XVIII.—The Histology of Disseminated Sclerosis.

By **James W. Dawson**, M.D., Neurological Histologist to the Royal College of Physicians' Laboratory; formerly Carnegie Research Fellow. To which is prefaced a Preliminary Communication on the subject made to the Pathological Society of Great Britain and Ireland by the late ALEXANDER BRUCE, M.D., LL.D., and JAMES W. DAWSON, M.D. *Communicated by* A. NINIAN BRUCE, M.D., D.Sc.

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[Plates XLV–LXXVIII.]

PREFACE.

The research of which this paper gives an account was originated by the late Dr ALEXANDER BRUCE and undertaken in conjunction with him; most of the material used had been accumulated by him during the later years of his life. The following preliminary communication made to the Pathological Society of Great Britain and Ireland in July 1910 represents in brief outline the position which had been reached at the time of Dr BRUCE's lamented death :—

PRELIMINARY COMMUNICATION ON THE PATHOLOGY OF DISSEMINATED SCLEROSIS. By A. BRUCE and J. W. DAWSON. (Reprinted from *Journ. Path. and Bacteriol.*, Cambridge, 1911, vol. xv, p. 126.)

The plaques in disseminated sclerosis, wherever they are situated, are distributed evidently without any relation to nerve tracts. Their character and appearance suggest a gradual infiltration from some central source into the surrounding or neighbouring tissues. In the cord their tendency is to pass inwards from the meninges in a more or less wedge-shaped form, their relationship to blood-vessels being often difficult or impossible to trace except in the earlier stages. The cerebrum and cerebellum are better adapted to give an idea as to their mode of formation because of the independence of the arterial and venous paths. Within the cerebrum the veins pass towards the wall of the ventricles and the choroid plexus towards the veins of Galen, and have in this way a distribution altogether different from that of the arteries. The same is true of the cerebellum. A study of a series of sections shows that the plaques are deposited in relation to the distribution of the veins and to the walls of the ventricles. An examination of sections of the cerebral hemispheres strongly suggests that the infiltration is along the lymphatic channels surrounding the veins. Similar conclusions are suggested by study of the sections of the pons, cerebellum, and medulla.

For some years Dr BRUCE's attention had been concentrated on the important part played by the lymphatics in disease processes in the central nervous system, and I had the honour of being associated with him in the investigations which he hoped would throw light on the subject. The earlier results obtained were recorded in the paper "On the Relations of the Lymphatics of the Spinal Cord," and more especially in that entitled "Multiple Neuromata of the Central Nervous System." As

the above abstract shows, Dr BRUCE found in disseminated sclerosis a disease which in his view accentuated the fact that in certain cases the effects of the causal agent fall especially on the lymphatic system. He was one of the first in this country to point out that in many cases the peri-ventricular sclerosis is the most important lesion in this disease, and that it frequently dominates the macroscopic and microscopic pictures. He formed the opinion that the lesions in the ependymal and peri-ependymal tissues are probably of especial significance, and he argued that the existence of such marked lesions around the ventricles raised the possibility of the cerebro-spinal fluid having toxic properties and that the causal agent entered along the lymphatics in the peri-venous sheaths. At the same time the peri-vascular distribution of the areas in the central nervous system led him to recognise that the causal agent might also be disseminated by the blood channels. He was strongly convinced that the process was toxi-infective, and that the plaques were caused by a gradual infiltration of the tissue with toxic lymph passing from a central focus, and, while recognising the limitations of the method, he hoped that the careful histological investigation of the morbid anatomy of the disease might ultimately throw light on the nature of the morbific agent which is at work.

Since Dr BRUCE'S death I have worked up more fully the cases on which our earlier joint observations were founded, and I have also investigated a considerable mass of new material which has more recently been available. This material includes a case which is of special importance from the fact that a full clinical record taken under Dr BRUCE'S personal supervision is in existence, and also on account of its having a fatal issue after a comparatively short course. This more recent work, and especially the observation of the acute case alluded to, brought new facts to light, and necessitated a reconsideration of some of the earlier conclusions.

It is a pleasure to acknowledge my indebtedness to the family of the late Dr BRUCE not only for the use of the material which belonged to him, but also for contributing to the expense of the research, and in particular to Dr NINIAN BRUCE for help in relation to certain points in pathological physiology and for reading the proofs of the paper.

During three of the years I have been engaged in this work I held a Carnegie Fellowship, and I desire to thank the Trust for the assistance given and for generous grants towards expenses and towards the cost of illustration. My thanks are also due to the Committee of the Royal College of Physicians' Laboratory, Edinburgh, for the facilities afforded for the research, and to Professor RITCHIE, the Superintendent of the Laboratory, for his sympathetic interest and criticism throughout the investigation. The coloured illustrations have been prepared by Mr RICHARD MUIR, of the University Pathological Department, and the micro-photographs by him, by Mr WILLIAM WATSON, of the Royal College of Physicians' Laboratory, and Mr THOMAS HAMILTON, my laboratory assistant; my acknowledgments are due to all of them for the care and skill they have exercised in executing the work.

CONTENTS.

I.

INTRODUCTION.

The following study is based upon the detailed histological examination of the nervous organs from nine cases of disseminated sclerosis. This name and its synonyms—multiple sclerosis, insular sclerosis, sclérose en plaques disséminées, Herdsklerose—indicate that the disease they designate has, as its chief anatomical feature, irregular sclerotic patches distributed throughout the central nervous system. Its manifestations, therefore, are protean, and an exact knowledge of its pathological anatomy is essential to the understanding of the various clinical forms of the disease.

The works of CHARCOT, who first gave classical pictures of the disease—the clinical and anatomical,—show that to him the condition was a distinct morbid entity, and that it bore no relation to the other non-system diseases of the central nervous system. All subsequent studies have been influenced by the fundamental observations of CHARCOT, and around the three cardinal points emphasised by him, proliferation of glia, degeneration of nerve fibres, and blood-vessel changes, have been grouped the various theories put forward to account for the origin of the process.

The etiology of the disease remains absolutely obscure. The supposition of a selective poison acting through the blood-vessels, which has received the support of most recent investigators, is justified as an hypothesis but remains undemonstrated as a fact. Chief interest has, therefore, centred in the pathological anatomy of the condition, and the object of this study has been to trace, by means of the most recent available specific staining methods, the characteristics of the pathological process and to determine, as far as possible, the histological changes which form its basis.

The earliest pathological studies in disseminated sclerosis were made in chronic cases of the disease, and the lesions described were the sclerotic areas found distributed in the brain and spinal cord. The recognition by later writers of acute stages of the disease and of cases of typical disseminated sclerosis running an acute course has caused me to direct special attention to the early changes and their relation to the development of the chronic sclerotic areas. In spite of the large number of works on the subject of disseminated sclerosis, its etiology and pathology present many problems for future elucidation. Our knowledge of the histology, especially of the early stages, has not kept pace with our recognition of the early clinical aspects of the disease. It was hoped, therefore, that a study of the earliest lesions, in tracing the rôle which falls to the various tissue elements before secondary factors had been introduced, would throw some light upon the nature and origin of the process.

No attempt has been made to give a complete representation of the literature of the subject. This is so extensive that it would scarcely have been possible, and, further, a detailed statement of all the hypotheses, often very vague and insufficiently based, seemed of little value. I have had in view, rather, a brief continuous account of the most important problems met with in the consideration of the pathological anatomy and pathogenesis of disseminated sclerosis. Having critically sifted all the available literature of the last twenty years, those writers have been chosen whose work has marked a new standpoint or an important step in our progressive knowledge of the subject. In the critical discussion on the nature, origin, and cause of disseminated sclerosis, the works of BORST (1904) and MÜLLER (1904) have been freely drawn upon, and readers are referred to MÜLLER'S monograph for a complete bibliography up to 1904. A list of the more recent anatomical researches will be found at the close of this study.

The clinical notes of the cases were very incomplete, and no attempt has been made to correlate clinical symptoms with the anatomical lesions in individual cases. The difficulty of bringing clinical symptoms into harmony with the anatomical findings in the central nervous system is a well-recognised fact, but, from the frequency with which certain areas are affected, attention has been drawn in the note on the Pathological Physiology to the possibility of predominant anatomical lesions explaining certain clinical symptoms.

As the significance and interpretation of our observations depend largely upon the judgment we pass upon, and the importance we attach to, the methods of investigation used, I have given in considerable detail an outline of the methods employed. During the last third of the nineteenth century neuro-pathology laid special stress on problems affecting the localisation of nerve fibres in an endeavour to define accurately the position of diseased processes, and to follow out secondary degenerations while almost neglecting the histo-pathology of the diseased processes

themselves. NISSL laid stress on the fact that practical neuro-pathology can and must be pursued without regard to definite ideas as to the functional significance of the individual component parts of the tissue. He pointed out that it is sufficient in the first place to collect pathological data regarding definite diseased conditions, and that for that purpose the changes in the supporting tissue—the glia and the vascular connective tissue—may be of greater importance and much more really decisive than the changes in the specific tissue elements—the nerve cells and nerve fibres—which are yet of greater functional importance. The classical methods of MARCHI for early, and of WEIGERT for late, fibre tract degeneration have, therefore, been supplemented by modern specific and diffuse staining methods. The examination of small sections for the recognition of these finer histological details has, on the other hand, been supplemented by large brain sections through the whole hemisphere. These sections, stained with Weigert's myelin sheath stain and a diffuse cell stain, give a very instructive comparative representation of the gyri and their associated sulci, and an idea of the extension of the process.

The pathological process may be disseminated through brain, pons, medulla oblongata, and spinal cord, and may produce symptoms of a very diverse character. The possibility of any useful clinical classification is, therefore, very slight, and an anatomical basis has been adopted for the classification of the various clinical types. According to the predominance of the symptoms, the disease has been divided clinically into cerebral, spinal, and cerebro-spinal forms, and the different possibilities of anatomical distribution and localisation have led to a similar pathological classification. Probably no cases are purely of one type, and experience has shown that, if sufficiently careful search is made, sclerotic areas will be found in nearly all cases distributed through both brain and cord, though perhaps much more marked in one or other position. As far as we know from the findings in other organs of the body, there is no widespread reaction to the etiological factor, such as is found in acute poliomyelitis. The anatomical findings point to a process localised in the central nervous system.

Before referring to some of the problems met with in the study of disseminated sclerosis, it will be convenient to give an indication of the pathological changes found in a well-marked case of the disease. WILLIAMSON (1908) in his text-book gives a brief, clear description of the main features of the pathological anatomy, from which we take the following detached statements :—

"The pathological examination of the nervous system reveals patches of sclerosis scattered about in the most irregular manner in the brain, pons, medulla, and spinal cord. Both white and grey matter may be affected, though the former is more frequently the seat of the disease. The patches are in some cases grey in colour and sharply defined ; in others greyish white and less sharply defined. Large patches in the cord, medulla, and pons may extend over the greater part of the transverse section. The largest patches are seen in the white matter of the brain.

The older patches are firmer than the normal substance of the brain or cord, but recent patches are occasionally seen which are gelatinous and softer than the normal tissues. The chief macroscopical characters of the lesions are their insular character, their irregular dissemination, the absence of secondary ascending and descending sclerosis in most cases. This feature—the absence of secondary degeneration—sharply distinguishes disseminated sclerosis of the spinal cord from other multiple lesions, such as disseminated myelitis and multiple syphilitic lesions.

"Under the microscope a striking feature of many patches is their sharply defined nature. This feature is well seen in the sections stained according to Weigert's method. Examination under a high power shows that medullated nerve fibres are generally absent in the sclerotic patches; but sometimes at the border of a patch there is a zone in which the medullated fibres are present, though scanty. At the periphery of some patches compound granular cells are found, along with indications that the morbid process is still active. In the patches of sclerosis the axis cylinders of the nerve fibres are very often present though the medullated sheaths have disappeared. The ganglion cells of the grey matter escape degeneration for a long period in the diseased patch; but at a very advanced stage they, like the axis cylinders, may finally disappear. The neuroglia connective tissue in a diseased patch is often greatly increased and converted into a dense fibrous tissue. Spider cells may be present, but the neuroglia is not richer in nuclei than in the normal condition. In other cases the neuroglia, though increased in amount, has an amorphous or homogeneous appearance under the microscope. In some patches the nerve fibres have degenerated, and spaces are left in the neuroglia from which the true nerve elements have disappeared, but the connective tissue itself has not proliferated. Compound granular cells are often present, especially at the periphery of a patch. They are most numerous in recent patches, but may be absent in old patches. Often there are large epithelial-like cells in cavities near blood-vessels. The walls of the blood-vessels in some cases appear normal; in some cases they are thickened and hyaline or present evidence of endo- or peri-arteritis; in other cases (in recent patches) the peri-vascular lymph sheaths are filled with round cells, compound granular cells, and fat globules. Often a large altered blood-vessel is found in the centre of a patch of sclerosis.

"Four forms of sclerosed patches may therefore be met with: (1) patches in which nerve fibres have degenerated, leaving sieve-like small cavities in the neuroglia, whilst the neuroglia connective tissue itself has increased very little; (2) patches in which there is marked proliferation of the neuroglia along with degeneration of nerve fibres; (3) patches presenting diffuse proliferation of neuroglia, whilst the nerve fibres and cells persist; (4) recent patches presenting changes very similar to those of cerebral softening—products of nerve degeneration and myelin drops, fat granular cells, and distension of the peri-vascular sheath of the blood-vessels with round cells. A point of importance is the presence of patches in various stages of development,

in the same case; some patches presenting firm sclerosis, whilst others are soft and recent, and may resemble ordinary softening."

A brief reference must now be made to some of the main problems met with in the study of the pathology and pathogenesis of disseminated sclerosis. Recent works show how widely views differ regarding these, and how vague and confused are the issues placed before the reader. One reason for this seems to lie in the absence of any distinction being drawn between the question of the nature and that of the origin of the process. These are undoubtedly the two most important problems: (1) what is the nature of the process underlying disseminated sclerosis? and (2) where has it its origin, *i.e.* in which structural element of the nervous tissue does it take its rise?

An attempt to answer the first of these questions has led many writers to a diffuse discussion regarding the distinction between inflammatory and non-inflammatory processes in the central nervous system. The views as to what constitutes true inflammation are nowhere so conflicting as when the term is used in connection with the central nervous system, and in the case of no other organ are the conceptions of different writers as to the relation of inflammation to pure degeneration so fundamentally opposed. The nature of chronic inflammation also is again nowhere so obscure as when the term is used in connection with the central nervous system. SCHMAUS (1903) has summarised the inflammatory process in the central nervous system under the general conception of a reaction process, which may express itself by an increase in the vital activity of any of the tissue elements, and, for the purposes of this paper, the term is used in this sense.

The pathological anatomy of disseminated sclerosis bears no analogy to any other known pathological process in the body. We know, *e.g.*, of no process in other organs in which the relative integrity of the specific functioning parenchymatous tissue is associated with the enormous increase of the interstitial tissue occurring in definite circumscribed areas.

Further, experimental investigation has as yet thrown little light on this question: it has proved only that disseminated areas of myelitis may result in a reparative growth of neuroglia, but it has not proved that areas of disseminated sclerosis proceed from an acute myelitis.

The attempt to define more clearly the nature of the process is rendered more difficult, therefore, by the difficulty of defining the term inflammation in the central nervous system, by the absence of analogies from the pathology of other organs, and by the absence of results realised from experimental investigations.

Two views in particular have been advanced to explain the nature of the process. BYROM BRAMWELL (1904) has succinctly summarised them thus: "(1) That the sclerotic lesions are the result of some irritant which is distributed through the nerve centres by the blood-vessels. (2) That the disease is due to some develop-

mental or congenital defect of the neuroglial or nervous tissue (perhaps similar to or analogous to the gliomatosis in cases of syringomyelia) which renders it more vulnerable or liable to be affected by irritation than the neuroglial or nervous tissue of the normal individual."

These views may be termed the exogenous and endogenous theories, using these words in their strictest meaning. The former ascribes to disseminated sclerosis an inflammatory process as its basis, and most observers accept the inflammatory nature of the process in some form. The latter view, strongly advocated by STRÜMPELL and supported by MÜLLER in his monograph, looks upon disseminated sclerosis as a disease independent of external factors, except as "agents provocateurs." MÜLLER distinguishes between true or primary disseminated sclerosis, a primary glia formation due to malformation of the glia—a disease *sui generis*—and secondary disseminated sclerosis, a myelitic form, one of a community of allied diseases. This standpoint, that a uniform explanation of all cases of disseminated sclerosis cannot be given, is taken up by many recent writers. Others, however, cannot recognise the existence of an acute or secondary disseminated sclerosis which differs in its evolution from the chronic forms, but whose pathological anatomy is yet almost identical.

Concerning the origin, as concerning the nature of the process, the views are no less divergent. Supporters of the endogenous theory see in disseminated sclerosis a multiple gliosis whose origin is, naturally, in the neuroglia tissue. Supporters of the inflammatory nature of the diseased process are, however, widely divided in their views regarding its origin. In a sclerotic patch changes occur in the three separate structural elements of the tissue: (1) the nervous elements—the myelin sheath of the nerve fibre; (2) the interstitial tissue—the glia; and (3) the blood-vessels. The differing views are related to these three components, and according to the anatomical change most in evidence writers have ascribed the origin of the process to a primary parenchymatous change, a primary interstitial process, or a primary vessel alteration. We must undoubtedly differentiate three groups of changes, and the question constantly arises, which is primary and are the others secondary, *i.e.* are they so related as to be cause and effect, or are they together due to the simultaneous action of the etiological factor? Many neuro-pathologists believe that here, as elsewhere, it is immaterial whether the reaction is discernible first in the parenchyma, or interstitial tissue, or vessels. It may be assumed that there are individual factors which, through the reaction of the tissues upon the unknown, though probably toxic, stimulation of the three components, determine the anatomical picture, allowing in one case one component and in another case another component to come to the front.

It is, therefore, clear that amongst the questions raised in any discussion regarding the nature and origin of disseminated sclerosis are the following:—its relation to acute, subacute, and chronic inflammatory processes in the central

nervous system, and, further, its relation to the different processes, *e.g.* diffuse cerebro-spinal syphilis and diffuse arterio-sclerosis, which have as their terminal product a sclerosed area.

In addition to its unexplained cause, nature, and origin, numerous other problems are met with in the study of disseminated sclerosis. A few of these falling within the scope of this paper, which is primarily concerned with histological data and those questions on which the anatomical picture may throw any light, may now be mentioned.

Disseminated sclerosis has been attributed to a variety of causes, some of which must be considered later, but, as has been stated previously, the etiology remains unexplained. A study of the cerebro-spinal fluid in disseminated sclerosis has as yet thrown little light on the disease, but investigations along this line have not been extensive. No culture has been obtained from the fluid, and such organisms as have been found in brain and cord sections must be regarded as having an accidental and not a causal relation to the disease. In the absence of any specific organism the morbid changes have been attributed to the action of a toxin. This hypothetical toxin has not been isolated, but it is suggested that it forms either in the body, possibly in the course of an infective disease, or is brought there from outside of it. For the distribution of this infective agent we have three paths: the blood-vessels, the lymph-vessels, and the central canal of the spinal cord. In view of the importance of the lymphatics of the central nervous system in the distribution of infective agents, and the distinction, emphasised in numerous recent works, between hæmatogenous and lymphogenous infection of the central nervous system, the histological data which give any aid in understanding this problem of the path of infection will be considered. Amongst the further questions raised by this consideration will be the following: why and how the toxin becomes circumscribed, and why, if it is carried by the blood-channel, it does not spread diffusely but should act arbitrarily on detached smaller blood-vessels or a portion of the distribution of such a blood-vessel.

Further, clinically, the course of the disease is marked by remissions and exacerbations, and histologically we find in nearly every case chronic areas side by side with areas of a more acute process. Two questions arise: what relation have these more recent areas to the original pathological process; and, if related, is it that the injurious agent has remained in the body for years or is re-formed there, or is it that the original "noxa" lowered the vitality of certain portions of the nervous tissues, so that, later, other exciting factors overturned the balance of repair and waste and, in WEIGERT'S sense (Wegfall von Wachstumhindernissen), disturbed the equilibrium between parenchyma and supporting tissue and removed the normal controlling influence which one tissue element of a complex structure normally exercises upon the other tissue elements?

Finally, in this connection must be mentioned one striking characteristic of the

picture. Most observers who have had the opportunity of examining cases clinically and anatomically have noted the disparity between the anatomical change and the disturbance of function. From the days of CHARCOT onwards this has been related to the persistence of the axis-cylinder and the comparative integrity of the ganglion cells in a sclerosed patch, with the consequent absence of secondary degeneration.

II.

HISTORICAL.

The lesions in disseminated sclerosis were figured by CRUVEILHIER in his *Atlas d'anatomie pathologique* (1835–1842), and the condition was first clinically described by FRERICHS (1849). RINDFLEISCH (1863) carefully examined the morbid anatomy: both CRUVEILHIER and he representing the lesions under the name "grey degeneration." The disease, however, was not generally recognised until CHARCOT published his famous lectures (1866). CHARCOT, working at the Salpêtrière, may be said to have given the classical account of the disease, both in its clinical manifestations and its anatomical features. The three cardinal symptoms—intention tremors, nystagmus, and scanning speech,—when present, were considered as diagnostic of disseminated sclerosis, and what may be regarded as the three cardinal and essential points of the anatomical picture—absence of myelin sheath, neuroglia proliferation, and persistence of the axis cylinders—were no less certainly thought to be distinctive of this disease. It has been named by the French writers "sclérose en plaques disséminées," by the Germans "Herdsklerose," and the appropriate and expressive term "insular sclerosis" was proposed by MOXON.

Since the time of CHARCOT, however, it has come to be recognised that the essential clinical features are the grouping of certain symptoms and their variability. Pathologically, too, it is now recognised that the anatomical features, once thought to be distinctive of disseminated sclerosis, may be the final stage of quite different processes. In the Introduction it has been stated that the two groups of theories put forward to explain the nature of the morbid process may be classified as Exogenous and Endogenous. As the latter term has come to bear a wider significance than that first attributed to it, it has been thought advisable to refer to it under the name "Developmental." The term "exogenous" must be admitted to be synonymous with "inflammatory," using this word in its widest sense, as a reaction process.

In the following survey of the literature, the writers will be referred to under the following groups:—those who support the inflammatory nature of the process, those who support its developmental nature, and a final group including the more recent investigators. It will be sufficiently evident that the views of many recent workers cannot be precisely defined.

Classification:—

(1) Inflammatory nature of the process:—
  A. Primary change in the neuroglia.
  B. Primary change in the parenchyma.
  C. Primary change in the blood-vessels.
  D. Disturbances in the lymph circulation.

(2) Developmental nature of the process:—
  A. Deficient "Anlage" of the nerve elements.
  B. Multiple gliosis.

(3) More recent researches, 1903–1913.

(1) Inflammatory Nature of the Process.

The views as to the inflammatory nature of the process are related to considerations regarding primary changes in the glia, the true nervous elements, and the blood-vessels. The final etiological factor or factors which bring the primary change into operation have, as yet, received no satisfactory explanation, but it is agreed that the postulated virus circulates in the blood-vessels or lymphatics and exerts its action primarily on the glia, the myelin sheath of the nerve fibre, or the blood-vessel wall itself.

A. *Primary Change in the Glia.*

According to the writers who support this view, the morbid process starts in a formative irritation of the glia, comparable to a chronic interstitial inflammation in other organs, *e.g.* liver or kidney. The thickening of the glia reticulum and the formation of the glia fibrils strangle, as it were, the myelin sheath of the nerve fibres, which gradually diminish in volume and then disappear, leaving the axis cylinders persisting for a long time.

Charcot (1866) and his followers held firmly to this view: they regarded the changes in the nerve fibres as secondary to the glia proliferation and the changes in the blood-vessels as a much later and not an essential part of the process. Charcot looked upon the neuroglia as a reticulated connective tissue, the meshes of which contained one or more nerve fibres. In the grey matter the meshes were much smaller than in the white, and in both the network served as a framework for the blood-vessels. At the nodal points of the reticulum were situated the neuroglia nuclei with a thin layer of protoplasm and numerous processes of different lengths. These processes seemed to unite with the trabeculæ of the reticulum, which continue them, as it were, without any line of demarcation. In his description of the topographical distribution of the areas he noted the frequent peri-ventricular localisation, that the spinal and cranial nerve roots were frequently affected, and that the dorsal sections of the medulla oblongata, where the cranial nuclei lie, show

special predisposition to the development of plaques. He remarks, however, that they are rarely found in the grey substance of the convolutions. Regarding the macroscopic characters of the areas, CHARCOT noted that they were sometimes turgescent, sometimes on a level with the surrounding parts, and sometimes depressed, of a firm consistence, and circumscribed. In colour they resemble the grey matter, with numerous vessels distributed through them, and on contact with the atmosphere they assume a rosy hue.

Microscopically CHARCOT showed that the apparently definite line of demarcation of a patch was an illusion. He distinguished three concentric zones in which, from the periphery inwards, the changes increased in intensity:—(*a*) a peripheral zone with thickening of the glia reticulum and increase in size and number of the glia nuclei; diminution in volume of the myelin sheath; and unaltered axis cylinders: (*b*) a transition zone in which the glia reticulum is still more hypertrophied and in places replaced by bundles of long and slender fibrils, which are disposed in a direction parallel to the long axis of the nerve fibres; the nerve tubes are still more atrophied and often represented by the axis cylinders, which may be very enlarged: (*c*) a central zone with the most marked changes. Here all traces of a reticulum have disappeared; the glia nuclei are shrunken, and may form groups between the closely arranged bundles of fibrils. In the midst of the fibrils persisting axis cylinders are present: these on longitudinal section are thicker than the glia fibrils and never rarefied. This long persistence of the axis cylinders was looked upon as one of the characteristics of disseminated sclerosis, and CHARCOT ascribed to this fact the absence of secondary degeneration. He so emphasised this finding as to make it a 'differential point in the diagnosis between disseminated sclerosis and disseminated myelitis.

CHARCOT further noted alterations in the blood-vessels within the areas. In the peripheral zone even the finest capillaries were prominent, and in the central zone the walls of the vessels were very thickened, and contained numerous nuclei. Fatty granulations were also found in recent areas, not only in the meshes of the recticulum, but also in the walls of the blood-vessel, especially in the transition and peripheral zones. These granulations were thought to be due to the disintegration of the myelin sheath. A peculiar alteration in the nerve cells was described, which was designated "yellow degeneration"; this was a form of atrophy of the cell, with a disappearance of the cell-processes.

CHARCOT related the peculiar intention tremor, so characteristic of disseminated sclerosis, to the absence of the myelin sheath from the long-persisting axis cylinders. The transmission of voluntary impulses would thus still proceed by means of the denuded axis cylinders, but it would be carried on irregularly in a broken or jerky manner, and would thus produce the oscillations which disturb the due execution of voluntary movements. It was thought possible also that the naked axis cylinders might again clothe themselves with myelin, and thus effect a *restitutio ad integrum.*

In reading CHARCOT'S lectures, one is struck by the accuracy of the observations, made with so limited a histological technique, and one must admit that, in spite of recent specific staining methods, little has been added to the classical histological picture of CHARCOT.

B. *Primary Change in the Parenchyma.*

All the writers in this group regard the change in the myelin sheath of the nerve fibre as the primary one: they contend that an infective or toxic "noxa" may act directly and primarily upon the nerve fibre before there is any trace of glia proliferation, and without a primary vessel disease.

REDLICH (1896) considers that the first impulse to the disease may be given, *e.g.* by infective diseases, in such a way that there is brought about an acute degenerative decay of the myelin sheath of the nerve fibre, analogous to that produced by experimental infection of micro-organisms or their toxins. He thinks that the acute degeneration of the myelin sheath finds an analogy in peri-axial neuritis, which likewise is found in toxic diseases. REDLICH suggests that a further advance of the disease may be caused by the original agent having caused, in addition to the evident areas, an alteration in the nutrition of other portions of the central nervous system, and later, through excess of function or strain, these parts may perish.

The vessel changes are looked upon as accessory phenomena, for the great irregularity in the distribution and form of the areas in the cord seemed to argue against the dependence of the foci on the vessels. The interstitial changes in the glia are regarded as dependent upon the parenchymatous degeneration, though it is admitted that the absence of definitely proved areas in the peripheral nerves argues for the presence of glia as essential to the process.

REDLICH thinks that all the actual histological changes found in disseminated sclerosis may be found in other conditions, but their actual grouping is characteristic of disseminated sclerosis. He distinguishes three types of areas:—

(*a*) Very dense patches which consist of very fine parallel fibrils with glia cells and nuclei. The processes of the cells are often very distinct, and give to the cell the appearance of beautiful spider cells; the cross-section of the fibrils gives the impression of granules. Within these areas few myelin sheaths are left, and the axis cylinders persist, but are swollen or atrophied. The transition to normal tissue is a gradual one.

(*b*) A large-meshed tissue with thickened glia trabeculæ but no definite area. In this tissue the vessels are more or less changed, the walls frequently hyaline, and the peri-vascular glia increased.

(*c*) A wide-meshed network with glia trabeculæ only slightly thickened. The nodal points of this meshwork are occupied by glia cells with their processes; the meshes are empty because the nerve fibres have completely perished, and the tissue has an areolar appearance. In the neighbourhood of these areas are found nerve

fibres, both myelin sheaths and axis cylinders, undergoing acute degeneration. Such areas are often accompanied by secondary degeneration, and REDLICH thinks that there is no connection between these and those of the first kind.

In the grey matter are found areas of the first and second types, in which the ganglion cells remain for a long time exempt.

HUBER (1895) also accepts the view of a primary parenchymatous change, *i.e.* "a simple degenerative decay, not an actual inflammatory decay."

