely in the subdural space, but also in enlarged lateral ventricles, without, however, any obstruction to the outflow such as occurs in chronic hydrocephalus. It is a noteworthy fact that excess of cerebro-spinal fluid of compensatory origin is not as a rule associated with distension of the intra-cerebral lymph-spaces. The only important exception is the condition of *état criblé*, in which the tissue-atrophy results in the formation around the vessels of more or less distinct spaces which are filled with lymph. True œdema of the brain is never merely compensatory for brain atrophy. It depends upon other conditions, the exact nature of which must still be regarded as obscure. It seems probable, however, that an abnormal state of the capillary walls, permitting of an excessive transudation of fluid, is one of the determining causes.

MORBID CONDITIONS OF THE CEREBRAL CIRCULATION.

Cerebral Congestion.—It is admitted on all hands that arterial hyperæmia and venous congestion may occur within the cranium. It is, however, disputed whether or not in these morbid conditions there is

really any important change in the total quantity of blood within the cavity. On the one hand it has long been believed by clinicians—some of them among the highest authorities of their day—that such general congestion is an important pathological state of frequent occurrence; on the other hand, ever since the enunciation of the *Monro-Kellie* doctrine, there have always been those who maintain that an arterial hyperæmia of the brain can only occur in conjunction with corresponding diminution in the amount of venous blood, and that conversely venous congestion can only occur in conjunction with a corresponding diminution in the amount of arterial blood. I have already endeavoured to show that the latter view is inconsistent with the anatomical and physical conditions that subsist within the cranium, and that, in spite of supposed experimental demonstration to the contrary, the induction of the clinicians remains perfectly accurate.

It may seem to some that, since the occurrence of arterial hyperæmia and venous congestion is admitted, it matters very little whether the total amount of blood in the cerebral vessels can vary or not. But this is not so. The point is really one of primary importance. For example, it has been asserted that venous congestion of the brain, such as may be determined by cardiac or pulmonary disease, really produces cerebral anæmia, since the volume of blood in the arterioles and capillaries is diminished in proportion to its increase in the veins; and the view has even been maintained that cerebral anæmia occurs as an important pathological condition in general paralysis owing to venous congestion. On the other hand, if it is true that the quantity of blood in the brain can vary, then belief in the opposite doctrine has evidently led certain writers into error upon questions that are of considerable pathological moment. This controversy, however, derives its chief importance from the physiological fact that the nutrition of a tissue is very greatly influenced by the state of distension of its blood-vessels. The processes of filtration and diffusion through the wall of the capillary in a condition of extreme dilatation (whether from high internal pressure or any other cause) differ considerably from those that take place when the vessel is normal in calibre. Therefore it does matter for us to know whether the total amount of blood in the cerebral vessels can vary or not, for it is certain that, if it is incapable of doing so, the greatest degree of general capillary distension that can occur is very much less than that which may take place if the total amount can vary.

Since the total quantity of blood within the cranium can vary to an important extent, general arterial hyperæmia of the brain implies far more than a mere increase of the rate of the blood-flow through the cerebral vessels. It implies unusual distension of arterioles and capillaries, and it may be also of veins, and the presence of a greater

amount of blood than in ordinary conditions. There is no reason why it should not have all the effects of active congestion in other organs. On the other hand, general venous congestion of the brain involves more than distension of the veins and slowing of the blood-stream. It implies at the same time distension of the capillaries, and it may be also of the arteries, and the presence again of a greater amount of blood in the brain than in ordinary conditions. It may seem that, as the cerebro-spinal fluid pressure rises with the venous pressure, venous congestion cannot cause diminution in the amount of cerebro-spinal fluid, and will therefore be accompanied by arterial anæmia. I scarcely think that this follows, for on account of the obstruction to the circulation the pressure in the arterioles and capillaries also rises.

The possible causes of active hyperæmia of the brain, which it is important to bear in mind may, within certain limits, be a physiological condition, are various. In the first place, high arterial pressure unquestionably determines the afflux to the brain of a larger proportion of the whole volume of the blood than is sent to it when the pressure is low. But we cannot yet exclude the possibility that there is a direct vaso-motor mechanism by which this increased supply may be, under certain circumstances, in some measure controlled, both as regards its entrance into the cerebral circulation as a whole, and as regards its local distribution. Then there is strong reason to believe that either in conjunction with such hyperæmia from elevation of the general arterial pressure, or independently of it, there may be a general or local cerebral hyperæmia from dilatation of the vessels. In how far such dilatation is due to purely nervous action, to a special chemical condition of the fluid in the adventitial lymph-spaces, to the condition of the blood, or to some other cause, is not at present definitely known. Lastly, morbid conditions of the vessel-walls may diminish their elasticity and determine the general or local dilatation of their lumen. Cerebral venous congestion is always secondary to high general venous pressure, except in so far as it may be due to obstruction of the veins, within or near the cranium, from thrombosis, external pressure, or other causes.

There can be no doubt that the evidences of congestion of the brain that may be recognised at post-mortem examinations are, for various reasons, apt to be untrustworthy. Hill (37), in endeavouring to strengthen the case for the *Monro-Kellie* doctrine, insists very strongly upon this fact, and goes so far as to say that "no sure evidence of cerebral blood volume can be gained by post-mortem examination." Most pathologists will, I think, agree with me in maintaining that so absolute a statement is scarcely warranted by the facts that may be observed. The only safe plan to adopt in regard to evidence of this kind that is known sometimes to be de-

ceptive, is to inquire carefully into the causes of fallacy, and to ascertain, if possible, how far they can be discounted.

The chief possible causes of fallacy are, I think, the following. A brain that has been in a state of active hyperæmia immediately before death may at autopsy appear of normal vascularity, or even anæmic, owing to the expulsion of the excess of blood from the cranium by contraction of the elastic vessel-walls when no longer expanded by the blood-pressure. This may be assisted by gravity in cases in which, after death, the head is kept above the level of the trunk. Probably in all cases in which the elasticity of the vessel-walls is not impaired by disease, such contraction takes place at death and renders the brain the pallid organ that it commonly appears, instead of the highly vascular one that it is during life. The space previously filled by the blood driven out of the cranium is taken by fluid which escapes chiefly from the large veins and from the lymph-channels of the dura, and occupies mainly the subdural space and the lateral ventricles. On the other hand, a brain which during life was not hyperæmic may be rendered so by an asphyxial mode of death, in which the general venous pressure is ultimately greatly raised, so that the cerebral vessels become distended with blood. The congestion will be the more marked if the elasticity of the vessel-walls is at the same time impaired by disease, and if, owing to the position of the body, the effect of gravity is such as to determine the flow of blood to the head. In some instances the action of gravity alone may be the cause of a congested appearance of the brain. The commonly observed relative congestion of the occipital region will be readily recognised as of this origin. Hill maintains that "the whole blood content of the brain may change at the moment that the pathologist opens the skull," in accordance with the direction in which gravity is permitted to act. I scarcely think that this statement is in accord with the general experience of pathologists. I have never myself observed evidence of such changes occurring to any important extent. It has not been my experience that, on opening the skull and reflecting the dura, an anæmic brain can be made a congested one by lowering the head of the cadaver, or that a congested brain can be made anæmic by raising it above the level of the trunk. It would indeed be very surprising if such extreme and rapid alterations could occur, for by the time that autopsies are commonly made the blood in the vessels has generally undergone more or less extensive clotting.

Unfortunately it is not possible in every case to discount these sources of fallacy, and for this reason, as well as on account of the present state of uncertainty as to many points regarding the physiology of the cerebral circulation, much caution is needed in coming to conclusions regarding the occurrence of cerebral hyperæmia in the various

forms of mental disease. Nothing is really to be gained by formulating conclusions that are not fully warranted by demonstrated facts, and therefore I wait for more information before committing myself to opinions upon a large number of questions that may seem to demand answer here.

The following are some of the few definite facts that in my judgment appear to emerge regarding the occurrence of active cerebral hyperæmia in mental diseases.

General paralysis is constantly attended with active congestion of the brain, which, however, specially affects the cerebral cortex. In the third stage this congestion often reaches an extreme degree, and is then accompanied by a loss of elasticity of the capillary walls, in consequence of which they do not contract after death. Hence the cortex appears more or less deeply congested, often in a patchy manner.

Senile mania is associated with cerebral hyperæmia, which tends to affect particular areas specially. The incidence and distribution of this hyperæmia are probably in large part determined by organic changes in the vessel-walls.

In acute insanities there is always hyperæmia of the cerebral cortex. In some cases, however, there is no distinct post-mortem evidence of such hyperæmia. It is probable that in these the dilated vessels have contracted after death owing to the fact that the elasticity of the capillary-walls has not been greatly impaired. In many other cases there is to be observed very distinct patchy congestion of the cortex, which may be interpreted as indicating that the elasticity of the capillary walls had been impaired to a greater extent in some areas than in others. In a large percentage of cases there is seen a condition of intense general congestion of the cortex. There is, further, sometimes to be observed at autopsy a condition of intense congestion throughout the whole encephalon, accompanied generally by multitudes of minute capillary hæmorrhages. This condition corresponds to what has been described as "hæmorrhagic encephalitis." In delirium tremens, which may be included among the acute insanities, there is post-mortem evidence of extreme general hyperæmia of the brain, with commonly very extensive permanent distension of the capillaries.

In choreic insanity there is always well-marked hyperæmia of the whole brain.

There are the strongest reasons for believing that such cerebral hyperæmia in mental diseases is essentially only a part of a complex pathological process, and that it is not in itself a primary cause of the cerebral disorder.

Cerebral Anæmia.—This subject is a wide one, and concerns general neurology rather than insanity. It may therefore be entered into only very briefly here.

On the grounds already very fully stated, I maintain that general cerebral anæmia does not necessarily consist merely in a retardation of the blood-stream, but may manifest itself as an actual diminution in the quantity of blood in the brain, and that congestion of the cerebral veins does not involve diminution in the amount of blood in the arterioles and capillaries.

The nutrition of the brain in common with that of other organs is undoubtedly seriously affected by general anæmia, whether of a quantitative or a qualitative character. Certain kinds of hereditary instability and feeble resistiveness of the brain appear to be specially liable to manifest themselves under such conditions of mal-nutrition. It is probable that to such concurrence of pathological factors a large number of cases of chronic melancholia, as well as of some other forms of chronic insanity, may rightly be attributed.

W. R. Dawson (65), in a recent highly instructive address upon the blood-supply in mental pleasure and pain, sums up as follows the views on this subject, which seem to be of most probable accuracy:

1. The emotional state produced by brain anæmia when gradual, not too profound, and of some duration, is depression.
2. Anæmia of rapid onset and considerable degree tends to produce convulsions and excitement.
3. The characteristic feature of the general circulation in mental depression is high arterial tension, which helps to maintain, if it does not cause, the painful mental state; but there is no conclusive evidence of the condition of the cerebral circulation.
4. In mental depression the blood is impoverished.
5. Under experimental conditions high oxygen tension in the blood supplied to the nerve-cells produces excessive action and possibly exhilaration, but there is no real evidence that such symptoms are ever due to this cause under ordinary circumstances.
6. The characteristic feature of the general circulation in excitement, and probably in exaltation, is low arterial tension, which helps to maintain, if it does not cause, the mental state. Here, again, there is no direct evidence of the state of the cerebral circulation.

Local cerebral anæmia, from narrowing and obliteration of the lumen of arterioles and capillaries by morbid alterations in their walls, occurs especially in senile insanity. It is, further, the immediate cause of the cerebral disturbance in that type of syphilitic insanity in which the cerebral arteries are narrowed by endarteritis obliterans.

PATHOLOGICAL INCREASE OF INTRACRANIAL PRESSURE.

There has been a long-standing controversy between two opposite schools of opinion as to the mechanism and effects of a pathological

increase of intracranial pressure. One side of this controversy is represented by the views of Bergmann (8, 9). This authority has maintained that, as the nerve-substance is incompressible, any foreign body or pathological effusion can only find room in the cranium by displacement of cerebro-spinal fluid; the tension of this fluid is therefore increased, and when it reaches a certain point the pial vessels are compressed and cerebral anæmia is produced; the clinical phenomena of "brain-pressure" are the immediate result of this anæmia. The other side has found its chief exponent in Adamkiewicz (1, 2, 3, 4). He maintains that the brain is compressible, that the cerebro-spinal fluid cannot transmit pressure, nor be raised above the physiological limit, owing to the readiness with which it may be driven out of the cranial cavity, and that the clinical phenomena attributed by Bergmann and others to "brain-pressure" and cerebral-anæmia are the result of irritation or injury of the nervous tissue by local compression.

A useful *résumé* of the observations and opinions of these and other writers who have taken part in this controversy, will be found in a paper by Giannelli (34), who points out that a certain number of facts have been accumulated which have to some extent shaken the theory of Bergmann in its premises. For my own part, I am strongly of opinion that the views of Bergmann are untenable, and that the teaching of Adamkiewicz is essentially accurate.

I think, however, that the pathology of intracranial pressure is capable of a more exact analysis than has yet been given of it. It contains elements that do not appear to have been hitherto detected. For example, none of the writers on the subject, with the exception of Elder and Fowler (27), have, I believe, taken into account the fact that obstruction to the outflow of cerebro-spinal fluid may occur as a pathological condition. In the following statement of my own views there is, consequently, much that is contrary to what at the present day is widely accepted as accurate pathology.

Pathological increase of intracranial pressure may be general or local. In the former case it consists in an abnormally high tension of the cerebro-spinal fluid, and is equally distributed throughout the cerebro-spinal cavity; in the latter it depends essentially on the elasticity of the cerebral tissues, and cannot be continuously transmitted by the cerebro-spinal fluid.

The pressure of the cerebro-spinal fluid is increased in a pathological sense when it is sustained at any point above the blood-pressure in the venous sinuses of the dura mater. There is only one possible cause of such increased pressure and that is obstruction to the outflow of cerebro-spinal fluid from the cranial cavity. The disease in which this specially occurs is general paralysis. There are two points that it is important to note regarding such increased intracranial or cerebro-

spinal fluid pressure, viz., (1) it must always be slight in degree, for it cannot rise above the cerebral capillary pressure; and (2) it must be governed more by the cerebral capillary pressure and less by the intradural venous pressure in proportion to the amount of obstruction to the outflow of fluid. It is to be borne in mind that this obstruction is probably never really complete. Hill (37) deduces from his experimental observations that "the pressure of the cerebro-spinal fluid can never mount above that of the cerebral veins on account of the rapid absorption that takes place through these veins," and, I suppose, as a corollary to this, that "the operation of trephining for such cases as general paralysis of the insane can receive no justification on any experimental grounds." But he has not reckoned with the possibility of obstruction to the outflow of cerebro-spinal fluid as a pathological condition. That such obstruction does occur to a very important extent in general paralysis admits of no dispute; and it is evident that it must result in the pressure of the cerebro-spinal fluid being raised, though only to a very slight extent. I am therefore of opinion that Batty Tuke (63), Claye Shaw (59), Macpherson (46), Wallace (45*a*), and others, who have advocated the operation of trephining in general paralysis, were right in maintaining that the intracranial pressure is raised in this disease. At the same time I think that they were in error in believing that the temporary amelioration of the patient's condition, which undoubtedly occurred in some cases, was due chiefly to relief of this pressure. The increase of intracranial pressure is very slight, it is equally distributed throughout the lymph-spaces of the brain, and therefore it cannot be regarded as doing injury by compression of the nervous tissues, which in many physiological conditions are subjected to a much higher cerebro-spinal fluid pressure than probably ever occurs in these asthenic patients. Nor is there any justification for the supposition that such increase of cerebro-spinal fluid-pressure is exerted as pressure of the brain against the skull. There are, I believe, really three different pathological conditions in general paralysis which are temporarily relieved by opening the skull, viz., (1) obstruction to the outflow of cerebro-spinal fluid, (2) a slight elevation of the general intracranial pressure, and (3) toxicity of the cerebro-spinal fluid. The first, independently of the others, tends to disorganise the mechanism by which variations in the arterial and venous blood-pressures are compensated for, in such a way that the physical conditions of the *Monro-Kellie* doctrine become in a large measure realised. The second must aggravate the effects of the first. The third directly affects the nutrition of the nervous tissues, and is probably of far greater moment than the other two combined.

If these views are in accord with the actual facts it will be seen that the endeavour to drain away the cerebro-spinal fluid by surgical

means in cases of general paralysis is given a new *rationale*. It may be well, however, to say here once more, lest there should be any misunderstanding about the matter, that as far as is at present known these three pathological conditions are merely of a secondary nature, and that their relief would still leave the primary morbid process entirely unaffected.

It may be added here that the occurrence of sustained negative intracranial pressure, which some writers have supposed to arise in certain chronic cerebral diseases, appears to be a physical impossibility. Such negative intracranial pressure might be defined as any tension of the cerebro-spinal fluid below that of the blood in the dural sinuses. But any tendency to such an inversion of the normal pressure relations is immediately met by arrest of the outflow of cerebro-spinal fluid from the cranial cavity and accelerated production of lymph by the cerebral capillaries.

What constitutes a local increase of intracranial pressure, and under what circumstances is it produced? I think it may be stated that when at any point within the cranium the extra-vascular pressure rises above that of the cerebro-spinal fluid (*i.e.*, the general intracranial pressure), it is pathologically increased, except in so far as the pressure exerted by the surface of the brain upon the dura mater may normally exceed this pressure. Such local pressure may be exerted by anything that can occupy space in the cranium without manifesting the same physical properties as the cerebro-spinal fluid. Thus normal salt solution injected slowly into the subdural space would not cause any appreciable increase of local pressure (granted that the channels by which the cerebro-spinal fluid escapes were not obstructed), while, on the other hand, air, or oil, similarly injected, would do so, and still more readily the introduction of any solid body.

Pathological increase of local pressure is produced commonly by blood-extravasations, tumours, depressed fractures and foreign bodies. Let us consider its effects as exemplified in a case of depressed fracture of the skull pressing, say, upon the top of a convolution. They may be divided into two classes, viz., (1) mechanical and (2) vital.