C. *Primary Blood-vessel Alterations.*

This view, stated in simple terms, is that the chief and essential rôle in the process is ascribed to the changes in the blood-vessels: these give rise to an altered nutrition of the surrounding tissue, leading to degeneration of nerve fibres or to an extension of the inflammatory process to the peri-vascular tissue, with subsequent or simultaneous glia proliferation.

RINDFLEISCH (1863) was the first to note the significance of blood-vessel changes in the areas of "grey degeneration," and the intimate relation of these areas to the blood-vessels. It was thought that a chronic irritative condition of the vessel wall introduced the process: that the consequent altered nutrition of the tissue led to changes in the nerve fibres, and, through the extension of the formative irritation, the surrounding glia was involved in a radiating direction. RINDFLEISCH found the walls of the small arteries and all their delicate ramifications enormously thickened and infiltrated with cells, even in the earliest stages of the process: the walls of the capillaries and veins were also surrounded by numerous nuclei.

RINDFLEISCH looked upon the glia as a fused protoplasmic mass with inserted nuclei. He thought that in "grey degeneration" there set in a redivision of the protoplasm around the nuclei, while the periphery of the cell elements, which thus arose, formed into fine fibres. The final result was a feltwork of fine fibres, which is saturated, like a sponge, with a mucoid fluid containing only a few nuclei. He also gave the first accurate description of the large multi-nucleated, ramified glia cells found in the early areas—the so-called spider cells, or monster glia cells, or Deiter cells, or Rindfleisch cells.

RINDFLEISCH gave no suggestion as to the nature of the final cause of the postulated alteration of the vessels, nor of the cause of its special distribution. The sequence of the process was as follows:—(1) the change in the vessels; (2) atrophy of the nerve elements from malnutrition; (3) metamorphosis of the connective tissue (glia).

RIBBERT (1882) related the areas in disseminated sclerosis to a primary disseminated thrombosis. He described in all the patches a congested vessel, and in several the vessel was so cut that it ran through the whole extent of the area. In two small patches cut in serial sections there were found in the lumen of the vessel white

blood-cells, partly adherent to the vessel walls and partly filling the vessel as emboli. RIBBERT looked upon these as multiple thrombi, and thought that they played an important rôle in the causation of the process, for in such thrombosed areas arose the commencing emigration of leucocytes. He thought that the characteristic form of the areas might well be accounted for by multiple emboli, and he also related to the blood-vessels the fact that the cerebral areas so frequently reached up to the cortex but did not involve it—explaining this circumstance by the few anastomoses between the vessels of the white and grey matter.

RIBBERT thought that the exciting cause of the inflammation circulates in the blood, and that owing to its presence a clot formed at some part of a small blood-vessel. At this point an irritation of the vessel wall is set up with a peri-vascular inflammation: this inflammation extends around the blood-vessel and invades the surrounding tissues, causing degeneration of the nerve fibres and an active proliferation of the glia. The glia nuclei proliferate and form large cells with an abundant protoplasm from which radiates the fibre-work of the glia. The fat granules, arising from the degeneration of the myelin sheath, are taken up by the emigrated white blood-cells and are carried to the lymph sheaths of the blood-vessels. The proliferated glia, after the removal of the fat, forms numerous fibrils, and thus arises a dense grey sclerotic area in which the protoplasm even of the large nucleated cells disappears.

French writers support chiefly the vascular origin of disseminated sclerosis. Amongst these may be mentioned the names of DÉJERINE and PIERRE MARIE.

DÉJERINE (1884) maintained that the configuration and dissemination of the areas could be explained only by relating them to changes in the blood-vessels. He found the blood-vessels altered, with a peri-arteritis and their calibre diminished, and that a vessel, thus changed, was the central point of each plaque. DÉJERINE thought that the causal factor, a microbe or a humoral agent of undetermined nature, circulated in the blood-vessels, modifying in some way their nutrition, and that this was the primary change. The effect on the surrounding tissue is seen first in the glia, which by its proliferation caused an "excentric compression of nerve tubes," leading to their disappearance.

PIERRE MARIE (1884–1895) has emphasised the special relation of disseminated sclerosis to infectious diseases, especially enteric fever, pneumonia, scarlet fever, and measles, and, of lesser importance, diphtheria, whooping-cough, erysipelas, dysentery, and even cholera. MARIE thinks that disseminated sclerosis is due, not to the different micro-organisms which produce these diseases, but to a combined infection occurring during their course. He suggests that the lesions in the brain and spinal cord are probably due to an ordinary pathogenic microbe, whose special action is due to its special localisation. The etiological influence of the infectious diseases is such that there may result changes of the vessels, and the sclerotic areas are therefore due to the localisation of infectious vessel disease in the central nervous

system. Most French writers, among whom PHILLIPPE and JONES may specially be mentioned, have accepted this conception of MARIE'S, which, as can be seen, is a deduction from RIBBERT'S.

Regarding the histological characters of the areas, MARIE laid special stress on the alterations in the blood-vessels and the persistence of the axis cylinders. The external coat of the vessel is specially affected, and on this account the lumen appears open and dilated in areas where the sclerosis is pronounced. The peri-vascular sheaths are full of granular bodies. From the persistence of the axis cylinders the following deductions are drawn :—(1) the absence of secondary degeneration in the path of the nerve fibres ; (2) the remission, improvement, and even cure which may occur, since the part of the nerve absolutely necessary for the transmission of the nervous current is retained ; (3) it throws light upon the pathology of tremor.

MARIE regards disseminated sclerosis as an interstitial process which has its origin in the blood-vessels. Possibly the infectious agent itself, rather than the materials which it secretes, brings this about, considering the dissemination of the lesions and their essentially embolic character. The presence of fat granular cells at the periphery of the islets points to the continued activity of the morbid process, since the products of the degeneration of the nerve fibres are not yet fully absorbed and are still being produced.

MARIE also points out that there are two forms of sclerosis : the one, in which the foci have a clear-cut appearance and in which numerous axis cylinders are found within the glia sclerosis ; and a second, with diffuse foci having very irregular and deeply indented borders and in which axis cylinders as well as myelin sheaths have often perished. He thinks that these two forms are distinct and are due to different causes, though both are probably a sequelæ of infectious disease. The latter is referred to under the name of "diffuse multilocular sclerosis," and the classical symptoms of disseminated sclerosis are frequently absent, especially the intention tremor, disorders of speech, and the eye symptoms. Paralysis is more often present, and its course is often rapidly fatal.

WILLIAMSON (1894–1908). A brief description of the pathological anatomy of disseminated sclerosis, as outlined by WILLIAMSON, has already been given. It remains to be added here that this author strongly supports the view of an alteration of the blood-vessel caused by a primary altered blood condition. The irregular distribution of the sclerotic patches, without any relation to nerve tracts or nerve fibres, seems to him suggestive of a primary change either in the blood or the blood-vessels or lymphatics. The frequent presence of marked vascular changes, *e.g.* the infiltration of the peri-vascular sheaths with round cells in the early areas, and the sclerotic or hyaline thickening of the vessel walls in older areas ; the presence of a vessel with altered walls in the centre of an area ; and occasionally the extension of an area of sclerosis corresponding to the area of distribution of a blood-vessel, all

point to the primary dependence on the blood-vessels. WILLIAMSON records a case where one of the areas corresponded roughly with the distribution of the anterior median artery of the spinal cord at one region, and the vessels in the anterior median fissure were dilated and surrounded by round cells and nuclei before they entered the substance of the cord. A thrombus was also present in the anterior median vein just at the commencement of the anterior median fissure, and several small thrombosed veins were found in the pia mater on the surface of the cord.

The pathological changes in disseminated sclerosis are thought to be very suggestive of the presence of some irritating substance in the blood, which stimulates the endothelium of the walls of blood-vessels and of the walls of the peri-vascular lymphatics, and which causes an extravasation of toxic lymph into the surrounding nerve tissue, with consequent degeneration of the myelin sheath of the nerve fibre. The presence of recent patches alongside old patches shows that the morbid agent persists in the organism and is able to cause the development of new patches of the disease long after the onset of the affection.

GOLDSCHEIDER (1896). The views of this writer are very similar to those of WILLIAMSON. He believes that the walls of the blood-vessels play an important rôle in the process, and that substances giving rise to cell-proliferation affect the walls of the blood-vessels by filtration and diffusion from the blood. The peri-vascular inflammation leads first to a solution of the surrounding myelin, and this leads to a reactive interstitial inflammation. GOLDSCHEIDER thinks that disseminated sclerosis is a disseminated myelitis running in acute and subacute stages.

D. *Disturbances in the Lymph Circulation.*

Changes in the lymphatics of the central nervous system have recently received considerable attention. In disseminated sclerosis the lymphatic spaces of the adventitia of the blood-vessels are frequently distended and filled either with fluid or with cells, or they are more or less obliterated by dense fibrous tissue. BORST was the first to bring these changes, which are dependent on a primary disease of the blood-vessels, into causal relationship to the areas of sclerosis. The disturbed lymph circulation expresses itself in characteristic serous infiltration, and the obstruction to the return of the lymph causes a lymph stasis in the area, which leads both to a myelin sheath degeneration and a forcing apart of the meshes of the glia, on the basis of a hyperlymphosis.

BORST (1897–1904) made a very careful histological investigation in five cases of disseminated sclerosis. He has also written a review of the whole subject (1904), a review to which I have already expressed my frequent indebtedness. On the grounds of his own investigations BORST thinks that the indications of lymph congestion and lymph stasis were sufficiently significant to account for the origin and for the dissemination of the areas. The areas were very sharply defined macroscopic-

ally, and within each a blood-vessel, cut longitudinally or transversely, could be traced, surrounded by a delicate peri-vascular space. Microscopically the pia of both brain and spinal cord was thickened, and all the vessels, especially the arteries, were also thickened: the vessels within the areas were hyaline and often obliterated, especially the paracentral vessels. Outside the areas the blood-vessels were also thickened and their lumen narrowed. In several cases the thickened vessel was the apex of an oval area. There was frequent marked glia proliferation around the central canal. BORST specially emphasises the presence of cystic spaces, often even macroscopically evident, around the obliterated vessels: these spaces were lined by cubical epithelium, probably arising from the glia, in virtue of its origin from the ependymal epithelium. These cystic spaces were regarded as having undoubtedly arisen in relation to the obliterated vessels, and, apparently, first as delicate peri-vascular spaces: they were, therefore, an expression of the obvious congestion of the lymph circulation.

As a further expression of this congestion there were found disseminated areas, usually round or oval and distinctly circumscribed, within which there was a rarefaction of the myelin constituents of the nerve fibres, while the axis cylinders remain naked. The glia in these areas is very delicate, and the glia cells are transformed into large protoplasm-rich forms. Such areas are described as "Lichtungsbezirke," are ascribed to a hyperlymphosis of the tissue, and are looked upon as a fore-stage of the sclerosed areas. When the increased pressure of the lymph is removed, the glia undergoes proliferation and invests the persisting axis cylinders with a more or less dense fibre feltwork. The proliferation of the glia need not always be solely a substitutive process which arises in consequence of the degeneration of the myelin: the existing hyperlymphosis may act as a stimulus to the glia, causing an inflammatory glia proliferation.

What the final cause is which acts on the membranes and the vessel walls, BORST concludes must be mere conjecture. The virus, in acute infections, courses in the first place in the blood, and from it passes through the walls of the vessel, causing an arteritis and a peri-arteritis in more or less intense degree. According to the degree of the lesion produced in the vessel we get abnormal permeability, diminished resistance to the oscillations of blood-pressure, and paralytic dilatation. Later, owing to a longer-acting irritant, the vessel changes assume a more or less productive character and express themselves chiefly in thickenings of the vessel wall and narrowing of the lumen. Through these processes in the vessel walls occur circulatory and nutritive disturbances. BORST'S view is, therefore, an extension of RINDFLEISCH'S view; he ascribes to the influence of the disturbed lymph-circulation the origin and extension of the process, but the changes in the vessel walls give occasion to the existence of the lymph-congestion.

ARNDT (1875) had, previous to BORST, laid emphasis on the influence of lymph-congestion in the production of areas of "grey degeneration." ARNDT looked upon

the glia cells and their processes as lymph bodies and canals, *i.e.* as the roots of the lymph vessels: he believed that in lymph-congestion these lymph-carrying elements swell and finally burst, setting free the lymph in the surrounding tissue. The nerve fibres then degenerate in consequence of the pressure of this congested lymph. Though ARNDT'S views on the glia texture of the central nervous system have been given up, his view of the influence of the disturbed lymph-circulation on the structural elements of the central nervous system, and especially in relation to "grey degeneration," is very important.

SCHMAUS (1901–1905) has also ascribed a considerable significance to the presence of lymph-congestion and œdema in a large number of general diseases, *e.g.* pernicious anæmia and chronic nephritis. The œdema leads to a dilatation of the meshes formed by the glia, to a swelling of the whole glia tissue, which may advance to such an extent that the fibrils blend to a homogeneous glassy or slightly granular mass, and to the presence of a homogeneous or granular substance in the lymph sheaths of the vessels. The myelin sheaths swell and become varicose, and the axis cylinders are swollen and twisted, on longitudinal section. That these signs are not pre-agonal or agonal is proved by the frequent presence of fat granular cells in the lymph sheaths of the vessels. In such diseases one is inclined to trace the origin of the œdema to toxic substances which circulate in the blood and cause an injury of the vessel wall, which thus becomes permeable to the serous fluid and allows of an increased transudation of (toxic) lymph.

In disseminated sclerosis SCHMAUS thinks that the dilatation of the peri-vascular lymph spaces can be explained only by the assumption of a congestion in the lymph stream, which, therefore, distends them. The changes in the blood-vessels, especially the frequently observed adhesions of their lymph sheaths, and the frequent adhesion and thickening of the meninges, lead to this obstruction to the lymph stream. The acute infection which precedes the disease (disseminated sclerosis) gives rise to these chronic inflammatory and proliferative processes in the vessel walls; these, on the one hand, lead to weakening of the vessel wall and dilatation of its lumen, and on the other hand to condensation and adhesion of its lymph sheaths. Thus is brought about an obstruction to the lymph flowing away, and, in dependence on this lymph stasis, a swelling and degeneration of the nerves fibres in the "Lichtungsbezirke." When the glia in such areas undergoes a compensatory growth, we get the formation of a sclerosed area. Thus a hyperlymphosis may be regarded as the "Grundlage" of the disease, and this may explain the various types of areas found in disseminated sclerosis. SCHMAUS thus supports BORST'S view of a hyperlymphosis, but attributes to it far less significance than BORST, for he thinks that the constancy of blood-vessel and meningeal changes is by no means proved.

(2) Process underlying Multiple Sclerosis founded upon a Disturbance of Development.

A. *Deficient "Anlage" of the Nerve Elements, with Hypoplasia or "Agenesie" of the Myelin Sheath.*

Schiff and other writers have thought it possible to trace disseminated sclerosis to partial or total absence of the myelin sheath formation. We know that the appearance of the myelin represents a definite stage in the development of the nerve fibre. This myelination sets in at different periods in different tracts, and even in different fibre areas of related tracts. The naked axis cylinders might, therefore, be looked upon as incompletely developed nerve fibres. Friedreich's ataxia has been traced to such a deficient development, and Schiff sees in the fact that in Friedreich's ataxia the glia development approximates in intensity to that found in disseminated sclerosis a possible analogy. He thinks that disseminated sclerosis may be due to a deficient or arrested development of the myelin sheath in the affected areas. Kahler and Pick have ascribed system diseases to such an arrest of development. Schmaus thinks this view worthy of consideration; but Borst, while acknowledging that certain parts remain at an early stage of development, thinks that such an explanation is possible only for system diseases, and that it is improbable that multiple scattered arrests of development can occur. Most writers have agreed with this attitude, and supporters of the developmental nature of the process relate it rather to disseminated defects in the glia framework of the central nervous system.

B. *Multiple Defects in the Glia Framework of the Central Nervous System.*

Strümpell (1896) was one of the earliest advocates of this view. He speaks of a "multiple gliosis," and draws comparisons with multiple fibromata, lipomata, neuromata, etc. He looks upon the etiological factors of an exogenous nature only as exciting causes, and he thinks it very unlikely that we should find a primary affection of the smallest vessels in the central nervous system and not in the other organs of the body. Strümpell further recognises it to be necessary, in other cord affections, *e.g.* hydromyelia and syringomyelia, in which we have marked glia proliferation, to have recourse to congenital anomalies of development. In disseminated sclerosis he thinks that the proliferation of the glia gives the impression of a primary process, and that it cannot be traced to a previous degeneration of the nerve elements.

Schmaus holds that both the view of a congenital hypoplasia or agenesia of the myelin sheath and that of the possibility of inserted islets of glia with a special capacity for proliferation are worthy of consideration, at least so long as no other proof is brought forward. He thinks that the most important objection to the

developmental theory is that from this kind of pathogenesis numerous forms of disseminated sclerosis must be excluded. He, therefore, distinguishes between primary disseminated sclerosis, due to developmental defect in some form, and secondary disseminated sclerosis, the consequence of an acute disseminated myelitis. This secondary form of disseminated sclerosis is only one of a group of allied diseases, which includes advanced vessel disease and disseminated syphilitic disease of the vessels, and all of which may lead to the formation of scattered sclerotic areas in the central nervous system. SCHMAUS further thinks that diffuse forms of disseminated sclerosis, or "diffuse multilocular sclerosis," in which the areas have not the defined outline nor the characteristic preservation of the axis cylinders, found in true disseminated sclerosis, must be regarded as "chronic myelitis."

ZIEGLER, in the last edition of his text-book, also differentiated primary and secondary disseminated sclerosis. Primary disseminated sclerosis may be due to the incomplete development of the myelin at certain parts, or to glia abnormality in the sense of an abnormal quantitative distribution of the glia, or deficient idioplastic differentiation of the glia. The areas typical of primary disseminated sclerosis contain dense sclerotic tissue, with persisting axis cylinders in the narrow meshes. Secondary disseminated sclerosis is thought to be due to multiple ischæmic areas, with secondary proliferation of the glia. The areas typical of this form are areolar, and contain few axis cylinders in the widened meshes.

BALINT (1900), BARTELS (1903), PROBST (1898), HOFFMANN (1902), and others likewise speak of an abnormal or inherent disposition of the glia, an early "invalidity" of the central nervous system, or an abnormal congenital "Veranlagung" of the glia.

MÜLLER (1904), in an important monograph, "Die multiple Sklerose des Gehirns und Rückenmarks," has made a careful survey of the whole subject of disseminated sclerosis, especially in relation to its clinical course, differential diagnosis and pathogenesis. He strongly support's STRÜMPELL'S view of the developmental nature of the disease, and emphasises the distinction between primary and secondary disseminated sclerosis. The views set forth in this monograph are more fully examined in a later section (p. 638). In a later paper (1906) MÜLLER urges the early diagnostic importance of the ocular disturbances: affection of the optic disc, especially in relation to the acuteness of vision and the field of vision, nystagmus, and paralysis of the ocular muscles. He looks upon these as more valuable signs than the so-called classical symptoms of the disease. The *formes frustes* are regarded as presenting a typical syndrome which permits of their ready recognition. In a further paper (1910) he relates the disturbances of sensibility, which are almost always present, at least to a slight degree, to affections of the cranial and spinal nerve roots in the glia-containing parts of their course.

(3) More Recent Researches, 1903–1913.

Bielschowsky (1903) has investigated five cases of disseminated sclerosis by means of a silver-impregnation method for axis cylinders (see p. 555). He found in sclerotic areas axis cylinders preserved in such large numbers that the areas could scarcely be distinguished, in consequence of the numbers of axis cylinders running in normal order and with normal calibre. The presence of thickened vessels in the sclerotic areas alone served to indicate the patch. In other areas the axis cylinders were sinuous and swollen or split up into a bundle of parallel-arranged fibrils, or, again, broken up into a series of pearl-like swellings. Bielschowsky discusses the question of the axis cylinders present being regenerated or persistent axons, and comes to the conclusion that they must be chiefly persistent. He bases his view chiefly on the facts that the topographical arrangement of the fibres is maintained, and that in longitudinal section myelin fibres could be traced directly into the sclerotic tissue, there to lose their myelin sheath and again to become connected with myelinated fibres at the limit of the area. Bielschowsky states that there was a far-reaching correlation between the clinical histories and the impregnation pictures, and claims that, by his method, the relationship between symptoms and anatomical findings is made more evident than by any other method. He thinks that the finest axis cylinders disappear first, the coarser ones being preserved longer, but admits that the coarser axis cylinders may be swollen fine ones. The possibility of a slight regeneration of nerve fibres is admitted, fork-like divisions being probably regeneration appearances, and brush-like splitting up probably degeneration signs.

Bielschowsky regards the nature of the process as essentially an inflammatory one, attacking both the parenchymatous and interstitial tissues, but affecting the nerve fibre more uniformly than the glia. He looks upon the vessel changes as secondary to the resorptive processes, and thinks that the circulating "noxa" passes through the vessel wall, leaving it intact.

Bartels (1904) has examined four cases of disseminated sclerosis, and supports Bielschowsky's view of the persistence of the axis cylinders in opposition to Strähuber's view of the regeneration. By means of Kaplan's, Strähuber's, and Bielschowsky's staining methods, he has demonstrated the direct transition of the fibres within and without the foci. He considers that the fibres stained with aniline blue are those in which the myelo-axostroma (axo-chromatenin) survives the destruction of the myelin sheath.

Strähuber (1903) thinks that the disposition to disseminated sclerosis might be occasioned by inborn defects as well as by minimal tissue injuries that have arisen in the place of earlier injuries or local anæmias. Such parts are "loci minoris resistentiæ" for bacteria or toxins reaching them from the blood. On the other hand, bacteria or toxins in the blood, in consequence, for example, of infectious

diseases, find favourable conditions for development in such parts with local tissue degenerations. These may be the result of capillary bleedings arising from concussion and other causes, or local anæmias arising from chill or nervous action (fear), etc. STRÄHUBER regards the process, on the whole, as an inflammatory one, affecting both the nerve fibre and the glia tissue simultaneously.

STRÄHUBER has found sclerotic areas in peripheral nerves, and looks upon these as an expression of the same process. BORST, however, thinks that the investigations were not sufficiently exhaustive, and certainly insufficient to prove STRÄHUBER'S contention that a primary proliferation of the glia is not the essential factor in disseminated sclerosis. MÜLLER interprets such areas in the peripheral nerves only in the sense of GOMBAULT'S peri-axial neuritis, and thinks that the cases in which they occurred were cases of true acute disseminated myelitis.

By means of a new staining method for axis cylinders STRÄHUBER concluded that a regeneration of nerve fibres must take place in the areas of sclerosis. He bases his arguments upon the finding of very fine nerve fibres with very small medullated sheaths and also on the presence of fine naked axis cylinders. These fine nerve fibres, he thinks, are too numerous to be persisting fine axis cylinders, and cannot be compressed nerve fibres, nor terminal stages of a previous swelling, nor primary atrophied nerve fibres.

SHOYER (1903) notes that a limited number of the patches in the cord in disseminated sclerosis assume certain primary forms, and that the remaining patches can be shown to be due to the coalescence of these primary forms. The primary forms, of which he distinguishes five, are related to the following structural features of the cord:—(1) the posterior fissure; (2) the anterior fissure; (3) the central canal; (4) the points of entry or exit of nerve roots; (5) a point in each lateral margin of the cord. SHOYER thinks that the shapes of the patches suggest that the changes which form them start in these points to which they are thus related. The oval shape of the first form, the wedge shape of the second and fourth, the circular shape of the third and fifth, all suggest that the active agent enters along the fissures, along the nerve roots, or from the central canal. The distribution of the lesions can, therefore, be explained by the assumption that they are caused by a poisonous agent conveyed by the cerebro-spinal fluid, which finds entry along these roots.

TREDGOLD (1904) has given an account of the microscopical examination of three cases of disseminated sclerosis, each of which was typical of a distinct clinical variety. These were, respectively, the spastic paraplegic, the transverse myelitic, and the cerebellar types. He notes that even in the absence of such symptoms as tremor and nystagmus a careful examination will often reveal some peculiarity in the grouping of motor, sensory, or reflex signs which could only be brought about by disseminated sclerosis. The chief symptoms may, therefore, simulate other diseases, but there are present other signs, not characteristic of such diseases, which could be produced only by disseminated lesions. In each case sclerotic islets were found in

both brain and spinal cord, and in each the peri-ventricular and peri-aqueductal localisation was marked.

The microscopic examination, which was very thorough, revealed areas of three types—hard, soft, and intermediate: frequently one area showed all three stages. The hard islets, most numerous in the cord, consisted of dense neuroglia fibrils with few glia cells and only an occasional axis cylinder: typical areas of softening were confined to the brain, and consisted of a loose reticulum, containing a semi-fluid material but no proliferated neuroglia, nor products of degeneration; the intermediate islets contained nerve fibres in all stages of degeneration and the products of degeneration, but no proliferated neuroglia fibrils. TREDGOLD thinks that the essential process is one of myelin degeneration independent of vascular disease, and that the initial changes are strongly suggestive of the presence of a circulating toxin.

BRAMWELL (1904) has studied disseminated sclerosis with special reference to the frequency and etiology and prognosis of the disease, and has discussed its pathology. The author inclines to the view that the disease is due to some developmental or congenital defect of the neuroglial or nervous tissue (perhaps similar to or analogous to the gliomatosis in cases of syringomyelia), which renders it more liable to be affected by irritation than the glial or nervous tissue of the normal individual. He thinks that the diversity of conditions which were thought to be the cause in individual cases makes it difficult to suppose that the alleged cause was in reality the starting-point or sole cause. With regard to the nature of the hypothetical toxin carried to, and distributed through, the nervous tissues by the blood-vessels, he writes: "The recurrence from time to time of the symptoms after periods of improvement and remission is very suggestive of repeated intoxications. If disseminated sclerosis is due to a toxin, the toxin, whatever it is, is probably produced within the body. It seems much more difficult to suppose that fresh doses of the toxin are introduced again and again into the body from without during a long period of years." BRAMWELL'S views as to the nature of this toxin are further referred to on p. 660.

DINKLER (1904) gives a description of the clinical and microscopical appearances in a case of disseminated sclerosis in which there had been spastic paraplegia of a slightly progressive character for eighteen years, but with no nystagmus, intention tremor, scanning speech nor sensory disturbances.

The distribution of the patches was peculiar in that the majority lay in the brain cortex. The myelin sheaths in these areas had undergone fatty degeneration, and the axis cylinders showed a distinct participation in the diseased process. Changes in the ganglion cells of the cortex accompanied the changes in the nerve fibres, not only in the actual areas but in the adjoining tissue. Nests of small cells, probably glious in origin, surrounded each ganglion cell, causing deformity and atrophy: their injurious action on the ganglion cell is compared by the author to that of osteolcasts.

The blood-vessels of the cortex and of the membranes and the membranes themselves were normal.

A further peculiarity was the presence of numerous tumour-like swellings on the anterior and posterior roots close to the cord. Microscopically these showed degeneration of the myelin sheath, marked proliferation of the Schwann nuclei, and persistence of the axis cylinders. Later, the axis cylinder disappeared and the central part of the nucleated hyperplastic zone became hyaline and structureless. The spinal ganglia and peripheral nerves were not preserved.

In correlating the clinical and anatomical appearances two points of importance stand out: (1) the considerable diffusion of the ganglion cell changes in the cortex and the apparently normal intellectual and psychical functions; (2) the appearance of posterior root changes without any sensory disturbances.

SPILLER and CAMP (1904) give an account of two cases, one of which was of the type of a multiple myelitis. They regard it as exceedingly difficult to determine the relation of disseminated sclerosis to multiple myelitis. In the latter disease the areas of sclerosis are much less sharply defined, and in some cases the peri-vascular cellular infiltration is marked without any close relation to sclerotic areas. The authors emphasise the frequent implication of the visual tracts in disseminated sclerosis, the most frequent seat being the optic chiasma. The disturbance of vision may be slight compared with the anatomical alterations. Ophthalmoscopic examination is of great importance, in every case presenting symptoms that can be attributed to disseminated sclerosis, and pallor or even atrophy of the discs may exist even when the vision is not complained of.

DERCUM and GORDON (1905) describe the anatomical findings in a case of disseminated sclerosis and briefly discuss its pathogenesis. They think it is unlikely that the relation of the blood-vessel changes to the sclerosed areas is that of cause and effect. They conclude that the origin of the process may be in the glia, but that at present it is impossible to go further than to infer that neither nerve cells, nor axis cylinders, nor blood-vessels are primarily involved.

CENI and BESTA (1905), in the course of a series of experimental researches upon the pathogenicity of aspergillus spores, observed a dog, which presented symptoms closely resembling disseminated sclerosis. CENI'S previous researches had led him to the conclusion that aspergillus infection is the essential cause of the pellagra, and that this condition is dependent upon the presence of the parasite in the spore form, in which it elaborates very virulent toxins. Animals inoculated intraperitoneally, frequently developed spastic paraplegia with tremors, and the spinal cords of such animals showed primary degeneration of the crossed pyramidal tracts and posterior columns. In this dog, the spastic paraplegia and tremors disappeared at the end of the second month, and the animal showed symptoms characteristic of both locomotor ataxia and disseminated sclerosis. The animal was killed three months after infection with the aspergillus fumigatus and, at the autopsy, the spinal cord,

especially in the cervical region, presented very numerous softened and gelatinous foci. These foci presented many of the characteristics of areas of "sclérose en plaques": the myelin sheaths had disappeared; the axis cylinders were persistent, though swollen; the neuroglia was somewhat hyperplastic; there were numerous fat granule cells in the vessel sheaths, and the vessel walls were infiltrated with numerous small round cells. The vessel alterations were present also in the surrounding normal tissue, and there was a complete absence of secondary degeneration.

The authors regard these areas as intermediate in position between disseminated myelitis and disseminated sclerosis, and also regard them as a proof of the vascular origin of the sclerotic process. They emphasise the fact that in those cases in which aspergillus infection produced a primary system degeneration, there was no trace of any vascular lesion, a circumstance which proves that alterations of myelin are unable of themselves to produce lesions of an inflammatory character.

CATOLA (1905) gives an account of a case in which trembling of the lower limbs developed a few days after the onset of an attack of cholera. Later, the classical symptoms of disseminated sclerosis appeared, and the gait was ataxic-cerebellar and spastic. Histologically there were marked sclerotic areas at various levels in the cord: in the lumbar cord the sclerosis was limited to the pyramidal tracts. In the cerebellum the nucleus dentatus was affected on both sides, but its cells were preserved. One superior cerebellar peduncle was atrophied in its middle portion, but the middle and inferior peduncles stained normally. The vessels both of brain and cord and membranes were thickened and homogeneous both in the sclerotic areas and in the rest of the tissue. The author thinks that the cholera was an etiological factor and that the process was probably of vascular origin. He also notes that although the areas had such an anatomical restriction, the classical symptoms of disseminated sclerosis were nevertheless present. Of special interest is the pronounced sclerosis of the dentate nuclei, in view of the cerebellar ataxia.

TAYLOR (1906) states, in evidence of the extraordinary interest which is being taken in disseminated sclerosis, that he has been able to discover eighty papers dealing with this disease in the literature of 1904 and 1905. He has personally examined several hundred specimens from eight cases. He was unable to find any trace of an inflammatory reaction in the areas of sclerosis. The blood-vessels in the various lesions showed no relation to the degenerated areas, nor did the blood-vessel walls show any alteration in the sclerotic areas as contrasted with normal areas. The symmetry, such as it was, appeared to the author to be entirely fortuitous, and both grey and white matter are involved. The peripheral nerves showed no degeneration, but numerous discrete patches were found in one dorsal nerve root with typical myelin degeneration and no other apparent change. "The conviction is strong that the lesions are localised sclerotic areas, characterised by the usual disintegration of myelin without either primary or compensatory neuroglial overgrowth."

TAYLOR notes that various types of lesion may co-exist in the same case: sharply defined clean-cut areas in contrast to a more diffuse type, in which the area shades off into the normal. He follows WILLIAMSON'S explanation of the sharp delimitation of the process in certain areas by suggesting the presence of a toxic agent, of unknown character, but with a special affinity for myelin, which spreads from a central focus until it exhausts itself. This causal agent reaches the tissue in all probability by the blood or lymph channel, but its manifestation may occur without evidence of local inflammation.

MARBURG (1906) in an important monograph, "Die sogenannte akute multiple Sklerose," gives a report of three cases and a review of others recorded in literature of disseminated organic disease of the nervous system which, from their resemblance to disseminated sclerosis, both clinically and pathologically, have been described as acute or subacute multiple sclerosis. The disease occurs usually between the ages of twenty and thirty. The symptoms indicate that there are multiple lesions in the brain and spinal cord; the onset is gradual; there is no fever; and though the affection is progressive, there is a tendency to remission and fluctuation in the symptoms. In the majority of the cases recorded, death occurred within three months, in some cases earlier, in some later.

The author considers that this so-called acute multiple sclerosis is a form of true multiple sclerosis which is characterised by a more rapid course of the disease. The symptoms indicate that it is a form of multiple sclerosis, especially the mode of onset, the advance of the disease in stages, the remissions and intermissions, and the indications of multiple lesions.

The pathological changes are characterised by degeneration of the medullated sheath of the nerve fibres, while the axis cylinder is relatively intact. At the same time, or soon afterwards, there is proliferation of the neuroglia cells and of cells in the walls of the blood-vessels. The process is analogous to peri-axial neuritis.

The pathological changes are inflammatory, and belong to the group of degenerative inflammatory changes. The nature of the degeneration of the medullated sheath of the nerve fibres indicates that it is due to a "lecitholysis," such as can be produced experimentally by "ferment" action. The pathological changes may, therefore, be regarded as the result of a toxin, and their final stage is the complete replacement of the degenerated nervous tissues by a finely fibrillated neuroglia tissue, which contains only few nuclei.

The affection is regarded by MARBURG as a form of degenerative myelitis, and he suggests for it the name of "encephalo-myelitis periaxialis scleroticans."

WEGELIN (1906) records a case which shows the great difficulty of drawing the distinction, emphasised by MÜLLER, between the acute cases, following disseminated encephalo-myelitis, and the true "sclérose en plaques." The disease in this patient ran a very rapid course, and at the autopsy typical areas of sclerosis were found disseminated through the brain and spinal cord, and in the upper three dorsal

segments there was a total transverse sclerosis. The vessels in most of the areas showed few changes, thus differing from the usual findings in cases of acute multiple sclerosis, and the extension of the areas in no way corresponded to the vessel-distribution. Ganglion cells and axis cylinders in the areas were not essentially changed; there was intense glia proliferation, and an absence of any considerable secondary degeneration.

In the clinical history there was nothing to indicate infectious disease, and during the course of the illness there was no rise of temperature till the onset of the broncho-pneumonia from which the patient died. The author claims that this case could not be regarded as a myelitis, and looks upon it as proving the existence of true acute disseminated sclerosis. He considers that MÜLLER'S grouping of all such cases as "secondary disseminated sclerosis" is arbitrary, as no distinction can be drawn between the acute and chronic cases.

STADELMANN and LEWANDOWSKY (1907) also describe a case, whose acute course (eight weeks) justifies the assumption of an acute multiple sclerosis or acute disseminated myelitis. Areas of sclerosis, composed almost entirely of neuroglial tissue, were found very widely distributed through brain and spinal cord. In the areas there was a distinct vessel proliferation with increase of adventitial cell elements, but no sign of small-celled infiltration. The writers look upon their case as one of acute multiple sclerosis, "in virtue of the absence of any marked signs of actual inflammation."

SCHOB (1907), in a careful histological analysis of the sclerotic areas in a typical case of disseminated sclerosis, lays special emphasis on the pathological changes found in the nerve roots. From these changes he claims that the process in the peripheral nervous system is analogous to that in the central nervous system—in both a myelin sheath degeneration, relative integrity of the true nervous elements, proliferation of the supporting tissue, and the essentially localised extension of the affected tissue. He states that the case belongs to the rare observations where "with certainty," in addition to areas in the central nervous system, circumscribed and analogous areas are found in the non-glial containing tissue, and relates it to a combination of a neuro-fibromatosis in the nerves and a gliomatosis in the central nervous system. The glia proliferation, therefore, cannot have the significance of an essential and primary process, as is claimed by STRÜMPELL and MÜLLER and others, who look upon disseminated sclerosis as an endogenous primary glia sclerosis.

The changes described are a connective-tissue proliferation which has arisen almost exclusively from the Schwann sheath or the finest endoneural septa, while the larger endoneural septa and the perineurium take no share in the proliferative process. In some cases the process is so advanced as to form fibroma-like tumours, in which the Schwann sheath has formed several concentric lamellæ, the central zone of which has become hyaline. In the midst of this lamellated tissue it is

possible to recognise a few axis cylinders. SCHOB has recognised the importance of examining the nerve roots in their longitudinal course. Several roots showed disease in their whole length: the emergent root zone showing a glious sclerosis, and the immediately adjoining tissue a connective-tissue sclerosis. On the other hand, in a few roots it was recognised that the affection was strictly limited to circumscribed areas, into which one could follow non-degenerated myelinated fibres, distal to the glious root emergent zone. Only one peripheral nerve, the right crural, was preserved, and in this similar degeneration was found. In criticising such findings it is necessary to state, firstly, that as the spinal ganglia were not preserved the portion of nerve roots attached was short, and secondly, that the only justification for asserting the non-glial content of the tissue seems to have been that these changes affected root sections where the nerve fibres are normally surrounded by Schwann sheath. It must be remembered that the glious zone reaches for a very varying distance into both cranial and spinal nerve roots, and that one can frequently recognise glia islets appearing in a part far into the connective-tissue portion of the root. It is difficult, therefore, to exclude the possibility of the glia-containing root emergent zone being primarily affected and the possibility of secondary degeneration.

VOLSCH (1908) describes very minutely the changes in a case of "acute multiple sclerosis." His choice of this designation instead of acute disseminated myelitis indicates, in his opinion, both the assumption of the influence of an exogenous factor, and also the supposition that the process depends on a primary proliferative process in the glia—this process depending only in part on the direct action of the exogenous factor. The illness set in with a gradually increasing weakness of the legs, which was followed by paralysis of the abdominal muscles, flaccid paralysis of the legs, and severe decubitus: the patient died four months after the onset of the illness. The characters of the sclerotic areas, which were very numerous in both brain and spinal cord, are very similar to those previously described as typical of disseminated sclerosis. In the centre of most areas was a compact glia proliferation, surrounded by a looser glia structure, which gave an areolar appearance to the periphery. In addition to these areas, the author describes diffuse alterations in the cord, which consist of a lighter staining of the myelin, together with a marked hyperplasia of the septal glia. The vessels in these latter areas were almost normal. This diffuse septal glia hyperplasia often extended over the whole transverse section, and in Marchi-stained sections the nerve fibres showed deeply stained granules of degeneration surrounding the axis cylinder.

VOLSCH looks upon the typical areas as the essential substratum of the disease: they were mostly at a uniform stage of development, already far advanced, and undoubtedly owed their origin to an unknown exogenous "noxa." On the other hand, he thinks that the areas of a more diffuse gliosis are related more probably

to a much more chronic process in which an endogenous factor—an increased tendency to glia hyperplasia—has played a part. In the brain there were no areas corresponding to this diffuse gliosis.

In a later paper (1910) VOLSCH returns to the question of the differential diagnosis between disseminated sclerosis and disseminated encephalo-myelitis. He states that both in acute and chronic multiple sclerosis he has found peri-vascular areas brought about directly by an exogenous "noxa," but that he cannot regard the glia hyperplasia as solely secondary and reparatory. On account both of its rapid onset and its profuseness, he assumes that the exogenous "noxa" causes nerve fibre degeneration, and at the same time stimulates the glia to proliferate. In this proliferation such an endogenous factor as a congenital predisposition of the glia to hyperplasia might play a rôle.

OPPENHEIM (GUSTAV) (1908) investigated histologically four cases of disseminated sclerosis. Successive sections of various parts of the brain and cord were stained by the various elective staining methods in order to obtain as complete and simultaneous a picture as possible of the changes in the component tissue elements. He was able to confirm the usual findings as to myelin sheath degeneration, relative integrity of the axis cylinders, and the frequent presence of fat granule cells in the sclerosis area. In three of the four cases examined there was marked plasma-cell infiltration of the walls both of arteries and veins. The presence of the plasma cells, the author regards as an expression of a more or less chronic inflammatory process. With the Weigert glia stain areas of a dense sclerosis were noted, together with those of a looser structure, the latter containing many large spider cells. A special study was made of the cortical areas, and those involving both cortex and subjacent white matter. While the subcortical portion of these patches presented a more or less dense feltwork of neuroglial fiibres, in the cortex itself this fibre increase ceased, except in the *Randzone*, and in the ganglion-cell layers only single spider cells were found. It was almost impossible to distinguish the cortical areas in the preparations stained by Nissl's and Bielschowsky's methods, on account of the persistence of the nervous elements: the glia fibril picture also was negative in the cortical area and positive in the subcortical white matter. The statements of those observers who worked with nuclear stains alone,—before the introduction of Weigert's medullated sheath stain,—to the effect that the subcortical patches did not extend into the cortex, is thus explained. OPPENHEIM has found in these cortical areas, in addition to the absence of the myelin sheaths, a diffuse, excessively delicate, protoplasmic reticulum. In spite of the similarity of this network to Held's diffuse protoplasmic glia reticulum, he doubts whether it can be looked upon as exclusively of glious structure.

BENIGNI (1908) describes a case in which there was complete absence of any of the classical symptoms of disseminated sclerosis, except intention tremor. Sclerotic areas were found only in the spinal cord, and there was a marked alteration of the

ganglion cells in the lumbar segments—an alteration *en rapport* with the muscular atrophy presented by the patient.

SCHLESINGER (1909) relates the case of a boy in whom the diagnosis of a typical multiple sclerosis, with subacute course, was made. The patient developed eye symptoms two weeks after an attack of measles and died ten months after the onset of the disease. Microscopical examination revealed the presence of a very large number of larger and smaller sclerosed areas in the brain and spinal cord.

The author was able to distinguish three types of areas: (1) in a few the nerve substance had in great part perished and only a few naked axis cylinders were left. The glia was markedly proliferated, and in the areas, especially in the walls of the vessels, were numerous fat granule cells. (2) Areas of an older date, typical of the classical picture of disseminated sclerosis, with absence of myelin sheath, marked glia proliferation, and persistence of axis cylinders, but no fat granule cells. (3) Areas described as *Markschattenherde*, in which the fibre layers are distinctly evident but weakly stained. The fibres have not only a lesser staining capacity, but are frequently abnormal in appearance, being either swollen or atrophied. These areas are also circumscribed, and on each side the fibre layers resume their normal staining and character. These areas were found distributed through the whole central nervous system, but especially in pons and medulla, where they occupy a large part of the transverse section. They were looked upon as transition stages to the development of patches of true disseminated sclerosis. The presence of areas of the second and third types justified the anatomical diagnosis of subacute multiple sclerosis, but the author regarded the areas of the first type as transitional to disseminated encephalo-myelitis.

SCHLESINGER also notes the finding of nephrolithiasis at the autopsy, and states that he has found this chiefly in relation to traumatic diseases of the spinal cord, and also in three cases of syringomyelia, and in three cases of encephalo-myelitis.

MARINESCO and MINEA (1909) have examined specially the changes in the axis cylinders in the sclerosed areas. They look upon the persistence of the axis cylinders neither as pathognomonic of, nor essential to, the picture of disseminated sclerosis. The persistence does not last indefinitely, and, therefore, there must be some secondary degeneration, but this affects not a tract nor even a bundle of fibres, but only a few groups of fibres. They regard regeneration as a necessary complement of degeneration, and by means of Cajal's and Bielschowsky's methods, they have found distinct evidence of terminal and collateral regeneration. The former is observed at the extremity of rather thick axons, but it is the collateral form which is more manifest in disseminated sclerosis. The thinness and the number of these new axis cylinders distinguish them from pre-existing collaterals of the axon.

LÉJONNE and LHERMITTE (1909) have examined clinically and anatomically three cases of disseminated sclerosis and give the histological analysis of one case. A young woman, twenty years of age, with the characteristic symptoms of dissemi-

nated sclerosis of five years' duration, died in hospital from typhoid fever. Plaques of sclerosis in every stage of development were found, from small inflammatory foci to old areas of neuroglial sclerosis.

In the cord the patches were quite typical: in some the vessels were apparently normal, in others they were surrounded by a proliferation of embryonic cells invading the lymphatic sheath and the vessel wall itself. In the brain, however, the picture was very variable, but in the centre of each plaque a blood-vessel was found, with embryonic cells and fat granule cells in its walls, or showing hyaline degeneration. In the areas, old and new, there was proliferation of the neuroglia with preservation of the axis cylinders. The axis cylinders were more or less hypertrophic or atrophic, but no secondary degeneration was found anywhere.

The recent areas showed typical inflammatory appearances, and all transitions could be traced to the old patches. The vessel changes are the more pronounced the younger the areas, and the authors consider it highly probable that the plaques owe their origin to an irritative agent brought by means of the blood-vessels. Nowhere was there any evidence of thrombosis or narrowing of the lumen. They exclude the possibility of a terminal infection, pointing out that the characteristic features of the latter are not present. They believe that there is no essential and fundamental difference between disseminated sclerosis and disseminated myelitis: it is a difference in degree rather than in kind.

LHERMITTE and GUCCIONE (1909), in the histological investigation of three typical cases of disseminated sclerosis, found identical lesions affecting the blood-vessels, the neuroglia, and the axis cylinders. In the wall of the blood-vessels in recent areas there was a marked infiltration of lymphocytes and plasma cells, and in older plaques the vessel wall was thickened and hyaline. In their opinion, the plasma cells in the vessel walls of the early areas develop into connective-tissue cells and give rise to the fibrous thickening of the older areas. The neuroglia was studied by means of their new staining methods for glia cells and fibrils (p. 556). The axis cylinders persisted in very diminished numbers, and there were marked alterations in those persisting.

In a later paper (1910) the authors review the psychic symptoms occurring in disseminated sclerosis, and relate them to anatomical alterations in the cortex.

In a further paper (1910) the authors describe specially the peri-ventricular changes found in two cases. In addition to numerous plaques in spinal cord and brain, there was marked neuroglia sclerosis of the peri-ventricular white substance. The ventricles were not dilated and the walls were of their normal smoothness. The sclerosed tissue was dense and poor in nuclei: the fibrils followed the lines of the nerve fibres, surrounding them completely. As a result, the latter were tortuous, rarefied, and moniliform; some were reduced to irregular spiral threads. The ependymal epithelium was normal, and dilated tortuous vessels, surrounded by small round-cell and plasma-cell infiltration, ramified through the glial tissue. A circular

band of sclerosis was also found to surround the aqueduct of Sylvius, but here the ependymal epithelium was greatly modified. The writers refer to the possible pathogenic significance of these peri-ventricular lesions, and think it probable that the toxi-infectious agent, whose nature is not suggested, may diffuse through two channels: the one the more constant, represented by the blood-vessels; the other, of lesser importance, the cerebro-spinal fluid.

MERLE and PASTINE (1910) also refer to a case in which the ependymal and peri-ependymal change was the dominant pathological feature. They agree with LHERMITTE and GUCCIONE in regarding the existence of lesions in such a special localisation as probably of great pathognomonic significance. References are given to other cases, which show that irritation of the ventricular walls must be considered a not uncommon feature of the disease.

WEISENBERG and INGHAM (1910). The most interesting points of the case reported by these authors are: (1) the atrophy of the brain—rare in disseminated sclerosis—and the undoubted hypoplasia of certain parts, which is here doubtless congenital; (2) the primary degeneration of the pyramidal tracts, which is in no way related to the sclerosis; (3) the presence of developmental anomalies.

SPIELMEYER (1910) has specially studied the relation between disseminated sclerosis and progressive paralysis. He distinguishes clearly between the diffuse cortical medullated fibre atrophy in general paralysis and the irregularly distributed patches which bear a striking resemblance to the cortical areas in disseminated sclerosis. He thinks that many cases of disseminated sclerosis in the intensity of their psychic disturbances bear a great similarity to the clinical picture of progressive paralysis. In general, in the latter disease there are no sclerotic patches found in the cord, but FÜRSTNER has found, in addition to the system degeneration in the posterior and lateral columns a more diffuse and patchy sclerosis in the cord, areas in which there was dense glia proliferation, and in the cord of the case which forms the subject of this article, SPIELMEYER also found, in the lumbar cord, definite patches with all the characters of the areas in disseminated sclerosis. In sixty other cases of general paralysis he has failed to find sclerotic areas in the cord, but thinks a definite relation exists between the cortical areas in the two affections.

In a case which clinically was general paralysis, there were found two varieties of medullated fibre atrophy: (1) the usual more diffuse fibre degeneration, and (2) a local accentuated form in which spots and striæ had led to a limited demyelination of the cortex and to changes which were designated as *cortical Markfrasse.* These spots and striæ were found most frequently in the radiations of the medullary ray, were sometimes limited to the region of the deep cortex, were sometimes in the intra-medullary cortex, and sometimes led to complete obliteration of the fibres in the cortex. The areas appeared sometimes only isolated in individual convolutions, and in other parts, especially in the anterior two-thirds of the hemispheres, were so numerous as to give the convolutions a moth-eaten appearance. In preparations

stained by the Bielschowsky method it was possible to recognise where the nerve fibre lost its medullated sheath and continued non-myelinated through the area, and in preparations stained for glia and for cells, the areas were not distinctly marked out from the surrounding tissue. Only occasionally was the impression gained that the large and small spider cells were more abundant in the patches. The changes in the blood-vessels also were not more marked than in the surrounding tissue, and it was found impossible to trace any special relationship between blood-vessels and the areas. From his histological analysis SPIELMEYER decided that the changes in the medullated sheath degeneration and the changes in the glia and blood-vessels in the cortex were in no sense proportionate, and in this negative finding he saw an agreement with what occurs in the cortical areas in disseminated sclerosis in which all anatomical changes in axis cylinders, cells, and glia fibres are absent.

In the form, however, of the cortical areas, there appeared in general a distinction between the areas in general paralysis and those in disseminated sclerosis. In the latter disease the areas are usually more extensive, more defined, and spread frequently from the medullary ray into the cortex. In general paralysis, on the other hand, the areas are smaller, indistinctly outlined and often ragged, and rarely spread from white matter to cortex.

SPIELMEYER has also microscopically investigated a case of NONNE'S, in which during the last nine months of life there were very marked psychic anomalies. He found numerous sclerotic plaques in the larger ganglia and in the cortex, and traced a complete agreement between clinical data and anatomical findings.

SIEMERLING and RAECKE (1911) put forward the suggestive view that underlying disseminated sclerosis there is an inflammatory process, which in its extent keeps to the distribution of the blood-vessels and leads first to the presence of capillary hæmorrhages. In all the plaques examined the evidence of the importance of capillary hæmorrhages as the first sign of the area was very striking, then followed fibre degeneration, with a subsequent glia proliferation. Such areas, with small hæmorrhages, often lay very close together, both in brain and spinal cord, and by their confluence large irregular plaques were formed. The authors investigated seven cases of disseminated sclerosis, and, to ascertain the number and distribution of the areas, made sections through the whole cerebral hemispheres in frontal and sagittal direction. Such large brain sections revealed how varied was the distribution of the sclerotic plaques: in three of the cases only the white matter of the brain was affected, and in two cases, in which psychic affections were marked, the plaques were prevailingly in the cortex. In the cortical areas the wedge-form, with base on the surface of the convolution, was most frequent, and over these areas the pia was thickened and infiltrated with round cells. In all the cortical areas the tangential and supraradial fibres were involved, and in almost all a blood-vessel or blood pigment was the central point of the area.

FLATAU and KOELICHEN (1902–1911) describe a case of disseminated sclerosis

which had clinically strongly simulated subacute transverse myelitis in the lumbo-sacral region of the cord, without any cerebral symptoms. Death occurred three and a half months after the onset of the disease. There were no macroscopical alterations in the brain or spinal cord. Numerous sclerotic areas were found throughout the whole length of the cord. These were divided into two groups: (1) those in an early stage of myelin sheath degeneration, without participation of the blood-vessels or glial tissue; and (2) further advanced areas with accumulation of fat granule cells in the vessel walls and glial proliferation. The whole of the lumbo-sacral cord was in a condition of advanced degeneration. In all the areas the participation of the vessels in the sclerotic process was quite evident, and the authors regard the vessel alterations as the key to the whole process. Disseminated sclerosis is looked upon as essentially a disseminated inflammatory process, *i.e.* a disseminated myelitis, with, however, certain special characteristics. The inflammatory changes are assumed to be not so intense as in myelitis, and, therefore, there are no "softenings" in the usual sense of the term.

In their later paper FLATAU and KOELICHEN again discuss the relation of disseminated encephalo-myelitis to disseminated sclerosis. They think that the infectious or exotoxic origin can be admitted for those cases of disseminated sclerosis running an acute course, but that the pathogenesis of most of the cases with a chronic course must be different, and is probably related to an autogenous toxin. Whether the supposed toxin forms in the body, and whether disturbed metabolism or an altered internal secretion plays a part is not stated. As in their earlier paper, the authors see in disseminated sclerosis a chronic irritative process of the whole central nervous system—a process which has acute exacerbations, and which, in the majority of cases, is dependent on autogenous intoxication.

NONNE (1911) has made a careful clinical and serological investigation into the phenomenon of inhibition of cobra poison hæmolysis. He has investigated all possible cases of organic disease of the central nervous system, and has also made very numerous control tests. He feels justified in stating, yet with a certain amount of reserve, that the cobra reaction is specially frequent in degeneration-neuroses and psychoses, and in hereditary diseases in the neuro-psychopathic sense. In the katatonic group also, and in the group of maniac-depressive psychoses, and in the chief representatives of endogenous psychoses, the reaction is likewise very frequent. Amongst organic diseases of the central nervous system, the reaction appears most frequently in disseminated sclerosis. In healthy individuals the authors found the reaction in 5 per cent., in people with diseases other than of the nervous system in 15 per cent., in psychoses in 65 per cent., and in disseminated sclerosis in 65 per cent. As the reaction appears even in the early stages of disseminated sclerosis, NONNE is tempted to value it as a differential diagnostic sign, especially as the Wassermann reaction, the globulin reaction, and the cytological examination of the cerebro-spinal fluid in disseminated sclerosis give no indication of

the disease. He thinks that as these very psychoses which are claimed as types of endogenous etiology are marked by the presence of cobra reaction, the fact of its presence in disseminated sclerosis appears to support the view of the endogenous nature of this disease, especially as it is very seldom observed in acquired disease of the nervous system, with the exception of general paralysis.

ROBERTSON (1912) records a case of disseminated sclerosis which is of special interest on account of the presence of hydromyelia, interstitial neuritis in several peripheral nerves, and changes in the posterior root ganglia, which suggested a chronic inflammatory condition. The absence of some of the characteristic features of disseminated sclerosis, *e.g.* nystagmus, scanning speech, intention tremor, etc., is explained by the author by the fact that the sclerosis had confined itself chiefly to the cord, the medulla and pons being only slightly affected, and the cerebrum and cerebellum scarcely at all. The presence of a hydromyelia is interesting in view of the theory that disseminated sclerosis is a multiple gliosis, but the author thinks that the cavity formation might as truly occur in glial tissue, formed as a result of chronic irritation, as in that resulting from congenital abnormality, and that the well-marked interstitial peripheral neuritis lends support to the view of the chronic toxæmic nature of the disease. The appearances of the posterior root ganglia would also accord with this view. There were no degenerative changes in the walls of the blood-vessels, but there was evidence of a cellular reaction in their adventitia.

WOHLWILL (1913) has given a short review of the recent literature on disseminated sclerosis. The pathological anatomy, pathogenesis, and etiology are carefully discussed, and various etiological factors are submitted to a close examination. The conclusion is reached that histological investigation has advanced in the direction of harmonising our ideas as to the exogenous nature and vascular origin of the disease, but that we are still far from determining its real nature.

III.

METHODS.

In order to obtain as comprehensive a view as possible of the distribution of the lesions and of their structure, a very large number of sections, both large and small, have been examined from the brain and spinal cord of each case. The brain was fixed in Pick's solution, and, after the tissue had acquired a certain consistency, was cut into pieces suitable for the respective methods. The spinal cord, after small pieces at various levels had been removed for Cajal's silver method for axis cylinders, was also placed in Pick's solution.

The cerebral hemispheres were removed from the pons and cerebellum by a section at the upper margin of the pons at right angles to the transverse fibres of the pons. They were then separated from one another by a vertical sagittal section. Each

hemisphere was then cut across horizontally by Pierre Marie's *coup d'élection*, a section which passes under and just touches the extremities, anterior and posterior, of the corpus callosum as it appears on the mesial aspect, and is carried horizontally outwards to the lateral aspect of the hemisphere. Successive cuts were made through the whole hemisphere above and below this section, and parallel to it. Each slab of brain tissue averaged one and a half centimetres, and from each hemisphere alternate slabs were mordanted in Müller's fluid for use with the Weigert and Marchi methods for fibre-tract degeneration. Two of these mordanted slabs from each hemisphere at corresponding levels were embedded in celloidin *en bloc*, and from the others, portions, which showed sclerotic areas either recent or old, were taken through for the Weigert or Marchi method. From the remaining unmordanted slabs pieces of tissue were removed, either including isolated areas when these lay, *e.g.* in the central white matter, or, when the sclerotic area involved cortex or subcortical white matter, the tissue section included the adjoining convolution on one or both sides. Such pieces of tissue were embedded in paraffin, or celloidin, or the combined celloidin-paraffin method, or finally were cut as frozen sections. Adjoining sections were then stained by as many of the available methods as possible, so that by the aid of differently stained sections, adjoining one another, a reconstruction of the complete histological picture was made possible.

The cerebellum, pons, and medulla oblongata were cut through by means of sections parallel to the original cut, *i.e.* at right angles to the transverse fibres of the pons, and the pieces of tissue were treated in a manner similar to that used for the hemispheres, with the exception that in one or two cases the whole of these portions was mordanted.

The spinal cord was cut transversely at levels corresponding, as far as possible, to the different segments. From each segment, except in the instances to be mentioned later, a portion was embedded in celloidin for the Weigert myelin sheath stain, a portion from each alternate segment for the Marchi method, and a portion from numerous levels for paraffin embedding or frozen sections. A segment from each region of the cord—cervical, dorsal, and lumbar—was in nearly every case cut longitudinally either in celloidin or paraffin sections, and in several instances, when a sclerosed area was distinctly outlined on the cord surface through the pia, such portions of the tissue were removed, embedded in celloidin or paraffin, and cut serially either in transverse or longitudinal sections. Longitudinal sections were found of special value in demonstrating changes in the myelin sheath and axis cylinder. In numerous other instances sclerosed areas were traced throughout their whole extent by means of serial sections, and in one case the pons and medulla were cut serially and three sections in every ten stained respectively for myelin sheath, axis cylinder, and cells. The smaller celloidin blocks were cut at 16μ in thickness; the larger, of the whole hemisphere, varied in thickness from 24 to 36μ; the paraffin sections were cut at 6μ.