In considering the mechanical effects, it is to be borne in mind that the brain is capable of conveying a fluid wave of pressure in virtue chiefly of the lymph permeating its tissue interstices and of the blood in its vessels, that it is compressible to a limited extent, and that its tissue-elements are all highly elastic. It is also able to transmit pressure to a certain extent, independently of the fluid it contains. At the moment that the depressed fracture is produced, a pressure-wave starts from the point of impact, and radiates through the brain. This pressure-wave, to a varying degree in accordance with its height, causes mechanical injury to the nerve-tissues, as has been shown by the

experimental observations of Miles (66) and others. The piece of depressed bone, carrying with it the dura mater, is now pressing upon the top of the convolution and indenting its surface. The displacement of cerebral tissue has been rendered possible chiefly owing to its compressibility and elasticity, not merely by emptying of the blood-vessels, as those writers maintain who insist that the brain is incompressible. The initial fluid-wave having passed, the pressure of the lymph in the tissues in the immediate neighbourhood of the indentation, and for some distance beyond it, is greatly raised. It is highest at the seat of compression, and from there gradually shades off to the normal. In consequence of this elevation of pressure the vessels are compressed, but only in so far as the pressure outside them happens to rise above that of the blood within them, and the lymph flows away from the tissue-interstices until its pressure is reduced as far as possible to the normal. With the reduction of the pressure of the lymph, many vessels that were compressed will be opened up again. In the immediate neighbourhood of the indentation there will be a zone in which both blood and lymph are permanently driven out, and in which the individual tissues are pressed closely against one another, and at the same time more or less stretched and lacerated. This first zone has not sharply-defined limits. It gradually shades off into a second zone, in which there are certain important changes. This second zone in its turn shades off gradually into the normal tissues. The changes in the second zone consist in closer approximation of the tissues, diminution of the quantity of lymph, and stretching of the individual tissue-elements. The compression and stretching of the tissues may involve, when extreme, rupture of nerve-cell processes, glia-fibres and capillaries, and occlusion of vessels by the narrowing of their lumen. These lesions will chiefly occur in close proximity to the first zone. At the furthest limits of the second zone they will not occur at all. If at this stage the depressed bone is elevated, the compressed and stretched tissues will return to their normal position, except in so far as their elasticity has been destroyed by its limits having been exceeded. If, on the other hand, the bone continues depressed, the remaining elasticity of the stretched tissue becomes gradually impaired. It is certainly lost within a few days. This gradual impairment of the elasticity must be accompanied by further rupture of nerve-cell processes, etc. But, as the impairment occurs first in the tissues that are most severely stretched, viz., in those in and near the first zone, the stretched tissues in the outer portion of the second zone will be relaxed before their elasticity is destroyed, and will therefore tend to return to their normal form. When the elasticity of the tissues has thus either ceased to exist or to be brought into action, the area affected by the depression of bone is no longer the seat of increased intracranial pres-

sure, provided that no vital changes have operated to produce new causes of such increased pressure. The increased pressure depended essentially upon the elasticity of the tissues which was brought into action by the displacement enforced by the depression of the bone. If the bone is now raised, the tissues, instead of returning in a large measure to their original position, will retain the shape that they have been made to take.

To maintain that such local increase of pressure is entirely vascular in origin is, I am convinced, erroneous.* Those who do so leave out of account the elasticity of the cerebral tissues. At the same time there is no reason to doubt that when vessels are compressed without their lumen being obliterated, or their continuity with the larger arteries interrupted, they must communicate the pressure within them to the other tissues.

The vital effects of such local compression as that we have been considering consist, in the first place, in part of abolition of functional activity and in part of abnormal stimulation of it. The former results, where the mechanical alterations are severe, the latter occurs where they are comparatively slight. Severe compression of the tissues, and obliteration of their capillaries, must immediately result in abolition of their functional activity; moderate compression and stretching of the tissues, local rupture of nerve-cell processes and dislocation of synapses, must cause abnormal stimulation or irritation. The vascular reaction consists in an active hyperæmia of the adjoining tissues, which invades the confines of the compressed area as far as pressure relations permit. Sometimes this active hyperæmia passes into an inflammatory condition. Lastly, there is to be recognised the occurrence of a certain amount of functional disturbance throughout the rest of the brain, which may in large part be due to the mechanical effects of the fluid wave, but must also have other causes.

All the clinical phenomena produced by local increase of intracranial pressure, whether caused by depressed fracture, hæmorrhage, tumour, foreign body, or other cause, are, I think, to be explained by reference to this local and general impairment of functional activity, as Adamkiewicz maintains, and not to anæmia as Bergmann, Hill, and others believe.

In the case of a hæmorrhage into the brain-substance, the mechanical and vital effects are essentially the same as those just described. The effused blood, forced into its position by the vascular pressure, acts as a foreign body which occupies a certain amount of space. The tissues with which it comes immediately in contact are more or less completely destroyed. The surrounding tissues are compressed and stretched just as they are beneath a depressed fracture, and lymph and blood are driven out from them in amount correspond-

ing to the volume of the foreign body. Supposing that the hæmorrhage ceases, the high pressure of the effusion is maintained essentially by the elasticity of the surrounding tissues. The theory that it is maintained purely by the arterial pressure is, I think, untenable. As the elasticity of the tissues is gradually destroyed, the pressure of the effusion falls to the level of the general intracranial pressure. If the increased local pressure were due to the arterial blood-pressure, there is no reason why it should not be maintained for an indefinite time.

The clinical phenomena of apoplexy result from the abolition of the functional activity of the lacerated and severely compressed cerebral tissues, and from the irritation of other tissues throughout a wide surrounding area by compression or stretching. They are not essentially due to anæmia, as so many maintain. Hill, who adopts this view, states: "It cannot be too forcibly insisted that it is not the rise of intracranial pressure but the cerebral anæmia that produces the symptoms of apoplexy. When a blood-clot lies in the cranial cavity, and all active hæmorrhage has ceased, the clot forms a foreign body which takes up a certain volume of the cranial capacity, and decreases to a corresponding extent the cerebral blood volume. For the amount of cerebro-spinal fluid that can be expressed from the cranial cavity is insignificant, and the brain matter is incompressible." This argument is based upon data that are either erroneous or imperfect. It does not take into account the important fact of the elasticity of the brain, which on the contrary has a few pages further back been described as "a viscous, inert mass of the consistency of a lump of putty." It does not recognise the existence of expressible lymph in the substance of the brain, and it is wrong in its assumption that the brain is incompressible. Expulsion of blood is not the only means by which more room can be made within the brain, and consequently the anæmia of the neighbouring tissues produced by the pressure of a hæmorrhagic effusion is not nearly so extensive as Hill supposes.

Hill has further contended that when the primary compression is extensive a *circulus vitiosus* may be established, in consequence of which the area of capillary compression gradually extends. He says: "The blood pressure which exists in these capillary areas surrounding the seat of complete vascular obliteration will lead to increased transudation of fluid, since plasma may pass more easily into the brain substance than blood through the compressed capillaries. The transudation will take place at almost arterial tension, will increase the volume of the foreign body, and so will lead to compression of other capillary areas. A *circulus vitiosus* is thus established and the cerebral anæmia may spread indefinitely." This seems very like saying that if the pressure within it is high a capillary can strangle itself by pouring out lymph until the external pressure becomes greater than the internal.

It may, however, be taken to imply merely that capillaries at some little distance, the pressure within which is less, may be obliterated owing to the high tension of the lymph which flows from the area of high capillary pressure. This, however, is scarcely more admissible. It does not recognise the fact of the rapidity with which the lymph can escape from the brain, more especially when under increased tension, nor that the tendency to obliteration of the capillaries would at once be met by an increase of the pressure within them. I am strongly inclined to think that this theory of the occurrence of a *circulus vitiosus* is erroneous. I am not aware of any pathological phenomenon that supports it, or of any that it helps to explain. Local increase of intracranial pressure can only obliterate the capillaries in so far as it exceeds the capillary pressure, and as far as mechanical effects are concerned there seems to be no reason why the area within which it does so, should extend further beyond the actual seat of the lesion than to a surrounding zone in which the pressure is sufficiently raised by actual compression of the tissues. But there are doubtless other vital effects that may come into operation, such as inflammatory action, rendering the changes of a much more complicated character than they would otherwise be.

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CHAPTER XII

CONGENITAL ABNORMALITIES OF THE BRAIN.

A FULL and systematic account of the congenital abnormalities that may be observed in the central nervous system, properly has its place in a text-book treating of general neuro-pathology, rather than in one with the special limits of the present work. I shall, therefore, consider the subject, which is a very large one, only very briefly, merely noticing in a somewhat cursory manner some of the more common abnormalities of the brain that have special importance in relation to mental diseases.

Congenital abnormalities of the brain may be divided into two classes. Firstly, there are those that are simply peculiarities of individual development, such as atypical arrangement of the convolutions, heterotopia of the grey substance, absence of the corpus callosum, etc.; and, secondly, there are those that arise in consequence of a pathological disturbance occurring in the course of intra-uterine life, such as congenital hydrocephalus, some forms of microcephaly, etc.

Some of the slighter congenital abnormalities of the brain may not infrequently be observed in persons who, during life, did not exhibit any noteworthy mental aberration or peculiarity; nevertheless such slight structural abnormalities are unquestionably far more common in the insane than in the mentally sound. They are especially common in cases of idiocy, imbecility and epileptic insanity. Some of the more gross congenital defects, such as microcephaly, are quite incompatible with normal intellectual development, while others, such as porencephaly, have only very rarely been discovered in persons who were not regarded as mentally abnormal.

Out of 288 brains of patients who died in Morningside Asylum, examined by myself, there were nine in which I found distinct congenital abnormalities. These consisted of the following conditions: Symmetrical depressions on the under surface of frontal lobes (in a case of epilepsy); imperfect definition of the fissures of Sylvius (epilepsy); abnormal complexity of the cerebral convolutions (senile insanity); local microgyria (idiocy); deep depression in the position of the superior parietal lobule, without evidence of any destructive lesion on section (senile insanity);

heterotopia of grey matter of cerebrum (senile insanity); abnormal simplicity of cerebral convolutions (imbecility); shallow, broad depression traversing both occipital lobes (imbecility); and, lastly, microcephaly associated with several remarkable structural features, including very extensive microgyria, a pale band (found on microscopic examination to be devoid of fully developed nerve-cells) in the middle of the cortex of the greater part of both cerebral hemispheres, and a deep abnormal fissure in both parietal lobes.

Absence of the Corpus Callosum.—Probably the most complete account that we have in English of this rare but important anomaly is that which was published some years ago by Alexander Bruce (1). He describes in minute detail a brain which presented complete absence of the corpus callosum and various other abnormalities, and gives an epitome of the records of fifteen previously published cases of a similar nature, as well as of nine others in which there was partial defect of the corpus callosum, and six in which the condition appeared not to be of a primary nature, but secondary to other pathological conditions, such as hydrocephalus and tumours. Since the publication of his monograph, quite a large number of additional cases have been described.

Bruce concludes that the majority of cases of partial or complete absence of the corpus callosum can be explained on the hypothesis of arrested development, and may be classified according to the period at which this arrest has taken place.

The point which most concerns us here is the relation of this anomaly to intellectual development. According to Bruce, certain of the cases recorded show that, if the brain is otherwise well developed, there may be no disturbance of mobility, co-ordination, general or special sensibility, reflexes, speech or intelligence, whether the defect of the corpus callosum be primary or secondary. He further states that, in cases associated with imbecility, the abnormality is always accompanied by some other grave brain-defect. Ireland (11) refers to a number of recorded cases which bear out the same conclusions. In the great majority of instances the condition is accompanied by other marked structural abnormalities of the brain (more especially in parts normally adjacent to the corpus callosum), and associated with distinct mental weakness.

Absence or Abnormal Development of other parts of the Brain.—The other local congenital abnormalities that may be observed in the brain are almost endless in their variety. The slighter of them are probably much commoner than is generally supposed, for they are readily overlooked at a post-mortem examination. The more prominent can hardly escape notice, and very numerous examples are now recorded in neurological literature. Among the abnormalities of this nature that

have been described the following may be enumerated: Absence of fornix, absence of anterior commissure of the third ventricle, absence of middle lobe of cerebellum, imperfect development of one lateral lobe of cerebellum, absence of corpora geniculata, imperfect separation of the cerebral hemispheres owing to defective development of the great longitudinal fissure, atypical arrangement of certain of the convolutions and sulci, microgyria, heterotopia of the grey substance, porencephaly.

The last four of these, perhaps, require some detailed notice here.

Atypical Arrangement of the Convolutions and Sulci.—This subject has been most minutely investigated by several observers, most of whom have recorded the results of their labours in exceedingly lengthy monographs. The various conclusions that have been arrived at can scarcely be briefly epitomised, and I would here simply refer the reader who desires to obtain a knowledge of the subject to the publications especially of Giacomini (2), Poggi (3), and Julius Mickle (4).

Microgyria.—The condition to which this term is applied consists in local sub-division of the cerebral surface by irregular, short and shallow sulci, in such a way as to produce the appearance of numerous abnormally small convolutions. It is most common in cases of idiocy and imbecility. It is frequently associated with a subjacent sclerotic change in the tissues, but may also occur quite independently of such sclerosis.

Heterotopia of the Grey Substance.—Smaller or larger portions of the grey matter of the cerebral cortex, basal ganglia, or other parts of the brain, are occasionally displaced from their normal position. The form in which this somewhat rare condition of heterotopia is, in most instances, observed to manifest itself, is that of one or more small isolated areas of grey substance in the white matter of the cerebral hemispheres.

Porencephaly.—To judge from the large number of examples that have now been described, this abnormality would seem to be a fairly common one. It consists in the occurrence of a cavity or fissure in one or other of the cerebral hemispheres, extending from the outer surface down to, or near to, the lateral ventricle, and situated generally in the parietal lobe, or island of Reil, or involving both.

Heschl (5), who first described the condition, regarded all examples of porencephaly as of congenital origin, but it is now known that, as was first clearly shown by Kundrat (6), some cases are determined by pathological disturbances arising at or after birth. Clinch (7) has described a typical case which clearly resulted from pressure of forceps upon the head during labour. An excellent account of the whole subject will be found in a somewhat recent paper by Conolly Norman

and Alec Frazer (8). The condition is now generally attributed to arterial rupture or occlusion, or to some other gross lesion, occurring at an early period in the growth of the brain.

While most of the described examples of porencephaly appear to have been observed in lunatics, the abnormality has occasionally been found in persons who had not been regarded as mentally defective.

Microcephaly.—The most authoritative account of the microcephalic brain is unquestionably that contained in the elaborate monograph of Giacomini (9). The best anatomical work that has appeared on the subject in this country is probably that of Professor Cunningham and Telford-Smith (10). A very full and interesting account of what is known regarding microcephaly, both on the clinical and pathological sides, will be found in Ireland's recent work upon mental affections of children (11).

Broca regarded as microcephalic all brains of 1019 grammes or less in the man, and of 907 grammes or less in the woman, but most other authorities have objected to such artificial delimitation of a pathological condition.

Giacomini has sub-divided cases of microcephaly into—(a) true microcephaly, (b) pseudo-microcephaly, and (c) combined microcephaly. In the first class, he includes those of purely developmental origin, or those in which at least there has been no distinct pathological process at work. In the second, he places cases in which there is evidence of the action of such a process; and in the third, those in which these two conditions are associated. This classification is now generally accepted as accurate, although some authorities, including Mingazzini (12), are inclined to regard all cases as determined by the intrusion of a pathological process. The old view that microcephaly depends upon premature closure of the cranial sutures is now recognised to be quite untenable.

A very full description of the appearances presented by the brain in two cases of true microcephaly (in the sense of Giacomini) will be found in the work of Cunningham and Telford-Smith. These authors state that, in all typical cases which belong to the extreme grade, the great and leading characteristic of the reduced cerebrum is the aborted condition of the occipital lobe, in consequence of which the cerebellum is only partially covered by it. The brain likewise shows a marked convolutionary disturbance.

A large amount of discussion has taken place upon the question as to whether or not the true microcephalic brain is to be regarded as "a partial atavism in which a phylogenetic stage in the evolutionary development of the brain is to some extent reproduced." This view was first advanced by Vogt in 1867, and although its accuracy has been disputed by several other authorities upon such questions,

Cunningham and Telford-Smith contend that a great deal may be said in favour of it.

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CHAPTER XIII

FOCAL LESIONS OF THE BRAIN.

THE subject of focal lesions of the central nervous system, like that of its congenital abnormalities, scarcely calls for full and systematic description in a text-book with the special limits of the present work. I shall, therefore, do little more than indicate the relationship of some of the more common morbid conditions of this class to mental diseases.

As factors in the pathogenesis of insanity, localised gross lesions of the brain are unquestionably of very considerable importance. They are present in a remarkably high percentage of cases examined after death. The form and degree of mental derangement that they occasion probably depend mainly upon their localisation, and the special reactive qualities of the individual brain. In a large majority of instances they are not, however, the only important structural alterations in the organ, being associated with well-marked pathological changes in various other situations.

Out of 288 cases of insanity examined by myself at Morningside Asylum, there were eighty-two, or 28·5 per cent., in which there were focal lesions of the brain. In twelve instances the lesions were of quite recent development, and therefore not to be regarded as factors in the production of the mental disease from which the patients suffered. In all of the cases, except one, the cerebral hemispheres were involved. The lesions were distinctly multiple in forty instances, single (as far as could be recognised) in only thirty-one. In sixty-six cases they were of such a nature as, in my opinion, to be classed as of vascular origin. There were three cases of tumour, six in which there were tubercular nodules, and five with extensive areas of sclerosis. There was no example of localised gumma, but in two cases of syphilitic insanity, presenting very extensive cerebral softening from recent thrombosis of narrowed arteries, there was diffuse gummatous infiltration of the pia-arachnoid in the neighbourhood of the morbid vessels.

GROSS CEREBRAL LESIONS OF VASCULAR ORIGIN.

As appears from the above statistics, by far the larger proportion of gross cerebral lesions that occur in cases of insanity are of vascular origin. An analysis of the sixty-six cases in which there were areas

of softening, atrophy, or sclerosis, regarded as of this nature, shows that four resulted from recent embolism of a large artery, two from thrombosis of a middle cerebral artery and its branches (following endarteritis obliterans), one from venous thrombosis, fourteen from hæmorrhage (recent in six cases, old in eight), whilst the precise nature of the vascular disease in the remaining forty-five could not be determined at the post-mortem examination. The lesions in this last group consisted almost exclusively of localised atrophies, generally multiple, and affecting most commonly the cerebral cortex, but also in many instances the white matter of the cerebral hemispheres, the basal ganglia, cerebellum and pons. The evidence in support of the view that such atrophic areas (the appearances presented by which are described below) are of vascular origin, is, I think, quite conclusive, although there are some authorities who maintain that many of them are secondary to degeneration of the nerve-cells. The latter theory, however, really receives no support from either experimental or histological observation. The destruction of the motor cells of the spinal cord which follows evulsion of a spinal nerve, does not result in local atrophic softening of the anterior horn; nor is the great loss of nerve-cells in the cortex that can be recognised to have taken place in some cases of profound secondary dementia, associated with such gross lesions in this situation. On the other hand, there is the clearest histological evidence that local lesions of the kind in question may follow obliteration of capillaries by hyaline fibroid degeneration or by acute hyaline degeneration, and obliteration of arterioles by endarteritis deformans. There are strong grounds for believing that such atrophic areas may also arise in consequence of the blocking of arterioles or capillaries by minute emboli, consisting of particles of degenerative material detached from the walls of larger atheromatous vessels. It is, moreover, certain that thrombosis plays an important part in determining occlusion of degenerated cerebral vessels. This last fact explains how the functional disturbances, associated with the occurrence of such cerebral softenings, are so commonly developed suddenly.

The fact that these atrophic areas are of vascular origin is already sufficiently clear; what has still to be investigated is their precise relationship to the various forms of vascular disease. It seems certain, however, that they result mainly from endarteritis deformans of the cerebral arterioles, and hyaline fibroid degeneration or acute hyaline degeneration of the capillaries, in consequence of which the vascular channels are gradually narrowed and finally obliterated. At the same time it is not possible in every instance to distinguish between a softening of such origin and one that is the result of an old hæmorrhage, although the latter is generally characterised by more or less distinct rusty staining.

The naked-eye appearances of the local softenings that follow cerebral hæmorrhage and cerebral embolism are fully described in other text-books, and I shall therefore not deal with them here. On the other hand, the lesions of which the origin has just been discussed, and which are perhaps most conveniently referred to as atrophic softenings, require some detailed description, for they have very special importance in relation to insanity. Although they are by no means confined to cases of mental disease, they are certainly far more frequently to be observed, and affect much more extensive areas, in such patients than in others. They are always accompanied by advanced degenerative changes in the vessels in other parts of the organ, as well as in their own immediate vicinity. Indeed, such atrophic areas merely represent the situations in which a general disease of the cerebral vessels has reached a stage that is incompatible with the continued nutrition of the nervous elements.

Atrophic softenings may affect any part of the brain, but the cerebral cortex seems to be the situation in which they most readily form. They appear as softened and wasted areas of a grey, yellow-grey or yellow-brown tint. They vary in size within wide limits. They may be so small as to be indistinguishable with the unaided eye, or so extensive as to involve the greater portion of the cortex, or of the white substance, of one cerebral hemisphere. They are practically always multiple, although the fact is often not apparent until a careful microscopic examination of various parts of the brain has been made. They have a remarkable tendency to bilateral symmetry, a feature which is perhaps most commonly exhibited on the under aspect of the frontal lobes, at the tips of temporo-sphenoidal lobes, and in the basal ganglia.

Dr Clouston¹ has specially directed attention to the fact that various vascular and trophic lesions of the brain are exceedingly apt to occur in both hemispheres in the same place and almost at the same time, and has insisted upon the great importance of keeping it in mind in brain study. Probably one of the most remarkable cases of the kind on record is that lately described by Drs George Mackay and Crauford Dunlop,² in which a rapid hyaline degeneration of the vessels had caused atrophic softening in the neighbourhood of the posterior part of the temporo-occipital convolution on both sides, and produced complete colour blindness.

When atrophic softenings affect the cortex, they appear as a distinct depression on surface view, unless hidden within a sulcus. The superjacent pia-arachnoid may be thickened as part of a general thickening of the membrane, but is often involved in the atrophic change. Very

¹ *Clinical Lectures on Mental Diseases.*

² *Scot. Med. and Surg. Journ.*, Dec. 1899.

extensive cortical atrophic areas may present islets of comparatively healthy cerebral tissue, the vascular supply of which must have been in some measure maintained. More commonly they contain one or more small, pale yellow nodules of a firm consistence, which are probably formed from such islets of cerebral tissue. The appearance of cortical atrophic areas on section varies greatly in different instances. The grey matter is generally much narrowed, and may be entirely lost. In the latter case, the area has a punched-out appearance, being bounded by a sharp wall of seemingly healthy tissue. Most commonly the entire depth of the grey matter is involved, and the softened tissue merges gradually with the subjacent white substance. Sometimes only the external layers of the cortex are affected, sometimes only its deeper layers, while very frequently the softening extends deeply into the subjacent tissues.

Atrophic softenings of the white substance have usually an appearance very similar to that of the cortical lesions, but in some instances their colour does not appreciably differ from that of the normal tissue. When they are of some standing, their centre is very often occupied by a cyst containing clear fluid. This cystic character is also common in atrophic lesions of the basal ganglia. In very old atrophic areas the softened matter has usually entirely disappeared, its place being taken by sclerotic tissue, or by a cyst surrounded by a zone of such tissue.

In paralytic insanity, the gross lesion involving the motor areas of the brain is probably most commonly the result of a hæmorrhage, but is often either an embolic or an atrophic softening. In senile insanity, atrophic softenings are exceedingly common, being present in from 40 to 50 per cent. of cases examined after death. Old hæmorrhagic softenings are also present in a very large proportion of cases. All of the aged insane appear to be exceedingly prone to suffer from gross cerebral lesions of vascular origin. In general paralysis, atrophic softenings, most commonly affecting the cerebral cortex, are very frequent. They specially tend to form near the summits of the convolutions. They appear to result from hyaline fibroid and acute hyaline degeneration in the capillaries, and from acute periarteritis, which blocks the small arterioles by inducing thrombosis in them. In choreic insanity, cerebral hæmorrhage is very prone to occur, and is the determining cause of a fatal issue in many cases.

CEREBRAL TUMOURS.

Primary tumours of the brain are, in the large majority of instances, either sarcomata or gliomata, of both of which several varieties are described. Other kinds of primary tumour have only very rarely

been observed. They include fibromata, osteomata, lipomata and angiomas.

A very considerable proportion of cerebral tumours are, however, secondary to malignant growths elsewhere. Both sarcomata and carcinomata frequently develop in the brain as the result of such metastasis. Further, the brain may be affected by tumours originating in its coverings, or in other structures closely connected with it, such as the pituitary body and the walls of the upper respiratory passages. Among the more important of the new growths originating from the coverings of the brain are endotheliomata, sarcomata and osteomata. The first may arise from the pia-arachnoid or from the dura, the last two especially from the dura and from the skull.

As already remarked, the form and degree of mental derangement occasioned by such growths depend mainly upon their localisation and the special reactive qualities of the individual brain. It is only exceptionally that patients suffering from intracranial growths are considered suitable for treatment in an asylum rather than in a general hospital.

INFECTIVE GRANULOMATA.

Tubercular Nodules.—It is now a well recognised fact that the insane are specially liable to suffer from the various manifestations of tuberculosis, and it is therefore only to be expected that caseous tubercular nodules in the brain, which are observed with considerable frequency at post-mortem examinations upon patients dying in general hospitals, should be of common occurrence in the subjects of mental disease. As already stated, I have found six examples of such lesions in 288 cases of insanity. In five cases the cerebrum was the part affected, in one it was the cerebellum. In each instance the cortical tissues were involved by the morbid growths, which consisted of single nodules in four of the cases and of two separate foci in each of the others.

Tubercular nodules in the brain vary greatly in size in different instances. They are commonly from one-eighth to one-half of an inch in diameter, but are often much larger. They are generally easily recognised by their pale yellow and cheesy appearance. The only other condition from which it is sometimes difficult to distinguish them is a localised gumma. It is very doubtful if they are important factors in the causation of insanity, appearing rather, when they occur in cases of mental disease, to be minor accompaniments of general cerebral disorder in tuberculous subjects.

GUMMATA.

Localised gummata of the brain seem to be much less common than a diffuse gummatous infiltration affecting a greater or less extent of the pia-arachnoid and subjacent nervous tissues, in association with endarteritis and periarteritis. Such diffuse gummatous infiltration is sometimes accompanied by distinctly localised caseous areas.

Like other new growths in the brain, gummata, especially when growing rapidly, may cause severe mental derangement and convulsions. They constitute the chief lesion in one of the forms of syphilitic insanity (see p. 356). They appear to be rare in other clinical types of insanity. It is certainly a remarkable fact that they are almost never found in the brain in cases of general paralysis, a disease which is now clearly proved to have a close etiological relationship to syphilis.

SCLEROTIC AREAS.

Sclerotic areas, consisting essentially of a dense overgrowth of neuroglia, may be observed with considerable frequency in the brains of the insane. They present various appearances, according to their extent, situation, and origin. It is certain that they may depend upon various different pathological conditions, some of which are still very imperfectly understood.

Very small hæmorrhagic, embolic, or atrophic areas, after some months or years, are generally represented by a sclerotic patch of corresponding size. Larger areas of the same kind, if situated deep in the substance of the brain, become cystic in the centre, whilst their walls are transformed into a zone of sclerotic tissue; if situated at the surface, a depression is formed, owing to absorption of the dead tissue, and the floor of this depression has the same structure as the wall of an old-standing cyst. Islets, or extensive areas of sclerotic tissue, which are evidently of essentially different origin from the foregoing, are also met with in the insane, more especially, but not exclusively, in epileptics. They resemble lesions of vascular origin, in respect of the fact that they have a distinct tendency to bilateral symmetry. Thus, in a case of epileptic insanity in a man who died at the age of forty, I found a condition of advanced, irregular sclerosis, affecting, roughly speaking, the middle third of each cerebral hemisphere, and in another case of the same kind, in a woman who died at the age of thirty-two, two large sclerosed areas on the under aspect of the frontal lobes, involving both cortex and white matter. The origin of such sclerotic lesions, which are common especially in cases of epileptic idiocy and imbecility, does not seem to have as yet been very satisfactorily explained. A special form of localised sclerosis of the brain

has been termed *hypertrophic nodular gliosis*. It also occurs especially in epileptic idiots and imbeciles. The nodules, which vary in size in different instances, are generally multiple, and affect chiefly the cerebral cortex. Pellizzi¹ has recently collected the records of most of the published cases, and has also given a very complete description of three observed by himself. From a consideration of their microscopic characters, he has been led to the conclusion that this form of sclerosis of the brain depends upon a defect of development arising at a time corresponding to the formation of the tertiary sulci in the cortex. If this view of its pathogenesis is correct, hypertrophic nodular gliosis ought, of course, to be classed among the congenital abnormalities of the brain.

¹ *Annali di freniatria*, 1899, f. 4 ; 1900, f. 1, 2.

CHAPTER XIV

PATHOLOGY OF SOME OF THE MORE IMPORTANT CLINICAL TYPES OF MENTAL DISEASE.

IN this concluding chapter it is intended to give a short account of the special pathology of some of the more important clinical types of mental disease. For various reasons it is impossible for me to attempt to deal with the subject in an exhaustive manner. For one thing its literature is now so enormous, and the present position of opinion upon most of the important questions that arise is still so much divided, that the ordinary limits of a chapter would be wholly inadequate for a statement of a tithe of the observations that have been recorded, or of the individual views that have been advanced. My purpose is simply to endeavour to place before the reader what seem to me to be, at the present early stage of investigation, the most important facts and probabilities with regard to the pathology of some of the more common forms of insanity.

ACUTE INSANITY.

From the pathological standpoint it is convenient, I think, in the present position of knowledge, to consider together those cases of mental disease that are distinctly acute in character, as contrasted with those that are chronic and with those that cannot properly be placed in either of these two categories. Such a group has, of course, neither clinically nor pathologically, any sharp line of demarcation from the other two, but those of its components with which I wish chiefly, though not exclusively, to deal here, namely, the various forms of acute mania and melancholia, fall quite definitely within it.

Etiology and Pathogenesis.—The vast importance of certain forms of inherent weakness of individual organisation as factors in the causation of insanity is now admitted on all hands. Some authorities even go so far as to maintain that without such faulty heredity there can be no insanity. Thus it has been stated by Macpherson (1) that "the difference between the person who may become insane and the person who will not become insane is one entirely of hereditary predisposition." This extreme view is, I think, scarcely admissible. To a certain extent, of course, its truth or falsity depends upon the

exact significance that we give to the term "insanity." But, even within the limits of technical insanity, there are numerous cases in the pathogenesis of which it is difficult to see how a morbid heredity can play any essential part. For example, in the vascular form of syphilitic insanity the mental derangement may be explained simply by the interference with the nutrition of those cortical nerve-cells which subserve the associative or intellectual functions. It is essentially independent of hereditary predisposition to insanity, although it is doubtless often intensified by the existence of such inherited weakness. Many other forms of vascular and gross lesion that could be mentioned must also, I think, be regarded as capable of producing insanity simply in virtue of their special localisation, without the aid of any constitutional weakness of nervous organisation. At the same time it is certain that a faulty heredity plays a part of essential importance in the pathogenesis of the vast majority of cases of insanity. The still vexed questions of the exact nature and mode of operation of a hereditary predisposition to insanity, and its relation to racial degeneration, are fully discussed in all the text-books upon mental diseases, and I shall not attempt to enter into them here.

The causes of insanity are generally divided into (1) the predisposing and (2) the exciting or determining. Some writers include many things in addition to hereditary predisposition in the former class, but in view of the altogether special position and importance of this factor in the pathogenesis of insanity, it is probably best regarded as the only predisposing cause, while all the others are classed as exciting causes.

In the pathogenesis of the acute insanities hereditary predisposition to mental disease is certainly a highly important factor, perhaps even a constant and essential one. The possible exciting or determining causes are extremely numerous. But the results of pathological research point more and more to the conclusion that in this, as well as in the great majority of other forms of insanity, we have to recognise the operation of toxic agents. Indeed the exciting causes of insanity that can now be excluded from this category are extremely few. Even such conditions as worry and anxiety, strong emotional excitement, excessive mental work, physical exhaustion and loss of sleep, all of which are commonly classed among the determining causes of mental disease, are now believed by many high authorities to act mainly through the alterations in metabolism and consequent auto-intoxications that they entail.

The toxic agents that determine the occurrence of insanity in predisposed persons may be classified as follows :—

1. Those that are introduced from without, such as alcohol, cocaine, morphia, etc.

2. Those that form within the body in the course of various infective and non-infective diseases, such as the poisons of influenza, syphilis, and rheumatism. They cannot always be separated from the next class.

3. Those that are generated within the body in consequence of various disorders of metabolism, producing *auto-intoxication*. In this class there are to be included the toxic agents present in cases of chronic Bright's disease, endarteritis deformans, myxœdema, diabetes, etc., all of which may determine the occurrence of insanity, and also those that develop as the result of living in bad hygienic conditions, and in consequence of various forms of mental shock and overstrain.

4. Those that arise in the contents of the alimentary tract in consequence of functional derangements of the various digestive organs, and are absorbed into the system, producing the condition generally referred to as *auto-intoxication from the gastro-intestinal canal*.

5. Those that are developed by the action of micro-organisms which have gained admission from the alimentary tract into the blood stream, producing the condition known as *auto-infection*.

Simple auto-intoxication and auto-intoxication from the gastro-intestinal canal have in late years been proved to be important determining causes of mental disease. The former may be brought about by many different conditions, including the defective functional action of various glandular organs and tissues (*e.g.* the liver, thyroid, kidneys, bone marrow and blood), and "physiological instability," in consequence of which the balance between waste and repair is not perfectly maintained. There can be little doubt that such abnormal conditions specially tend to arise in certain individuals owing to particular forms of constitutional weakness.

The whole subject of the modern conception of the toxic basis of insanity will be found very fully and clearly explained in the recent work of Macpherson (1), who was one of the first in our own country to direct attention to the vast importance of this branch of neuropathology (2). This authority justly remarks that "The toxic basis of all forms of insanity is a presumption for which there is fairly good foundation, but no direct proof." But this foundation is now being very rapidly strengthened, and with regard to many individual forms of mental disease, the direct proof is already abundant.

I shall briefly note here the results of some of the recent observations bearing upon the question of the infective and auto-toxic origin of the acute insanities.

One of the most important points that has been investigated is the possible relation of acute delirious mania, or acute delirium, to infective organisms. Although some observations pointing to a possible close connection of acute delirium with bacterial infection were recorded by

earlier writers, the first really important work on the subject seems to have been that of Bianchi and Piccinino (3), of which an account was published in 1893. These observers discovered a special bacillus in the blood and meninges of two cases. In the following year they reported the results of the examination of seven other cases in which they were able to confirm their previous observations (4). They concluded that there is a special form of acute delirium, to which they applied the name "Acute Bacillary Delirium," clinically distinguished by the greater intensity of the phenomena, by an adynamic phase which quickly succeeds that of excitement, and by the rapid course and fatal issue of the illness. Pathologically it was distinguished by the presence in the blood and nervous tissues of the special bacillus that they had succeeded in isolating. The only independent observer who seems to have been able to confirm these observations is Hitzig (6). Others have either obtained negative results, or have isolated organisms of a different character. Ceni (7, 9), who has certainly been one of the most able of the many investigators in this field, failed to find the bacillus of Bianchi and Piccinino in four cases presenting the special symptoms of acute bacillary delirium. From two of the cases he obtained cultures of the *staphylococcus pyogenes albus*, from the third the *staphylococcus pyogenes aureus*, and from the fourth a streptococcus and the *micrococcus tetragenus*. In another investigation, Ferrari (8) and he obtained cultures of various different organisms from the blood of seven out of eighteen lunatics in whom "the psychical disturbances agreed in some measure with the classical and characteristic picture of acute delirium." The organisms were staphylococci in two of the cases, and streptococci in the other five. The authors concluded that in such cases there were organisms in the blood only when fever was present, and that these organisms had no etiological value in relation to the mental disease. Recently Bianchi and Piccinino (5) have recorded observations upon two additional cases of acute delirium. The results obtained bear out their previous conclusions. In a third case, which recovered, they found only micrococci in the blood. They suggest that there may be a coccal form of acute delirium, as well as a bacillary form. Ceni (9) does not doubt the existence of the bacillary form of acute delirium described by Bianchi and Piccinino, although he has been unable to find the special organism in his own cases, and therefore has not had an opportunity of studying the disease. He maintains, however, that it is very probable that the various pathogenic organisms that are found in acute delirium do not represent more than a secondary auto-infection, which nevertheless may form a true and grave complication of the disease, influencing its course and issue. Very numerous other observers, including Batty Tuke (10) in this country, have isolated, either the same organisms as

those obtained by Ceni, or various other forms, from cases of acute delirium. At present there is no absolute proof that these organisms have in any instance a definite etiological relationship to this disease, but there are many grounds for believing that they have such a relationship in certain cases. It is well known that the toxins generated in the course of several of the specific fevers are capable in some people of causing maniacal symptoms, and it seems very probable that many other bacterial toxins, more especially when the organisms producing them are actually circulating in the blood, may, in pre-disposed persons, be capable of causing similar disturbance of the cerebral functions. The subject is one presenting many difficulties in the way of investigation, and will still require much patient observation for its complete elucidation.

The numerous observations that have now been made upon the composition and toxicity of the gastric juice, urine, and sweat in various forms of insanity, although in many respects contradictory in their evidence, and also the remarkable cures obtained by Marro (11) and others by the washing out of the stomach of patients suffering from acute mania, go far to confirm the opinion that this disease is often dependent upon auto-intoxication from the gastro-intestinal canal.

The conclusions recently formulated by D'Abundo and Agostini (12) regarding the rôle of intoxications and infections in the pathogenesis of nervous and mental diseases, representing as they do the present consensus of authoritative opinion among Continental neurologists upon this subject, may perhaps be fittingly quoted here :—

1. In the pathogenesis of nervous diseases in general, infections and intoxications are the most frequent, conspicuous and active element, and this at all periods of life, intra and extra-uterine.

2. An infective-toxic heredity (*e.g.* syphilis, alcoholism, etc.) favours in the descendants the development of infective-toxic nervous diseases with typical lesions.