Three groups of staining methods were used :—

(1) Methods for fibre-tract degeneration. The Weigert myelin sheath stain and the Marchi method are of special value in giving a topographical distribution of the areas, but they permit of very limited histological observations.

(2) The elective staining methods. These render possible the isolated representation of certain tissue constituents, but for this reason they do not give a complete histological picture. The methods for representing fibre-tract degeneration must also be regarded as elective staining methods.

(3) The diffuse stains. These, on the other hand, *e.g.* Van Gieson's stain and hæmatoxylin and eosin, do not sharply distinguish between the individual elements of the central nervous system, yet are of great value in giving an insight into the detailed structural changes, especially when controlled by elective staining methods.

The Kulschitsky-Pal modification was found to be the best of the many modifications of Weigert's classical method of demonstrating the medullated sheath. This has been used by numerous recent workers as being that which allows sufficient differentiation of the medullary layers without decolorising the finest fibres of the cortex. WEIGERT used as a test of a satisfactory differentiation the supraradial network which lies between the tangential fibres and the pyramids of Ferrein : any staining which did not show this clearly he regarded as unsuitable. In the preparations through the whole hemisphere it was found impossible to differentiate the medullary layer sufficiently without decolorising this supraradial network, and an endeavour was made to have two sets of preparations in different stages of differentiation.

As a substitute for the Weigert method, with unmordanted celloidin sections and frozen sections, Heidenhain's iron-hæmatoxylin stain was used. This stain brings out the finest fibres in the grey matter of the cord, and in the cerebral cortex the fine fibre network is stained. Frozen sections thus stained are extremely brittle, but sufficient may be left of the section for comparative examination.

The Marchi method used was Orr's modification, in which the penetration of the osmic acid is assisted by a small proportion of acetic acid. It was found, however, that instead of bringing the thin pieces of tissue direct from Müller's fluid into the Marchi fluid, it was preferable to begin with a proportion of 3 : 1 of Müller's fluid and Marchi fluid, and, later, increasing the proportion of Marchi fluid to finish with Marchi fluid of full strength. The results in tissues thus treated were invariably constant. The Marchi-stained sections were frequently counter-stained with safranin.

For the staining of the axis cylinders two specific staining methods were employed. Cajal's silver impregnation method (for myelinated axis cylinders) was used when the tissue could be fixed directly in 96 per cent. absolute alcohol : when the tissue, however, had been already placed in formalin or in Müller's fluid, the Bielschowsky method, or, in the latter case, the Bielschowsky-Williamson method, was used. These staining methods depend on the reducing action of formaldehyde, which acts on an ammoniated silver solution and deposits metallic silver. It stains

not only axis cylinders deprived of their myelin sheath but also those "naked" axis cylinders which no longer contain myelo-axostroma (a cement substance enclosing and holding together the neurofibrils which, as its name indicates, histogenetically and chemically resembles the myelin of the medullated sheath). The extreme uncertainty of the Bielschowsky method and its various modifications has been frequently emphasised. It is undoubtedly "a method full of surprises and disappointments even for the experienced technician." In numerous instances the glia fibrils are also stained, and as these run longitudinally in the same direction as the axis cylinders the result is confusing; at other times the medullated sheath is stained—a point very forcibly brought out in comparing frozen sections stained with iron-hæmatoxylin. The method, however, often gives very serviceable, and even beautiful, results, and is applicable to both celloidin and frozen sections, but one must accept a negative picture with very great reserve. Two non-essential modifications were adopted, both of which seemed to make the result less capricious. The one, recommended by SCHLEMMER, has for its object the obtaining of an ammoniated silver solution, of uniform strength, which will not become cloudy or discoloured when exposed to light; the other is an addition of a slight trace of acetic acid to the alcohol in which the sections are immersed before being brought into the ammoniated silver solution.

A third specific staining method for axis cylinders was also tried: Strähuber's aniline blue method, differentiating the sections with saturated sodium hypochlorite solution. The aniline blue, however, while bringing out axis cylinders very beautifully in normal tissues, distinguishes them very insufficiently from the glia fibrils in sclerosed tissue. Strähuber's method stains only those axis cylinders which still retain the myelo-axostroma, or as STRÄHUBER named it, the chromatenin or axo-chromatenin—terms which seemed to him to indicate that the material to which it refers is only one of the constituents of the peri-fibrillar substance. Fibres which have lost their myelin sheath are, therefore, merely non-myelinated axis cylinders, not necessarily naked axis cylinders.

Before leaving axis-cylinder methods, it must be mentioned that there is no specific method analogous to that of MARCHI to represent the degeneration of the axis cylinder. Eosin and picro-fuchsin and several other stains frequently bring out the axis cylinders very clearly, but they are not elective stains, and BARTELS states that the homogeneous granular masses, which are recognisable in sclerosed areas by means of the diffuse stains, are not seen with silver impregnation.

Elective glia-staining methods still leave much to be desired. VIRCHOW noted the extreme susceptibility of the glia fibrils to post-mortem changes and the necessity of bringing material into the fixing fluid fresh. The Weigert glia method, to which we owe our present knowledge of the finer structure of the neuroglia both in normal and pathological conditions, is very difficult to work, very capricious, and, in particular, frequently fails in staining the cerebral cortex. Its success, too, is

conditioned by the absolutely fresh state of the tissue, and it is also unsuitable for tissue obtained from experimental animals. The method was not available in this work, as the autopsies were made from twenty-four to forty-eight hours after death. By Mallory's neuroglia method the glia fibrils are said to be brought out very prominently, but in our hands it stained the tissue with such an intensity that it was difficult to distinguish between glia fibrilis, axis cylinders, and connective-tissue fibres. Dense glia proliferation is certainly extremely perceptible by this staining method under a low magnification.

Recent glia methods have had in view a simplification of the technique and more constant results than those yielded by either Weigert's or Mallory's methods. Perhaps the simplest of these are those devised by LHERMITTE and GUCCIONE (1910) for the study of neuroglia cells and fibrils respectively. These writers claim for their methods that they are available for either normal or pathological material fixed within a reasonable time after death, that they are absolutely constant and specific, and that the exact conditions for success in staining are easily secured. Further, on account of the very exact differentiation of the tissue elements the staining allows of the share taken both by the neuroglia and connective tissue in inflammation and in other processes being exactly defined, and also brings into evidence the relation of the neuroglia nucleus, protoplasm and fibrils to one another, thus solving the much disputed question of the mode of formation of the fibrils. One great advantage of both methods is that the preliminary fixative is formalin. Frozen sections are taken from distilled water into an osmio-chromo-acetic mixture; from this transferred to Gram's solution and then to the stain—1 per cent. Victoria blue solution for the staining of the fibrils, and phosphotungstic acid hæmatoxylin for the staining of the cell protoplasm. In normal longitudinal sections of the cord thus stained it was possible to follow the neuroglia fibrils of the white matter as interlacing fibrils—the axis cylinders being almost unstained. In areas of sclerosis also the neuroglia fibril proliferation was clearly brought out, with frequently more or less altered, but unstained, axis cylinders in the meshes. But in the preparations the fibrils, at first stained an intense and beautiful blue, became decolorised very rapidly. Though only moderately successful, therefore, with these stains, I am satisfied of their great value. They are used with frozen sections: the technique, though elaborate, is much simpler than that of the other methods, and the tissue need not be absolutely fresh.

Neuroglia, if well preserved, stains with all simple methods, *e.g.* Van Gieson's stain, and of these non-specific staining methods the most valuable were found to be the Heidenhain iron-hæmatoxylin and Ford-Robertson's methyl-violet stains. This iron-hæmatoxylin method is extremely simple and often gives very beautiful pictures of the glia fibrils, nucleus, protoplasm cell bodies and processes, and their mutual relations. By means of it the structure of the neuroglia cells and the mode of their proliferation and hyperplasia are well brought out, and all phases in the development of the glia fibrils can be followed. The methyl-violet stain is of special value in

representing the structure of the patches in the cerebral cortex, and gives a less confusing picture than the iron-hæmatoxylin stain.

For the representation of the ganglion cells, Unna's polychrome methylene blue was used as the modification of Nissl's method. At first introduced by NISSL as an elective stain to reveal a certain portion of the ganglion cells (the chromatophile granules), this method was found to stain not only these granules but certain component parts of the cell nuclei, not only ganglion cells and glia cells, but connective-tissue cells, and all cell elements in the vessel walls. It stains specially beautifully young actively proliferating elements, *e.g.* the nuclei, protoplasm, and protoplasmic processes of glia cells in proliferation. Nissl's method was the first which made possible the study of the finer internal structure of the cellular constituents of the central nervous system, but it threw no light upon the elementary fibrils in ganglion cell bodies, nor upon the relation of the glia fibrils to the glia cell bodies. For the latter the glia methods above mentioned have been adopted, but for the former none of the neuro-fibril methods have been used in this study.

Van Gieson's method was used as the routine diffuse stain. Such sections revealed the changes in the blood-vessel walls and the relation of the structural elements of the tissue to one another. In densely sclerosed areas, however, the distinction between axis cylinders and glia fibrils was not sufficiently brought out. The Kulschitsky-Pal sections were also counter-stained with picro-fuchsin to bring out the relation of the vessels to the sclerosed areas.

Heidenhain's iron-hæmatoxylin is a diffuse stain which, as already mentioned, stains the medullated sheath of the nerve fibre, the axis cylinders, and the glia fibrils, but in addition it stains the cell elements of the tissue. This renders the interpretation of the picture a little difficult, but allows of the recognition of the relationship which exists between the different structural elements. This is of great importance in the study of cortical areas of sclerosis, as it brings out the changes in the nerve cells, the glia cells, and the medullated fibres. The medullated sheath of the nerve fibre and the axis cylinder are stained in different shades of greyish blue, the nuclei of the cellular constituents of the tissue have their chromatin structure well brought out, the protoplasm of the nerve cells is pale yellow, and the chromatophile granules a deep blue. As the medullated fibres are decolorised before the complete structure of the nuclear elements is brought out, it is necessary to have preparations in differing degrees of differentiation.

Numerous other stains were used to bring out individual points, *e.g.* Weigert's elastic tissue stain, Mallory's connective-tissue stain, Gram's stain, Ford-Robertson's palladium methyl-violet stain, and Scharlach R., etc. Many sections stained by Levaditi's silver method for the spirochæta pallida were also examined, but with negative results.

In the foregoing sketch an attempt has been made to indicate the methods which

have been relied upon in the histological analysis of the changes in the several tissue constituents. For the myelin sheath Marchi and Weigert's methods have been employed, supplemented by the iron-hæmatoxylin method; for the axis cylinders Cajal's and Bielschowsky's methods; for the neuroglia Heidenhain's iron-hæmatoxylin supplemented by Van Gieson's stain; and for the cellular constituents Unna's polychrome methylene blue and the diffuse stains. For use with frozen sections iron-hæmatoxylin for the myelin sheath, Bielschowsky's method for axis cylinders, Lhermitte and Guccione's stains, and Ford-Robertson's methyl-violet for the glia cells and fibrils, Van Gieson and hæmatoxylin and eosin for the cell elements, and Scharlach R. for fat granular cells.

IV.

HISTOLOGICAL STUDY.

(1) INTRODUCTION.

It has already been briefly mentioned that this study is based upon the observations made in the histological investigation of nine cases of disseminated sclerosis. The brain and spinal cord from most of these cases were equally thoroughly examined, but in only one instance was there the possibility of following the case clinically and anatomically. That case, therefore, has been taken, more or less, as

a standard of comparison, and it is proposed to begin this part of the paper by giving a short account of the clinical history of this patient. In the Appendix will be found the available clinical notes and post-mortem reports in the other cases, as well as an account of the general histological features and topographical distribution of the areas of sclerosis in Weigert-Pal sections.

Clinical History.

L. W., aged twenty-eight, a kitchenmaid by occupation, was admitted to the late Dr ALEXANDER BRUCE'S wards on 4th April 1910, complaining of weakness in both legs, inability to walk, and tremors in both arms and legs, the duration of these symptoms being about two years.

History of Present Illness.—At the end of March 1908, the patient, who was then employed at one of the baths in Edinburgh, was reaching up to clean the wall with a long brush, when she stepped too far back and fell into the deep end of the bath. She was pulled out immediately, but was, of course, wet through to the skin. This gave her a great fright, and she screamed for about ten minutes. When she had quietened down, she had a hot bath, put on dry clothes and went home. She said also that a menstrual period came on about two hours before she fell into the water; after this it completely stopped and did not return until a fortnight later. The above accident took place in the forenoon, and by the afternoon she felt so much better that she returned to her work.

She continued at her work until the end of June, when one morning she found that both her legs had become swollen and tender, that she had shooting pains down her right leg, and that she had great trouble in rising out of bed. She sent for her doctor, who thought the symptoms were due to muscular rheumatism, and treated her accordingly. She was slightly feverish at this time and remained in bed for a week, and at the end of a fortnight returned to work. She noticed, however, that she did not seem to be able to walk so quickly as previously, that she was slightly lame, and that her right knee was stiff.

She worked steadily at the baths until March 1909, when she began to find her work too heavy, and she, accordingly, took an easier situation as kitchenmaid at a golf club-house. She succeeded so well at this that after a month she became waitress. After four months this post became too heavy for her, and she returned to her old post of kitchenmaid, but two months later had to give this up also, and has done no work since 12th November. Two months before admission her symptoms had become more marked. Both legs became very stiff, and she could only walk with the help of a stick. Her arms became shaky, and one of the reasons why she left the club-house was that if anyone gave her a sudden start her arms became very shaky, and once or twice she dropped a tray full of dishes. Although usually constipated, she was subject to sudden precipitate action of the bowels as well as to incontinence. Her friends had noticed that she had been getting very slow in her

speech, and that sometimes she had difficulty in pronouncing words. The menstrual periods had been somewhat irregular, usually occurring too frequently, but lasting only a very short time. As these symptoms became progressively worse, she was sent to the Royal Infirmary, Edinburgh, to be examined by the late Dr ALEXANDER BRUCE, who at once admitted her to his ward.

Previous Illnesses.—Patient had always been remarkably healthy as a girl, and, with the exception of occasional "bilious headaches," can remember of no other illnesses.

Condition on Admission.—Her appearance was that of a strong healthy girl with a good fresh colour. Smell and taste were normal. The pupils were circular and equal and reacted both to light and to accommodation. The eyes were freely movable in all directions. There was slight lateral nystagmus on looking to the left and slight rotatory nystagmus on looking upwards. Both discs were normal.

Sensation to touch, heat and cold, and pain was intact; and there was some tenderness on deep pressure of both calves.

The knee-jerks were both exaggerated, the left rather more than the right. Both Achilles jerks were also exaggerated, and Babinski's sign was positive on both sides. The abdominal and upper limb reflexes were all present and apparently normal. There was no wasting of any muscles. There was slight inco-ordination in the finger-nose test with the right hand, but no intention tremor and no inco-ordination of the lower limbs.

The heart was not enlarged, the apex-beat not displaced, and the pulse was 70. There were no murmurs present, and the arteries were not thickened nor the blood pressure raised.

The chest was well formed and the expansion good. Neither percussion nor auscultation revealed anything abnormal.

There was no enlargement of the liver or spleen. The stomach was not dilated, the digestion was good, but there was considerable constipation. The urine contained neither albumen, sugar, bile, nor pus, the specific gravity being 1017. She has occasional attacks of precipitate micturition.

Progress.—She was put to bed and at first made good progress, but on 25th May numbness in the left arm developed suddenly. On the 29th she felt deaf in the right ear, with dull buzzing sounds, and noticed that her right eye watered exceedingly. She complained of feeling her face squint on speaking. On examination a right facial paralysis was found. The right eyelid scarcely moved on attempting to close the eye. The electrical reactions on the affected side of the face were normal both to Faradism and to galvanic stimulation. On the 3rd of June she developed diplopia on looking to the right, and was found to have a paralysis of her right external rectus. The other movements of the right eye were normal, and the left eye was unaffected. The pupils were equal, rounded, and dilated, and reacted to light and to accommodation sharply. Five days later the tongue was seen

to protrude to the left side, and slight difficulty in speech was observed, which was followed two days later by difficulty in swallowing. Dr J. S. FRASER, who at this time examined the ears, reported that both vestibular apparatuses were functional, although possibly the activity of the right was slightly diminished. By the 8th of August the weakness in the legs had become very marked and they were painful on attempting any movement. Spasticity in the legs soon developed. On 14th August severe vomiting set in, which was scarcely affected by any treatment. On the evening of 15th August she complained of dimness in seeing, and next morning was found to be blind in both eyes. On examination the discs showed some pallor but no neuritis. Muscular wasting now developed and proceeded rapidly, especially in the legs. The face became more hollow and sunken, diarrhœa and vomiting set in, and a catheter had to be passed every eight hours. From now onwards she went rapidly downhill, sometimes slightly better and sometimes slightly worse. She had an extremely septicæmic look, and died suddenly and unexpectedly on the morning of the 5th of September, after having passed a better night and had a little breakfast.

Post-mortem Report.

Body is small, well developed, and fairly well nourished. Rigor passing off in upper limbs and in lower limbs. Slight amount of œdema of lower limbs. Pupils are slightly contracted and equal.

Serous Sacs.—No adhesions and no fluid in pleural cavities. No excess of fluid in pericardium.

Heart.—230 grams. Rather small. Shows a few small milk spots on anterior aspect of ventricles. Tricuspid valve at C.C., 12 cm. Appears healthy. Pulmonary valve competent. C.C., 9 cm. No pathological change. No dilatation of either ventricle. No subepicardial fat. No thrombi in cavities. No post-mortem clot. Mitral valve C.C., 11 cm. Healthy in appearance. Heart muscle rather pale but firm. Coronaries healthy. Aorta and aortic valves also healthy. Aortic orifice C.C., 8 cm.

Lungs.—Lungs are voluminous and pale. General atrophic emphysema, especially along anterior border. Adhesions between upper and lower lobe in left lung. Collapse in lower lobe. On section the lung shows œdema in both upper and lower lobes. Bronchi contain a good deal of frothy mucus. No special change in their walls. Right lung: adhesions between upper and middle lobes. There is a stony, hard nodule in lower part of upper lobe. On section the lung is œdematous and has slight congestion of lower lobe. Left lung, 290 grams. Right lung, 400 grams.

Liver.—1470 grams. Normal in size. Gall-bladder is very small and contains a small quantity of brownish-red bile. No evidence of gall stones. On section liver substance is pale in colour, rather friable and soft. There is some diffuse fatty change, slight in extent.

Kidneys.—Left, 220 grams. Left suprarenal gland is large. No special change. On section, kidney slightly enlarged. Cortex as a whole is diminished in breadth. It is pale. At upper end there are several opaque white areas with hæmorrhage around them. General dilatation of pelvis. Capsule strips easily and leaves smooth lobulated surface (fœtal). Right kidney, 200 grams. Right suprarenal is also large but shows no special change. Right kidney distinctly enlarged. On section shows numerous abscesses. Pelvis dilated and shows pyelitis.

Other Abdominal Organs.—Spleen, 75 grams. Not abnormal in size. Pale colour and soft in consistence. Hæmorrhage into substance. Stomach dilated. Mucous membrane pale. Covered with glairy mucus. Shows minute hæmorrhages. Some chronic gastritis. Early marked dilatation of veins in lower part of œsophagus. Mucous membrane of duodenum is somewhat congested and shows a few small hæmorrhages. Pancreas is pale and appears healthy. Small and large intestines show nothing abnormal in mucous membrane. Bladder shows some thickening; interior grey and necrotic in places. Uterus and appendages appear normal.

Brain.—No clots in superior sinus. Convolutions atrophied. Some general opacity of pia arachnoid. Fluid in subarachnoid space.

Cord.—Shows irregularly scattered areas of bluish-grey colour varying in size and shape. Cord as a whole is small. Similar areas in pons and medulla.

Macroscopically the cerebral and spinal meninges were in the main normal, but in places where the grey and greyish-blue areas in the cord reached the surface the pia over these areas appeared slightly opaque. On section of the cord at various levels, numerous gelatinous grey areas were found, and also parts of a softer consistence with a whiter colour than the normal tissue of the cord. Sections of the medulla oblongata and pons indicated the same two types of areas, parts of the pons appearing so affected that there were only islands of normal tissue, and the floor and immediate neighbourhood of the IVth ventricle were also markedly involved. Numerous areas were found in the horizontal sections of the cerebral hemispheres at various levels, not only in the basal ganglia and white matter, but also in the cortex and subcortical white matter. There was a well-marked peri-ventricular sclerosis, especially of both the posterior horns of the lateral ventricle extending down into the descending horn on both sides. The ventricles were not dilated, and their surface was smooth but cloudy, and raised in slight ridges corresponding to the venous branches which are present underneath the ependyma, especially at the posterior and anterior horns of the lateral ventricle. These veins were distinctly outlined and surrounded by a zone of gelatinous tissue.

The size of the areas varied very considerably: in the cord it was impossible to define macroscopically, either on the surface or on section any of the areas, as they seemed to run into one another. In the brain, however, isolated areas were the rule, though here also irregular areas of different size and form coalesced. Those

isolated in the white matter varied in diameter from 1 to 10 or 12 millimetres, and were mostly oval or circular. The largest were found in the immediate neighbourhood of the roof of the lateral ventricle, and gave the impression of being upward extensions of the peri-ventricular sclerosis of the roof.

In examining the microscopic findings it is important to recognise that different stages of the disease come under observation, and it would appear natural to differentiate acute, subacute, and chronic stages, for they are often enough found close together in one and the same case. The finding at the autopsy of patches at different stages in their evolution accords with the clinical history of the affection, which has usually progressed with remissions and relapses. It is, however, by no means universally admitted that the recent areas are transformed into those which would seem to represent a chronic process, in which all traces of inflammation have disappeared. If such chronic areas do not develop on the basis of the former, it must be acknowledged that there is a strong justification for looking upon them as a multiple gliosis, related to an anomaly of development, and upon the recent areas as an acquired form of sclerosis, whose origin lies probably in toxi-infective conditions.

This study, therefore, begins with a short description of these two types of areas; the one an old area, typical of the "sclérose en plaques" of the earlier writers; the other, a recent area, corresponding to those found in the so-called acute multiple sclerosis of recent writers. It will then be necessary to endeavour to trace all the stages in the development of an actual sclerotic area, and further to describe other types of areas present. A second section will deal with the structure of areas in special situations, *e.g.* peri-ventricular sclerosis, cortical and combined subcortical and cortical areas, areas in the grey matter of the cord, areas in the cerebellum, nerve roots, etc. A further section will deal with the changes in the individual structural components of the central nervous system, and a final section with other features, *e.g.* the form, symmetry, and distribution of the areas, and changes such as secondary degeneration outside of the area.

(2) Structure of Different Types of Areas.

1. *An Actual Sclerotic Area.*

(*a*) *In the Spinal Cord.*

(i) Nerve fibres cut longitudinally (figs. 4, 31, 331–336, and 341, 342), *e.g.* in the ventral third of the posterior columns.

The histological structure of such an area is a very simple one. It consists almost entirely of newly-formed fibrils which are arranged parallel to the original course of the nerve fibres. In sections stained by means of Weigert's medullated

sheath stain and counterstained with picro-fuchsin,* under a low magnification we recognise at once three of the outstanding characteristics of an old sclerotic area (fig. 335): the disappearance of the myelin sheath of the nerve fibre, the proliferation of the glia, and the alterations of the blood-vessels. By means of a glia stain (fig. 333) and a diffuse stain (fig. 336), these changes are confirmed and their details revealed; by an axis cylinder stain the fourth histological characteristic is represented—the persistence of numerous axis cylinders (figs. 334, 424); and, by the Marchi method, it is seen that this old sclerotic area contains no degenerating nerve fibres nor granular cells containing the products of the degenerated myelin.

The shape of this area is brought out clearly by Weigert's stain as an elongated oval with its long diameter in the long axis of the cord (fig. 31). The continuity, therefore, of the nerve fibres is broken by this oval area, and the absence of the myelin at the sides is more or less sharply defined from the surrounding tissue, the margins forming more or less sinuous lines, but the limits of the area, on longitudinal section, are never straight or even curved outlines, for individual nerve fibres or bundles of such pass into the borders. The myelin sheath of these fibres stains irregularly and weakly, and the termination is usually broadly broken off, or it may be swollen or narrowed (fig. 406).

Numerous fine glia fibrils course in regular, undulating lines parallel to and close to one another (figs. 3, 334). The neuroglia nuclei lie often in short rows or in groups, but more often, as in this area, isolated with the long diameter in the long axis of the fibrils, and, as a rule, quite independent of them. The number of the nuclei is smaller than in the normal tissue, but in structure and form they are slightly larger, clearer, and more oval. Between the glia fibrils and surrounded by them are found numerous axis cylinders, which are mostly thin and fine but thicker and more homogeneous in structure than the glia fibrils (fig. 334). They do not run in such regular lines, and frequently show as faint diffusely-stained bands. The impression is often given that in place of the myelin sheath there has been a substitution of glia fibrils, forming a glious sheath to the axis cylinder. LAPINSKY has wrongly interpreted this process of substitution as a metamorphosis of the medullated sheath—a conception which accentuates the enveloping character of the glia fibril proliferation.

The blood-vessels stand out clearly in this sclerotic tissue. Those cut transversely show, with picro-fuchsin stain, thickened, homogeneous, pink-stained walls, and on longitudinal section the numerous longitudinally-running small vessels (fig. 342) have a similar structure, with few cell elements even in their adventitia. The lumen of the smallest capillaries is often obliterated and that of the larger vessels narrowed. Weigert picro-fuchsin sections show beautifully the arrangement and distribution of these smaller vessels and bring out the abundant vascular supply of the various tissues.

* Such sections will in future be designated Weigert sections.

At the periphery of the area, especially at its upper and lower limits, diffuse stains bring out a zone where intensely-stained nuclei are in great abundance: these nuclei, in iron-hæmatoxylin stain, are seen to occupy the spaces between the nerve fibres projecting into the sclerotic tissue, and their increase can be traced for a small distance among the fibres of the normal tissue on all sides. The glia fibril proliferation and thickening of the vessels are here also evident, and this zone can be looked upon as a zone of transition between normal and sclerotic tissue—a zone where the pathological changes gradually cease till normal tissue is reached.

(ii) Similar area in the cord with nerve fibres cut transversely (figs. 258, 259, 353, 354, 358–360).

To understand the structure of such an area it must be remembered that in the posterior columns, according to WEIGERT, the usual glia fibrils very largely run longitudinally, and the pathological glia fibril formation takes place almost wholly in this direction. Exceptions to such an arrangement will be noted later. When the glia proliferation has taken the simple course represented in the former paragraphs a transverse section of the areas seen in figs. 258, 259 will represent the glia fibrils as minute fine points which more or less surround as a ring larger, more diffusely stained, and more homogeneous points—the axis cylinders. If the section is directly transverse to the direction of the fibres we get so dense a picture that, under low power, no details can be recognised (fig. 354). But a higher magnification shows that the normal meshes of the glia and the space originally occupied by the myelin sheath of each nerve fibre is replaced by those fine points. Amongst them, lying almost isolated and in no way forming the nodal points of a reticulum, are rounded nuclei, with smooth nuclear membrane and clearer nuclear structure than the small normal glia nuclei. In this dense tissue is found the cross-section of numerous thickened capillaries and pre-capillary vessels (fig. 443). Around each vessel is a narrow zone where the glia fibrils radiate almost perpendicularly to the vessel wall—forming the "corona ciliaris" described by BORST and STORCH. It is not a question of a central vessel but of many transverse and oblique vessels. These give the impression that not one single vessel, but the branches of a vessel system are affected. Weigert sections show the complete absence of myelinated fibres within the sclerotic tissue, but at the periphery the transition to normal tissue is a gradual one—isolated well-stained myelin sheaths being found within definitely sclerotic tissue (fig. 258). The transition zone is again seen to consist of a large number of small deeply-stained nuclei, amongst which are found larger nuclei with a distinct amount of protoplasm and several protoplasmic processes (fig. 357). Here a more reticular arrangement of the glia fibrils can be recognised: the glia trabeculæ which, in the normal tissue, separate groups of nerve fibres, are in this transition zone more evident, and the processes of the cells cut into the larger meshes, dividing up the bundles into smaller and smaller groups, till, finally, the meshes contain only individual

nerve fibres, and the granular appearance of the sclerotic area is reached. Sections of such an area stained by the Marchi method again show no black staining: the characteristic transverse section of the myelinated fibre is absent, but no traces of degenerating myelin are found either in the fine tissue spaces or around the blood-vessels.

The impression is received that here again the normal architecture of the tissue is preserved; that the myelin sheaths have disappeared (fig. 258) (Weigert stain), and have been replaced by a fine close fibre formation (fig. 354) (glia stain); that the walls of the blood-vessels, even the small capillaries, have thickened walls with few cell elements (fig. 440) (diffuse stains); that the axis cylinders have, at least to a considerable extent, been retained (fig. 427) (silver impregnation stains); that there are present in the area or its periphery no indications of the degeneration of myelin (Marchi method)—thus allowing it to be supposed that the process which caused the myelin destruction has come to a standstill; and, finally, that there are evidences at the periphery of the area, in a nuclear proliferation and diminution in myelin fibres, of a process which has left these traces of a reaction to its further progress.

These areas, just described, in longitudinal and transverse section, are typical of the sclerosis which is the essential substratum of the disease known as disseminated sclerosis. They show a compact glia fibril proliferation, apparently without spaces, for only here and there are there traces of the original glia meshes. The area of dense sclerosis is regularly surrounded by a peripheral transition zone, which interposes between it and the healthy tissue. This transition zone shows very numerous nuclei of small and large glia cells, with more or less developed glia trabeculæ.

(*b*) *In the Cerebral White Matter.*

The first points to be noted in comparing such an area with a similar one in the spinal cord are that in the brain it is much more usual to get a more defined outline of the patch, and also that a central vessel, cut transversely or longitudinally, is more frequently present.

(i) Nerve fibres cut longitudinally, *e.g.* at the base of or within a medullary ray (figs. 288, 372).

The shape of the area is again often oval and its structure is very similar to that described in the longitudinal direction of the cord. Weigert sections show again a complete absence of myelin (fig. 284); the presence often of one thickened vessel, which sometimes is found to extend centrally almost the whole distance of the patch (fig. 287); and the presence also of numerous other smaller vessels cut transversely, obliquely, and longitudinally—all with walls thickened, almost homogeneous and structureless. The general substance of the area is again composed in great part of fine glia fibrils (fig. 372), which run longitudinally and parallel to each other, and surround the persisting axis cylinders (fig. 422). The glia cells in this area are, as a rule, much less numerous than normal; they have, however, more elongated and

lighter-staining nuclei. Along with these many darkly-staining smaller nuclei are found, which agree in form and staining with the normal small glia cells of the cerebral white matter. The preserved axis cylinders are, as a rule, much fewer in number than in the cord, and they show, even in the dense sclerosis, more evident indications of a previous involvement. They are usually thicker, more diffusely stained, and have more irregular contours as compared with the axis cylinders of adjoining medullary rays. Marchi-stained preparations again show a complete absence of any degerating myelin either in nerve fibre or in the presence of fat granule cells. The affected area stands out much lighter in colour than the surrounding tissue, and gives a contrast almost as marked as the negative picture of the Weigert section. In glia sections this condensed tissue is, on the other hand, much denser and darker than the surrounding tissue, and its limits are often very defined —that towards the central white matter being abrupt, that towards the radiations of the convolutions being very frequently in the form of a wedge with its apex to the radiations (*cf.* fig. 405). The transition zone at this limit is also much more marked and consists of a narrower or broader zone of deeply-staining round nuclei, amongst which a few larger, protoplasmic forms are found. This nucleated zone extends for a short distance into the normal myelinated tissue.

(ii) When the sclerosis affects a portion of the brain substance in which the nerve fibres normally run in very varied directions (figs. 292, 293; 364; 397, 398; 430), *e.g.* a small defined area in the central white matter above the roof of the lateral ventricle, the resulting tissue is a very dense network in which the original glia spaces are replaced by fine fibrils.

On Weigert picro-fuchsin sections the central vessel stands out clearly as the mid-point of a yellow-stained zone, at the periphery of which there is usually an abrupt transition to normal myelinated tissue (fig. 294). If bundles of longitudinal fibres are cut across, these often pass for a short distance into the sclerotic zone, breaking the otherwise almost defined circular or oval outline of the area (fig. 292). At their terminations such fibres do not show any evidence of degeneration but are simply faintly-staining normal fibres. In this sclerotic zone there are found as a rule, in addition to the central thickened vessel, several cross-sections of capillaries, each standing out as a pink thickened ring, which encloses a narrow lumen. Individual capillaries are quite obliterated and form a dense solid fibrous cord. Marchi-stained preparations again show a complete absence of signs of disintegration of myelin: the affected area again appearing lighter in colour than the normal tissue.

Sections stained for glia and for cell structure show that the sclerotic tissue is composed almost entirely of glia fibrils. These fibrils are very unequal in size: the larger form larger meshes into which the finer fibrils cut and make finer meshes. The tissue becomes denser and denser till the meshes are inconceivably fine (fig. 364).

The size of the glia cells varies very much, but the body of the cell is in general round or slightly elongated and may contain one or more nuclei but little protoplasm. Around the blood-vessels (fig. 398), even the capillaries, is a zone in which this fibril formation is even more dense; the fibrils rarely form a "corona ciliaris," but rather concentric layers of fibrils closely pressed together, with few nuclei, form an outer dense glious sheath to the vessel. The axis cylinder content of these areas has been exceedingly difficult to ascertain, for the brains of most of the cases in which such areas occurred were already fixed in formalin, and the Bielschowsky impregnation method in cerebral areas gave no absolutely reliable results. A comparison with other areas, stained by means of Cajal's silver method, showed how extremely difficult it was to differentiate between glia fibrils and fine axis cylinders and their branches. The intimate network formed by both is so alike that it was never possible to be satisfied that in these dense sclerotic cerebral areas there could be so abundant an axis cylinder network persisting, and the conclusion was come to that in such areas the glia network had been stained. Other areas which had been cut in two by the section of the hemispheres were taken through—one part by Cajal's method, and one for glia and cell staining. These showed that when the fibrillar network of the glia was not quite so dense as above described, there was a very abundant network of axis cylinders and their finest branches persisting (fig. 430). Such areas will be referred to in a later section.

The nucleated transition zone of these dense sclerotic areas was, as a rule, a narrow one, and the nuclei were all relatively small and darkly staining (fig. 403). Even in the sections stained with diffuse stains the contrast between the sclerotic tissue and the normal was very evident.

Such areas, therefore, consist of a dense-meshed fibrillar tissue, poor in nuclei, with thickened vessels. The areas give the impression again of tissue in which the normal architecture is retained: they also seem to show that the change consists in a demyelination, a complete substitution of the spaces by fibrillar tissue—which in its arrangement forms simply a condensation of the original glia meshwork (fig. 364), a thickening of the walls of the vessels originally present in the tissue (fig. 440), and, finally, the formation of a narrow but dense nucleated peripheral zone (fig. 403), which forms the transition to normal tissue.

2. *An "Early" Area.*

(*a*) *In the Spinal Cord.*

(i) Nerve fibres cut transversely (figs. 10; 260, 261; 66, 313; 350), *e.g.* in the middle or anterior third of the posterior columns.

On Weigert sections an irregular non-medullated area can be recognised (fig. 260), which extends approximately from the middle of the posterior median septum forwards to the posterior commissure. The area is, roughly speaking, triangular in

shape, with its base to the commissure, and under low power has a more or less definite sinuous outline. At the periphery on all sides there are isolated nerve fibres passing for a short distance into the area, and under high power it is seen that their myelin ring is very thin, or stains diffusely, and shows evident signs of degeneration. This area has formed with the posterior median septum and its vessels as a centre (fig. 313), and on either side are found numerous cross-sections of small vessels and capillaries and longitudinally-running branches of the posterior median fissure vessels. Individual branches of these longitudinal vessels can be followed up into the surrounding normal tissue. The tissue of this area, even in Weigert sections, is seen, notwithstanding the absence of myelin and the presence of changed vessels, not to correspond to the dense sclerotic fibrillar tissue seen in the former area described. The blood-vessels—arteries, veins, and capillaries—are all dilated and engorged with blood, and their walls, instead of the homogeneous, thickened, structureless tissue, show in the intima and media little recognisable change from normal; but the adventitia has its lymphatic spaces dilated and filled with nucleated elements, and these same nucleated elements are scattered irregularly through the non-myelinated tissue, and in the blood-vessel walls of the transition zone (fig. 10).

The most characteristic features of this area are seen best with diffuse stains. Hæmatoxylin and eosin, or Van Gieson's stain, or, even better, Heidenhain's iron-hæmatoxylin stain, show the presence of a very large number of nucleated cell elements with a considerable amount of protoplasm. Most of these large cell elements correspond roughly to pathological examples of the proliferated spider cells of the normal tissue (fig. 9). The nucleus is large, vesicular, with a very light chromatin framework, and one or more distinct nucleoli. It lies usually excentrically in the protoplasm: this is large in amount, usually homogeneous, and stains slightly with hæmatoxylin, or yellowish green with the picro-fuchsin. From the protoplasm radiate in all directions very fine branching, protoplasmic processes, which break up into a fine network. Many of these cells are multi-nucleated, and vary greatly in shape and size from star-shaped forms to those with crescentic outline and bi-polar forms. Their processes bear very frequently a very definite relationship to the vessel walls—a relationship which will be more fully emphasised when describing recent areas in the cerebral white matter. Smaller and darker-stained nuclei, with little protoplasm and no processes, can also be found in considerable numbers. In the spaces formed by the large branching processes of these cells and in the adventitial spaces of the blood-vessels lie the second tissue elements characteristic of such an area. These are larger, rounded, nucleated cells, with a large amount of vacuolated protoplasm: they correspond to the phagocytic cell of the central nervous system, and their vacuolated appearance is derived from the solution of the fine degenerated myelin granules in the process of hardening. NISSL has given to these cells the name "Gitterzellen" from their morphological appearance, but they are more generally known as compound granular or fat granular cells ("Fettkörnchenzellen")

(figs. 9, 10), from their function of absorbing the products of the disintegration of the myelin. These cells lie not only in all the tissue interstices, surrounded by the branching processes of the glia cells, but in the lymphatic spaces of the adventitia of the blood-vessels—whither they have in all probability been drawn in from the tissue spaces by the suction influence of the lymph flow in the adventitial lymphatics. Round even the smallest capillaries these cells form a complete ring, and the area under low power assumes a very characteristic appearance. The presence of such large numbers of fat granular cells gives to the blood-vessel walls an appearance of a cell-infiltration, for in the vessels larger than the capillaries they are present in several rows, often closely compressed. In addition to these cell elements in the adventitia, other nucleated elements add to the nuclear abundance of the vessel wall. The endothelium, especially of the capillaries, frequently shows evidence of a distinct proliferation, and in the adventitia are found dark-stained nuclei, together with nuclei of a vesicular clearer character, both of which have probably arisen from the proliferation of the cells of the adventitia and the endothelial cells of its lymphatic spaces. Diffuse stains, *e.g.* Van Gieson's stain, bring out, although feebly, one further tissue component—the axis cylinders. These are no longer the sharply defined, homogeneous points of the dense sclerotic tissue, but a faintly-staining, almost unrecognisable, swollen structure, which is a lesser degree of the intense swelling of the axis cylinders seen in marked œdema of the cord. These swollen axis cylinders are usually found lying in the tissue meshes, with no trace, or only slight traces, of myelin around them, and often closely compressed between the fat granular cells and the protoplasmic processes of the large glia cells (fig. 10). The iron-hæmatoxylin stain shows that in this area there is as yet almost no attempt at fibril formation on the part of these glia cells, although the processes at their lateral margin and terminations show a definitely darker staining.

It has been seen that Weigert sections show the almost complete absence of myelin in this area; that diffuse stains give (1) the characteristic appearance of the two cell elements—proliferated glia cells with numerous processes and the fat granular cells—(2) the numerous dilated blood-vessels, and (3) the persistence of numerous swollen axis cylinders; and that glia stains give as yet no definite fibril formation. There remains now to be mentioned the appearance with Marchi-stained sections (figs. 66, 313). This is the most characteristic of all, and has given to the areas the name of "fat granule cell myelitis." Each of the large vacuolated cells in the tissue spaces and walls of the blood-vessels is found to be composed of a very large number of minute granules of a substance staining black with osmic acid. Most of these granules are quite round, but a few show irregular contours from compression. Granules are found also in the spaces between the cells. Under low power the area is thickly studded with these black granular cells, which also form concentric rings around the blood-vessels. No trace of normal myelinated fibres can be found within the area, but in the transition zone are recognised numerous fibres in all

stages of degeneration. The blood-vessels in this zone also have their sheaths filled with similar cells, but the numbers in the tissue spaces themselves are still too many to allow the radial appearance to be recognised, which is characteristic of the areas in which the blood-vessels radiating from the area have their walls filled with cells which have passed from the tissue spaces to the lymphatic spaces of these vessels, leaving the tissue more or less clear. In this transition zone, in addition to numerous degenerating myelin fibres and vessels with rows of fat granular cells in their walls, we find also a marked proliferation of the glia cells and protoplasmic processes, and a widening of the normal glia meshes, but the degeneration of the myelin has not advanced to the stage of complete disintegration and its absorption by cells. The glia meshes of the adjoining normally myelinated tissue are distinctly widened, the cells also enlarged, and the blood-vessels engorged and dilated.

(ii) Similar "early" area in the cord—nerve fibres cut longitudinally (figs. 1, 2; 18–20; 326, 338).

In Weigert sections under low power, this area is both laterally and at its upper and lower limits very irregularly defined. The transition zone on all sides shows that the fibres, though still staining with hæmatoxylin, are markedly altered (fig. 406). Longitudinal sections are very valuable in showing the changes in the nerve fibre as it passes into the area. Those changes will be referred to in detail in a later section. In the area itself are numerous globular and granular remains of the myelin which have not undergone complete disintegration into fat droplets (fig. 407), and one can also recognise, even within cell elements, such remains which still retain the myelin stain.

Marchi preparations (figs. 316–318) show the characteristic appearance of long rows of fat granule cells, which seem to occupy the spaces left by the removal of the degenerated myelin of the nerve fibre and also the longitudinally-running vessels surrounded by elongated layers of similar cells (fig. 433). In sections stained with Scharlach R. and hæmatoxylin (figs. 18–20), the smallest capillaries can be followed, marked out by a single or double row of such cells, the nuclei of which is either central or pushed to the periphery by the accumulating granules of fat. In the transition zones of the area the disintegration of the projecting nerve fibres can be followed and the formation of the fat granule cells, which can be traced not only into the transition zone but even between the nerve fibres of the normal tissue.

In sections stained with diffuse stains, the large glia elements, already referred to, are beautifully seen, lying often in rows (figs. 337, 379), with the nuclei of two adjoining cells lying close to one another, as if they had arisen from the division of one cell. The long branching protoplasmic processes extend round and almost envelop the rows of fat granule cells, and in some parts the direction of these processes is already becoming longitudinal. Almost pushed aside between the rows of cells and the protoplasmic processes can be found faintly-stained, homogeneous,

swollen bands, which represent axis cylinders (figs. 1, 2), and here and there are large numbers of rows of finer and larger granules staining with the same tone as these bands. These are the remains of disintegrated axis cylinders, which seem, after the stage of severe swelling, to become broken up into large granule formations and gradually into finer granules before they ultimately disappear (figs. 425, 426). These remains of axis cylinders can be distinctly recognised not only with eosin, picro-fuchsin, and iron-hæmatoxylin, but also with the elective axis cylinder stains, *e.g.* Cajal's and Bielschowsky's methods.

(*b*) *In the Cerebral White Matter.*

(i) Nerve fibres cut longitudinally (figs. 284, 304, 370, 373–376), *e.g.* an oval area at the base of or within a medullary ray.

Such an area is again very similar in structure to that described in the spinal cord. Weigert sections show that there is a gradual transition on all sides into healthy tissue (fig. 284), and that the adjoining nerve fibres show marked traces of swelling, diffuse staining, and granular disintegration. The blood-vessels appear very numerous and even the capillaries are dilated, engorged with blood, and, in nuclear staining, show an evident increase of the endothelial nuclei, together with a very abundant presence of fat granular cells in their adventitial spaces. The two most characteristic features of the cord area are here again present: (1) the rows of fat granule cells, which seem to occupy the tubular spaces of the degenerated myelin fibres (fig. 373); and (2) the presence of rows of large, protoplasmic glia cells (fig. 375), whose processes entwine between the rows of fat granule cells and separate them into more definite layers. These processes divide into numerous, fine, interlacing and anastomosing branches which tend to take a longitudinal direction, the protoplasm of some of the cells being drawn out also in a longitudinal direction and giving off numerous processes from either pole. The glia nuclei are vesicular and elongated and frequently one or more are at either pole of a cell. Together with the larger nuclei are found many smaller, darker-stained nuclei, with little protoplasm and no processes.

The adventitial wall of the longitudinally-running vessels is again infiltrated with fat granule cells, which form a single or double layer, and when the capillaries join the smaller vessels the whole tissue in the angles between the vessels seems permeated with such cells. In the walls of the vessels are found other nucleated elements which are rounder, denser, and have only a small cell body, and similar cells are found frequently in small groups or isolated in the tissue immediately adjoining the capillaries. The axis cylinders are here very thickened and vesicular and in many parts transformed into clumps of larger and smaller globules and granules. In all cases they seem pushed aside by the large glia cells and rows of fat granule cells, and take the direction between these rows. Marchi-stained preparations (figs. 304–306) bring out very beautifully the enormous number of fat granule cells and the

changes in the nerve fibres as they pass into the affected area. The transition zone is a very broad and irregular one, and can be more clearly understood from transverse sections of such an area.

Such an area, therefore, consists of elongated rows of fat granule cells, almost alternating with rows of large, protoplasmic glia cells with long-branching processes. In between the rows are numerous capillaries and larger vessels, cut mostly longitudinally, and surrounded by one or more layers of fat granule cells. Numerous axis cylinders have perished, and those persisting are markedly altered. There is a complete absence of myelin within the area, and the transition into normal tissue is a very gradual one.

(ii) Small "early" area in cerebral white matter, with nerve fibres cut in various directions (figs. 5, 6; 68; 361, 362).

The most important and characteristic feature of such an area is the enormous number of large cell elements. These are of two kinds: the one the round vacuolated fat granule cell with central or peripherally-placed nucleus (fig. 365); the other the large protoplasmic glia cell with branching processes (fig. 6). Both of these cell elements are seen here at their most distinctive stage of development. This area (fig. 5), situated in the central white matter at the base of one of the parietal convolutions, measured less than 2 millimetres in diameter. It was almost circular, and was surrounded by a well-marked nucleated transitional zone. In Weigert sections one saw a well-marked central engorged vessel with an increase of nucleated elements in its walls, a complete absence of myelin within the area, and the presence of numerous rounded spaces, almost equal in size, which gave the non-myelinated tissue a very characteristic fenestrated appearance. With cell stains it was recognised that these spaces are fat granule cells, so closely arranged together that one might almost think of them as forming irregular tubular lines made up of cell units—the tubules almost as closely arranged as the rows of liver cells in a lobule. Between groups of these cells lie large glia cells such as are nowhere found in the normal glial tissue. These are large cells with homogeneous cell body: their size sometimes as large as that of a motor ganglion cell of the cord. They have large-branching, protoplasmic processes which wind around the individual fat granule cells and almost surround and isolate them. Their nucleus is large and vesicular, and contains a very defined membrane and one or more deeply-stained nucleoli—its position is usually excentric but is sometimes central. These cells differ from the Deiters or spider cells only in degree and are pathological spider cells, and they may be multinucleated. They are found specially numerous in the neighbourhood of the small blood-vessels, and their processes are frequently attached to the adventitial wall (*cf.* figs. 435, 436). With glia stains it is seen that the margins of the processes of these cells are already becoming differentiated into fibrils (fig. 382) which are found lying between and surrounding the fat granule cells. The central vessel is dilated

and engorged with blood, and in its adventitia is an increase of nucleated elements. These are mostly small, round, deeply-staining nuclei with little protoplasm, together with a few fat granule cells. The capillaries within the area are also dilated, but changes in their walls are not marked. The presence of swollen axis cylinders in cross-section and in short pieces in longitudinal can be proved in the narrow spaces between the fat granule cells and the glia cell processes.

At the periphery is a more or less broad transition zone. This shows (1) a very irregular loss of myelin, the myelinated fibres showing all stages of degeneration; (2) a very marked nuclear proliferation, which in the outer part consists mostly of small nuclei and in the inner part of the larger, protoplasmic cells similar to those just described; and (3) the presence of a few fat granule cells lying in the wide meshes between the processes of the large glia elements.

Marchi sections of such a small recent area (figs. 13, 68) show the central vessel surrounded by concentric layers of cells filled with closely compressed fat granules. Similar cells lie irregularly but closely scattered in the tissue, and the picture enables one to recognise how such areas received the designation of "fat granule cell myelitis." Marchi sections counter-stained with safranin and mounted in Canada balsam give a very instructive picture. The fat granules within the cell elements dissolve in the Canada balsam, leaving a skeleton structure of the tissue with the nuclei and the processes of the large glia elements and the nuclei of the fat granule cells stained with safranin. Such sections frequently gave the most characteristic representation of the close relation of glia cell processes to the fat granule cell—the latter apparently lying in the large meshes formed by the processes of different glia cells. The Marchi preparations also showed that the fibres in the transition zone were in a condition of disintegration. This degenerating myelin did not dissolve out when mounted in Canada balsam—thus showing the different constitution of the fat granules within the cells and the globules and fragments of disintegrated myelin.

Such an area, therefore, again consists largely of closely arranged fat granule cells, between which lie the large protoplasmic proliferated glia elements; of dilated vessels with fat granule cells and other nucleated elements in their adventitial spaces; of markedly altered persisting axis cylinders; and of a gradual transition zone in which these changes are less marked and in which degenerating myelin fibres may be found.

If now the old sclerotic areas are briefly contrasted with those which have been termed recent areas, it is found that the areas typical of the "sclérose en plaques" of CHARCOT are marked by the following histological characteristics: the complete absence of myelin (Weigert stain); the presence of a dense fibrillar tissue (glia stain); the persistence of numerous axis cylinders (silver impregnation method); the presence of numerous blood-vessels with condensed, sclerosed walls (diffuse stains); and the complete absence of any evidence of myelin degeneration (Marchi

method); and, finally, a nucleated transition zone, which gives frequently an abrupt passage to normal tissue. On the other hand, the recent areas, while presenting a striking contrast to the former, have also some of these characteristics, but in a lesser or different degree: the absence of myelin within the area; a very slight commencing glia fibril formation, but a very intensive glia cell proliferation; the persistence, to a much less extent, of axis cylinders and those persisting being markedly altered; the presence of numerous dilated blood-vessels with nucleated elements in their adventitial spaces; the marked indications of a previous myelin degeneration in the presence of fat granule cells which fill up all the interstices of the tissue and the adventitial lymph spaces of the blood-vessels; and, finally, a very gradual nucleated transition zone in which all these changes are less marked, but are combined with an evident degeneration of the myelin of the nerve fibres in this zone.

The question naturally arises: What relation do these two types of areas bear to one another? The finding of both types side by side in the same case, and the clinical history—with its remissions and relapses—argue for a close connection between them. Yet numerous writers, while not denying that the end result of the recent areas is a sclerotic tissue which bears a close agreement to the old sclerotic areas typical of the disease first designated by CHARCOT disseminated sclerosis, claim that true or primary disseminated sclerosis arises solely on the basis of areas of the first type, in whose evolution there is no stage corresponding to that of "fat granular cell myelitis." Areas of sclerosis which pass through the stage of the second type must be designated as secondary sclerosis, and those areas arise on the basis of a disseminated myelitis.

The questions must then arise: What is the evolution of the first type? and what are the stages in the evolution of the so-called secondary sclerosis? In the next two sections an endeavour will be made to trace their respective evolution.

3. *Evolution of an Actual Sclerotic Area.*

A. Through Stages of increasing Glia Hyperplasia.

The supporters of the view of a primary form of disseminated sclerosis claim that the essential lesion lies in the neuroglia tissue. By some anomaly of development this tissue, in certain areas, undergoes an intensive proliferation, which, by a gradual constriction of the glia meshes, produces a slow atrophy of the myelin sheath of the nerve fibre. The myelinated nerve fibre, therefore, in certain areas, undergoes a progressive reduction in its volume till it is completely replaced by the glia fibril proliferation, leaving the axis cylinder preserved. This proliferation goes a stage further than a mere substitution of glia fibrils for myelin sheath, for it is of such intensity that in no other condition is the glia proliferation so marked as in disseminated sclerosis (WEIGERT). It is claimed that not only is there a

direct action on the nerve fibres by direct compression of the proliferating glia, but that there is an indirect action upon their nutrition. By accumulating around the vessels the glia, if it does not close their lumen, is said at least to limit their expansion, and diminish the blood-flow, and interfere with the circulation in the peri-vascular lymphatics. In this simple atrophy of the myelin sheath the degenerated products, owing to the slowness of the process, are removed just as formed, in the form of very fine granules or in solution, without requiring the presence of true granular cells. These cells are said to appear only when the process is more rapid: they may occur at the periphery of an area of true, primary sclerosis, where the affected tissue causes a reaction in the normal tissue and an excentric spread of the process occurs.

In the description of an area of old sclerosis in the cord (p. 563) an oval area in the posterior columns was chosen, because here the glia fibrils normally constitute a very uniform fine network and the pathological increase of the fibrils appears to take place much more regularly in a direction parallel to the normal nerve fibres. In the lateral columns, however, the gradual increase of glia in a sclerosed area, on transverse section, can be followed up much more easily because of the more definitely reticular structure of the normal glia in this situation. The glia trabeculæ, in the lateral column, run out transversely to the long axis, both from the marginal glia zone and from the lateral grey matter. In the substance of the white matter they break up into a reticulum which is much coarser and more transverse than in the posterior columns, and the resultant meshes enclose the fibres and groups of fibres, which in their turn are larger than the average fibres of the posterior columns.

Fig. 343 shows an area in the lateral column, in which there is a commencing thickening of the glia trabeculæ and of the finest fibres forming the reticulum. This gradually increasing thickening (fig. 344) can be followed up till the finest glia meshes are almost obliterated and a dense fibrillar feltwork takes their place (fig. 345). With glia and cell stains it is seen that the septa which are formed by the glia fibres around the groups of nerve fibres become thicker and denser and richer in fibrils: they, as it were, force the groups of nerve fibres more and more apart and divide them into smaller groups, and the fibrils penetrate amongst individual nerve fibres. There is thus produced a feltwork of glia tissue, composed of glia fibrils, becoming more and more dense. As this condensation increases, even under low power it can be recognised that the ring of myelin around individual nerve fibres is becoming thinner, and finally the brilliant yellow-green ring (Van Gieson's stain) disappears altogether and leaves a naked axis cylinder. Sometimes this condensed glia has a granular, but more often a homogeneous, appearance, as if the individual fibrils had fused. Simultaneous with the thickening of the glia trabeculæ and reticulum the glia nuclei in the nodes of the reticulum and within the trabeculæ have enlarged and proliferated, becoming large protoplasmic cells with long-branching processes (fig. 347). In the glia septa, large and small, in which the blood-vessels

run, numerous examples of these may be found—the large ramifying processes joining the general glia reticulum. In such a condensed glia tissue the axis cylinders may be recognised for a long time (fig. 345). They appear little altered either in quantity or quality, but may be atrophied and gradually disappear or appear to fuse with the general glia tissue. The blood-vessels present thickened, condensed walls, with few cell elements. No compound granule cells can be found either distributed in the tissue or in the adventitial lymph spaces of the vessels. The proliferated glia cells seem to remain for a long time enlarged in this condensed tissue and their very defined processes can frequently be traced for a long distance, with no relation to the close feltwork of the glia in which they lie. Cross-sections of such areas are seen in figs. 345, 347, in which the dense glia tissue appears almost fused and stains lightly with Van Gieson's stains: the numerous glia cells are still larger than the largest spider cells of the normal cord. Weigert sections of such an area show a complete absence of myelin in the fully sclerotic area, but in the earlier stage of thickening of the glia trabeculæ, the myelin ring appears only thinned and atrophic and gradually lost. A low-power view of such an area gives the impression merely that the myelin sheath is faintly stained compared to the normal tissue, the transition to which is more abrupt than the glia-stained sections would indicate. In Marchi-stained preparations of the fully developed area, there is a complete absence of any indication of myelin degeneration.

It must be noted, however, that in some areas which also give the impression of a primary glia change, which has gradually encroached upon the nerve fibres and led to the dissolution of the myelin, compound granular cells have been found at the periphery of the areas and in the walls of the small vessels within it, and also for a time very isolated examples in the tissue itself. Such cells are always very isolated and give the impression that the process has been a slow one, and that somehow, in the gradual withdrawal of these cells from the tissue spaces into the lymph channels, a few have been left behind.

Such areas, from the slowness of the demyelination process; the absence of all, or almost all, signs of reaction except in the neuroglia tissue; and the frequent absence of granular cells, may be looked upon as evolving gradually to a complete sclerosis without any intermediate stage of fat granule cell myelitis.

B. Evolution of an Actual Sclerotic Area through a Stage of so-called "Fat Granule Cell Myelitis."

(*a*) *Spinal Cord.*

(i) Nerve fibres cut transversely (figs. 8–12; 349–354).

It will be convenient again to take an area in the ventral third of the posterior columns of the cervical cord, for such are very numerous in our preparations. To trace the gradual changes by which the normal tissue is replaced by sclerotic tissue

it will be necessary to refer to stages. These, it must be admitted, are somewhat artificial, yet they are marked in general by definite histological characteristics.

(1) The first indications of change (fig. 8) are best brought out by Van Gieson's stain and seem to us related to the glia cells. The normal spider cells show a distinct enlargement not only of their nuclei, but of their protoplasm and protoplasmic processes, and the small darkly-stained glia nuclei in the tissue also show a lighter staining. As yet there is no proliferation of such cells nor of any of the tissue cells, *e.g.* cells in the blood-vessel walls. Very closely related to this glia cell enlargement is a change in the nerve fibres and in the glia reticulum. This seems to start in a slight œdematous swelling of the tissue meshes, a swelling and faint staining of the myelin sheath, and a diffuse pink staining and swelling of the contained axis cylinder. These alterations are very slight, and though analogous in kind to the similar changes found in acute myelitis, are not so in degree. The small capillaries are dilated and engorged with blood, and show a slight participation, in the dilatation of their adventitial lymphatic spaces, in the slight œdema of this localised area.

This swelling of the structural elements increases till large protoplasmic glia cells are formed, some of which show indications, in the presence of two nuclei, of a previous mitosis, though we have never been able to recognise definite mitotic figures, and it is possible, as many writers assert, that a direct division of such cells may occur. The myelin sheath of individual nerve fibres is so swollen and faintly staining as to be unrecognisable; around others only a faintly-staining ring of myelin can be found, and in some the swollen axis cylinder lies apparently free at one side of the distended glia meshes. Under low power the nuclear content of this area is already definitely increased. These nuclei belong in part to the enlarged spider cells, in part to the swollen glia nuclei, and in small part to an increase in the endothelial nuclei of the vessels, and, where a distinct adventitia is present, to an increase in the lining cells of the adventitial spaces. The share these vessel cells take is extremely difficult to decide, for numerous areas have been examined in which, under low power, the affected tissue was found distinctly to contain more nuclei, and yet none could be traced to any change in the cells of any of the vessel walls.