3. Infections and intoxications in the parents, or in the mother during gestation, very often produce in the fœtus a most marked retardation in the process of myelinisation in the different systems of nervous connection.

4. Some of the degenerative neuroses are to be regarded as due to defective cerebral and spinal organisation, arising from intra-uterine toxic pathological processes that have been cured.

5. Infections and intoxications of the nervous system favour the development of secondary intoxications which feed, reinforce and complicate the clinical phenomena, and together produce the forms of disease due to poly-intoxication.

6. The action of infective-toxic agents can display itself in any part of the nervous system, leading to peripheral or central, systemic or disseminated localisation, and resulting in the acute or chronic neuropsychoses.

7. Mental confusion is merely the most frequent clinical type of infective-toxic action; other psychopathic types may also have a toxic origin.

8. Acute delirium may be regarded as a clinical manifestation caused by various infective-toxic agents.

9. Recent researches upon the etiology of general paralysis greatly strengthen the theory of its infective-toxic origin.

10. The clinical manifestations of infections and intoxications of the nervous system are the resultant of more or less profound nutritive disturbances, which at certain stages are capable of arrest, even when the symptomatology is such as to make us doubt the possibility of recovery.

The relation of simple auto-intoxication to the acute forms of insanity is a subject of great difficulty, and one about which very little of a definite character appears yet to be known. That this form of intoxication plays an important part in some cases is, however, now believed by many authorities.

I shall not enter upon the various physiological and psychological problems connected with the subjects of mania and melancholia, although I freely recognise that no discussion of the pathogenesis of these morbid conditions can be regarded as complete if it evades these problems.

There are now, I think, satisfactory grounds for regarding acute insanity as the expression of the action of toxic agents upon the cortical nerve-cells. This conclusion is supported by the results of the microscopic examination of the brain. It seems necessary to suppose, however, that in the person who suffers from an attack of acute insanity the cortical nerve-cells are in some way specially susceptible to the injurious influence of the toxins that are present, since, to all appearance at least, similar toxic conditions may occur in other individuals without producing either the same symptoms or the same anatomical lesions. This special vulnerability of the nerve-cell must, in the meantime, be looked upon as an inherent individual character. But, even if we take all this as proved, we are still a very long way from having a complete pathology of acute insanity. We have little more than a sound basis for further research. There are still innumerable problems that await answer. What are the various toxins that may determine an attack? When not simply introduced from without, where do they develop, and under what circumstances? Is their injurious influence upon the cortical nerve-cells continuous, or does it act simply as a spark that starts a conflagration? Is the hyperæmia of the cortex merely secondary to the nerve-cell lesions, or is it a primary effect of the toxæmia and a factor of essential importance in the production of the nerve-cell lesions? Is the defective resisting power of the nerve-cells a constant condition, or is

it only one that corresponds to a particular phase of a physiological periodicity? To these and a hundred other related questions there is as yet no definite answer.

Pathological Anatomy—(a) *Macroscopic*.—In the cases of acute insanity that I have had an opportunity of examining post-mortem, the most conspicuous morbid appearance has generally been intense local or general congestion of the cerebral cortex. In some cases of acute melancholia, evidence of congestion was, however, entirely absent (see p. 314). Some of the other abnormal features that have been present are slight general softening of the cerebral tissues, an abnormal yellow-grey tint of the cortex, and indistinctness of its layers. The pia-arachnoid has generally been slightly milky, but never markedly so.

Local atrophic softenings, of recent origin, have been found in some cases.

(b) *Microscopic*.—The dura mater and pia-arachnoid constantly show slight but distinct recent proliferative and degenerative changes in their endothelial elements. In the cases that I have examined there has always been evidence of an irritative action upon the intracerebral vessels in the form of some proliferation of the connective tissue corpuscles of the adventitia, and slight infiltration of the vessel-walls with leucocytes. But such changes have never presented themselves with the intensity that characterises them in advanced general paralysis and in the vascular form of syphilitic insanity. On the other hand, the morbid alterations in the cortical nerve-cells have always been exceedingly well marked. I therefore cannot agree with those who state that in acute delirious mania the recognisable changes are chiefly in the blood-vessels and perivascular spaces. The neuroglia may show an occasional hypertrophied element, but there is rarely any very distinct pathological alteration in this tissue. The changes that occur in the cortical nerve-cells are described at page 262, and are illustrated in plate xxviii.

Cristiani (13) and Crisafulli (14) have found that the spinal and cerebellar nerve-cells are affected to some extent, as well as those of the cerebral cortex; and Donaggio (15) has shown that systemic primary degeneration, both in the posterior and lateral columns of the cord, is of frequent occurrence.

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GENERAL PARALYSIS OF THE INSANE OR PARALYTIC DEMENTIA.

The pathology of general paralysis has probably been more extensively investigated than that of any other form of insanity. Very numerous important facts with regard to it have now been definitely ascertained, nevertheless the essential nature of the disease still remains in dispute. The subject is a vast one, and I can do little more than touch the fringe of it. I append a list of some of the more important publications that may be consulted by those who desire information upon the many points with which it is impossible for me to deal here.

Etiology and Pathogenesis.—Recent investigations have conclusively proved that general paralysis has a most important relationship to syphilis. Some authorities now go so far as to maintain that without previous syphilitic infection there can be no general paralysis. But the preponderance of authoritative opinion is still against the view that it is always and essentially a syphilitic, or "parasyphilitic," disease. Chronic alcoholism, lead-poisoning, and all causes of brain-irritation and exhaustion are generally admitted to be other important factors in its etiology. Hereditary predisposition to insanity does not appear to play an important part. It has been observed, however, that there is very commonly a family history of the occurrence of other forms of cerebral disease, such as apoplexy and allied morbid conditions.

Many different opinions have been advanced in explanation of the essential nature of the morbid process in general paralysis. The following are some of those that are still discussed:—

1. That the disease is primarily a chronic meningitis, or a chronic meningo-encephalitis.
2. That it is a chronic cortical encephalitis.

3. That it is a premature senility.
4. That it is primarily a hypertrophic change in the interstitial tissues of the brain, comparable to cirrhosis of the liver.
5. That it is primarily an irritative process in the arterioles of the pia and brain.
6. That it is primarily a degeneration of the nervous elements of the cerebral cortex.
7. That it is the result of a general toxic condition, which affects specially, but not exclusively, the cerebral tissues.

The old theory that the disease is essentially a chronic meningitis, which develops into a meningo-encephalitis, is now generally regarded as insufficient. The examination of early cases has clearly demonstrated that the signs of meningitis may be entirely wanting. Closely allied to this theory is the contention that general paralysis is a chronic cortical encephalitis. There can be no question that in the later stages of the disease there is, as a rule, abundant evidence of the occurrence of inflammatory changes in the cerebral tissues, but it is certain that many at least of these changes are merely of a secondary nature. Moreover, to regard the disease simply as a chronic encephalitis does not enlighten us much as to its essential nature. Modern pathology demands more precise information than is conveyed by such a term. The view that general paralysis is simply a premature senility is one that is now very widely taught. Even if accurate, it explains almost nothing regarding the essential nature of the pathological process, for the pathology of premature senile decay is still in dispute. The belief that the disease manifests itself primarily as a hypertrophic change in the neuroglia has been proved to be erroneous by studies with modern histological methods. The view that it is primarily an irritative process in the arterioles of the pia and brain, is that which is advocated in this country by Bevan Lewis (1). It is to be noted that he does not attach any importance to a cerebral capillary lesion.

In my opinion none of the theories just mentioned offers an adequate explanation of the essential nature of the morbid process in general paralysis. Only the last two in the above list need at the present day be seriously discussed.

The view that general paralysis is primarily a degeneration of the nervous elements of the cerebral cortex was first advanced by Tuzcek (2), who directed attention to the extensive destruction of the medullated fibres of the cortex. Its more recent supporters, of whom there are now a very large number, naturally speak rather of the degeneration of the cortical neurons. As is well known, this view of the pathology of general paralysis has lately been very strongly advocated in this country by Dr Mott (3-6). In essential opposition to at least one form in which this view is maintained, there is another which

is now also advocated by a considerable number of neurologists, but which has probably received its most able exposition from Angiolella (7). According to this authority, the disease is the result of a general toxic condition, which leads primarily to morbid changes in the small cortical arterioles and capillaries, although at the same time the nerve-cells may be affected by the toxic agents. But the alterations in the nerve-cells and neuroglia are, for the most part, the consequence of the alterations in the vascular walls. Many others maintain this toxic theory in a more general sense, hesitating to regard the implication of any single cerebral tissue as of primary importance.

It is certain that neither of these two hypotheses regarding the essential nature of general paralysis has as yet been definitely proved. It is possible that both are wide of the truth, and that the real nature of the disease has still to be discovered. But as they are unquestionably at present the two most important theories regarding the pathology of this disease, it may be well to examine them in some detail here.

I take the theory of the primary degeneration of the neuron as stated by Mott, who has certainly been its strongest exponent in recent years. He says (3): "In general paralysis there exists a primary progressive decay of the nerve-cell which ontogenetically and phylogenetically may be looked upon as a regressive metamorphosis, a degenerative process which starts in the highest and latest phylogenetically developed structures, *e.g.* the centres of verbal and written speech; the molecular layer with the tangential system of fibres and the association systems of the frontal and parietal lobes. This premature decay of the highest controlling structures is progressive and cumulative, it causes phenomena of irritation, manifested by mental and physical symptoms, such as motor irritation, with rise of blood pressure, cerebral anæmia and venous stasis, local and general auto-intoxication respectively by products of degeneration and imperfect metabolism. A vicious circle is established which continually is enlarging." He further states that general paralysis "is a primary decay of the neuron itself with secondary inflammatory changes affecting the vessels, lymphatics and membranes, due to irritation of the products of degeneration." In another paper (4) he says: "The nervous units decay and die because they are unable to assimilate from the lymph environment the material necessary to repair the waste occasioned by the bio-chemical changes incidental to their aroused vital activities. The morbid process is essentially one of defect of specific vital energy of the neuron itself, although subsequently vascular complications may arise which lead to traumatic death of neurons and establishment of a vicious circle" In the same paper he describes the disease as "essentially a parenchymatous degeneration due to loss of durability of the nerve-cells—a premature

decay of tissue in which inherited and acquired conditions take part with the result that progressive decay of the latest and most highly developed nervous structures ensue as soon as their vital energy is unable to cope with the antagonistic influences of environment." He further maintains (5) that locomotor ataxia and general paralysis are one and the same morbid process affecting different parts of the nervous system. "They are both a primary and progressive decay of the nervous elements, and are etiologically, clinically, and pathologically related."

It will be seen from these quotations that Mott maintains this theory in a somewhat special sense. He regards general paralysis as essentially the result of a premature failure of the specific vital energy of the higher cortical neurons, while locomotor ataxia depends upon a similar failure on the part of the sensory protoneurons. Some other writers regard the primary degeneration of the neurons simply as the result of the direct action of toxins circulating in the blood, which is a different thing from a primary decay owing to exhaustion of their specific vital energy.

There are, in my opinion, many serious objections to the acceptance of this view, more especially in the form in which it is advanced by Mott. But I think that it is absolutely necessary to recognise that the same may truthfully be said of each of the other theories that have been advocated. The pathogenesis of general paralysis has not yet been sufficiently elucidated to justify any dogmatic statement being made with regard to it. All that is permissible in the present position of knowledge is to put forward what one considers to be the most probable hypothesis and to endeavour to point out how the known facts support it. This, I take it, is precisely what the distinguished director of the Claybury Laboratory has done with respect to the view that he has so ably championed. My own studies upon the subject incline me to regard the auto-toxic theory, in the special form in which it was advanced by Angiolella in 1894, as the hypothesis in favour of which the strongest case can at present be made out.

It is to be observed, in the first place, that Mott does not adduce any direct evidence in favour of his contention that the cortical neurons are the first elements to be affected in general paralysis, such as ought to be obtainable from the study of the nerve-cells in early cases of the disease; he argues indirectly from other considerations, many of which are purely of a clinical nature. One of the facts upon which he has laid special stress is the unquestionably close relationship of the disease to tabes dorsalis. To my mind this clinical fact, instead of supporting his thesis, furnishes an argument of some weight against it. There may, as yet, be no evidence that serves to exclude the possibility that general paralysis is essentially a premature failure

of the specific vital energy of the cortical neurons, but there is proof that tabes does not depend upon a similar morbid condition of the sensory protoneurons. It is now a well recognised fact that the nerve-cells in the posterior root ganglia, which are the trophic centres of these neurons, are not necessarily affected by morbid change in the latter disease. Mott admits that this is so, but does not see that he thereby gives his case away as regards tabes. A disease in which the trophic centres of a set of neurons remain essentially intact, cannot depend upon a failure of the specific vital energy of these neurons. The portion of the sensory protoneuron that undergoes degeneration in tabes is that which lies within the spinal cord. It has been proved that destruction of this central prolongation of the spinal ganglion cell is not followed by degeneration of the whole cell, as generally occurs after destruction of its peripheral prolongation. Lugaro (9), who was the first to demonstrate this important fact, has gone very fully into its bearing upon the pathology of tabes dorsalis. He recognises in this disease the action of a toxin upon the sensory protoneurons, which tends specially to implicate their central branches, and he finds in the results of his experimental observations an explanation of why such local action should not be followed by degeneration of the cell-bodies in the spinal ganglia. Whatever the precise cause of this degeneration of the central prolongations of the spinal ganglion cells may be—whether it is the direct action of toxic agents as many suppose, or the indirect action of such agents, through inflammatory changes in the membranes, which lead to constriction of the posterior roots at their point of entrance into the cord, as Obersteiner, Bruce (10), and others maintain—the lesion certainly cannot be regarded as a premature decay of these elements from failure of their specific vital energy, and it therefore seems to me that the very fact that tabes is in some way closely allied to general paralysis, is presumptive evidence against the theory that the latter depends upon a like defect of certain of the cortical neurons.

Further, Mott's statement that the vascular and neuroglial changes in the cerebral cortex result from the action of irritative products, formed in consequence of the degeneration of the nerve-cells, seems to me to be contradicted by certain well-established facts. For example, experimental secondary degeneration of intra-spinal and cerebral nerve-cells is not attended by irritation of the neighbouring vessels and neuroglia; and in many cases of acute mania there is a far more rapid destruction of cortical neurons than in general paralysis, but no corresponding irritative changes in the surrounding tissues. He regards the nerve-cell lesion as primary, and the vascular lesion as secondary to it. In support of this view, he mentions that he has found that wherever the degeneration of the nerve-cells is most ad-

vanced, so also are the vascular lesions. This anatomical fact is well known, but from many it has received an exactly converse interpretation, which he does not show to be untenable.

The theory that general paralysis depends upon a general toxic condition, which specially implicates the small vessels of the nervous system, is summarised by Angiolella (7) as follows:—"It appears that the anatomico-pathological process at the root of general paralysis is the effect of toxic substances circulating in the blood, which are either products of syphilitic infection, or certain special poisons, such as alcohol, nicotin, etc.; or substances which, perhaps, are produced in an organism thereby debilitated, in consequence of excessive work on the part of the nervous system. . . . The point in which the anatomical process appears to begin is the vascular system, and the interstitial and parenchymal alterations are the consequence of the vascular lesions. In part, however, the nerve-cell degeneration may be produced directly by the action of the toxins circulating in the blood. The process is diffused throughout the nervous system, although it appears that in individual cases some parts of it are involved in preference to others." With regard to the exact nature of the vascular lesions, he considers that there are to be distinguished—(a) An endo- and peri-arteritis syphilitica, which specially affects arterioles and capillaries, and is diffused throughout the nervous system, in which it leads to interstitial and parenchymal alterations; and (b) an endo- and peri-arteritis, which has the same site, diffusion and anatomical form, and which is followed by the same lesions, but is due to other etiological factors. He has found (8) that the outer walls of the renal arteries, hepatic arteries and hepatic veins constantly show inflammatory changes, in the form of a round cell infiltration, and maintains that this observation confirms the hypothesis that the primary cause of the morbid process in general paralysis is a toxic condition of the blood.

The theory that the disease depends upon a general toxic condition is also maintained by numerous other authorities. It has been very ably advocated in this country by A. W. Campbell (11), whose conclusions on the subject are based largely upon the results of original observations, which have been independently confirmed by several Continental workers. Campbell (12) thinks, however, that it is absurd "to wrangle over the point of attack of the poison, for its ubiquity renders judgment impossible." Macpherson (13), also adopts a similar theory, maintaining that general paralysis is "due to toxins, the result of auto-intoxication from previous infection of the system by syphilis or other poisons."

It is certain that the morbid tissue-changes in general paralysis are of wide distribution, and that they may implicate practically the entire

nervous system, and also the non-nervous organs. Some of these changes are doubtless secondary to the alterations in the cerebral cortex, but many of them cannot be satisfactorily explained in this way. There is a steadily increasing mass of direct and indirect evidence in support of the view that a general toxic condition is at the root of the disease. As already indicated, according to my own observations the changes that occur in the brain can be most satisfactorily explained upon this hypothesis. Further, I agree with Angiolella that special importance is to be attributed to the capillary lesion that occurs in the cerebral cortex. It is naturally difficult, and probably with the present available histological methods impossible, to determine precisely by microscopic examination whether the vessels or the nervous tissues are the first to be affected by the action of the toxins. The latter tissue-elements are so sensitive to many different toxic agents that it is highly improbable that any poison could act upon the capillaries and not at the same time directly influence the adjacent nerve-cells in an injurious manner. The early cases that I have had an opportunity of examining show an apparently simultaneous implication of both tissues. In such cases the capillary change consists in proliferation of the cellular elements of both intima and adventitia, or in hyaline or slightly granular swelling of the wall, the one being the proliferative and the other the degenerative phase of the same lesion. Only a limited number of capillaries are distinctly affected, but at the same time the lesion is widely distributed throughout the cortex. The short vessels of the first layer are among the earliest to suffer. The alteration in the nerve-cells is a primary degeneration, which affects only a small percentage of cells in a distinct form. We cannot in the meantime, I think, entirely exclude the possibility that this lesion is in a large measure the result of a terminal auto-intoxication. The capillary lesion is probably not merely secondary to the nerve-cell degeneration, because a similar capillary change neither attends nor follows the extensive degeneration of the cortical nerve-cells that occurs in many cases of acute mania, nor does it follow secondary degeneration of nerve-cells experimentally produced. On the other hand, there is conclusive evidence that it is capable of being set up by a toxic condition of the blood. Although it must be admitted that the circulating toxins may have a direct action upon the cortical nerve-cells, I am strongly inclined to think that such direct action plays only a minor part in the pathogenesis of general paralysis. The histological study of the brain at all stages of the disease has confirmed me in the belief that the one essential tissue-alteration in general paralysis is the capillary lesion just described. It can be demonstrated in a large number of cerebral capillaries in the earliest cases of general paralysis that can be examined. In advanced stages

of the disease it is constantly a wide-spread and severely marked condition. Strong evidence can be produced in support of the view that, as it spreads throughout the cortex, it is followed by, and directly induces, the morbid changes that occur in the nervous elements and in the neuroglia. That so many observers have failed to recognise the important extent to which the capillaries are involved in general paralysis is scarcely surprising, for the histological methods at present most in use do not satisfactorily serve to reveal the lesion in question. The methods which I have hitherto found of most service for this purpose are the fresh aniline black method of Bevan Lewis and my own methyl violet method. The platinum method also occasionally serves to reveal its presence in a striking manner.

In connection with this subject it is to be borne in mind that the capillaries of the central nervous system are peculiar in structure. Not only do they, unlike the capillaries of most other organs, possess an adventitial coat, but the fibres of which this coat is composed, consist of an elastic tissue, differing both from ordinary white fibrous tissue and from ordinary yellow elastic tissue. There is strong evidence that in various different toxic conditions the capillaries of the central nervous system are prone to undergo degenerative changes, while those of other organs escape. I maintain that the true explanation of this remarkable selective action is to be found in the fact of this higher structural differentiation. The capillaries of the central nervous system have acquired their special strength and elasticity at the cost of a peculiar vulnerability to the action of certain toxins. This fact explains why the toxæmia of general paralysis specially implicates the central nervous system. It may be more difficult to understand why the capillaries of the frontal and central convolutions should be specially liable to involvement, but many possible explanations could be suggested.

It can be shown that the cerebral vessels are more or less distinctly altered in structure throughout their whole course. The lesion of the cerebral capillaries acquires its special importance from the fact that it is through the walls of these vessels that there take place those processes of filtration and diffusion by which the nutritive materials are brought to the special cerebral tissues, and the effete products of metabolism in part conveyed away. These processes cannot be carried on in a normal manner through structurally altered capillary walls, and hence the nerve-cells and neuroglia undergo morbid changes. Those who, like Bevan Lewis, attribute the parenchymal changes simply to an irritative process in the arterioles of the pia and brain, and attach no special importance to the capillary lesion, miss what is probably one of the most important facts in the pathogenesis of general paralysis. As far as my own observations go, round cell infiltration of

the adventitia of the cerebral arterioles is a non-essential and generally late occurrence. It is always localised. On the other hand, proliferative or degenerative changes in the intima, are present from an early period of the disease, and soon become generalised. They are accompanied by similar changes in the adventitia, which are to be distinguished from the round cell infiltration that marks the occurrence of acute periarteritis.

I would summarise what appears to me the most probable hypothesis regarding the pathogenesis of general paralysis as follows. The disease depends upon the occurrence of a general toxic condition, the exact nature of which is still obscure, but which is certainly in many cases the result of antecedent syphilitic infection. The first important effect produced by the toxins is a proliferative and degenerative change in the walls of the vessels of the central nervous system, including those of the capillaries of the cerebral cortex. This alteration in the capillary walls interferes in various ways with the nutritive exchanges between the blood and the cerebral tissues. Consequently the adjacent cortical neurons undergo primary degeneration, and the neuroglia also tends to suffer certain morbid alterations. At the same time these tissues are to some extent affected directly by the toxic agents circulating with the blood.

The reaction of the neuroglia is not constant, consisting sometimes in an atrophic change, and sometimes in more or less active hyperplasia. In the great majority of instances, such hyperplasia is very well marked in the outermost layer of the cortex. As the morbid alterations progress and extend, it is probable that the action of the circulating toxins, and the disorder of cerebral nutrition depending upon the capillary lesion, are in some degree reinforced by toxic agents developed as the result of the altered metabolism and the disintegrative changes occurring especially in the nervous tissues. From an early period the cerebral lymph, in consequence of the above enumerated morbid conditions, is altered in composition, so that it becomes unsuitable for the healthy nutrition of the tissues which it bathes. Hence the walls of the lymphatic channels within the brain, in the pia-arachnoid, and in the dura, undergo proliferative and degenerative changes which gradually lead to more or less complete obstruction to the outflow of the lymph. This obstruction probably gives rise to some derangement of the cerebral circulation in the manner already explained (pages 308 and 317). It also leads to the retention in the cerebro-spinal fluid of the products of cerebral metabolism. From these various causes the morbid process gradually tends to increase in intensity, until in the later stages of the disease it assumes a distinctly, and even acutely, inflammatory character.

Pathological Anatomy. (a) *Macroscopic.*—In advanced cases, the

calvarium is practically always more or less condensed, and at the same time thickened (see page 68). The dura mater is often firmly adherent to the skull. It is constantly thickened (p. 78), and is generally congested. On its inner aspect there is almost always discernible some distinct morbid alteration, consisting, in its slighter manifestations, in the presence of minute granulations, or of yellow or rusty staining. Subdural false membranes are more common in this disease than in any other. The pia-arachnoid is always more or less thickened and milky (p. 122), and the outer surface generally presents numerous minute granulations (p. 123). If a portion of the membrane is stripped off from the cerebral cortex, a lacerated surface is often left at the summits of certain of the convolutions (p. 128). The large cerebral vessels almost constantly show milkiness of their adventitia, and frequently distinct, but slight, diffuse thickening of the intima. In advanced cases the brain is always much atrophied, more especially in its anterior half. Its weight is generally several ounces below the average. The cerebro-spinal fluid is always greatly increased in amount. The lateral ventricles are commonly somewhat dilated. Their walls, as well as the floor of the fourth ventricle, are in most instances studded with fine granulations. On section the brain is always more or less cedematous and abnormally soft in consistence. It is generally congested, often extremely so, but may be anæmic. The cortex especially tends to show deep, often irregular congestion. It is, at the same time, narrow and of an abnormally dark colour, frequently having a peculiar slaty tint. Its layers are generally indistinguishable. Areas of atrophic softening are very common especially in the cortex (p. 333). Recent hæmorrhages into the brain, or into its soft membranes, are frequently to be observed.

(b) *Microscopic*.—The changes that occur in the dura and pia-arachnoid are fully discussed in chapters v. and vi. The arterial and capillary lesions are described at pages 156 and 143, and the nerve-cell changes at page 262. The results of my observations upon the condition of the neuroglia have also already been stated (p. 185). Dr John Macpherson (13), in his recent work, has in error attributed to me the assertion "that in about two-thirds of all cases, excepting the subpial increase of Deiter's cells, there is no marked change in the neuroglia." He very naturally questions the accuracy of this observation. The passage in my paper in the *Edinburgh Hospital Reports* to which he refers, is reproduced on pages 185, 186, under *General Paralysis*, and a comparison of it with the above quotation will show at once that I did not put the matter nearly so strongly. I recognise that there are distinctly marked hypertrophic and proliferative changes, both in the cortex and white matter, in the large majority of cases.

In sections of the cerebral cortex, stained with basic dyes, there is

generally to be observed a very decided increase in the number of small dark nuclei throughout the tissues. This appearance is commonly attributed to an emigration of leucocytes from the vessels. Two of the highest authorities upon questions of neuro-histology have, however, lately denied that leucocytes are to be found beyond the vessel-walls in the brains of general paralytics. If this observation is correct, these nuclei must represent only proliferated neuroglia cells, mesoglia cells, and corpuscles of the capillary adventitia.

The medullated nerve fibres of the cortex, but more especially those of the outermost layer, are generally extensively destroyed in advanced cases.

Whilst these morbid changes are usually most pronounced in the frontal and central convolutions, they implicate, in some measure, practically the whole encephalon.

There are very commonly, but by no means constantly, well-marked degenerative changes in the medullated tracts of the spinal cord, but opinion on the subject is still much divided. Some observers assert that there is frequently a lesion of the posterior columns exactly corresponding to that which occurs in tabes, while others doubt the identity of the two. There is more general agreement with regard to the statement that there is usually some degeneration of the pyramidal tracts, more especially in cases in which there have been convulsive seizures.

Vascular and nerve-cell changes, similar to those that occur in the brain, have been found in the sympathetic ganglia.

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SYPHILITIC INSANITY.

Syphilis is now recognised to be one of the commonest and most important causes, not only of nervous diseases in general, but also of insanity. It is probably the most potent factor at present in operation in the production of racial degeneration, and hence of congenitally defective nervous organisation and predisposition to mental disease. It is also the chief determining cause of a very considerable proportion of cases of acquired insanity. Our Continental neighbours seem for long to have been aware of these facts, but it is only within the last few years that alienists in this country have been fully awakened to them, thanks chiefly to the extensive and precise investigations upon the subject that have been carried out by Dr Mott. This authority (1) maintains that from the pathological standpoint syphilis may operate in two ways as a factor in the production of insanity. "Firstly, the poison may produce a specific inflammatory process affecting the membranes and blood-vessels of the central nervous system, either of which may be affected separately or together. The process may be local or general. The inflammatory process may produce direct irritation or destruction of the nervous elements, the blood-vessels may be partially or completely occluded, and the effects on function will depend on the extent of the process. The inflammatory process may also give rise to neoplastic growths, which may undergo regressive metamorphosis in the older parts (gummata), but all the processes are pathologically identical, and it may be observed that there is really no absolute specific character about them, yet experience has taught us that the lesions are pathognomonic of syphilis."

"Secondly, syphilis, whether acquired or inherited, may lower the specific vital energy of the component cells of the body as a whole, or the cells of particular tissues or organs."

He further states that in his experience of cases upon which an autopsy has been performed, all of the various manifestations of syphilitic brain disease—namely, basic meningitis, meningitis of the convexity, cerebro-spinal meningitis, arteritis and neoplastic formations and encephalitis—are combined in the severe and early forms of the disease.

For full information regarding the occurrence of these morbid alterations and the various appearances that they present, I would refer the English reader to the easily accessible papers of Mott (1, 2), Mickle (3), Dawson (4, 5), and Welsh (7), in which numerous references will also be found to the foreign literature upon the subject.

Clouston (6) recognises four chief forms of syphilitic insanity, namely :—

1. Secondary syphilitic insanity.
2. Delusional syphilitic insanity.
3. Vascular syphilitic insanity.
4. Syphilomatous insanity.

Dawson (5) has lately suggested another classification, in which the parasymphilitic affections are included :—

- I. *Insanity of early syphilis (primary and secondary).*
 1. Acute toxic insanity (analogous to delirium or *mania a potu*).
 2. Melancholia with or without dementia, probably due to cerebral anæmia.
- II. *Insanity of late (tertiary) syphilis.*
 1. Insanity due to syphilitic disease of the base and vessels.
 2. Insanity due to syphilitic disease of the convexity.
- III. *Metasyphilitic (parasymphilitic) insanity.*
 1. Insanity of tabes (so far as due to other than "moral" causes).
 2. General paralysis of the insane.

Several authorities have denied that insanity is ever caused by syphilis in its primary and secondary stages, but so many cases of the kind have now been described by competent observers, that there appears to be ample warrant for the first division of the two foregoing classifications. We may provisionally regard such cases as the result of the direct action of the syphilitic poison upon cortical nerve-cells of persons with a strong predisposition to mental disease.

In the insanity of tertiary syphilis the functional disturbance in the cortical nerve-cells is chiefly secondary to narrowing and occlusion of cerebral arteries by endarteritis obliterans, and to the mechanical and other effects of gummatous and meningitic lesions. The pathogenesis of parasymphilitic affections has already been discussed in the preceding section.

Apart from the last named conditions, which it is still doubtful if we are entitled to include among the syphilitic insanities, the most common and important cases appear to be those that are dependent upon the occurrence of endarteritis obliterans of the cerebral vessels. The microscopic characters of this vascular lesion have been described on page 156. The associated intra-cerebral changes (excepting the extensive softening resulting from the thrombosis that commonly

determines death) are usually slight, but have certain characters of special interest. In each of the three cases of this kind that I have had an opportunity of examining, there was a slight but distinct infiltration of the adventitia of the arterioles with round cells, that is to say, an acute periarteritis similar to that found in advanced general paralysis. In each case there were also to be observed, scattered throughout the cortex, a few hyaline capillaries presenting the same features as the thickened capillaries so characteristic of general paralysis. The neuroglia changes were slight, consisting in a moderate degree of hyperplasia in the first layer in all three cases, and of a similar condition in the white matter of one. According to the evidence of these three cases, the intra-cerebral vascular lesions associated with endarteritis obliterans of the large cerebral arteries do not differ from those of general paralysis in their form, but only in their extent. It is further to be remarked that in some cases of vascular syphilitic insanity the inflammatory change in the intima is exceedingly acute, and the new formation of tissue very rapid. In others this morbid process is comparatively very slow. In most cases of general paralysis it may be observed that there is slight new formation of tissue in the intima of the large cerebral arteries and pial and intra-cerebral arterioles. The cerebral vascular lesions in these two diseases would therefore appear to form a continuous series. On these and other grounds, I am strongly inclined to believe that the vascular form of syphilitic insanity and general paralysis of syphilitic origin are pathologically very closely related to each other, and that they blend at their confines. Both are determined by a toxic condition which develops as a result of previous syphilitic infection; the differences in the site and intensity of the vascular changes may depend upon certain special characters of the toxæmia, or merely upon the individual reaction.

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SENILE INSANITY.

The pathology of the mental disorders that arise during the period of senile involution presents many complex and still obscure problems. Moreover, the gross and minute changes that have now been observed in the nervous system of persons who have suffered from such disorders, are exceedingly numerous and varied in character. The subject is therefore an extremely large and difficult one. Only the merest outline of it can be sketched here. For fuller information, more especially regarding the question of pathogenesis, I would recommend the reader to consult the papers of Clouston (1 and 2) and Verga (4).

Etiology and Pathogenesis.—Physiological senile involution is a process of which the exact nature and significance are still in dispute. Some authorities regard it as consisting merely in a gradual failure of the vital energies of the tissues, more especially of those composing the central nervous system. Others maintain that it is largely the expression of a chronic auto-intoxication, due to the gradual failure and perversion of the functional activity of various organs and tissues. In the present position of knowledge, it is probably impossible to determine definitely which of these two views contains the greater element of truth. Microscopic investigation throws considerable light upon the matter, but with the present available means of observation cannot settle all the points at issue. The most healthy senile brains that can be obtained show very numerous abnormalities. The physiological regressive changes in the nerve-cells, which are always present in such cases, have already been described (pp. 226-227). That they can be correctly regarded as physiological is, of course, somewhat doubtful. Various vascular and neuroglial changes are also constantly present. Many of the capillaries of the first layer of the cortex show distinct hyaline fibroid thickening; the same morbid change is always recognisable, though it may be only slightly developed, in the pial and intra-cerebral arterioles and venules. The neuroglia of the first layer always shows some degree of hyperplasia.

The constant presence of distinct vascular lesions appears to me very strongly to favour the auto-toxic theory of normal senile involution. If such auto-intoxication is really an important factor in the process, then the slow degeneration of the nerve-cells cannot be regarded as simply the expression of the natural failure of their trophic energy, but must be looked upon as, in part at least, a true primary degeneration of toxic origin.

In many aged persons who have died in general hospitals from acute diseases that could not have produced lesions that are essentially of slow development, these same tissue-changes may be observed in a

much more marked form. These patients probably in some instances showed distinct mental symptoms. They at least form a pathological link between uncomplicated senility and senile insanity. In each of the three types the same kind of histological changes can be observed; the essential difference consists only in the severity of the lesions, which in senile insanity may proceed even to extensive destruction of tissue.

It is therefore probably accurate to regard senile insanity as representing "a special intensity or irregularity in the physiological decay of the brain" (Clouston, 3). It is right to state, however, that this view is not accepted by all authorities. Verga (4) has eloquently protested against the statement made by some that "the natural end of man is the asylum," and has insisted that physiological senile involution—regarding the nature of which he would appear to maintain the first of the two theories mentioned above—cannot pass into insanity. He contends that senility is not a cause of insanity, and that when mental disease does occur in old age it is determined by other factors. It seems to me that this view would be perfectly tenable if a distinctly senile brain could be produced in which the effects of auto-intoxication, as evidenced by irritative and degenerative changes in the walls of the vessels, could be shown to be entirely absent. Until then, I think, we are logically bound to admit that normal senile involution is associated with auto-intoxication, and that senile insanity essentially represents a more intense, and in some respects irregular form of the same condition, although, no doubt, additional factors are often added.

In typical cases of senile insanity, the evidence in support of the essentially auto-toxic nature of the pathological changes is, to my mind, absolutely conclusive. Indeed I would regard senile insanity as the best example that we have of mental derangement determined by auto-intoxication. The kidneys are cirrhotic; the liver is atrophied, or shows some other form of chronic morbid change; the lungs are often emphysematous, or present evidence of chronic congestion; there is frequently chronic bronchitis; the stomach is commonly dilated and there are generally signs of imperfect intestinal action. All of these morbid conditions of the internal organs imply incomplete and perverted metabolism, and consequent auto-intoxication. One of the results of this auto-intoxication is chronic irritation and mal-nutrition of the vascular walls, of which there is always abundant evidence in various parts of the body. The cerebral arteries, arterioles, capillaries and venules are always more or less severely implicated. The two chief forms assumed by this vascular disease are endarteritis deformans (p. 144) and hyaline fibroid degeneration (p. 140). They lead to gradual narrowing of the lumen of the affected vessels, to obstruction of the intra-adventitial lymph-channels, and to obliteration of many

of the capillaries and small arterioles. Hence the nervous tissues are imperfectly nourished and undergo degenerative changes; where the vascular lesions advance so far as to cause obliteration of the lumen, actual death of the nervous tissues takes place and atrophic softenings are produced. Further, the vascular disease may lead to the occurrence of hæmorrhages of small or large extent, and also to embolism and thrombosis of capillaries and arterioles. The intracranial lesions may become of such extent as to determine death, but more commonly derangements of the abdominal and thoracic viscera are immediately responsible for this event.

I regard both senile insanity and general paralysis as dependent upon chronic auto-intoxication, which in the case of the latter would in very many instances appear to be in some way brought about by antecedent syphilitic infection. As is now well recognised, there are some cases of supposed senile insanity in which the cerebral tissue-changes are practically identical with those in a typical case of advanced general paralysis. Distinct capillary thickening, instead of being general only in the first layer of the cortex and merely local in the other layers, is diffused throughout the cortex, and is at the same time attended in a greater or smaller measure by the marked neuroglia hypertrophy and extreme degeneration of nerve-cells that usually accompany this capillary change in general paralysis. I have now seen several cases of this kind. Clinically they were regarded as cases of senile insanity. Histologically they were examples of general paralysis. It may be that in such cases there has been syphilitic infection, but it is not necessary to suppose so. The similarity of the pathological picture to that presented by general paralysis may be accounted for simply by an unusual intensity of the auto-intoxication. Indeed I think that the fact that general paralysis and senile insanity thus merge with each other at their borders, is evidence of some weight in support of the contention that general paralysis is not exclusively a parasymphilitic disease.