(2) The next steps in the process (figs. 9 and 349) are characterised by the presence of a few large "epitheloid" cells, which, after the extraction of their contents with alcohol, appear vacuolated. This stage may be termed that of a commencing formation of fat granule cells. At first these are very isolated in the tissue, but as increasing numbers of myelin sheaths undergo degeneration their number increases very rapidly. The development of such cells at this stage must be largely traced to an increase in size of the small darkly-staining glia nuclei: the change in the nucleus of, and the increase in the protoplasm around, these cells may be followed till round cells are found, with a central nucleus in which the chromatin structure is quite visible and, with the protoplasm, taking a faint hæmatoxylin tinge.

Such a cell is seen in fig. 9 lying in the bay formed by two protoplasmic processes of an enlarged, multi-nucleated, spider cell. From such a cell all transitions can be traced to the fully-developed fat granule cell, in which the protoplasm between the vacuoles stains light purple and its outer rim forms a distinct membrane. When this stage is reached, it is found that numerous glia spaces appear empty or are occupied by fat granule cells in process of development; that the long ramifying processes of the enlarged glia cells extend for long distances and frequently envelop the fat granule cells; that numerous naked, swollen axis cylinders are found attached to the original glia meshes, which are now only faintly visible; that the nuclear increase is largely related to the presence of deeply-staining nuclei with a small amount of protoplasm; and that all the blood-vessels in this area are dilated and engorged with blood.

Slightly later in the development of the process, it is found that as the fat granule cells increase in number, there is often a definite reaction both in the endothelium of the small vessels and in the adventitial wall of the pre-capillary vessels. A special study was made of the recent areas to endeavour to trace proliferating endothelial cells in the vessel walls and their possible migration into the tissue. In many capillaries it seemed that the endothelial cells had proliferated and detached themselves from connection with the vessel. Some of the nuclei were perpendicular and oblique to the vessel wall, and appeared as if passing into the surrounding tissue. In the immediate neighbourhood of the vessels were frequently found, especially in cerebral areas, small groups of cells, similar in their nuclear structure to the cells in the vessel walls. Stages could be traced in the further development of these into cells with distinct zone of protoplasm, which in its turn appeared vacuolated till true fat granule cells were formed. It is thus seen that at this stage of maximum development of fat granule cells, the cells of the blood-vessel walls take a share in their formation, while at an earlier date they seem to arise from the proliferation of the small glia nuclei. Everywhere in the area were numerous small vessels, which give the impression of a new vessel-formation, but this might well be only an apparent increase, because all are so dilated and perceptible. In the cerebral areas this impression was much more marked than in the cord area, where the general architecture of the tissue seemed retained, in spite of the large increase in the cell elements.

(3) Following this is a stage (figs. 10 and 350) in which the formation of fat granule cells has reached its maximum. The whole affected tissue seems permeated with these characteristic cells, which lie not only in every possible tissue space, but fill the adventitial lymph spaces of all the vessels within the area—even the smallest capillaries being surrounded by a uniform, cellular ring, which gives the cross-section a very characteristic appearance. This stage may be termed that of a granular cell myelitis, and is the type of area we have described under heading 2 as representing the so-called acute multiple sclerosis. The presence of the fat granule cells in the

vessel walls indicates that the cells containing the products of the disintegration of the myelin are already commencing to be removed in the lymph sheaths of the vessels. Probably as a result of the presence of these foreign bodies in the lymphatics there is a reaction in the cell elements of the adventitia, with the production of a certain number of small, round cells, with darkly-staining nuclei and a small amount of protoplasm. These cells can be recognised in the adventitia together with the presence of the fat granule cells, and it is at this stage that the tissue gives the appearance of an inflammatory reaction in the vessel walls. Especially under low power, when the significance of this nuclear accumulation is not recognised, it seems that the tissue bears all the signs of an infiltrative myelitis. As the process advances, the protoplasm around the nuclei increases in amount, and the cell content of the adventitia can be differentiated into its various constituent elements (figs. 434–436): (1) the fat granule cell, with its vacuolated protoplasm and its nucleus, which has now undergone regressive changes and appears darker, and its chromatin texture denser, and later still the whole nucleus becomes crenated and fragmented; (2) the large vesicular nucleus of the proliferated endothelial cells; (3) the darker, smaller nuclei of the proliferated connective-tissue elements of the adventitia; (4) small lymphocyte-like cells whose nucleus is scarcely to be distinguished from the former.

(4) The stage succeeding this (figs. 10 and 350) may be termed that of a commencing fibril formation. Up till now the tissue at first glance appears as if large round nucleated elements had simply distended the glia meshes and taken the place of the nerve fibre; that these were specially numerous around the vessels; and that in place of the few spider cells of the normal tissue with the delicate glia reticulum, numerous large, proliferated, frequently multi-nucleated glia cells had arisen, whose long-branching processes entwined between and around the fat granule cells.

It is at this stage that there appear the first glia fibrils, as distinct from the glia cell protoplasmic processes. This fibril formation is beautifully brought out by Heidenhain's iron-hæmatoxylin stain, and specimens stained by this method and Van Gieson's method will be drawn upon for the description of the gradually increasing sclerosis of this area, which has so many of the characters of an area of acute myelitis. The essential feature of the rest of this evolution is the further development of the fibrillar glia tissue, which takes place at the expense of the protoplasm and protoplasmic processes of the large spider cells. The lateral margins and terminations of the processes are the first to develop into differentiated deeply-staining filaments, which at first retain their connection with the cell body, but as the differentiation is completed they become independent of the process and of the cell body, but retain a close relation to the cell nucleus. The nuclei seem finally to be the nodal points from which the fibres radiate. The evolution of these fibrils will be later more fully described, and here it is sufficient to state that these fibrils gradually assume a longitudinal position parallel to the longitudinal direction of the original nerve fibre. They are found gradually to increase in amount and to interlace and almost to form

a sheath with elongated meshes around the fat granule cells. On cross-section of the nerve fibres it is difficult to trace this, but it can be seen that the fat granule cells are gradually compressed by the increasing fibril formation between them. It is probable that this compression aids the suction influence of the lymph flow in drawing the fat granule cells out of the tissue spaces into the lymphatic spaces. Many of the large protoplasmic glia cells are now found to have their protoplasm entirely transformed into fibrils. Along with the increase of the fibrils and the diminution of the fat granule cells in the tissue spaces, it is recognised that many of the axis cylinders which have survived the swelling have now returned to their former volume and are more readily recognised than at an earlier stage, lying in the meshes of the condensing tissue.

(5) The next stage, that of advancing sclerosis (figs. 11, 12, and 351), is one which seems to occupy a long time. It is a gradual increase of the fibres, which seem able to become more abundant, possibly through fibrillation, even after their emancipation from the cell protoplasm. It is further a gradual diminution in size of the glia nuclei, and an increasing withdrawal of the fat granule cells from the tissue spaces, till only isolated examples are found. These may remain for a long time as vacuolated or granular spaces in the dense tissue, their nuclei very crenated or lost, and their membrane no longer recognisable. All the vessels, not only in the area, but the vessels radiating from it into the adjoining tissue, have their adventitial spaces crowded with similar cells. When the fibre formation has developed slowly and regularly, the pathological increase has taken place, according to WEIGERT and also in my experience, in a longitudinal direction, so that the transverse section represents the glia fibrils as fine granules, which surround the remaining preserved axis cylinders. Most of the glia cells have undergone regressive changes, but some large examples are still found.

(6) The final stage, that of complete sclerosis (figs. 353, 354), can scarcely be separated from the former: its complete evolution must be a very slow one, but the final result is a tissue which cannot be distinguished from that described under heading 1, as an old sclerotic area. In this area no fat granule cells remain either in the tissue spaces or in the vessel walls; the glia nuclei are mostly small and may be fewer in number than in the normal cord; and the fine granular points, representing the fibrils, surround the axis cylinders, giving the impression that a fine fibril formation has taken the place of the degenerated myelin sheath.

The blood-vessel changes, during the advancing sclerosis of the tissue, correspond to a very gradual condensation of the vessel walls (figs. 442, 443). The fat granule cells are gradually drained away, leaving the adventitial spaces still dilated. Many of the nuclei of these cells are left, crenated or broken up, in the adventitial wall, and add to its nuclear abundance. The numerous nuclei at this time may be attributed to several sources, but the small round cells predominate. As the surrounding tissue becomes more and more dense, all the walls of the vessel seem to

fuse and become homogeneous, and with Van Gieson's stain take a faint pink or yellow tinge. The outer layers of the adventitia remain for a long time separated, and contain cells of various kinds, granular debris, and blood pigment, but finally these all disappear, leaving a dense, homogeneous ring, in which almost no cell element can be recognised, except a very rare endothelial cell.

The glia changes correspond to the age of the process; on the one hand glia cell proliferation is found, and on the other glia fibril formation, and the tissue has altered to a dense feltwork. It is undoubtedly the large, pathological spider cells that produce the fibrils, and then in great part the nuclei perish. To such a disappearance and degeneration is to be traced the comparative nuclear poverty of the old sclerotic area.

It may be noted here that the glia fibril formation rarely takes place so uniformly parallel to the longitudinal direction of the nerve fibres. Where the large lateral blood-vessels course inwards from the surface at right angles to the long axis, they interrupt the direction of the fibrils. This may partly explain the almost constant radial arrangement of the glia fibrils around blood-vessels in an old sclerotic area. When, too, a greater degree of degeneration has occurred or a more rapid proliferation, the resulting glia fibrils will run much more irregularly (fig. 359), and, especially round the blood-vessels, will form the tourbillons or whorls so frequently found in sclerosed posterior columns, and also in the lateral columns.

The above stages may be briefly described in the following terms, which characterise their dominant feature:—

(1) That of a commencing reaction of all the tissue components.

(2) That of a glia cell proliferation and a commencing fat granule cell formation.

(3) "Fat granule cell myelitis."

(4) That of a commencing glia fibril formation.

(5) That of an advancing sclerosis.

(6) That of a complete sclerosis.

In Weigert sections of an area in its process of evolution it is found that, in the earliest stage, the low power indicates little alteration, but a higher magnification shows that the myelin is swollen and diffusely and densely stained, and has not the clear, ring-like defined character of the normal myelin sheath. In the second stage this is even more marked amongst some nerve fibres, while others have their myelin sheath broken up into a group of globules, and still others show an almost complete absence of myelin within the area, but many of the fat granule cells contain granular globules that retain the hæmatoxylin stain, and still other granules and even fragments so stained are found free in the tissue (fig. 408). In the succeeding stages the Weigert picture within the area is an entirely negative one.

Marchi-stained preparations show, even in the earliest stage, traces of a commencing degeneration of the myelin of the swollen nerve fibre, and frequently within this can be recognised, especially in sections counter-stained with safranin, a

swollen axis cylinder. In the second stage the picture is very definitely one of degeneration in most of the affected nerve fibres, while the few fat granule cells present are filled with fine granules of a Marchi-staining substance, and numerous other cells show a commencing fat granule formation in their protoplasm. In the next stage the whole area is beset with large black formations—fat granule cells—scattered through the tissue and grouped around blood-vessels and septa (fig. 313). In the two succeeding stages the Marchi reaction is confined to the remaining fat granule cells chiefly around the vessels (fig. 315), while in the final stage the sclerosed tissue stains lighter than the normal, and the picture, like the Weigert one at this stage, is again a negative one.

Reference must be made to the transitional zone of such an area ere its complete evolution can be understood. The area which served as the illustration for our description was a roughly triangular one, with its base to the posterior commissure (*cf.* figs. 260 and 356). This well-marked layer of dense glia tissue around the central canal seemed to act as a barrier to the further development of the area in this direction, but at its point of greatest development the two lateral sides curved gradually to the apex about the middle of the posterior septum. Along these lateral sides there was a very gradual transition to the normal tissue which bordered the posterior horns. In this transition zone the stages were very similar to those described within the area, but were later in their development, so that, for example, when the fibril formation had commenced within the area, there was still nothing of it to be seen in the transition zone. It was, however, in the two final stages that the transition zone was most marked, for here, long after no trace of fat granule cells could be recognised even in Marchi preparations, there was a well-marked peripheral zone of such cells, and in this zone the vessels still retain traces of fat granule cells in their adventitia at a stage when the central sclerosis has been long complete. The presence of this zone containing fat granule cells and other changes characteristic of an earlier stage of development, *e.g.* degenerating nerve fibres and proliferated glia cells, justifies the assumption that the process develops excentrically. When the transverse section of a sclerosed area in Marchi sections shows up lighter under low power than the surrounding normal tissue, and no degenerating fibres nor fat granule cells can be found either in the area itself or within the vessel walls at its extreme limit, the impression is given that the area has reached its climax of development, and that the process is stationary. All the products of degeneration have been removed, and the glia fibril formation has also reached its climax, except in the transitional zone, which seems also stationary. Here a nuclear proliferation is very evident, mostly of small round cells; the nerve fibres have a thin, faintly-staining myelin sheath, but not a degenerated one; and it can be seen that the glia cell enlargement is continued into the normal myelinated tissue around—the glia cells showing an enlargement of their protoplasmic processes, without any apparent change in myelin sheath or axis cylinder.

(ii) Spinal cord area—nerve fibres cut longitudinally.

The series of drawings (figs. 1–4) and photographs (figs. 325–336 and 337–342) of a part of an area in the posterior columns cut in longitudinal direction almost sufficiently indicate the nature of the changes. A glance at these figures shows the two outstanding features of the earlier process: the development (1) of an enormous number of large glia cells with a wide zone of protoplasm and numerous branching processes which quite mask the outline of the cell body, and (2) of rows of fat granule cells which tend to occupy the position of the degenerated myelin tubes. The latter figures show (1) the gradually increasing fibril development at the expense of the glia cell protoplasm and processes, (2) the increasing diminution of the fat granule cells in proportion to the increase in fibrils, and (3) the presence of large numbers of axis cylinders in this fibrillar tissue.

Here also the first change visible is an enlargement of the protoplasmic processes and nucleus of individual spider cells. This is closely followed by a swelling both of myelin sheath and axis cylinder, both of which swell out to occupy the whole space of the distended glia meshes, without, however, breaking through the glia reticulum which forms the meshes. Together with this change in axis cylinder and myelin sheath is an increase in the number of the normally present small glia nuclei, which may be seen, often in short rows, lying between the swollen nerve fibres (fig. 325). It is in such a section that it is possible more easily to follow the gradual increase in size of these cells and their development into the first fat granule cells, which lie closely applied to the swollen and degenerating myelin sheath. At this stage numerous dilated longitudinal capillaries and larger transverse and oblique vessels can be recognised in the affected tissue.

The development of the large spider glia cells occurs *pari passu* with the development of the small glia nuclei, and long rows of hypertrophic cells (fig. 379) of very varying shape may now be found, their long-branching processes passing in between the degenerating nerve fibres. The increase in the formation of fat granule cells takes place in a very close relation to the number of the degenerating fibres, and soon the whole tissue is composed of these rows of the two cell elements, pushed aside amongst which may be found very swollen axis cylinders or granular remains of such (figs. 1, 326, and 338).

The stage of " fat granule cell myelitis " has now been reached, and the description of the early area described under heading 2 applies to this area. The further evolution to the old sclerotic area described under heading 1 consists in the further development of the fibrillar glia tissue already described in transverse section. Here, however, it is much more easily recognised how the fibril formation tends to take place in a longitudinal direction. When the tubular rows of fat granular cells are fully formed, the glia cell processes twine around them and, when the fibril formation commences, the fibrils not only form between the rows, but pass in transversely or obliquely between

groups of three, four, or more granule cells, thus forming interlacing bundles of fibrils (figs. 2 and 329). In the elongated meshes formed by this interlacing there would seem to be a gradual compression of the granule cells, for many seem to undergo a gradual breaking up *in situ*. The nuclei become hyperchromatic and crenated, and the definition of the cell membrane is lost, till finally only nuclei are left with a few traces of vacuolated protoplasm around them. These nuclei remain long in these glia meshes, and add to the nuclear abundance of the areas at this time. With the gradual disappearance of the fat granule cells the interlacing bundles of fibrils gradually become more parallel (fig. 330); the glia cell nuclei diminish in volume as their protoplasm is differentiated into fibres; the axis cylinders, which have survived the early swelling, are now more defined (fig. 331), though many are still swollen and weakly stained; and, finally, the numerous vessels in the fibrillar tissue, which up till now have had their sheaths widened and filled with cell elements, gradually undergo the regressive changes already described.

For the stage of complete sclerosis, reference may be made to the area described under heading 1 (figs. 3, 4, and 331–336).

Weigert sections of such an area, during its evolution, show the successive changes of diffuse swelling of the myelin sheath, gradual loss of staining, and, finally, a negative picture with at first numerous fragments and granules, retaining the hæmatoxylin stain, scattered throughout the tissue. The transition zone is often a broad one on all sides, and both at its upper and lower limits it is wedge-shaped, the lateral margins of the wedge forming a zone in which all the changes are characteristic of an advancing process. If such an area undergoes complete sclerosis, this wedge-shaped zone shows (1) a looser structure than the central area—its fibril formation being not nearly so dense—and (2) a marked nuclear proliferation, of small and large glia cells, which extends for a short distance into normal tissue.

Marchi sections (figs. 319–323) and frozen sections, stained with Scharlach R. (figs. 18–20), reveal very beautifully the gradual changes in a degenerating nerve fibre—the presence of fine granules and globules or small and large irregular particles. Those changes may take place in a portion of a nerve fibre which in its subsequent course stains normally and then again shows degenerative changes. At the stage of maximum development of fat granule cells both Marchi and Scharlach R. specimens show their almost tubular arrangement in the tissue, and as the tissue becomes cleared, the arrangement in long rows around the longitudinal vessels, and in the vessels, cut transversely, which reach the pia. In the latter their numbers gradually diminish as the pia is reached, and those that are left pass into the lymph spaces in the inner layers of the pia (fig. 315). In the stages of advancing and complete sclerosis, fat granule cells are left for a long time in the walls of the vessels radiating from the sclerosed area: the transition zone also shows a complete layer of such cells in the tissue spaces. As the process becomes stationary, these also are drained away, leaving the whole area and the transition zone staining lighter than the normal tissue.

(*b*) *Cerebral area*: *e.g.* in the central white matter.

(i) Nerve fibres cut in various directions (figs. 5, 6, and 361–369).

It is when we come to trace the evolution of such an area that we recognise how complicated is the resultant sclerosis. The nerve fibres, instead of running parallel in one direction, here run in every possible direction—not only in straight lines, but in curves. It is a web in which, in addition, the threads in bundles and groups of bundles cross each other and also curve round to cut across the longitudinal, transverse, and obliquely-running threads. Those who have studied, by means of the various elective stains, the structure of an area, *e.g.* of the central white matter, have realised how difficult it is to define the plexus formed even when only one of the structural elements is stained. When, however, in consequence of the degeneration of the myelin sheath, or of both myelin sheath and axis cylinder, their place is taken by a dense fibrillar tissue, which more or less follows the varying direction of the lost fibres, it will be seen how aptly such a tissue may be described as an inextricable tangle, in which the finest meshes are invisible under low power.

Here also the first stage is one of reaction of all the tissue elements: at times it seems as if the glia cell enlargements were distinctly the primary change; at other times it is equally clear that a myelin sheath alteration, or even its complete dissolution, has preceded the glia cell change; and again it occurred that both changes are coincident. Heidenhain's iron-hæmatoxylin stain is of great service in allowing both the change in the myelin sheath and the change in the cell elements to be recognised in the same section, and frozen sections were found likewise of great help in coming to a decision as to which was the primary tissue element involved. It was distinctly evident that both changes preceded any recognisable alteration in the vessel walls. The frequent centrally-placed vessel and all the capillaries and pre-capillary vessels were dilated and engorged. In Van Gieson's stain the smallest capillaries are brought out distinctly, for the outer membrane of the endothelial cells stains intensely with fuchsin—and, in addition, a fine double contour, frequently present, gives the impression of a distinct adventitia or elastic coat even to these fine capillaries. At this stage, also, there is an increase in the small normal glia nuclei of the cerebral white matter, and an indication of a commencing enlargement of the nucleus.

At a later stage the large glia cell proliferation (figs. 13 and 434–436) is the most outstanding characteristic: the rapid appearance in such large numbers of those large protoplasmic cells with homogeneous protoplasm and long-branching processes is closely related to the numerous dilated vessels everywhere present in the affected tissue. It would seem that it is the glia cells, which normally lie within and close to the peri-vascular glious sheath, which first enlarge and proliferate, and several of their broad processes end in the outer wall of these vessels. Closely following this proliferation both of the large and small glia nuclei, appear the first fat granule cells,

which in size and structure closely resemble those found in the cord area (figs. 13, 361–363). These likewise develop in such profusion that soon the whole area is permeated by them, and under low power the tissue appears fenestrated and areolar —the spaces being occupied by round nucleated elements, and the intercellular spaces being filled by large protoplasmic glia elements whose branching processes again entwine around the cells. When the climax of fat granule cell development has been reached, Weigert and iron-hæmatoxylin sections indicate the almost complete absence of myelin within these areas; the progressive changes in the nerve fibres are not so easily followed as when the nerve fibres run only in one direction, but both Weigert and Marchi sections show the characteristic appearances of an early degeneration, the Weigert sections giving a myelin sheath diffusely or faintly stained, and the Marchi, the different stages of its disintegration. At the stage of "fat granule cell myelitis" the whole area is again beset with granular cells, both in the tissues and in the vessel walls. Marchi preparations (figs. 68, 301) show the structure and arrangement of these best, but cell stains, and Marchi sections counter-stained with safranin, in which the fat has dissolved out of the fat granule cells—leaving the skeleton structure of the tissue—show best the relation to the other tissue elements.

With the onset of the fibril formation, the walls of the blood-vessels, both within the area and leading from it, are even more densely packed with fat granule cells, amongst which may be found other nucleated elements, the result of the reaction of the adventitia to the cells in its lymph spaces. It must again be emphasised that it is areas at such a stage of development that have given the justification for regarding the process as developing on the basis of an acute myelitis, for the cell infiltration of the vessel walls and the presence of fat granule cells in such abundance in the tissue gives all the appearance of a softened and infiltrated area. At an earlier stage we have seen that the blood-vessel changes are not constant, and that only on the onset of the removal of the fat granule cells in the lymphatics is there any definite cell infiltration of the vessel wall. Later, as we shall see, the blood-vessel changes again recede in their prominence. Figs. 362 and 365 give a clear idea of the commencing fibril formation and the gradual separation of the fat granule cells by the fibrils, and figs. 436 and 437 give a conception of the vessel changes at this stage.

The stage of advancing sclerosis is well represented by figs. 6, 363, and 366. It will be seen in the low-power view that in a large area the sclerosis advances by no means uniformly—small areas being present in which there is an almost dense tissue, while others still contain numerous fat granule cells. The blood-vessel changes correspond very closely to those described in the spinal cord area, and will be more fully referred to in a later section. Weigert sections give a completely negative picture within the area; Marchi sections give a negative picture in the sclerosed parts, but the fat granule cells are well brought out in the tissue spaces and surrounding the blood-vessels. The further development of the fibrillar tissue,

at the expense of the glia cell protoplasm, and the gradual removal of the remaining fat granule cells, leads to the formation of a dense sclerosis, the meshes of which are so fine that under low power almost no spaces can be recognised (fig. 364). Within this area the glia nuclei gradually diminish in size and number, and, finally, they are fewer than in the normal tissue of the neighbourhood. Both Weigert and Marchi sections give a completely negative picture of such an area—the areas standing out clear against a dark background (figs. 292–294, 397). Glia stains, on the other hand, give a dense positive picture—the area standing out deeply stained against a lighter-stained background (figs. 398 and 401).

The transition zone of such areas must now be referred to. Here, also, we have a gradual but slower evolution of the same changes as within the area, but the sclerosis never reaches the stage of a final, dense meshwork. In this transition zone are found at successive stages degenerating myelin fibres, with hyperplastic glia cells and fat granule cells both in the tissue and in the vessel walls—signs of an advancing process, which frequently remain long after the sclerosis within the area is complete. When, finally, all indications of myelin degeneration have been removed, the transition zone is markedly different from the adjoining sclerotic tissue on the one side, and the normal tissue on the other—from the former in the lesser degree of glia fibril formation, and from the latter in the diminished number of myelin fibres, and the thinness of the ring of myelin around such as persist in this zone. Again, as in the cord area, there is a marked small glia cell proliferation in this transition zone (fig. 403), together with a few enlarged glia cells (fig. 404). The latter may also be found extending for a short distance into the surrounding, otherwise healthy tissue. In this description of the evolution, few references have been made to the persistence of the axis cylinders. Nowhere is the distinction more difficult to draw between glia fibrils and axis cylinders than in such cerebral areas—not only with the ordinary diffuse stains, but with Bielschowsky's method, which here so frequently stains the glia fibrils—a finding which numerous writers have noted in cerebral areas. In two areas stained by Cajal's method, there were found a very large number of persistent axis cylinders; in one case (fig. 430) the whole fine reticulum of axis cylinders and their branches were retained, but in three other small areas no axis cylinders could be found. By the diffuse stains, in numerous instances, it could be asserted that almost the whole axis cylinder content of the area was retained.

(ii) Cerebral area cut in longitudinal direction of the nerve fibres (figs. 370–377).

Such an area shows no essential changes from those described in the longitudinal direction of a spinal cord area. In my experience the preserved axis cylinders were very much less numerous than in the cord. Fig. 422, taken from an area at the base of a medullary ray, shows the appearance presented in a specimen stained by the Bielschowsky method.

4. *Other Types of Areas.*

So far the histological description has been confined to areas which may be looked upon as typical of a late and of a recent process respectively, and to the evolution of a sclerotic area, on the one hand by a gradually increasing hyperplasia of the glia, and on the other by stages which include the formation of a large number of fat granule cells. As different stages occur in the same case, and as the process by no means always follows the same uniform course of development, it will be evident that the histological picture met with is a very varied one. Yet before a comprehensive view of the complete process can be obtained, it is necessary to add to this complicated picture a brief description of other areas—areas so frequently met with as to constitute types almost as definite as those already taken of an old and a recent process.

(*a*) *Areolar Areas.*

The "areolierte" areas of German writers. At first sight it would be natural to relate such areas simply to an arrest of the fibril formation before a dense sclerosis had taken place. An examination of the transition zone around most of the old areas, where the process has become stationary, and yet the fibril formation is not so abundant as in the centre of the area, would seem to justify this explanation. A close examination, however, shows that this cannot be accepted as the constitution of all such areolar tissue. Under a high magnification the glia is found to be often relatively unaltered, and to show only a distension of the network. Wide meshes are thus formed, with cells at the nodal points of the network, and frequently larger spaces result from the opening into each other of adjoining meshes by the breaking down of the glia fibres separating them. Within the meshes the myelin sheath has disappeared, leaving the axis cylinder at one margin, or this also has disappeared, and the space is empty, or contains only granular remains of regressively changed fat granule cells. An area of dense glial sclerosis is frequently quite completely surrounded by such a peripheral areolar zone, which interposes between it and the healthy tissue. This peripheral zone contains numerous nuclei and dilated vessels, with nuclear accumulations in their dilated adventitial sheaths: its mode of formation is to be distinguished from that of the transition zone already described—the latter being distinctly an arrest of the development of the fibrils before complete sclerosis had occurred, while this areolar zone around a compact area, and the areolar areas described in this paragraph, are to be traced in all probability simply to an acute and rapid degeneration of the nerve elements, with a distension of the original glia meshes before fibril formation had occurred. In the spinal cord such a distension of the glia meshes, swelling of the myelin, and distension of the adventitial lymph spaces of the vessels, extends sometimes over the whole transverse section of the cord. At other times at the periphery of the cord we get a widening

of the glia meshes. This is only in small part due to the retraction under the influence of hardening agents. The abnormal dimension of the interstices points to the presence of liquid in excess in the tissue. A primary degeneration of the nerve elements, at least of the myelin sheath, as an explanation of "areolar" areas, has been assumed by those who see in such areas a proof of the change in the myelin sheath as the essential and primary feature of disseminated sclerosis. It is not denied that later, if there is time, a proliferation of the glia may be associated. On the other hand, REDLICH and others see in "areolar" areas a process quite distinct from the essential substratum of a typical sclerotic area.

It must here be added that very large numbers of the areas found in all the cases, especially cerebral areas in which the process was quite stationary, as far as the degeneration of the myelin at the periphery was an indication, showed under low power a much less dense sclerosis than that described as compact sclerosis. In such areas fat granule cells were absent both from the tissue spaces and the vessel walls; Marchi and Weigert sections also gave a completely negative picture, but cell stains and glia stains showed that numerous large, multi-nucleated glia cells were still present, and that each was the central point from which a marked fibril formation radiated. This fibril formation, however, had not been sufficient to form the inextricable tangle of the denser areas, and yet was quite distinct from the simple distension of original glia meshes of the areolar areas (figs. 367, 368). We thus draw a sharp distinction between these two forms, which have both received the name of "areolar" areas, and reserve this name for the areas in which the original glia meshes are retained or distended, and reserve "areolar zone" for the zone sometimes found around compact areas, which has a similar structure.

(*b*) *Peri-vascular Sieve-like Areas.*

Non-myelinated areas are frequently found, especially in the brain, in which large open spaces are met with around all the vessels found within the affected area. The wall of this space is, on the side of the nerve tissue, represented by a dense ring of glia fibrils, often with very few nuclei. The walls of these vessels seem often little modified: they may be slightly thickened and infiltrated, but the essential change is a separation of the constituent elements of their adventitial sheath so that the connective-tissue fibrils stretch across and form a very wide-meshed reticulum between muscle coat and condensed glia (figs. 448–450). Within these meshes a fine coagulum (fig. 441) is frequently found, together with a few cells, often containing pigment or the remains of fat granule cells. The vessels thus affected lie together in groups, and give the tissue a sieve-like character, which, when advanced, has been termed "l'état criblé." The impression is received that it is the branches of one vessel stem (fig. 448) that are concerned in this change. Around each vessel the myelin fibres are dissolved, the glia meshes are widened, and both large and small glia cells are proliferated

(fig. 449), and the areas affected, around each vessel, usually coalesce to form a more or less large irregular non-myelinated area. Frequently half the vessels affected lie within non-myelinated tissue, and half within tissue in which the myelin as yet stains normally (fig. 450). BORST considered that these areas are the result of a circumscribed peri-vascular lymph congestion and that they are a pre-stage of areas of true dense sclerosis, which, he considers, develops on the basis of a lymph stasis in the tissue.

(*c*) "*Markschattenherde.*"

As a rule, at least at the commencement of the process, sclerotic areas have a very limited longitudinal and transverse extent. This characteristic has given to the disease the name "insular sclerosis," because the areas appear isolated. We have seen, however, that areas frequently coalesce on one or several sides, and the original outlines are quite indistinct. In addition to this, there are often found between individual non-myelinated areas, extensive patches which, with Weigert staining, show a weak staining of the myelin. The fibre bundles are distinctly perceptible and yet scarcely stained: this is well brought out on longitudinal sections, where it is seen that the fibre layers correspond in arrangement and position to the normal bundles, and one can recognise the immediate transition of normal fibres into those with deficient staining. Such areas, in which the myelin sheaths are simply shadows or very thin, adjoin areas of complete demyelination, and may involve the whole transverse section or the longitudinal section over several segments. ALZHEIMER looks upon this deficient staining as a condition of the myelin sheath antecedent to degeneration. Marchi staining sometimes gives a very extensive early degenerative process, and there may be an equally extensive commencing glia proliferation. Yet this change may sometimes indicate a simple atrophy which results in a progressive reduction of the volume of the sheath without affecting the remaining myelin. The process might then be looked upon as a slumbering one, and not necessarily immediately antecedent to degeneration. In the former case the glia proliferation would be more abundant, as the slow, chronic stimulus would be more likely to lead to a greater reaction in the interstitial tissue. Thus VOLSCH has described areas in which there was a very extensive "Aufhellung" of the myelin sheath, which was associated with an equal or even greater degree of glia hyperplasia—a condition which he has termed "diffuse multilocular sclerosis."

It may finally be noted that in Marchi sections there was frequently found, extending outside the sclerosed areas uniformly over the whole transverse section of the cord, an early myelin sheath degeneration. This could be noted even in the nerve roots and must, probably, be traced to the septic fever from which the patients suffered.

(3) Histological Characteristics in Special Situations.

1. *White Matter.*

This has already been fully considered, as the areas described in the previous sections were all in the white matter of the brain and cord.

2. *Grey Matter.*

(*a*) *Central Grey Matter.*

Where the sclerotic process affects the grey matter of the spinal cord and the corresponding nuclei of grey matter in the medulla oblongata and pons, we find that the changes in their evolution correspond very closely to those in white matter in which the nerve fibres form a reticulum.

The myelin network quickly disappears, and in its place we get a thickened glia reticulum with large meshes and numerous hypertrophied glia cells. These spider cells, with relatively numerous processes, varying in length and thickness, give rise to a fibril formation analogous to that already described—the resulting meshwork being very close. The formation of fat granule cells is always much less marked than in the white matter; their size is smaller and the structure of their granules more delicate. This corresponds to the lessened quantity of myelinated fibres in the grey matter, but the process of their formation, the absorption of the degenerated myelin, their presence in the glia meshes, and their gradual removal in the lymphatic spaces of the vessels is quite similar to that elsewhere. The vessels passing from the borders of the grey matter into the white matter form often radial lines, the commissural vessels and the vessels in the anterior median fissure also take their share in this removal of degenerated products.

The ganglion cells in this reticulum seem to remain long preserved (fig. 417), and in this investigation changes, which could be distinctly traced to the sclerotic process, were found only when an advanced degree of sclerosis had been reached (fig. 419). The cells undoubtedly remain long with their normal form and minute structure preserved. The processes first lose their structure and, as the sclerosis becomes denser, the cell bodies share in this change. In the later stages they show all the possible changes which are traceable to a slow simple atrophy from loss of function (fig. 409) or from compression on the part of the developing cells and fibrils of the interstitial tissue (fig. 419). Diffusely extensive changes in the ganglion cells (fig. 411) should probably be referred to somatic general disturbances which accompany the disease, *e.g.* the fever, anæmia, exhaustion, or direct septic absorption from bed-sores or a pyelitis, and can thus not be looked upon as specific to disseminated sclerosis. In numerous affected segments which microscopically showed complete demyelination, many of the ganglion cells showed no changes—completely normal cells being found alongside those with marked chromatolysis or atrophy.

As the glia reticulum becomes denser and encroaches more and more on the ganglion cell processes and cell body, there takes place a gradual atrophy of the cell (fig. 415). For a long time an atrophic, rounded or oval cell, with no processes and no chromatophile granules and usually without nucleus, may be recognised (fig. 418). But gradually this faintly or diffusely staining body can no longer be recognised as a cell, and this dense tissue consists of the deeply-staining glia nuclei and the abundant delicate fibrils (fig. 419).

It is frequently stated that sclerotic areas are never found solely in the grey matter, but that these are always extensions from sclerosis of the white columns. In serial sections, however, it could be proved that small sclerotic areas may be confined, throughout their whole longitudinal extent, to the grey matter. An affection of the myelin reticulum around and between one or other group of cells (figs. 137 and 155) has frequently been the sole trace of demyelination in many sections of the lumbar cord. A peri-central sclerosis (fig. 197), limited at first entirely to the commissures, is often the starting-point of an extension into each anterior and lateral horn. The spread may take place forwards along each lateral margin of the anterior fissure or posteriorly along the posterior median septum as a central line, or the extension may be along all of these planes, giving rise to a cruciform area of sclerosis, which in its further extension may involve the whole transverse section, leaving sometimes four lateral and symmetrical peripheral areas situated near the posterior and anterior roots respectively (fig. 210).

Undoubtedly, however, the affection of the anterior horn of grey matter of the cord starts very frequently from the extension inwards of an area of sclerosis situated at the margin between white and grey matter (fig. 241). In the transition of an area from grey to white there is such marked glia proliferation that the transition can no longer be recognised. MÜLLER looks upon this border line as an area in which the glia is more fully developed: this is certainly so in the region of the formatio reticularis, which is the most frequent site of development of a gradually increasing glia hyperplasia. The development of areas at this transition zone has been explained by other writers with reference to the breaking up of both central and peripheral vessels, and it is not difficult to trace the direct passage of a lateral vessel to such an area (figs. 241 and 253), or of thickened commissural branches passing to areas in the lateral and anterior grey matter.

The definition of the area in the grey matter was never a sharp one: the nerve fibres of the reticulum passing into the area for very varying distances (fig. 412). It was also found that where an areolar zone surrounded an area which involved both white and grey matter, it ceased almost abruptly at the transition and was never present in the grey matter.

When sclerosis affects the cranial nuclei, as is so frequently the case, the process may again be confined to the grey matter, but this is rare, and it is much more often an extension of a process which involves the floor of the IVth ventricle. The

histological characters in no way differ from that just described. Fig. 417 shows an involvement of the hypoglossal nucleus.

Sclerosis of the olivary bodies and of the dentate nuclei leads to a gradual thinning of the lamellæ. In numerous specimens there is present a very advanced degree of sclerosis of the fibres entering at the hilum and passing to the grey matter before there is any noticeable involvement of the glia reticulum of the lamellæ, unless these are involved in a general extension inwards from the surface of the medulla or ventricle. The ganglion cells (fig. 375), as far as it was possible to interpret their changes, seemed to undergo a gradual and uniform structureless appearance, and to retain a deeply-staining nucleus till the cell body was almost completely atrophied.

Numerous areas at all stages of development were found in the basal ganglia (figs. 265–267). In the evolution of these areas there is little distinctive to be added. The numerous bundles of parallel nerve fibres which pass through these ganglia and intersect each other frequently give to the resulting glia reticulum a more uniform appearance over short stretches. It was also noted that in such areas it was possible to prove how the process advanced without any relation to any conducting tract of fibres, and simply involved the immediately adjoining tissue bundles in whatever direction they ran. It was found impossible to relate any specific changes in the ganglion cells to the sclerotic process: these underwent a gradual atrophy as the fibril formation became closer. Very large and very numerous spider cells were found in all the early areas, and the fibril development was a very close-meshed one, the sclerosed tissue being formed by a web of very closely arranged fibrils oriented in all directions. The special changes in the branches of the lenticulo-optic and lenticulo-striate vessels will be considered later.

(*b*) *Cortical Grey Matter.*

It is now well recognised that the cortex is affected in disseminated sclerosis. Before the introduction of the Weigert medullated sheath stain, such areas were often overlooked, and by many their existence was denied. Two deductions may be drawn from this circumstance: the one, that cortical areas are difficult to recognise except with a medullated sheath stain; the other, the completement of the first, that the glia, axis cylinder, and cell changes in the cortical areas are very slight. Both deductions are, in my experience, justified. A very large number of portions of tissue from the cerebral convolutions, in which macroscopically—after fixation in formalin or after mordanting in bichromate—cortical areas could be distinctly made out, were taken through both for celloidin, paraffin, and frozen sections. In only a small proportion of these could the demyelinated area be recognised in cell stains, even after the most careful comparison with the control Weigert or iron-hæmatoxylin-stained section. The cortical portion, which showed a complete absence of myelin (figs. 298, 385), seemed to show no other change related to the process of

disseminated sclerosis. In comparison with the adjoining cortex on either side, with the cortex of adjoining convolutions, or with the cortex of an altogether different portion of the hemisphere, there seemed to be no change in the ganglion cells, glia cells, or axis cylinders. Yet there were many areas in which recognisable alterations in these structural elements in the demyelinated area did occur (figs. 299, 386–396), and it is these which will now be described. It has seemed impossible to reach any explanation of why certain areas showed changes and others did not do so.

Minute areas were found in all the layers of the cortex, but before referring to these it will be simpler to trace the changes in an area which passes over from the subcortical white matter into the cortical layers. The earlier writers, as we have seen, asserted that this transition never occurred, and that the grey matter formed a barrier to the extension of the process. Sections stained with Weigert's glia method were largely responsible for this statement, for such preparations showed an almost abrupt cessation of the glia fibril formation at this border, and recent writers emphasise the complete absence of a glial sclerosis as one of the essential characteristics of a cortical area. Is, then, the process that attacks the cortex different in its nature and origin from that which affects the rest of the central nervous system? Those who see in disseminated sclerosis a primary proliferation of the glia must admit that in the cortex, at all events, this is not the origin of the process, and that a primary degeneration of the myelin sheath is often the sole change. The examination, however, of a very large number of sections from very numerous areas in several cases, by means of the Heidenhain iron-hæmatoxylin method, both in celloidin and paraffin and frozen sections, and a comparison of such sections from the same block of tissue, stained by Ford-Robertson's methyl-violet method, Scharlach R., Bielschowsky's silver impregnation method, and the routine diffuse stains, has led to the conclusion that, while a fibril formation in the layers of the cortex is proportionate in its development to the normal glia fibril content of the layers, a change in the glia cells and fine glia reticulum of the cortex is very closely related to the loss of its myelin fibre content.

In the area represented in fig. 286 it is seen that the absence of the myelin affects a portion of the medullary white matter and the radiating fibres in the cortex. The demyelinated tissue is roughly wedge-shaped, with its broad apex in the white matter and its base on the surface of the convolution. Its outline is clearly defined from the surrounding radiating fibres. The great majority of areas in which changes in the cortical layers were found in association with subcortical changes were in the condition of recent areas. The structure of that portion in the white matter, therefore, was similar to that described under heading 2. The enormous spider cell proliferation and fat granule cell formation attained, at this transition border (fig. 389), its maximum intensity, and passed over into the deepest layers of the cortex so that the border could no longer be recognised. Specially prominent was the development of the glia cell processes which attached themselves to the walls of the

capillaries and pre-capillary vessels (fig. 436). Each of these was surrounded by rings or layers of fat granule cells, and to the outermost of these the glia cell processes formed almost a radial arrangement. Each ganglion cell in the stellate layer and in the layer of the deep pyramids was in a condition of marked degeneration and atrophy. Many were mere ghost-like forms with no structure; in others only the large nucleus remained, and still others were replaced by nests of small round cells from five to ten in number (fig. 381). The whole tissue of these deeper layers was so crowded with the two proliferated cell elements, large glia cells, and fat granule cells, and with the numerous dilated small vessels, that the ganglion cells were almost lost sight of. Where the area involved, as in fig. 387, the Betz cells, these also were found to show all stages of degenerative change, and many of them had disappeared. The changes gradually receded in intensity as the upper limit of the deep pyramids (figs. 392, 395) was reached: the cells in the granular layer were found to be surrounded by nests of small round cells (fig. 393), but here the glia spider cell and fat granule cell formation was very limited. The fat granule cells present had also a finer structure than that in the deeper layers (fig. 396).

The intensity of the process gradually lessened as the upper layers of the cortex were reached. Amongst the large pyramids were found still a large number of proliferated glia cells, but now the processes of these were of a fine, almost uniform calibre, and reached a very long distance from the small nucleus from which they radiated. Marchi sections showed a very characteristic appearance in these layers. All the satellite cells, which are normally round and have no visible protoplasm, were found to have developed a protoplasm cell body, of various shapes, often spindle-shaped and star-shaped, and to surround with their processes the ganglion cell (fig. 396). Their protoplasm was studded with the minutest black granules, and transition forms could be traced between those surrounding the ganglion cell and rounder forms lying free in the tissue spaces or in the sheaths of the larger vessels. The finest capillaries were surrounded by similar granular cells of varying shapes, which had evidently arisen from the rows of small round cells which in these cortical layers normally surround the capillaries. It is to these cells and to the very similar round cells in the white matter that FORD-ROBERTSON has given the name mesoglia cells, and to which he attributes phagocytic properties. Of their phagocytic character their protoplasm, loaded with fine fat granules, is a direct proof. Here also the fine uniform processes of the glia cells have a very intimate relationship to the vessels, especially to the very abundant capillary plexus in this region. When we reach the surface layer we find again a very abundant development of glia cells, many of which are multi-nucleated and in the process of fibril formation. Diffuse stains—for here specific axis cylinder stains failed—showed that numerous axis cylinders could be recognised, but that very many had perished in the dense zone of reaction.

To sum up briefly the changes in a recent combined subcortical and cortical area,

it is sufficient to emphasise these related to the glia cell and fat granule cell development, for the myelin sheath and axis cylinder changes do not differ from those in other areas. In the transition from white matter to cortex the deepest layer of the cortex is no longer recognisable (figs. 388–390). In the layer of the deep pyramids (fig. 392) and Betz cells (fig. 387) both glia cell proliferation and fat granule cell formation are still very marked: from the granular layer upwards, however, the intensity of the cell reaction is much less. Nests of small round cells are found around nuclear remains of atrophied ganglion cells (fig. 393), and around others and around the capillaries is found a fine fat granule formation in the satellite cells (fig. 396), together with a very delicate glia fibril formation, which requires the highest magnification to recognise. In the marginal zone there is again a marked glia cell and fibril reaction.

If the evolution of such an area be followed, it is found that in the white matter and deepest layers the process often follows the lines one would expect from the presence of the large, protoplasmic, potential fibril-forming glia cells. This sclerosis extends to involve the deepest layer of the cortex. Above this, in the layer of deep pyramids and Betz cells, the glia cell nuclei are left as the nodal points from which radiate a glia fibril formation which is insufficient to cause sclerosis; the fibrils, however, merge into a very delicate reticulum, which may be the syncytium claimed by HELD to form the groundwork of the cortex. In the superficial layers of the cortex the long, uniform, delicate processes of the glia cells also unite with this reticulum, and in the surface layer the proliferated glia cells form fibrils which extend downwards—also to merge with the syncytial reticulum.

The ganglion cell changes in relation to these areas will be taken up under the heading of ganglion cells.

When an area is confined to the cortex, the changes are, as a rule, not nearly so marked, especially those in the deepest layers. The demyelination may reach from the surface of the convolution to varying depths (*cf.* figs. 269, 273), even to the border between cortex and white matter. It may lie wholly within the cortex and cut through a portion of the radiation or simply affect Baillarger's stripe. These areas are often in association with a markedly dilated vessel which penetrates from the surface almost to Baillarger's stripe, and a number of dilated changed smaller vessels lie within the area. Marchi sections of such areas show that the myelin sheath is not attacked as a whole: the black staining gradually increases to involve the whole myelin ring, and the axis cylinder shows by its swelling a distinct participation in the process. The ganglion cells in such areas show everywhere nests of glia cells around them: these changes are by no means confined to the actual demyelinated area, but are more marked there than elsewhere, and most constant in the granular cell layer (fig. 393). The glia cells in the layer of the deep pyramids show the changes represented in figs. 392, 395—a marked proliferation and fibril formation, which, however, is again insufficient to cause

sclerosis. In the layer of stellate cells (figs. 391, 394) also there are the same changes with a more marked disappearance of the ganglion cell bodies, leaving only nuclei surrounded here and there by nests of cells.

3. *Peri-ventricular Sclerosis.*

This special localisation, noted by CHARCOT, BORST, STRÄHUBER, WESTPHAL, and others, has been emphasised as the dominant feature in the cases reported by LHERMITTE and GUCCIONE, MERLE and PASTINE, and also by SCHOB. It is of special interest in relation to the pathogenesis of disseminated sclerosis, and at once raises the question whether the development of the peri-ependymal areas may not be conditioned by the presence of the causal agent in the cerebro-spinal fluid itself. In horizontal sections through the cerebral hemispheres, there was frequently found a sclerosis which, macroscopically, seemed limited to the walls of the ventricles (figs. 200, 201), and very numerous sections at various levels were studied to determine the exact limits of this alteration, in what it consisted, and whether the apparently isolated areas in the adjoining grey nuclei or white matter were really offshoots from the areas on the ventricular surface. In all the cases which showed a peri-ventricular sclerosis, this was much more marked around the horns, especially the posterior horn (figs. 23, 24), but sections cut at lower levels, *e.g.* through the temporo-sphenoidal lobe (fig. 29), horizontally or sagittally, showed the almost equally marked involvement of the descending horns on both sides, and sections of the hemispheres cut at levels immediately above the corpus callosum showed large round isolated areas in the central white matter, some of which, in serial section, proved their connection with the sclerosis of the roof of the lateral ventricle (figs. 25, 26). It is thus seen that not only were the walls of the ventricle involved, to a varying degree, throughout their whole surface—lateral walls, horns, floor and roof,—but that this sclerosis extended inwards from the ventricular surfaces, forming a zone from one-half a centimetre to 1 centimetre broad in the adjoining grey nuclei or white matter. Further, that from this zone at numerous points processes—sometimes finger-like, sometimes cup-shaped—passed deeper into the surrounding tissue. Such areas appeared naturally, in some sections, isolated from the peri-ventricular sclerosis or attached to this by a narrow neck, in which often lay a central vessel with walls changed according to the degree of sclerosis reached.

Horizontal sections through the hemispheres at Pierre Marie's *coupe d'élection*, or immediately above or below this level (figs. 23, 24; 70–73; 93–96), showed that the occipital horn was surrounded by a hood of changed tissue, macroscopically greyish-white and gelatinous (fig. 200), or of a whitish-yellow colour and softer consistence. From the point of this hood the sclerosis is prolonged in a series of small elongated or rounded areas towards the posterior extremity of the occipital lobe, involving the optic radiations, the inferior longitudinal fasciculus, and the tapetum at several points, and in some cases involving the medullary rays and cortex of the convolu-

tions of the calcarine fissure. The sclerosis of the anterior horns is less marked, but is also prolonged in the direction of the frontal lobe, and laterally involves the lenticular nucleus and the cortico-pontine fibres. Between these two horns the thickness of the sclerotic tissue varies greatly at individual levels—sometimes the lateral walls of the ventricle are scarcely involved, again there may be a sinuous narrow margin along its whole extent, and again the outer border at parts may be half a centimetre broad, with well-marked processes extending into the grey nuclei and adjoining white matter. The fornix and the corpus callosum, on the ventricular surface both of the splenium and genu, were also involved, and isolated areas were also found in both, which seemed to have no connection with the ventricular border.

Horizontal sections near the roof of the ventricle usually showed an involvement of the entire surface extent of the ventricular walls, with well-marked pouches passing inwards into the corpus callosum on the one side and the central white matter on the other (fig. 26), and also passing upwards. One such area above the roof of the ventricle (fig. 25), three-quarters of a centimetre in diameter, was traced not only to its connection with the roof sclerosis, but upwards till it gradually diminished and broke up into a series of smaller areas. In this large area there was no one central vessel, but a large number of dilated vessels—arteries, veins and capillaries—with their walls all filled with fat granule cells. The tissue was very soft and fell out in the large celloidin section; in the bichromate it had appeared chrome-yellow in colour and much lighter than the surrounding white matter.

Horizontal sections through the temporo-sphenoidal lobe (fig. 29) on both sides showed that the sclerosis of the descending horn was very marked, and below the floor of the ventricle it had extended to involve almost the whole of the adjoining white matter, reached into almost every one of the medullary rays passing off from this, and that there were also numerous areas in the cortical grey matter in close relation to the affected medullary rays. Sagittal sections through the temporo-sphenoidal lobe in other cases gave a very instructive picture of the extension outwards of the ring of peri-ventricular sclerosis into each medullary ray and of the very frequent involvement of the white matter of the hippocampal convolution, of the fimbria, and of the gyrus dentatus.

The ventricles, in most of the cases, were not dilated: their walls also were smooth, and presented neither granulations nor glandular indentations. In one case (figs. 70–73) the lateral ventricles were very dilated, and the outline of the sclerosis between anterior and posterior horns was so irregular and passed on both sides so deeply into the optic thalamus, in which were also numerous apparently isolated areas, that the substance of the optic thalami, the internal capsules, the lenticular nuclei and external capsules presented a moth-eaten appearance. In one case especially (fig. 201) the numerous veins in the sub-ependymal glious tissue, especially near the posterior horns, were macroscopically outlined on the ventricular surface by a gelatinous, deeply-stained zone, and, microscopically, it was found that this

corresponded to a zone of denser sclerosis—the vessels, however, in which had dilated adventitial sheaths filled with very numerous cellular elements. Only one distinct ependymal granulation (fig. 455) could be found throughout the whole investigation: this consisted of a dense mass of deeply-staining glia nuclei and glia fibrils. The ependymal epithelium over it and over the whole sclerotic tissue in general, was retained and apparently normal—any apparent proliferation of epithelial cells could be traced to the oblique level of the section.

The histological structure of the peri-ventricular areas need not be entered into in any detail. Weigert sections showed the complete absence of myelin in the areas at all stages—the preserved nerve fibres passing into the areas were very tortuous and varicose. Marchi preparations (figs. 181, 308) again gave the long rows of fat granule cells in the tissue spaces and around all the blood-vessels, especially around the groups of venous vessels at both posterior and anterior horn: the branches of these vessels could be traced for long distances towards both occipital and frontal poles, and similarly numerous vessels could be traced into the lateral peri-ventricular tissue. The closely arranged longitudinal fibres of the corpus callosum (fig. 307) showed beautifully the tubular arrangement of the fat granule cells, the rows of enlarged spider cells, and the gradually increasing dense longitudinal fibril formation. Both Cajal's and Bielschowsky's methods and diffuse stains showed the very large number of retained axis cylinders. When the immediately sub-ependymal tissue had reached the stage of dense sclerosis, it presented an extremely close fibrillar web, poor in nuclei—the fibres mostly parallel to each other, parallel to the direction of the normal nerve fibres. Numerous dilated vessels twined in this fibrillar tissue. Before the onset of this advanced sclerosis the glia meshes were often very elongated and rarefied (fig. 376); the glia cells were markedly drawn out in a longitudinal direction, and showed often a nucleus at each pole, and a sheaf of fine fibrils passing from each pole of the cell to interlace with similar bundles of fibrils.

In the zone of unaffected tissue around the ventricle it was found that there was frequently a proliferation of the sub-ependymal glia cells. But such areas sometimes showed a lighter staining of the myelin: similar "shadow" areas often united wholly demyelinated areas of the lateral wall or extended inwards from them. It could thus be assumed that the originally primary areas became fused by these transition areas becoming wholly demyelinated, till the whole ventricular surface was affected.

Around the aqueduct of Sylvius and around the floor of the fourth ventricle and its lateral angles (*cf.* figs. 76–82) the degree of sclerosis was often very marked. The extent of this in individual cases is well brought out in the very numerous figures taken from Weigert sections, and is more fully described elsewhere in the individual cases. Its structure was everywhere on similar lines. The final web formed was simply an exaggeration of the closely arranged fibrils, which are normally oriented in all directions. The involvement of the cranial nuclei in this extension has been also elsewhere described.

4. *Changes in Nerve Roots and Meninges.*

(*a*) *Optic Nerve.*

The optic nerve and olfactory lobe must, embryologically, be looked upon as parts of the central nervous system. They therefore contain neuroglia, and must be considered apart from the other cranial nerve roots. The olfactory lobe was examined in only two of the cases: both peduncle and lobe in each case showed distinct signs of demyelination. Owing to the extreme flattening of the tissue before embedding, it was found impossible to get very satisfactory preparations, and only Weigert and Van Gieson stained sections were examined.

The optic nerve, chiasma, and anterior portion of the tract, investigated in seven of the cases by numerous staining methods, in every instance showed marked involvement. In one case Weigert sections, both longitudinal and transverse, showed complete absence of myelin in the whole of the intra-cranial course of both optic nerves, and the chiasma was similarly degenerated. Figs. 64, 65; 100, 101; 163, 165; 225; 431, 432; 444 show the degree of myelin involvement in six separate cases: the chiasma, as will be seen, was the site most frequently affected, and the first evidences were manifested in its anterior border. In one case the optic tract on both sides was cut in celloidin sections from the chiasma to the corpora geniculata interna, and both showed a very characteristic discontinuous degeneration: the degeneration in the chiasma passed into both optic tracts and then ceased—to begin again at a point midway in its course. Weigert counter-stained sections brought out very beautifully the advanced septal and blood-vessel change which accompanied the sclerosis in the optic nerves (fig. 444). Van Gieson sections showed that this had commenced in a proliferation of the fine connective tissue elements between the nerve fibres, and that this active proliferative process had then extended to the larger septa and the inner layers of the optic sheaths. The glia elements had shared in this reaction, and there resulted rows of large protoplasmic glia cells with long branching processes. Later, the glia fibril formation seemed almost masked by the great connective tissue increase, which the very numerous blood-vessels of the septa had shared. The degeneration of the myelin sheath appears to take place very rapidly, and long tubular rows of fat granule cells are found in Marchi sections (figs. 64, 65): the mode of their removal in the blood-vessel lymphatics is in every way comparable to that in the central nervous tissue. REDLICH and others have noted the long persistence of the axis cylinders in the optic nerve sclerosis. In one case, macroscopically, there was very evident involvement of the optic chiasma and nerves: they presented a completely gelatinous, almost transparent, appearance, and yet Cajal-stained sections showed an almost complete preservation of the axis cylinders in nerves, chiasma, and tract (figs. 431, 432).

The characteristics of the areas in the optic nerves and chiasma are therefore related to the presence of both glia and connective tissue interstitial elements, for

both are affected. The sclerotic areas in these regions are amongst the most constant appearances in disseminated sclerosis, and may be related to the early eye changes so frequently found clinically.

(b) Changes in the Nerve Roots, Cauda Equina, and Peripheral Nerves.

Changes in the nerve roots are comparatively seldom referred to in the literature of disseminated sclerosis, and where noted they are usually described as insignificant. DINKLER, however, in one case found the whole of the spinal cord roots thickened near the cord; SCHOB, in addition to fibroma-like thickenings of the nerve roots, describes discontinuous areas of myelin degeneration in non-glious containing tissue, and STRÄHUBER and MARBURG have reported similar findings. These areas contained a connective tissue proliferation of the endoneurium and a proliferation of the Schwann's sheath in place of a neuroglia sclerosis. In one peripheral nerve similar discontinuous areas were found.

In this investigation the nerve roots in only one case were systematically examined in longitudinal section, but in several other cases portions of the nerve roots remaining attached to the cord segments (figs. 125–128; 240) reached the length of one-half centimetre, and in other cases very numerous ganglia (fig. 227) were examined with nerve roots attached, and in most of the cases the cauda equina (fig. 92) was examined in longitudinal sections extending from two to three centimetres. In the frequent neuroglial involvement of the intra-medullary portion of the cranial nerves, the extra-medullary portion seldom shared. The loss of myelin or the deficient staining of the myelin extended often for a short distance into the nerve roots, and then these resumed the normal staining. The extent of this demyelination and neuroglial involvement of the nerve roots varied greatly, and it was looked upon as proportionate in extent and form to the varying degree in which the glia normally passed into the nerve roots. In the spinal nerve roots, however, especially in the posterior roots of the lumbar cord, this limit was frequently overstepped, and small circumscribed areas of neuroglial sclerosis were found, as if the glious zone had extended far into the normally non-glial portion of the root (see figs. 263, 264). Serial sections showed that these areas were very minute and that the axis cylinders passed through them.