Pathological Anatomy. (a) *Macroscopic.*—The skull is commonly thickened, and either sclerosed or softened (pp. 67, 68). The dura is very often morbidly adherent to the calvarium; granulations, rusty staining and false membranes are common upon its inner surface. The pia-arachnoid over the convexity of the cerebral hemispheres is always thickened and milky, and often contains numerous opacities; its surface generally presents very abundant minute granulations; the membrane strips off readily, and without any laceration of the convolutions, except in rare instances. The large cerebral arteries are generally atheromatous, often extremely so; in some cases, however, they present little change that is appreciable with the unaided eye. Localised opacity of the pial arterioles from atheromatous disease is

often recognisable in various situations; in such cases, minute dark red points, representing true and pseudo miliary aneurisms, may not infrequently be recognised. Very occasionally they occur in large numbers. The whole brain is generally distinctly atrophied, more especially in its anterior half, and the sulci appear wide. There is at the same time corresponding increase in the amount of cerebro-spinal fluid, especially in the subdural space and lateral ventricles. The brain weight is commonly several ounces below the average. On section, the cerebral substance presents various morbid appearances. The cortex is generally somewhat narrowed and its layers indistinct. To its normally warm grey colour there is always added a distinctly yellow tint. The surfaces of the lateral and fourth ventricles are commonly slightly granular, occasionally very markedly so. Atrophic, hæmorrhagic or embolic softenings are present in over 40 per cent. of cases. They are described in chapter xiii. Miliary aneurisms, having an appearance similar to those that may be seen in the pia-arachnoid, may occasionally be observed. The condition of *état criblé* is very common (see page 159).

(b) *Microscopic*.—The histological changes that occur in the brain and its membranes have already been described in preceding chapters. The vascular lesions are especially dealt with in the sections commencing on pages 138, 140, 144, 149, 154 and 159. The morbid changes presented by the neuroglia are described on page 186, and those that affect the nerve-cells on page 262.

In addition to the various gross lesions already referred to, minute atrophic softenings, or sclerotic areas representing old softenings, can be discovered, both in the grey and in the white matter, by microscopic examination in practically every case. Occasionally they are very numerous. As already contended (p. 188), these microscopic atrophic areas are different from the condition that has been described as "miliary sclerosis," which in its typical form is an artificial production.

The medullated nerve fibres of the brain always show extensive degenerative changes. There is evidence that many of them have disappeared.

These morbid alterations are not confined to the cerebrum. They affect practically the whole of the central nervous system. Slight diffuse sclerotic changes in the spinal cord are exceedingly common. A senile peripheral neuritis has been described.

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CHRONIC ALCOHOLIC INSANITY.

Alcoholic insanity is generally regarded as divisible into the following five chief forms (Clouston):—

1. Acute alcoholism, or delirium tremens.
2. Chronic alcoholism.
3. Mania a potu.
4. Dipsomania.
5. Alcoholic dementia.

Only the second and last of these are considered here. The pathology of alcoholism in general will be found very fully discussed in the works enumerated at the end of this section.

Etiology and Pathogenesis.—There are, I think, three great factors that it is necessary to recognise in the pathogenesis of chronic alcoholic insanity, namely (*a*) the direct toxic action of alcohol, (*b*) a secondary auto-intoxication, and (*c*) the special reactive qualities of the individual brain.

It has been clearly proved that alcohol acts directly and specially upon the neurons, and that it is capable of producing rapid and severe morbid alterations in their structure. When its action is experimentally pushed to near its lethal point, a certain number of the cells suffer degenerative changes of so profound a nature that they cannot recover in any measure, and consequently they atrophy and disappear. But alcohol does not act upon the nervous tissues alone. It probably leaves no organ in the body unaffected. Its long continued excessive use leads to grave structural alterations, more especially in the kidneys, liver and stomach, and hence after a time a state of auto-intoxication is established, which tends gradually to increase in severity, although up to a certain stage it seems to be capable of arrest by removal of its original cause. This secondary auto-intoxication, which is really of the utmost importance in the pathogenesis of chronic alcoholic insanity, is a factor which seems to have been lost sight of by most writers upon the subject. The third factor, the special reactive qualities of the individual brain, would almost appear to have more essential importance in this form of mental disease than in any other. The

very wide differences in the effects both of the occasional and the prolonged action of alcohol upon various individuals is, unfortunately, a matter of common observation. The special liability of certain brains to be progressively damaged by this particular toxin, probably depends upon various forms of inherent weakness, but microscopically it manifests itself in a comparatively feeble resistiveness or special vulnerability of the neurons.

On the ground of now clearly established facts regarding the general pathology of the nerve-cell, and of personal observation upon the human brain, I affirm that no man with such inherent feeble resistiveness of his nervous system can indulge in alcohol to the extent of suspending for a time the normal functional activity of his higher nerve-cells, without suffering the total destruction of thousands of these tissue-elements. To use a simile already employed in a previous chapter, in such persons the action of alcohol upon the nerve-cells may be likened to the effect of a storm sweeping over a great forest. While the storm rages, every tree bends before it, and, as it were, struggles to ward off its attack. When the storm has passed, the forest may seem on distant view to be very little changed in its general appearance; but, if a walk is now taken through it, one observes that, while most of the trees have suffered no apparent damage, very many of them have had branches broken off, and that here and there a giant or a sapling has been uprooted and destroyed. So also it is in the case of the nerve-cells; all of them are temporarily affected by the alcoholic storm; the vast majority successfully weather it; but certain of them, somehow placed at a disadvantage as compared with the others, yield before the blast; degenerative change has proceeded beyond those limits within which repair can still take place; speedy death and subsequent removal are their inevitable fate.

This complete destruction of large numbers of the cortical neurons by the direct action of the toxic agent, is the first great fact in the pathogenesis of chronic alcoholic insanity. Each successive drinking bout implies the death of more of these elements, just as the next gale causes further damage to the forest. But at one important point the simile breaks down. Young trees may grow up and take the place of those that have been destroyed. But in the case of the nerve-cells there can be no such substitution (see page 238). There are no units held in reserve to step into the place of those that fall in the fight; all that is possible is a closing up of the ranks.

It is very probable, and indeed may be regarded as certain, that injury to protoplasmic and collateral branches has some importance in the production of functional defects and disturbances. But the methods at present available for the detection of such partial damage are in-

sufficient for its satisfactory demonstration, or, at least, for the clear distinction of it from other partial alterations that are of totally different significance (see pages 248-250 and 258). Moreover, there are the strongest reasons for believing that when acute primary degeneration does not pass that stage, which when overstepped is fatal for the element, the nerve-cell possesses a remarkable power of recuperation, being able even to throw out new processes and to re-establish broken connections. It is further true that there are certain permanent structural alterations in the cell-bodies, which must have an influence upon the symptomatology of the disease. But to endeavour to find the sole explanation of the phenomena of chronic alcoholic insanity in such partial degenerations of the cortical and other neurons, as some have lately done, is to miss the most important fact in the pathology of this form of mental disease, namely, that a large number of these tissue-elements have suffered total destruction.

But, as already indicated, we have not to deal only with the direct effects of alcohol upon the neurons. Other organs as well as the brain have had to meet the shock of the successive alcoholic storms, and few of them can long remain unaffected by it. Slowly, but with steady progression, excretion is rendered imperfect and metabolic processes become perverted. Auto-intoxication has set in, and consequently vascular changes, closely resembling those that have already been described as occurring in senile insanity and in general paralysis, take place throughout the body. The cerebral capillaries pay their penalty for the physiological advantage they possess in having a special adventitial coat, and the nervous elements and the neurologia suffer in their nutrition. To the occasional direct action of alcohol upon the cortical nerve-cells, there is thus added a continuous toxic action, which is in part direct, and in part indirect, through the alterations in the vessel-walls.

In many cases of chronic alcoholic insanity, the changes in the cerebral tissues are practically indistinguishable from those that are regarded as typical of senile insanity, and in some they closely approximate to those that are most characteristic of general paralysis. These facts have often been observed and remarked upon, but, as far as I have seen, no one has satisfactorily explained them. I maintain that the true explanation is simply that each of these three diseases has an auto-toxic basis.

Pathological Anatomy. (a) Macroscopic.—Both the gross and minute tissue-changes in this disease naturally differ considerably according to whether the case under examination has terminated at an early or a late stage. In the early stage the brain often presents little abnormality to the unaided eye, except some milkiness of the pia-arachnoid

and slight general atrophy of the organ. In the advanced stages of the disease the morbid appearances do not differ essentially from those in senile insanity. The vascular changes are, however, generally much less pronounced, and atrophic and hæmorrhagic softenings are less frequent.

(b) *Microscopic*.—In advanced cases the dura mater and pia-arachnoid constantly present the chronic proliferative and degenerative changes described in chapters v. and vi. Endarteritis deformans is probably never entirely absent from the cerebral arteries, but it is seldom a prominent change, except in senile cases. Hyaline fibroid degeneration is generally a well developed lesion, both in the pia-arachnoid and within the brain. In the cases that I have examined, it has very commonly manifested itself especially in its formative and fibroid phases. The vessels consequently appear unduly cellular. In some cases there is added to this simple proliferative change in the adventitia a degree of acute periarteritis, manifested by distinct, but almost always slight, leucocyte infiltration of the vessel-walls. Hyaline fibroid thickening of the capillaries of the first layer of the cortex is a well-marked condition in all advanced cases; it may also occasionally be observed in the deeper portions of the cortex and white matter. Aneurismal dilatations of the arterioles and other vessels, which some observers have described as characteristic of chronic alcoholic insanity, have not been a prominent feature in the cases that I have had an opportunity of examining.

The changes that commonly affect the neuroglia are described on page 186. Lying in the sclerosed tissue, immediately subjacent to the pia-arachnoid, there are often numerous "colloid bodies," which appear as colourless or pale blue globules in fresh aniline black preparations. They closely resemble "amyloid bodies," but differ from them in their staining reactions. They are generally regarded as droplets of myeline. In the light of recent observations it is difficult to accept this view of their nature in all instances, although it is certainly accurate in some. It seems to me very probable that "colloid bodies," like "amyloid bodies," represent not one, but several different degenerative products.

The nerve-cell changes are discussed on page 263. In correspondence with the loss of a considerable proportion of the cortical nerve-cells and the advanced degenerative changes presented by those that remain, there are always, in advanced cases, well marked alterations in the medullated nerve-fibres of the brain.

As already indicated, in many cases the histological changes are practically identical with those in senile insanity. The two clinical forms of mental disease are, of course, often combined.

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EPILEPTIC INSANITY.

The subject of the pathology of epilepsy occupies at the present moment a position of extreme interest. The deplorable prevalence of the disease in almost every country, and the untold suffering that it occasions, have always given it a special importance. For long it has almost completely baffled every effort of scientific investigation to discover its essential nature. But, during the last five or six years, investigations have been carried out which, it is not too much to say, have so far advanced our knowledge of the subject that to-day we stand within measurable distance of one of the greatest triumphs of medical science. There is good reason to be confident that this triumph will not be long delayed. Already the way to it is opened up, thanks to the splendid work that has been done by Agostini, Krainsky, Ceni, Voisin and Petit, as well as by numerous other able investigators. Such researches have only to be continued for a little time, and then we shall understand fully, as we now understand in a large measure, the pathogenesis of idiopathic epilepsy. Already we know enough to make it practically certain that the disease is one that we shall yet be able to arrest in the great majority of cases.

It is chiefly through work in the chemical department of pathology that this great advance has been made. I can here do little more than very briefly outline the results of the more important recent observations and conclusions regarding the pathology of idiopathic epilepsy and its relations to insanity.

Etiology and Pathogenesis.—It is now regarded by most authorities as clearly proved that idiopathic epilepsy is essentially a disease of the cerebral hemispheres; and not of the bulb, as it was at one time very generally believed to be. The most conclusive evidence upon this point appears to be that of the experimental observations of Bechterew (1).

The disease manifests itself especially in a sudden and tumultuous discharge of nervous energy in the sensory-motor centres of the cerebral cortex. Similar explosive discharges can be produced experimentally in lower animals in various different ways, such as by faradisation of the cerebral cortex, of which they may be an immediate

or somewhat remote effect ("after-actions"), and by intra-venous injection of absinthe, ammonium carbammate, and various other toxic substances. They may also follow the experimental production of sudden and extreme cerebral anæmia.

It is now maintained by the great majority of those who have made a special study of the subject, that there are two great factors in the pathogenesis of the disease in the human subject, namely (a) a special defect of cerebral organisation which predisposes to the epileptic discharge, and (b) a toxic action which determines the discharge. Some believe that the toxins act directly upon the nerve-cells of the cortex, others maintain that they influence these elements indirectly by producing cerebral congestion, or cerebral anæmia from vaso-motor spasm.

The precise nature of the defect of cerebral organisation which predisposes to the epileptic discharge is still unknown, but many important facts in regard to it have been definitely ascertained. In a certain proportion of cases, the predisposition is associated with the presence of a gross lesion in the brain, not necessarily directly implicating the motor areas. But in the great majority there cannot be discovered any abnormality, either of a gross or microscopic character, that might help to explain the explosive tendency. In the meantime we are obliged simply to regard the condition as "a certain unstable quality" of brain. This motor instability is generally, though by no means always, an inherited character. It has a distinct relationship to the predisposition to insanity. Congenital and acquired insanity, epilepsy and various other neuroses tend to run in the same family. Many idiots and imbeciles are at the same time epileptics. Clouston (2) considers that "to have epilepsy we must have an inherent motor instability in the convolutions, just as we must have essential mental instability in the convolutions in order to have insanity in most cases." Binswanger (3) believes that various forms of chronic intoxication and infection (alcoholism, syphilis, tuberculosis, etc.) in the parents, and also traumatic injuries to the foetus, are important causes of congenital predisposition to epilepsy. Marinesco (4) considers that infections and intoxications in the parents of epileptics can produce such weakening of the nervous system of the descendants that they are not able to resist the epileptogenetic action of toxic substances, which in themselves would not be able to produce epilepsy. Tonnini and Agostini (5) maintain that the most constant, almost pathognomonic, fact in all forms of epilepsy, which is capable of being regarded as a polymorphic degenerative state, is somatic and functional asymmetry; the tendency to the disease is essentially hereditary and of a degenerative nature. Lewis C. Bruce (6), from a study of cases of unilateral epilepsy, has been led to "suggest that, in some cases of epilepsy at least, the disease is due to a want of equal education

or development in the two cerebral hemispheres, thus rendering the patient liable to unusual brain exhaustion when active mental work is undertaken, or at the developmental periods of life, when new cortical areas are suddenly called into action." Voisin (7) regards the predisposition to epilepsy as essentially consisting in an unstable equilibrium of the nerve-cells.

The nature of the toxic action which determines the discharge has, as already indicated, been very extensively investigated in recent years. Pommay (9), Massalongo (10), Zacchi (11), Herter (12), Herter and Smith (13), Voisin and Petit (8), and numerous others, have clearly shown that epileptic fits are in certain cases associated with the absorption from the gastro-intestinal canal of toxic substances developed in consequence of disorders of digestion. Agostini (5) has carried out a most laborious series of experimental investigations which have given this fact a solid scientific basis. He has studied the toxicity of the gastric contents and urine, and also their chemical and physical characters, at various periods in relation to the fits. Of the value of his work it is scarcely possible to speak too highly. He has certainly done more than any other investigator to advance our knowledge of the pathology of epilepsy. A fuller account of his researches than can be given here will be found in the *Journal of Mental Science* of July, 1897, at page 603.

The condition of the urine has also been studied by a large number of observers, including Féré (26), Mirto (14), Voisin and Petit (8), Teeter (15), Ferrannini (16), Mairet and Vires (17) and Galante and Savini (18). The alterations in the blood have been investigated by Haig (19), Krainsky (20), Lui (21), Charon and Briche (22), Mairet and Vires (17), Caro (23) and others, and the toxicity of the sweat by Cabitto (24). Ceni (25) has investigated the relative teratological actions of the blood of healthy persons and of epileptics, using the well-known method of Féré.

I can state here only the general conclusions to which the results of these researches seem to lead, and must refer the reader to the original papers for the various details. Among the investigations with which anyone who wishes to go fully into this subject of the toxic basis of epilepsy should make himself conversant, are especially those of Agostini, Krainsky, Ceni, Galante and Savini, Voisin and Petit, and Lui. In this connection there should also be mentioned the recent monographs of Binswanger (3), Voisin (7) and Hallager (27), as well as a paper by Marinesco (4).

I would briefly sum up what appears to be the present position of knowledge regarding the toxic basis of idiopathic epilepsy, as follows:— It is fully proved that the fits are preceded and determined by the accumulation in the blood of certain toxins, the exact origin and nature

of which is still uncertain, although a great amount of light has now been thrown upon the subject. It is probable that the toxins consist of various substances, and that they differ considerably in individual cases. Krainsky has, however, obtained very strong evidence in support of his contention that in many cases the essential irritant is ammonium carbammate; he appears to have disproved the theory of Haig that epilepsy depends upon a retention of uric acid in the blood. In persons who are subject to epilepsy, metabolism tends to be imperfect; the average elimination of azotised products, phosphoric acid and chlorides is below normal in the inter-convulsive periods; there is diminished excretion of azotised substances in the prodromal period; after a fit there is increase in the density and acidity of the urine, and in the quantity of all the regressive products of metabolism contained in it; the urine of epileptics is constantly more toxic than normal urine when injected into lower animals; the toxicity increases in the period immediately preceding the fit, and is in strict relation to the gravity of concomitant gastro-intestinal disturbances; after the fit the urine is hyper-toxic (Agostini). The formation of the toxins is greatly favoured by gastro-intestinal disturbances, which, indeed, are able to determine the occurrence of fits; these can often be prevented, or greatly diminished in numbers, by washing out of the stomach, and by the use of purgatives, saline enemas, etc. (Agostini). The gastro-intestinal disturbances consist chiefly in the occurrence of abnormal putrefactive processes in the contents of the alimentary canal. It has been proved that before a fit occurs there is an increase in the excretion of ethereal sulphates, which may be taken as the index of the amount of putrefactive change occurring in the alimentary canal (Galante and Savini). It has also been shown that in association with the accumulation of toxins in the system, and in anticipation of a fit, there is constantly a diminution in the alkalinity of the blood (Lui; Charon and Briche).

The problem of the immediate future is to determine more fully the source, nature and causes of formation of these toxins which determine the occurrence of the fits, and it is one that numerous able workers are now endeavouring to elucidate. It is to be remarked, however, that in the absence of precise knowledge as to the nature of the predisposition to epilepsy, we may still regard it as probable that future investigation will show that this factor in its pathogenesis is also capable of being modified and controlled, as is, indeed, already done in some measure by the administration of bromides.

With regard to the causation of the mental disorders, and more especially of the progressive dementia, that are so often associated with epilepsy, very little of a definite nature can yet be said. But when we bear in mind that the fits, which in themselves can scarcely fail to be a cause of cerebral injury, are attended by a severely toxic condition of

the blood, and that the patients are generally to be classed among those who have a strong inherent predisposition to insanity, it is not difficult to understand in a general way why mental deterioration should occur.

Pathological Anatomy. Macroscopic.—The brain may present practically no abnormality. As a rule, however, one or more of various chronic morbid changes, or atypical structural features, may be observed. In long-standing cases the pia-arachnoid is slightly thickened and milky, and the brain shows some general atrophy. Several observers have found that an important difference in the weight of the two hemispheres is a very constant feature. Congenital lesions, more especially atypical arrangement of the convolutions and microgyria, are very common. Various forms of gross lesion are also frequently met with. The most important are the sclerotic areas, which have already been considered at page 335. Sclerosis of the cornu Ammonis, of one or both sides, has been found to be present in a considerable proportion of cases, by several observers (see p. 186). When death has taken place in a fit, the whole brain is found to be much congested. After death in *status epilepticus*, there is generally intense congestion and œdema of the brain, and some flattening of the convolutions.

Microscopic.—The brain may be devoid of any discoverable structural defect or chronic morbid change. This, however, is quite exceptional. But the fact justifies us in the belief that the various chronic changes that may generally be recognised on microscopic examination are of a non-essential and, for the most part, secondary nature. The most common alterations are those that affect the neuroglia. They are described on page 186. The vessels are not, as a rule, much altered in their structure, but evidence of old hæmorrhages of small size is often to be found in the form of hæmatoidin granules in their neighbourhood. In cases in which there has been dementia, there is always considerable diminution in the number of nerve-cells. The nuclear vacuolation in the cells of the second layer described by Bevan Lewis, and regarded by him as of high importance in the pathology of epilepsy, is certainly not special to this disease, as he himself admits. Moreover, the weight of evidence with regard to the nature of this change in the nerve-cells points to the conclusion that it is either of immediately *ante-mortem* or of *post-mortem* development, and that it can rarely have any special significance in the pathology of chronic diseases of the brain. In cases which die in *status epilepticus*, very profound structural alterations, of the character of a rapid, acute and almost universal primary degeneration, are generally present. They have recently been very fully described and figured by Mott (28).

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IDIOCY AND IMBECILITY.

The modern pathology of idiocy and imbecility has recently been so fully gone into by Dr Ireland in his *Mental Affections of Children*, a standard work which is doubtless in the medical library of every asylum in this country, that I may perhaps be excused by the reader if I dismiss the subject in a few words.

It may be said that it is now clearly established that in well-marked cases of idiocy and imbecility, corresponding to the imperfect

development of the mental faculties, there are always demonstrable structural defects, or pathological alterations, in the brain. Some of these abnormal conditions are of a gross character, others are recognisable only upon careful microscopic examination. The various forms that they take are being studied and classified now by numerous observers, but the work is still far from having been completed.

In addition to the very numerous references given by Dr Ireland to publications dealing with the pathology of idiocy and imbecility, there are some more recent or contemporary contributions to our knowledge of the subject, to which the attention of those specially interested in the matter may be directed, namely, the papers read before the Section of Psychiatry at the Paris International Medical Congress, which will be found fully reported in the *Epitome of the British Medical Journal*, in the issue of Sept. 22nd, 1900; those of Tanzi upon myxœdematous idiocy (*Riv. di patol. nerv. e ment.*, 1899, p. 145) and upon the relation of idiocy to infantile cerebroplegia (*Do.*, 1899, p. 193); numerous papers by Kœnig upon the last-named subject (*Deutsche Zeits. f. Nervenheilk.*, 1897, Bd. ix. H. 3-4; *Do.*, 1898, Bd. xiii. H. 1-2; *Monats. f. Psych. u. Neurol.*, 1898, Bd. iii.-iv.; *Neurolog. Centralbl.*, 1900, N. 7; *Journ. Ment. Sc.*, July, 1900); one by Bourneville on tuberculous sclerosis (*Arch. de Neurol.*, 1900, N. 55); and the important clinical and anatomical studies by Pellizzi (*Annali di Freniatria*, 1899, f. 4; 1900, f. 1, 2 and 3).

INDEX OF SUBJECTS

- ABSENCE or abnormal development of various parts of the brain, 326.
 Achromatic or achromophile part of protoplasm of nerve-cell, 195, 196, 197, 222.
 Achromatic substance, coagulation of, 243.
 " " intense colourability of, 293.
 Achromatolysis, 242.
 Acute bacillary delirium, 340.
 Acute insanity, 337.
 " " pathological anatomy, 343.
 " mania, 262, 337.
 " delirium, 339.
 " melancholia, 262.
 Albumenized slides, 15.
 Alcoholic insanity, 263, 362.
 " " pathological anatomy of, 364.
 Alveolar point, 55.
 Amœboidism of nerve-cells, 227.
 Amyloid bodies, 187, 188, 365.
 Anæmia, effects of, upon nerve-cells, 237.
 Anastomoses of pial arterioles, 137.
 Aniline black fresh method, 27.
 Arterioles, cerebral, normal structure of, 133.
 Arterioles, cerebral, morbid conditions of, 138-160.
 Arterio-sclerosis, 148.
 Asterion, 55.
 Atheroma, 144.
 Auricular hæmatoma, 34.
 Auto-infection, 339.
 Auto-intoxication, 339, 341, 342, 359, 367, 368.
 " " from the gastro-intestinal canal, 339, 368.

 BACTERIA, invasion of nerve-cells by, 247.
 Bacterial infection in acute delirium, 339.
 Basion, 55.
 Bichromate hardening, 13.
 " and formalin hardening, 13.
 Blood in epilepsy, 368, 369.
 Blood-supply of the brain, regulation of 297.
 Blood-vessels, morbid conditions of intracranial, 132.
 " normal structure of intracranial, 133, 288.
 Bregma, 55.
 British skull, normal measurements of average, 58.

 CALCIFICATION of cerebral vessels, 158.
 Capacity of skull, 56.
 " method of estimating, 56, 59.
 Capillaries of dura mater, 73.
 Capillaries of dura mater, morbid changes in, 93.
 " cerebral, normal structure of, 136.
 " cerebral, morbid changes in, 138-159.
 Centrosome and sphere, 199.
 Cephalic index, 56.
 Cerebral circulation, physiology of, 283, 288, 303.
 " " morbid conditions of, 283, 310.
 " congestion, 310.
 " anæmia, 314.
 " embolism, 155.
 " hæmorrhage, 154, 320.
 " thrombosis, 155.
 " tumours, 333.
 Cerebro-spinal fluid, 284.
 " " morbid conditions of, 309, 310.
 Choreic insanity, 263.
 Chromatolysis, 241.
 Chrome alum-copper hardening, 13.
 Chromophile part of the protoplasm of nerve-cells, 200, 222.
 Classification of nerve-cells, 214.
 Clinoid processes, abnormalities of, 64.
 Coats' method, 22.
 Colloid bodies, 365.
 Colloid degeneration of cerebral vessels, 158.
 Concentric bodies, hyaline, 97, 126.
 " starch grain, 98.
 Congenital abnormalities of the brain, 325.
 Convolutions, atypical arrangement of, 327.
 Corpus callosum, absence of, 326.
 Cortex, cerebral, nerve-cells of, 217.
 Cox's modification of Golgi's sublimate method, 22.
 Crania progenæa, 63.
 Cranial diameters, lengths, etc., in the insane, 60.
 Cranial capacity in the insane, 60.
 Craniology, 51.
 Craniometer, Hepburn's, 53, 59.
 Craniometry, 54.
 Craniometrical observations at autopsy, 53, 58.

- DACEYON, 55.
 Dementia, secondary, 262.
 Dentary arcades, absence of normal over-riding of, 64.
 Dextrine freezing method, 14.
 Dilatation, diffuse, of cerebral arterioles, 159.
 Dura mater, normal structure and functions of, 73, 302.
 " morbid conditions of, 73.
 " morbid adhesion of, to skull, 77.
 " morbid adhesion to pia-arachnoid, 78.
 " thickening of, 78.
 " thinning of, 78.
 " bony formations in, 79.
 " degenerative changes in, 80.
 " congestion of, 80.
 " inflammation of, 80.
 " false membranes under, 81, 101.
 Dynamic polarisation, law of, 223.

 EAR-CARTILAGE, normal structure, 38.
 " changes in, preliminary to hæmatoma auris, 37, 39.
 Ectasis, 159.
 Elasticity of the cerebral tissues, 281, 293.
 Embolism, 155.
 Endarteritis deformans, 144.
 " obliterans, 156.
 Endocellular reticulum of Golgi, 211.
 Endothelial cells of dura mater, morbid changes in, 91.
 " " of pia-arachnoid, morbid changes in, 125.
 Ependyma, granulations of, 182, 353, 361.
 Epilepsy, idiopathic, 366.
 Epileptic insanity, 366, 369.
 État criblé, 159.

 FATTY degeneration of cerebral vessels, 139.
 " " of nerve-cells, 246.
 Focal lesions of the brain, 330.
 Formalin hardening, 12.
 Freezing method, dextrine, 14.
 Fresh method of Bevan Lewis, 27.

 GASTRIC CONTENTS, toxicity of, in insanity, 341, 368, 369.
 Gemmule of the protoplasmic prolongations of nerve-cells, 198, 228, 264.
 General paralysis, nerve-cells in, 262.
 " etiology and pathogenesis of, 344.
 " pathological anatomy of, 352.
 " relation to tabes dorsalis, 347.
 Glabella, 54.
 Glenoid fossa of temporal bone, absence of, 64.
 Gnathic index, 57.
 Golgi's sublimate method, 22.
 Granular changes in nerve-cells, 252.
 Granular degeneration of muscular coat of arterioles, 157.
 Granular patches in tissues of dura mater, 101.
 Granulomata, infective, 334.
 Granulations on surface of dura, 87.
 " on surface of pia-arachnoid, 122, 125.
 " of ependyma, 182, 353, 361.
 Gross cerebral lesions of vascular origin, 330.
 Gummata, 335.

 HÆMATOIDIN granules in dura mater, 94.
 " " in pia-arachnoid, 127.
 Hæmatoma auris, 32, 34.
 " " in the mentally sound 34, 47.
 Hæmatoxylin and eosin staining, 20.
 Hæmorrhage, cerebral, 154, 320.
 " into subdural space, 94.
 Heidenhain's fluid, 12.
 Heller's method, 20.
 Hepburn's craniometer, 53, 59.
 Hereditary predisposition to insanity, 337, 338.
 Heterotopia of the grey substance, 327.
 Histological methods, 12.
 Hyaline degeneration of tissues of dura mater, 97.
 " " of tissues of pia-arachnoid, 126.
 " " of intra-cranial blood-vessels, 139.
 Hyaline fibroid degeneration, 140.
 Hypertrophic nodular gliosis, 336.
 Hypertrophy of the scalp, 33.

 IDIOCY and imbecility, 371.
 Inanition, effects of, upon nerve-cells, 234.
 Infections, relation of, to nervous and mental diseases, 341.
 Insomnia, effects of, upon nerve-cells, 237.
 Intoxications, relation of, to nervous and mental diseases, 341.
 Intracranial blood-vessels, morbid conditions of, 132.
 " " normal structure of, 133, 288.
 " " pigmentary deposits in walls of, 138.
 " " fatty degeneration of, 139.
 " " hyaline degeneration of, 139.
 " " hyaline fibroid degeneration of, 140.
 " " endarteritis deformans of, 144.
 " lymphatic system, 283, 284, 306.
 " pressure, 283, 304, 315.
 Intra-neuronic and inter-neuronic elaborations, distinctive functional values of, 229, 264.
 JORES' method, 30.
 KINETOPLASM, 196.

- LAMBDA, 55.
 Law of dynamic polarisation, 223.
 Lewis, Bevan, fresh method, 27.
 Lymph canaliculi of nerve-cell protoplasm, 211.
 Lymphatic system, intracranial, 284, 306.
- MARCHI's method, 25.
 Maxillary upper facial index, 57.
 Meningitis, purulent, 124.
 Mental point, 55.
 Mesoglia cells, 164.
 " " normal histology of, 177.
 " " functions of, 179.
 " " changes in, under conditions of irritation, 181.
 " " morbid changes affecting, 187.
- Methods, histological, 12.
 " of fixing and hardening, 12.
 " of staining, 17.
 " of rendering Golgi - preparations permanent, 23.
- Methyl violet method, 18.
 Metopism, 64.
 Microcephaly, 328.
 Microgyria, 327.
 Miliary aneurisms, 149.
 " sclerosis, 188.
 Mirto's method, 23.
 Monro-Kellie doctrine, 289, 292, 311.
 Mulberry bodies, 100.
- NASAL EMINENCE, 54.
 Nasal index, 57.
 Nasio-mental complete facial index, 57.
 Nasion, or nasal point, 54.
 Nerve-cells, normal structure of, 195.
 " terminology of, 195.
 " achromatic part of, 197, 222.
 " chromophile part of, 200, 222.
 " gemmule of protoplasmic prolongations of, 198.
 " physiological pigment of, 202.
 " nucleus and nucleolus of, 204.
 " pericellular reticulum of, 208.
 " endocellular reticulum of, 211.
 " lymph canaliculi of, 211.
 " protoplasmic prolongations of, 223.
 " achromatolysis or plasmolysis of, 242.
 " coagulation of achromatic substance of, 243.
 " intense colourability of achromatic substance of, 243.
 " partial or superficial coagulation in, 243.
 " pigmentary or yellow-globular degeneration of, 243.
 " fatty degeneration of, 246.
 " vacuolation of, 246.
 " invasion of by bacteria, 247.
 " varicose atrophy of, 247.
 " varicose hypertrophy of axis-cylinder process of, 250.
 " displacement of nucleus of, 251.
 " homogeneous degeneration of nucleus of, 251.
- Nerve-cells, loss of, 251.
 " granular changes in, 252.
 " morphological classification of, 214.
 " mode of connection of, 216.
 " of cerebral cortex, 217.
 " physiology of, 218.
 " alleged amœboidism and plasticity of, 227.
 " functions of body of, 224.
 " functional contractility of the gemmule of, 228.
 " structural changes in, accompanying modifications of functional state, 225.
 " physiological regressive changes in, 226.
 " morbid conditions of, 194.
 " experimental pathology of, 230.
 " general pathology of, 253.
 " special pathology of, in relation to mental diseases, 258.
 " changes following section of prolongations of, 231.
 " changes produced by poisons in, 234, 257.
 " effects of inanition upon, 234.
 " effects of elevation of temperature upon, 235.
 " effects of uræmia upon, 236.
 " effects of anæmia upon, 237.
 " effects of insomnia upon, 237.
 " proliferative capacity of, 238.
 " post-mortem changes in, 239.
 " types of morbid change affecting, 241.
 " chromatolysis of, 241.
- Nerve-fibres, medullated, morbid conditions of, 265, 354, 361.
 Nerves, of dura mater, 75, 302.
 " in walls of pial arterioles, 137.
- Neuroglia, development of, 165.
 " functions of, 178.
 " normal histology of, 168.
 " morbid conditions of, 164, 183, 184.
 " reaction to irritants, 179.
 " rôle in processes of repair, 179.
 " hypertrophy and hyperplasia of in disease, 181.
 " pigmentary degeneration of, 183.
 " in general paralysis, 185.
 " in senile insanity, 186.
 " in chronic alcoholic insanity, 186.
 " in chronic epileptic insanity, 186.
- Neuron theory, 218.
 Nucleus and nucleolus of nerve-cells, 204, 251.
- OCCIPITAL point, 55.
 Opisthion, 55.
 Ophryon, 55.
 Orbital index, 57.
 Orr's methods, 26.
 Osteoid plates, in dura mater, 79.
 " in pia-arachnoid, 123, 127.
 Osteoma of skull, 69.
 Osteoporosis of skull, 68.

- Osteosclerosis of skull, 68.
 Othematoma, 34.
- PACCHIONIAN VILLI, 284.
 Palate, abnormalities of, 65.
 Palato-maxillary index, 58.
 Paraffin embedding method, 14.
 Paralytic dementia (see under general paralysis), 344.
 „ insanity, 154, 333.
 Periarthritis, 156.
 Periarthritis nodosa, 157.
 Pericellular reticula of nerve-cells, 208.
 Perichondritis auriculæ, 35.
 Physical properties of the brain, morbid variations in, 278.
 Pia-arachnoid, normal structure of, 116.
 „ morbid conditions of, 116.
 „ milkiness, thickening, opacity, etc., of, 121.
 „ morbid adhesion of, to the cortex, 128.
 Pigment granules in walls of cerebral vessels, 136, 138.
 „ physiological, of nerve-cells, 202.
 Pigmentary degeneration of endothelial cells of pia-arachnoid, 126.
 „ „ of neuroglia, 183.
 „ „ of nerve-cells, 243.
 Plagiocephaly, 63.
 Platinum method, 28, 117, 134, 135, 164, 166, 177, 197, 207, 284.
 „ processes for rendering Cox-preparations permanent, 24.
 Photoxylin method, 16.
 Polyneuritic psychosis, 263.
 Porencephaly, 327.
 Post-mortem examinations, 4.
 „ changes in nerve-cells, 239.
 Pressure, normal intracranial, 304.
 „ pathological increase of intracranial, 315.
 Proliferative capacity of nerve-cells, 238.
 Pseudo-aneurisms, 152.
 Pterion, 55.
- ROYAL EDINBURGH ASYLUM, form for making pathological records, 5.
- SAGITTAL SUTURE, bilateral elevation along-side, 64.
 Scalp, morbid conditions of, 32.
 „ morbid adhesion of, 32.
 „ hypertrophy of, 33.
 Sclerosis, cerebral, 180, 181, 184, 335.
 „ miliary, 188.
 „ arterial, 140, 148.
 Sclerotic areas, 335.
 Secondary dementia, 252, 262.
 Section-cutting, 14.
 Senile insanity, 262, 358.
 „ involution, 358.
 Skull, morbid conditions of, 51.
 „ abnormalities in form and size, 60.
 „ macrocephalic, 62.
 „ microcephalic, 61.
 „ asymmetry of, 62.
- Skull, "the insane type" of, 64.
 „ changes in thickness, texture and weight of, 66.
 „ alterations in weight of, 68.
 „ histological changes in, 68.
 „ tumours of, 69.
 Softenings, atrophic, 331, 333.
 „ hæmorrhagic, 331, 333.
 Special histological processes, 21.
 Specific gravity of the brain, 280.
 Spinal cord, in acute insanity, 343.
 „ „ in general paralysis, 354.
 Spinal point, 55.
 Spiral vortices of Levi, 199.
 Spongionplasm, 196, 197.
 Staining, methods of, 17.
 Status epilepticus, brain in cases of, 370.
 Stephanion, 55.
 Subdural false membranes, 81, 101.
 Sublimate fixation, 12.
 Subnasal point, 55.
 Surface sections, method of preparing, 21.
 Symmetry, bilateral, of focal lesions, 332.
 Syphilis, relation to insanity and other nervous diseases, 355.
 Syphilitic insanity, 355.
- TEMPERATURE, elevation of, effects upon nerve-cells, 235.
 Thickening of the skull, 66.
 Thinning of the skull, 67.
 Thionin stain for nerve-cells, 17.
 Thrombosis, 155.
 Toluidin blue method, 17.
 Toxic agents, causation of insanity by, 338.
 Trophoplasm, 196, 197.
 Tubercular nodules, 334.
 Tumours, cerebral, 333.
 Turner, Sir William, scheme for study of human skull, 55.
- URÆMIA, effects upon nerve-cells, 236.
 Urine in epilepsy, 368, 369.
 Urine, toxicity of, in insanity, 341, 368, 369.
- VACUOLATION of nerve-cells, 246.
 Varicose atrophy of nerve-cells, 247.
 „ hypertrophy of axis-cylinder process of nerve-cells, 250.
 Vertical index of skull, 56.
 Vitreous degeneration of endothelial cells of dura mater, 92.
 Vitreous degeneration of endothelial cells of pia-arachnoid, 126.
 Vortices, spiral, of Levi, 199.
- WATERSTON'S method of making cranio-metric observations at post-mortem examinations, 53.
 Weigert's chrome alum-copper fluid, 13.
 Weight of the brain, 278.
- YELLOW-GLOBULAR degeneration of nerve-cells, 243.

INDEX OF AUTHORS

- ACQUISTO, 75, 236, 249, 302.
 Adamkiewicz, 214, 266, 286, 316, 320.
 Adler, 127.
 Agostini, 238, 280, 341, 366, 367, 368, 369.
 Althaus, 85.
 Alzheimer, 158, 362.
 Amadei, 279.
 Andriezen, 164, 166, 168, 169, 248.
 Angiolella, 160, 346, 349.
 Anglade, 246.
 Apathy, 196, 197, 198, 199, 217, 218.
 Arnold, 168.
 Aubanal, 81, 82.
 Auerbach, 216.
 Azoulay, 248, 250.

 BABES, 247.
 Baillarger, 81, 82, 83, 281.
 Baistocchi, 62, 280.
 Ballet, 231, 233, 237, 263.
 Barbacci, 240.
 Barker, L. F., 194, 219, 221.
 Barr, T., 49.
 Bartels, 279.
 Barthez, 82.
 Bastian, 282.
 Bauchet, 81, 84.
 Bayle, 81, 122, 124.
 Bayliss, 290, 297, 301, 304.
 Beach, Fletcher, 281.
 Beadles, 67, 160.
 Bechterew, 166, 366.
 Becker, 197.
 Benda, 196.
 Benedikt, 56, 60, 62, 64.
 Berger, 246.
 Bergmann, 316, 320.
 Berkley, H. J., 195, 248.
 Bernardini, 304.
 Bethe, 196, 197, 198, 199, 210, 213, 217, 218, 219, 225.
 Bianchi, L., 340.
 Bianchi, S., 64.
 Binswanger, 157, 355, 367, 368.
 Bird, Frederick, 34.
 Bischoff, 281.
 Boll, 168.
 Bondurant, 82.
 Bonne, 170, 175.
 Bouchard, 149.
 Boudet, 82.
 Bourneville, 372.
 Boyd, 279.
 Bra, 281.
 Bradbury, 290.
 Bramwell, Byrom, 150, 154, 158.
 Briche, 368, 369.
 Broca, 281, 328.
 Brown, J. J., 151, 153, 158.
 Browne, Crichton, 82, 84, 85, 278.
 Browne, Lennox, 35.
 Bruce, Alexander, 326, 348.
 Bruce, Lewis C., 367.
 Brunet, 82.
 Buchstab, 281.
 Buck, 246.
 Bucknill, 281.
 Bühler, 196, 199, 200, 207.
 Bullen, F. St John, 67, 77, 78, 123.
 Bunzl-Federn, 231.
 Burrows, 290, 294.

 CABITTO, 368.
 Calmeil, 81.
 Campacci, 240.
 Campbell, A. W., 246, 349, 362.
 Campbell, J. A., 35.
 Camuset, 64, 79, 82.
 Capobianco, 166, 170, 174, 180, 216.
 Caporaso, 238.
 Cappie, 323.
 Caro, 368.
 Cavazzani, A., 323.
 Cavazzani, E., 287, 288, 299, 301.
 Ceni, 233, 246, 248, 340, 366, 368.
 Channing, W., 65.
 Charcot, 81, 137, 149.
 Charon, 65, 368, 369.
 Chiozzi, 234, 249.
 Christian, 81.
 Clapham, 64, 279.
 Clark, A. Campbell, 62.
 Clarke, 64.
 Clinch, 327.
 Clouston, T. S., 35, 65, 79, 81, 83, 109, 153, 156, 158, 179, 332, 356, 358, 359, 362, 367.
 Cobbold, 37.
 Colella, 180, 248, 251, 362.
 Colenbrander, 231.
 Colucci, 203, 214, 215, 239, 243, 244, 246, 251.
 Corrado, 246, 250.
 Cowan, J. J., 33.
 Cox, W. H., 22, 231.
 Craig, M., 304.
 Crisafulli, 343.
 Cristiani, 244, 343.
 Cruveilhier, 149.
 Cullerre, 70.
 Cunningham, D. J., 52, 62, 328.

 D'ABUNDO, 285, 302, 341.
 Daddi, 234, 237, 246.
 Dagonet, 79, 169.
 Danilewsky, 282.
 Dawson, W. R., 86, 304, 315, 356.
 Dean, 323.
 Dehler, 199, 204.
 Deiters, 168.
 Dejerine, 165.

- Demoor, 248, 250.
 De Sarlo, 304.
 Donaggio, A., 170, 174, 197, 202, 209, 210, 212, 213, 216, 251, 343.
 Dotto, 233, 248, 249.
 Down, Langdon, 35, 62, 65.
 Duncan, J. A. H., 21.
 Dunlop, C., 332.
 Durand-Fardel, 159.
 Duret, 137.
 Dutil, 237.
 Duval, 228.

 EICHLER, 151, 153.
 Easterbrook, 4.
 Elder, George, 285, 289, 290, 294, 316, 323.
 Ellis, Havelock, 70.
 Elkins, F. A., 246.
 Eppinger, 151, 152.
 Erlitzki, 166.
 Eurich, 165, 169, 180.
 Eve, 195.
 Ewing, 236, 241, 246.

 FALKENHAIN, 323.
 Faure, 231, 233, 263.
 Ferrannini, 368.
 Ferrari, 340.
 Féré, 368.
 Fick, 304.
 Field, M. D., 34.
 Fieschi, 238.
 Findlay, J. W., 98, 100, 136.
 Fischer, Franz, 36.
 Fish, 246.
 Flatau, 216, 223, 235, 256.
 Flechsig, 23.
 Fleming, R. A., 231.
 Flemming, W., 197, 204.
 Flesch, 195.
 Foà, 231.
 Foster, 196, 323.
 Fothergill, J. Milner, 323.
 Fowler, J. F., 316.
 França, 240.
 France, 30.
 Fränkel, 63, 68.
 Fragnito, 166, 170, 174, 180, 216.
 Frank, 228, 250.
 Frazer, Alec, 328.
 Friedmann, 180, 238.
 Fromman, 168.
 Funaioli, 62.

 GAERTNER, 298.
 Galante, 368, 369.
 Ganfini, 234.
 Gehuchten, A. van, 165, 168, 175, 179, 194, 195, 202, 206, 207, 215, 219, 221, 222, 223, 224, 231, 233, 241, 246, 254.
 Geigel, 297.
 Giacomini, 62, 327, 328.
 Giannelli, 316.
 Giese, 165.
 Gieson, Van, 195, 222, 228.
 Giuffrida-Ruggeri, 62, 63, 64, 65.
 Goldscheider, 216, 223, 235, 256.
 Golgi, C., 22, 23, 165, 168, 179, 208, 210, 211, 216, 218, 223, 238, 248, 251.

 Gonzales, 310.
 Goodall, 37, 180.
 Gowers, Sir William, 155, 225.
 Grashey, 297.
 Greenfield, 82, 86.
 Greenlees, 134.
 Gudden, 36.
 Guerrini, 226.
 Guillain, 285.
 Gull, 140.
 Gulland, 137.

 HAIG, 368, 369.
 Hallager, 368.
 Halliburton, 287, 288, 309.
 Hamilton, D. J., 68, 323.
 Hasse, 63.
 Heimann, 207.
 Held, 201, 210, 216.
 Hepburn, David, 54, 59.
 Herter, 368.
 Heschl, 81, 327.
 Heubner, 137.
 Hewitt, Prescott, 82.
 Hill, Alexander, 199, 216.
 Hill, Leonard, 284, 286, 287, 288, 289, 290, 297, 301, 302, 303, 304, 312, 317, 320, 321.
 Hill, William, 49.
 His, 166, 168, 196.
 Hitzig, 340.
 Hochhaus, 158.
 Hodge, 226.
 Holmgren, 213.
 Huber, 137.
 Huguenin, 81, 82, 84, 85.
 Humphry, Sir George, 61, 62.
 Hunter, W. K., 245.
 Hunter, William, 190, 210, 216.
 Hürthle, 298.
 Hutchison, R., 203, 243, 323.
 Hyslop, Theo. B., 366.

 ILBERG, 281.
 Ireland, W. W., 61, 65, 326, 328, 371.

 JACK, William R., 12, 23.
 Jacobsohn, 161.
 James, Alexander, 324.
 Jastrowitz, 169.
 Jeannerat, 79.
 Jelgersma, 254.
 Jensen, 279.
 Jores, 30.
 KAPOSÍ, 34.
 Kellie, 289.
 Kempson, 62.
 Key, 134.
 Kingsley, N. W., 65.
 Klippel, 248, 254, 355.
 Kölliker, 165, 168, 195, 196.
 Kollman, 70.
 Koenig, W., 81, 82, 86, 372.
 Köppen, 161.
 Köster, 246.
 Kremiansky, 82, 85.
 Krafft-Ebing, 355.
 Krömer, 123.

- Kromayer, 151, 152.
 Kronthal, 136.
 Krainsky, 366, 368, 369.
 Kundrat, 34, 327.
 Kussmaul, 157.
 LABORDE, 82.
 Lachi, 166.
 Lancereaux, 81, 85, 86.
 Langley, 224.
 Lannelongue, 61.
 Lapinsky, 134, 136.
 Lavdowsky, 173.
 Legendie, 82.
 Lee, Bolles, 12.
 Lelut, 82.
 Lenhossek, 165, 168, 177, 195, 199, 204,
 206, 207, 219, 222.
 Lépine, 228.
 Leubuscher, 36.
 Levi, Giuseppe, 195, 197, 198, 199, 204,
 205, 215, 222, 238.
 Levi, Giulio, 240.
 Lewis, Bevan, 27, 67, 68, 77, 78, 82, 84, 85,
 123, 124, 128, 134, 154, 156, 159, 168,
 179, 183, 222, 243, 244, 246, 252, 345,
 351, 370.
 Lewis, M., 199.
 Lewy, 324.
 Lombroso, 63.
 Lord, 203, 244.
 Löwenfeld, 146, 154, 155, 157.
 Lugaro, 183, 195, 196, 197, 199, 201, 204,
 208, 209, 210, 213, 217, 219, 222, 223,
 224, 225, 228, 229, 231, 232, 234, 235,
 242, 244, 246, 248, 249, 250, 251, 252,
 255, 264, 348.
 Lui, 368, 369.
 Luys, 70, 282.
 Luxemburg, 225.
 Luzenberger, 227.
 MABILLE, 37.
 Macalister, 51.
 Macdonald, James H., 24.
 Mackay, George, 332.
 Macpherson, John, 317, 337, 339, 349, 353.
 Mackenzie, J. C., 324.
 Maclure, 199.
 Magendie, 289, 294.
 Mairet, 368.
 Major, Herbert C., 3.
 Mallory, 158.
 Manicatide, 234.
 Mann, G., 206, 223.
 Manouelian, 250.
 Manouvrier, 282.
 Mantegazza, 56.
 Marchand, 282.
 Marchi, 25.
 Marimo, 64.
 Marina, 231.
 Marinesco, 195, 196, 197, 203, 215, 222,
 223, 225, 227, 231, 233, 236, 237, 238,
 241, 242, 243, 244, 246, 251, 252, 253,
 254, 256, 367, 368.
 Marro, A., 341.
 Marracino, 170, 174.
 Marshall, 282.
 Martinotti, 149, 208, 209, 210.
 Massalongo, 368.
 M'Dowall, 33.
 Mayer, 157.
 Mendel, 153.
 Mercier, 282.
 Meyer, Adolf, 71, 244.
 Meyer, L., 36, 39, 63, 125.
 Meyer, Semi, 210, 216.
 Meynert, 278.
 Mickle, W. Julius, 327, 355, 356.
 Middlemass, James, 3, 27, 32, 34, 37, 67,
 69, 77, 78, 79, 86, 96, 100, 101, 109, 116,
 119, 123, 246, 278, 279.
 Miles, Alexander, 319.
 Mingazzini, 71.
 Mirto, D., 231.
 Mirto, G., 23, 368.
 Modena, 275.
 Monakow, 233.
 Monro, 289.
 Monti, A., 234, 238, 248, 250.
 Montyel, 282.
 Morison, Alexander, 137.
 Morselli, 60, 280.
 Mosso, 304.
 Mott, F. W., 156, 161, 309, 310, 345, 346,
 355, 356, 370.
 Moxter, 236.
 Müller, 165, 169, 234.
 Mya, 288.
 NANSEN, 165.
 Naunyn, 323.
 Nawratski, 287.
 Nelis, 213.
 Nepi, 240.
 Nissl, 169, 187, 195, 196, 198, 201, 204,
 210, 214, 219, 231, 234, 247, 252.
 Norman, Conolly, 327.
 OBERSTEINER, 74, 76, 83, 86, 99, 134, 137,
 154, 155, 156, 158, 159, 278, 285, 348.
 Obregia, 23.
 Obreja, 203.
 Odier, 250.
 ettinger, 149.
 Oliver, 47.
 Onuf, 231.
 Orange, 263.
 Ormerod, 81.
 Orr, David, 18, 26, 208, 226, 227, 250, 251,
 252, 262.
 Ottolenghi, 184, 237, 249.
 PALADINO, 170, 174.
 Pareidt, 36, 39.
 Paton, S., 165.
 Peli, 68.
 Pellizzi, 36, 37, 168, 182, 225, 336, 372.
 Penta, 71.
 Pergens, 225.
 Pernice, 234, 248.
 Peters, 250.
 Peterson, Frederick, 65.
 Petit, 366, 368.
 Petrone, 169.
 Piccinino, 246, 247, 340.
 Pick, 225.

- Pietersen, 36, 37.
 Pilez, 202, 243.
 Pilkington, 34.
 Pirotais, 85, 86.
 Poggi, 33, 327.
 Pollack, 12, 23.
 Pommay, 368.
 Popoff, 169.
 Prenant, 207.
 Prus, 81, 82.
 Pugnât, 225, 226, 252.
 Pusateri, 75, 233, 236, 249, 302.
 QUAIN, 81.
 Querton, 250.
 RABL-RÜCKHARD, 228.
 Raggi, 64.
 Ramon, P., 178.
 Ramon y Cajal, 165, 168, 178, 179, 204, 207, 210, 222, 223, 249.
 Ranvier, 168.
 Reiner, 324.
 Reinke, 170.
 Retzius, 134.
 Rey, 280.
 Richter, 282.
 Righetti, 237, 246.
 Rilliet, 82.
 Rindfleisch, 82, 85.
 Robertson, Alexander, 37.
 Robertson, G. M., 47, 81, 83, 84, 85, 86, 108.
 Roncali, 324.
 Roncoroni, 204.
 Rosin, 203, 204.
 Roth, 151.
 Roy, 298, 301.
 SACERDOTTI, 184, 237, 249.
 Sanarelli, 238.
 Sankey, 280.
 Sappey, 73.
 Sarbò, 237, 246, 251.
 Savini, 368, 369.
 Scabia, L., 47.
 Scagliosi, 234, 248.
 Schäfer, 165, 168, 195, 202.
 Schaffer, J., 199.
 Schaffer, K., 234, 254.
 Schnitzler, 324.
 Seppilli, 282.
 Shaw, Clave, 65, 317.
 Shennan, Theodore, 30.
 Sherrington, 298, 301.
 Shuttleworth, 61.
 Simpson, F. O., 71, 282.
 Skae, 282.
 Skae, F., 246.
 Soukhanoff, 237, 246, 250.
 Spampini, 169.
 Sperling, 82.
 Spina, 302.
 Stanziale, 156, 161.
 Stefanowska, 250.
 Strahan, 34.
 Straub, 149.
 Stroebe, 238.
 Studnicka, 213.
 Sutherland, G. A., 85.
 Sutton, 140.
 Symington, 289.
 Szczawinska, 200.
 TALBOT, 65.
 Tamburini, 62.
 Tanzi, 224, 372.
 Tatuses, 203.
 Tedeschi, 63, 238.
 Teeter, 368.
 Telford-Smith, 52, 62, 328.
 Terrazas, 169.
 Testut, 62.
 Tétard, 49.
 Thoma, 128, 147.
 Thomson, John, 86.
 Thomson, St Clair, 287, 288.
 Thudicum, 280.
 Tigges, 279.
 Timofeew, 207.
 Tirelli, 238, 239, 240, 248.
 Tischkow, 36.
 Tomkins, H. H., 34.
 Tonnini, 367.
 Tuczek, 345.
 Tuke, Sir J. Batty, 3, 116, 124, 136, 137, 138, 250, 304, 306, 317, 340.
 Tuke, Hack, 281.
 Turner, Sir William, 55, 64, 282.
 Turner, W. Aldren, 190, 210, 216.
 Turner, John, 228, 244, 252, 263, 287.
 URQUHART, A. R., 62.
 VALENZA, 166, 238.
 Vallon, 34.
 Vassale, 25, 36, 216, 266.
 Veratti, 212.
 Verga, 71, 310, 358, 359.
 Vignal, 165.
 Virchow, 36, 51, 61, 81, 149, 168.
 Vires, 368.
 Vitzou, 238.
 Voisin, 123, 366, 368.
 Vogt, 282, 328.
 WAGNER, 282, 298.
 Waldeyer, 195.
 Wallace, David, 317.
 Walsem, 278.
 Warrington, 231.
 Waterston, David, 53.
 Weigert, 13, 165, 168.
 Weil, 229, 250.
 Welsh, D. A., 37, 45.
 Welsh, G. A., 356.
 Whitwell, 190.
 Wigglesworth, 82, 83, 84, 85, 104.
 Wilks, 81, 82.
 Wilson, G. R., 366.
 Woodhead, 123, 124, 168.
 Wright, H. K., 250.
 Wright, Hamilton, 263.
 ZACCHI, 368.
 Zanke, 59.
 Zenker, 151.
 Ziegler, 82, 84, 123, 124, 127.

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