In addition to these small areas of sclerosis, there were frequently found in the fibres of both cranial and spinal nerve roots three other types of changes: (1) a diffuse change comparable to the "shadow" staining of the myelin in the central nervous tissue; (2) a definite secondary degeneration of isolated fibres or groups of fibres (fig. 451), related probably to the loss of the axis cylinder in a sclerotic area; and, finally (3), in Marchi sections, as already mentioned, the nerve roots shared in an early degree of myelin degeneration, which affected the whole transverse section of many cord segments—a change which is probably related to the presence of a terminal infection. ORR and ROWS have demonstrated the evidence of a continuous

flow of lymph upwards along the nerves, the main current of which lies at the periphery of the nerve immediately under the fibrous sheath. It was presumable, therefore, that we ought to find in the cord of cases in which some septic focus existed, *e.g.* bed-sores or an extensive pyelitis, lesions of the posterior columns, caused by toxins ascending in the lymph stream. The evidence for this was carefully sought for, but the lesions were already so extensive—and the terminal infection, if this were the cause of the general myelin degeneration, affected the whole transverse section, including the attached nerve roots—that no conclusion could be come to on this point.

Two points of interest may be added: (1) that the intra-medullary portions of both anterior and posterior nerve roots seemed frequently to withstand the sclerotic process much longer than the white matter through which they passed, and (2) fig. 250 indicates how normal nerve roots may be attached to a segment of the cord entirely deprived of myelin, and figs. 452, 453 that a similar condition of the nerve bundles of the cauda equina may exist though the whole lumbo-sacral cord shows, in Weigert sections, complete sclerosis. In both the longitudinal section (fig. 90) and at every level of the cord from which fig. 92 was taken, Bielschowsky preparations showed an almost normal number of retained axis cylinders (fig. 427). The posterior root ganglia related to numerous segments were investigated.

In only one case (L. W.) were the peripheral nerves examined. In both Marchi and Weigert preparations, both transverse and longitudinal, from two levels, at least 5 centimetres distant from each other, showed a complete absence of early or late degeneration in the following nerves: popliteal, peroneal, and median on both sides, and the right sciatic (fig. 454). In the left sciatic nerve, however, there was a distinct Marchi degeneration (fig. 324).

(*c*) *Changes in the Meninges.*

BORST has described, in all the four cases examined by him, adhesions and thickenings of the cerebral and spinal cord membranes. The significance ascribed by him to these changes is of great importance in relation to the pathogenesis of disseminated sclerosis, and this subject will be more fully dealt with when considering general changes in the lymphatics. A few histological details may, however, be given here. In uncomplicated cases the meninges were found almost normal: the pia was frequently slightly thickened, contained a slight increase of cells, and the pial vessels showed changes very similar to those within the sclerosed tissue. In the earlier stages the vessel walls and inner layers of the pia contained fat granule cells. In other cases, however, the cerebral and spinal soft meninges were infiltrated with cells, chiefly lymphocytes, and a few plasma cells, which also passed in with the vessels into the substance of the cord. Many dense glia fibres—radiating from the glia marginal zone into the pia—were found around the venous vessels as they passed out of the cord, and also around these vessels there was a marked accumula-

tion of small round cells. These meningeal changes, when present, are usually diffuse and in no way confined to the meninges overlying areas of sclerosis.

(4) Changes in the Individual Tissue Elements.

1. *Nerve Fibres.*

(*a*) *Medullated Sheath.*

In the actual sclerotic areas the medullated sheaths have entirely perished, but in recent areas and at the advancing peripheral zone of older areas the changes present themselves in very various forms, according to the stages of the degenerative process, and according to the greater or lesser intensity of the process. In Weigert transverse section, the myelin sheath may appear deficiently stained, or there may be only a thinning of myelin, but more often it is diffusely stained and swollen, or the whole ring of myelin may be broken up into a number of finer and larger globules (fig. 408). On longitudinal section, however, the process may be much more readily studied in its individual stages, and the fibres, especially in the transitional zone of an advancing area, may show all conceivable types (figs. 406, 407). The varicosity so frequently found even in normal fibres is greatly exaggerated, and the whole fibre may be represented by a series of large oval vesicles, the outer rim of which stains with hæmatoxylin. Frequently, and this seems to me the most usual type, a number of very fine granules and balls are attached to the outer border of the myelin sheath; some of these tiny balls seem to burst, and gradually others re-form till the myelin sheath projecting into an area is gradually more and more thinned, and is finally represented by a series of very delicate globules. Some of these may be found for a considerable time in the degenerated area, retaining the hæmatoxylin stain. One rarely meets with the very swollen, tumefied, badly-staining fibres such as are found in softenings, although the destruction of the myelin seems to start in an œdematous swelling analogous to that found in acute myelitis.

In Marchi sections (figs. 319–323) the actual degeneration shows first as long parallel rows of droplets which darken with the osmic acid. These are again most frequently on the outer edge of the nerve fibre, and may be only on its one side. Such fibres on transverse section would appear as if a crescentic part of the sheath were affected. Sometimes there are double rows of droplets or granules within one myelin sheath. The appearance of these rows of granules is often, but not always, preceded by a varicose condition of the fibres, extending over long distances; the swelling affecting the whole sheath and appearing either in the form of small beads or large spindle-shaped vesicles, which may perhaps represent an acuter process, or one accompanied by more œdema. Within these swellings the sheath may then show the fine granular degeneration, and these granules may run together. On transverse Marchi sections it is frequently possible to recognise that an entire

outer rim of the sheath is stained black, and that this degeneration gradually extends inwards to involve its whole extent.

In Heidenhain's iron-hæmatoxylin sections, the nerve fibres bordering on the degenerated zone have their neurokeratin framework beautifully brought out, and in the spindle-shaped swellings above referred to this is seen to be a very wide-meshed one. MARBURG has represented the chemistry of this process as a degeneration first of the lecithin, which supplies the fatty products, while the chief mass of the hæmatoxylin substance (protagon) is spared longer, so the fibres which in Marchi sections show degeneration are still stained in Weigert's hæmatoxylin.

In longitudinal sections of the cord it may be seen that this degeneration may affect the nerve fibres "discontinuously." This is specially easily recognised in Marchi sections, counter-stained with safranin, in which the retained axis cylinder is seen surrounded by a pink-stained zone, which becomes gradually interrupted by a portion of the fibre in which granular disintegration has commenced. The axis cylinder within this affected portion may be swollen and homogeneous, but can be recognised till a late stage of the degeneration. Thus this form of degeneration can be distinguished from secondary degeneration by its limitation, by its late affection of the axis cylinder, and, finally, by the character of its disintegration into granules and globules (fig. 320) instead of at once into coarse balls and fragments (fig. 324) which fill the whole myelin sheath. The fat granule cells, which are found in such large numbers, could only in rare instances be found to contain large fragments of myelin. It seemed rather as if a gradual absorption of dissolved substances had taken place, and that these within the cell had become transformed into fine fat-like granules.

In the "Markschattenherde" we may have simply a deficient staining of the whole myelin sheath, or there may be only a thin ring of myelin around an almost normal axis cylinder. VOLSCH assumes that in the latter case there has been a gradual atrophy of the myelin, and then a persisting condition of the remainder.

It may finally be noted that in some areas certain fibre-systems seem to be more resistant. In areas of sclerosis involving both the anterior horn and the entire antero-lateral tract the intra-medullary anterior root fibres were frequently found intact, or showing only slight Marchi degeneration. Similarly the external arcuate fibres in the medulla oblongata seem to be relatively long preserved.

(*b*) *Axis Cylinder.*

The comparative persistence of the axis cylinders in the sclerotic area has long been regarded as one of the essential characteristics of disseminated sclerosis. CHARCOT himself, from the apparent disproportion between the symptoms and the anatomical lesions, argued for their persistence. The earlier observers undoubtedly, with diffuse stains, frequently mistook the longitudinal glia fibrils, which run parallel to the degenerated nerve fibres, for true axis cylinders, yet modern specific staining

methods have proved that CHARCOT's conception was justified. Yet this persistence is only a relative one, and in the foregoing study attention has been drawn to the numerous alterations which axis cylinders undergo. The most frequent change is that of a slight homogeneous swelling, and this may be found even in old sclerotic areas, in which, as a rule, the axis cylinder becomes attenuated, and, with diffuse stains, is only with difficulty distinguished from the coarser fibrils. The changes in the axis cylinders are much more easily recognised in longitudinal sections of the nerve fibres.

In early areas degenerative changes (figs. 425, 426) set in with a moniliform appearance, which may later take the form of spindle-like enlargements of various size, and these may finally lead to disintegration, with the formation of homogeneous clumps and granules. This qualitative change may affect a large number of the axis cylinders in an affected area, or most of the fibres may show spindle-shaped swellings and only a few go on to the stage of disintegration. It is probable that the fibres which survive the swelling may persist into the stage of sclerosis as homogeneous, condensed elements which, as the sclerosis becomes denser, are compressed into thin, even spiral threads.

In the stage of abundant fat granule cell formation the swollen axis cylinders become pushed aside between these cells and the proliferated glia elements (figs. 1, 2; 328, 329), but with specific stains it can be seen that as these cell elements diminish in number and size, the axis cylinders course straight again and are surrounded, almost as by a sheath, with the proliferating, wavy glia fibrils (figs. 3; 334). At the margin of a demyelinated and even sclerotic tissue, the direct transition of the still remaining axis cylinders into those of the normal tissue can be followed, and if the area be not a very long elongated one, a normal myelinated axis cylinder can be traced, deprived of myelin, right through the sclerosed tissue to its transition into a normal myelinated axis cylinder again. In other cases the transition from normal tissue into sclerotic is marked by a fainter, grey-staining of the axis cylinder, which in the depth of the area becomes a mere shadow (fig. 423), or the transition may be represented by a swelling and tortuosity, which it must be remembered are present to a limited extent in quite normal tissue. If the axis cylinder, too, terminate at the transitional zone, their ends are often swollen and granular. On tranverse section the remains of such degenerated axis cylinders may be recognised as faintly-staining granules—with eosin or picro-fuchsin—or dark-stained, cloudy granular debris—iron and hæmatoxylin and silver—lying in the meshes of the glia cell protoplasmic processes, and in the walls of the blood-vessels.

The density of the non-myelinated axis cylinders is rarely the same (fig. 422) as that of the normal fibres, but sometimes they are found of normal calibre and numbers. A striking illustration of this may be seen in figs. 16, 17; 421. In considering the relative proportion of axis cylinders preserved, it must be taken into account that the sclerosed area is relatively smaller than normal, *e.g.* where the

sclerosis affects the entire transverse section of the cord the area is frequently little more than half the normal. In this very shrunken area impregnation methods show a dense arrangement of the axis cylinders, yet one must admit that many must have perished.

Numerous writers have claimed that after the degeneration of the axis cylinders there comes a regeneration. POPOFF, MARINESCO and MINEA, and others base their contention on the presence of axis cylinders with a brush-like formation of fine fibres at their end, or on the presence of *boules terminales* at the end of both terminal and collateral fibres. This possible regeneration has been supported by SCHMAUS and HUBER, and also by STRÄHUBER, on the strength of his aniline-blue staining methods. BIELSCHOWSKY, while claiming that most of the fibres in a sclerotic area are "persistent," admits the possibility of a regeneration. BORST, however, who has investigated the regenerative powers of fibres in the brain, and ascribes to them a very considerable regenerative new-formation, thinks that both BIELSCHOWSKY'S and STRÄHUBER'S special methods stain certain kinds of glia fibrils so similar to axis cylinders that it is impossible to draw any conclusion.

MARBURG claims that the first effect of the "toxine" is a lecitholysis: when this effect is carried further or is more intense there is a marked axolysis with the formation of fine granules. But it must be admitted that a change short of this, the demyelination and the swelling of the axis cylinder—which is an indication of its sensitiveness and a proof of its sharing in the changes in the myelin sheath—may be present.

2. *Nerve Cells.*

The relative resistance ascribed to the axis cylinders has also been extended to the ganglion cells, both in the cord and brain. Numerous writers have emphasised their quite normal appearance, both in outer form and minute structure, till a late stage of the process. CATOLÀ found normal cells even when sclerosis was complete, and SCHLAGENHAUFER, in a case of disseminated sclerosis which ran its course as a transverse myelitis, found the nerve cells normal at all levels of the cord, even in the most affected segments.

The relation of the cell changes, when present, to the sclerotic process is difficult to decide, and the majority of the changes should probably be referred to the intercurrent disease, with possible elevation of temperature, which caused death, or to the exhaustion and anæmia and decubitus which accompanied the nervous affection. In judging how seriously diseased a cell is, and specially as to whether it is capable of restoration, the variations in the nucleus have always been counted as affording more useful data than those of the protoplasm. In one case (C. S.), in which every level of the cord showed not only an almost complete demyelination, but cell and glia stains showed that the fat granule cells had been almost completely removed from the tissue, and already an advanced fibril formation was in process,

many ganglion cells at very numerous levels retained an almost normal nuclear structure and an almost complete retention of the chromatophile granules (fig. 410). The only recognisable change was an absence of the processes, a rounding of the cell body, and an increase in the cell pigment. At other levels, all the cells present showed a marked diminution in volume (fig. 409), and a marked pigmentation (fig. 413), including cells which had become already transformed into a rounded, small, non-nucleated mass of pigment. These changes occur in areas in which the sclerosis is not very advanced and the intercellular tissue is composed of a network of capillaries and branching glia cells. In a later stage such cells become wholly lost in the sclerotic tissue, or small traces of pigment may still be found.

Another type of change, and a more frequent one, is a gradually advancing atrophy (figs. 415, 416), proportionate to the increasing density of the sclerosis. This first affects the minute structure of the processes, and then reaches the cell body, in which the chromatophile granules become powdery or are dissolved, and the nucleus becomes peripheral. Such atrophying cells may assume very varied shapes according to the intensity of the process, and traces of non-nucleated cells with complete chromatolysis may be found in the sclerotic tissue for a long time. In the cells of Clark's column, where we have normally an excentric nucleus and a peripheric disposition of the chromatophile granules, the nucleus undergoes a marked shrivelling and condensation, or at times a vacuolation before its extrusion. The cells very frequently assume a spindle shape, and have been described by NISSL as "Fisch" cells.

The mechanism of these changes in the spinal cord cells seems to be a simple atrophy, and one factor in its causation is probably compression on the part of the developing cells and fibres of the glia (fig. 419). Nowhere was there found any evidence of the accumulation of small round cells around ganglion cells in the cord, such as are to be described later around the ganglion cells of the cortex. The changes described are those related to a slow, chronic process, but more extensive and general changes, *e.g.* complete chromatolysis (fig. 411) or deeply-staining cytoplasm, are also found, which must be related to the general somatic disturbances. The "coagulation necrosis," described by MARINESCO as an acute cellular change in which there is a dense fusing together and coagulation of the individual constituent elements, is rarely present.

The cells in the different cranial nuclei undergo changes which are closely analogous to those described above. The cells of the hypoglossal nuclei are frequently very pigmented, and have the pigment distributed throughout the whole cell. The glia cell proliferation may be very marked before there is any appreciable atrophy of the cells, but as the sclerosis advances, here, too, there is a gradual diminution in their number (fig. 418). Cells with normally staining granules may be found alongside cell remnants or pigment accumulations.

The cells in the cortex, in a demyelinated area, when involved, are much more uniformly so than those of the cord. The large pyramidal cells are never normal

(fig. 386), but show chromatolysis and have their dendrites thickened or weakly-stained or absent, and the cell contour is rounded or pear-shaped (fig. 22). These changes involve not only the demyelinated area but also the adjoining stretches of the cortex to a varying extent. But the most characteristic appearance in a cortical area, and that which enables it, under low power, to be readily recognised, is the nuclear increase around the ganglion cells. The majority of the ganglion cells, in the lower layers of the cortex and in the layer of the large pyramids, are surrounded by small nests of cells (figs. 381, 393), from five to ten in number. These with diffuse stains have a small deeply-staining nucleus with little protoplasm, and cause, according to their number and arrangement, more or less deformity and atrophy of the ganglion cell, but we have never seen the penetration of such cells into the ganglion cell body. They have probably arisen from the pre-existing satellite cells, and their proliferation is taken as an indication of the inter-relation between ganglion cell and its satellite cells ("Trabantzellen"). MARINESCO thinks that in health the former secrete substances which exercise a controlling influence on the size and development of the latter: if any noxious or toxic agent affects the former, this controlling secretion is diminished in quantity and quality, and the neuroglia cells react accordingly by increasing in size and numbers. This change is again not limited to the demyelinated areas, but passes over to the adjoining stretches of the cortex.

Comparatively little change was found in the cells of the posterior root ganglia (fig. 420). Those that were present indicated a general reaction, probably in no way related to the sclerotic process in the cord.

3. *Neuroglia.*

The changes in the neuroglia represent, in the opinion of numerous observers, the dominant and essential histological feature of disseminated sclerosis. Whilst the changes in the nerve fibres show little variation in the individual cases, the glia components show wide differences. In an early area we have seen that the most important and characteristic finding is the enormous number of large cell elements (fig. 380) which in their further evolution are transformed into glia fibrils (fig. 384) and glia nuclei. In an actual sclerotic area we have a dense glia fibril mass, apparently without spaces (figs. 354, 364). The histological characters of the glia, therefore, depend on the length and the intensity of the process. In the final result the name "sclerosis" is justified by the amount of neuroglia present in the areas, and WEIGERT has stated that the glia hyperplasia is greater here than in any other form of sclerosis. The neuroglia, though not from a histogenetic, yet from a morphological and biological standpoint, may be looked upon as a true fibrous connective tissue. It is thus of great significance that the glia begins to proliferate when component parts of the specific nervous tissue are destroyed, even where any stimulus capable of causing primary proliferation is absent. The classical example of this is the secondary degeneration of the white substance, where the secondary glia proliferation sets in

probably as a reaction to the irritation caused by the products of degeneration. At the same time it may happen that one and the same "noxa" destroys the specific nerve tissue, and in an equally primary manner causes the glia to proliferate. Again it is possible that we may have isolated primary proliferative processes in the glia—which in their turn cause secondary degeneration of nerve cells and fibres. STORCH has pointed out that in chronic diseases, in which the plan of the nerve tissue remains unchanged, the newly-formed glia fibrils show exactly the same arrangement as the original fibres, whereas in cases of acute destruction of tissue, this regularity does not hold good. He, therefore, distinguishes between an isomorphous and a reparatory sclerosis. The glia proliferation may, therefore, be merely a substitution process, or an inflammatory process, or, more rarely, a primary glia proliferation.

It is impossible to discuss here the question of the spatial relation of the glia fibres to the glia cell protoplasm. All that can be done is to indicate the stages in the elaboration of the glia fibrils (figs. 382–384). These can be followed very beautifully in the evolution of an early area into a sclerotic area by means of Heidenhain's iron-hæmatoxylin method and Ford-Robertson's methyl-violet stain. In the rapidly proliferating glia cells, the first stage in their transformation is an enlargement of the nucleus (fig. 8), by which its chromatin structure becomes clearer. This is followed by the development of a considerable amount of deeply-staining protoplasm around the nucleus and the further development of large, branching, protoplasmic processes (figs. 9, 349), till forms of very varying size and shape are produced. In many of these large glia cells, two or more nuclei may be found (fig. 379): this may represent a karyokinesis which has remained incomplete. After cell division the new cells rapidly increase in size, and form protoplasmic processes, and are potential fibril-forming cells (figs. 379, 380). From a close consideration of the specimens the conclusion was reached that the formation of fibrils can take place in the enlarged pre-existing glia cells without cell division. The first indication of the formation of fibrils consists in a definition of the edge of the protoplasmic processes (fig. 382): when this can be followed throughout the concave border of two adjoining processes (fig. 383), it gives to the fibril formation the appearance of recurving fibres (fig. 384) with their convexity near the cell nucleus. The general arrangement of the fibrils corresponds at first to the general outline of the borders of the protoplasmic processes. At a later stage the relation to individual nuclei is less easy to determine. FORD-ROBERTSON thinks that each branching process becomes converted into several plain processes by gradual splitting at the forks down to the close vicinity of the nucleus. His methyl-violet method shows very clearly that many of the fibres are attached to the walls of a vessel by an expanded "foot," but frequently, especially around the capillaries in the cortex, the new formed fibrils of adjacent cells were found to form a network, with elongated meshes, around the capillary wall (figs. 21, 391).

Glia cells, that have produced fibrils, undergo slow and gradually regressive

changes: almost the whole of the protoplasm seems used up and shrivels into an irregular border around the doubly-staining nucleus. In later stages, too, the nuclei may disappear, and thus account for the comparatively few nuclei found as a rule in actual sclerotic areas.

Weigert's method does not stain the cell body, and therefore his statement as to the spatial separation of the glia fibrils from the cell protoplasm may be overdrawn, but this does not undermine the "Verhalten," the distribution and the specificity of the fibrils, and the fact that they stain at a certain definite stage of their development. FIEANDT'S recent work has seemed to support the HARDESTY-HELD conception of the syncytial structure of the glia tissue. HELD believes that the glia represents a widely-ramified but connected syncytial meshwork of protoplasmic character, which envelops the functioning elements of the central nervous system. At its nodal points are nuclei, and within the protoplasm, not separated from it, are Weigert's specific fibrils. The glia, therefore, represents a continuous reticulum, which holds together the ganglion cells and nerve fibres, and the differentiated fibrils are deposited in this as supporting or stiffening elements. By Nissl's stain the cell nucleus and protoplasm immediately surrounding it are stained, and the cell protoplasm gradually merges in a surrounding meshwork. The sharp concave edges of the bodies are formed by light, strongly refractive lines, which consist of fibrils that do not stain with basic aniline dyes. FIEANDT thinks that glia granules—gliosomes—play an important rôle in the new formation of glia fibrils, and that they may be looked upon as an intermediate stage between the undifferentiated protoplasm and the specific fibres. In specimens fixed in Heidenhain's sublimat-trichloracetic acid mixture, and stained by iron-hæmatoxylin, granules were present, arranged in rows, in the large star-shaped glia cell processes and in different parts of the cell body. In some cases rows of granules are seen to radiate towards the centre of the cell, thus giving the cytoplasm a radial structure. These granules are very fine, and similar granules may be distinguished in the fine meshes of the glia, arranged almost in streptococci-like rows.

The HARDESTY-HELD conception of the syncytial structure of the glia tissue would reconcile WEIGERT'S teaching with that of his opponents, and show that in the neuroglia tissue cells — nuclei and protoplasm and protoplasmic processes — differentiated fibres, whether anatomically independent or not, and, finally, intercellular protoplasmic fibreless glia, may all exist together.

In the grey matter of the brain the ganglion cells and fibres are embedded in a tissue which shows a uniform finely granular structure. This is probably constituted by the dendrites and axis cylinder processes of the ganglion cells; the axis cylinder ramifications from other parts of the grey matter; the fine intercellular fibril lattice work originating from both; and by the diffuse protoplasmic glia meshwork with its specific glia fibrils. In this glia meshwork nuclei are fairly evenly distributed, and are specially met with in close relation to the larger ganglion cells—the so-

called satellite cells or "Trabantzellen"—and around the vessels. These elements, together with arteries, veins, and a fine capillary network, constitute the grey matter of the cortex. The specific glia fibrils vary much in amount in the different layers. In the marginal zone and amongst the tangential fibres they are abundant, but from this downwards they rapidly decrease in amount, but in the transition between white and grey matter they are again abundant. On the other hand, the protoplasmic glia meshwork is apparently equally developed at all levels. Radial glia septa, such as are found in the cord, are never present in the cortex. The nuclei in the grey cortex are small and round, 5 to 7μ in diameter, or flattened, and have a dense chromatin content in the form of fine granules. Larger and lighter-stained nuclei are also met with, and both types have, with certain stains, fine thread-like processes, which ramify and anastomose with each other.

We have stated that one portion of the proliferated glia cells both in the white and grey matter probably form the first fat granule cells. This double function of the neuroglia cells, that of fibre-formation and phagocytosis, has been emphasised by NISSL, MARINESCO, and FORD-ROBERTSON. The increasing zone of protoplasm around the nucleus becomes gradually laden with granules, which often outline the cell body and its processes—at first spindle-shaped, then star-shaped, and gradually becoming rounder till the cells are set free in the glia reticulum (figs. 18–20). These glious granular cells have a lattice or "Gitter" structure in their protoplasm, in preparations in which the fat granules have been dissolved out (figs. 9, 10). They emigrate from the tissue, or rather are carried along with the lymph stream, and are found later in the adventitial spaces of the blood-vessels and there give up their contents, or are carried still further on. This evolution may be traced beautifully in the advancing zone of an area in the white matter where the nerve fibres are cut longitudinally. Here the pre-existing small glia cells, lying far into the normal myelinated tissue, may be found proliferating and undergoing the changes described above. In the cortical grey matter this evolution is slower, and the commencing granule formation in the "Trabantzellen" is well brought out in fig. 396.

4. *Blood-vessels; Lymphatics; Cell Elements in Vessel Walls.*

(*a*) *Blood-vessels.*—Note on the normal structure of the vessels of the central nervous system.

The arterial vessels of the cerebral cortex arise altogether from the pia. Short radial branches, referred to as "cortical" vessels, pass into it perpendicular to the surface, and soon after their entrance break up into the very smallest arterioles and capillaries. The outermost layers of the cortex are supplied, not by lateral branches from the larger of those radial arteries, but by a special system of very short vessels, which break up into a capillary network in the first and partly in the second cortical layers. One division—of longer radial branches, referred to as medullary—penetrates

further down and supplies the superficial portion of the subcortical white matter. The larger portion of the cortical white matter and the basal ganglia are supplied by central arteries, which arise from the circle of Willis : their terminal branches ramify on the surface of the ventricles (BORST). One division of the veins likewise passes to the pia, and another, that draining the central white matter and basal ganglia, joins the great veins of Galen beneath the splenium of the corpus callosum. Numerous venous branches can be recognised, immediately sub-ependymal, coursing mostly obliquely towards this point, and grouped especially around the posterior horn of the lateral ventricle. In the spinal cord the white columns are supplied by vessels radiating from the pia, and the grey matter by vessels passing in from the anterior fissure. The transition zone between white and grey matter receives its blood-supply from the terminal branches of both central and lateral vessels. The lateral vessels, as they penetrate the cord, run at first almost in the transverse section of the cord ; many lateral transverse branches are given off, but the majority widen out in vertical directions. These vertical branches, on account of their small calibre, represent terminal vessels, pre-capillary arterioles, and capillaries, and may be traced, in longitudinal section, for long distances. In consequence of this arrangement, the areas supplied by the radial vessels and their lateral branches would, therefore, have a wedge-shaped form, with base on the surface of the cord, and those supplied by the vertical branches must have a shape in the long axis of the cord.

The discrimination, in individual sections, of small arteries and veins is by no means always easily made, and, when a condensation of the vessel wall occurs in sclerotic tissue, is impossible. As in other tissues the venous walls are thinner, contain irregularly distributed muscle cells and adventitial nuclei, but small veins proceeding from capillaries cannot be distinguished from pre-capillary arterioles. It is generally taught that no elastic lamina is present in the arteries and arterioles, but SCHROEDER and LAPINSKY state that a very delicate elastic membrane can be recognised even in the capillaries, and that elastic fibres are present in the media and the adventitia, wherever a distinct adventitia can be found. With Weigert's elastic stain the capillary walls certainly stain sharply and frequently with a double contour, which some have looked upon as the expression of a rudimentary elastic membrane. It is generally admitted that even the capillaries have traces of an adventitia, the nuclei of which are found only at intervals. The capillaries, therefore, consist of an endothelium and traces both of an elastica and an adventitia. In pre-capillary arterioles we get, in addition, detached muscle cells, which in the larger arterioles form a layer of circular cells. FORD-ROBERTSON states that by far the most important feature in the structure of the intracerebral 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 but also venules and capillaries. The capillaries of the central nervous system, therefore, unlike the capillaries of most other organs, possess an adventitia, the fibres of which

differ both from white fibrous tissue and yellow elastic tissue. He thinks that there is strong evidence that in various toxic conditions the capillaries of the central nervous system are prone to undergo definite change, while those of other organs escape. The explanation of this selective action is to be found in the fact of their higher structural differentiation, which has been obtained at the cost of a peculiar vulnerability to the action of certain toxins.

The adventitia is immediately bounded on its outer side, without the presence of any peri-vascular space, by a condensed layer of glia—the glia peri-vascularis limitans. This glia layer is a continuation inwards of the glia superficialis limitans which was carried inwards by the in-growing vessels of the pia when they invaginate the embryonic nerve tube. The inner layers of the pia form the adventitia coat of these penetrating vessels, and this intimate relation between glia and adventitia is maintained till the finest capillaries are reached. In these the glia limitans may be formed by a very fine protoplasmic reticulum in which the glia "Fuss" of immediately adjoining cells are inserted.

It was formerly supposed that there was no evidence of the existence of vaso-motor nerves in the intracerebral arteries, but LAPINSKY has demonstrated that medullated fibres reach the media and are distributed to the muscular fibres as non-medullated fibres.

The disposition of the areas in relation to the blood-vessels has led to the supposition that these play an important rôle in the genesis of the areas. This topographical relation is frequently obvious even macroscopically, especially in areas in the cerebral white matter, and numerous illustrations point to its microscopic proof. This dependence on the vessels is brought to light only where the areas are isolated: in later stages, through coalescence, the original relationship is no longer recognisable. A parallelism between the sclerosis and the area of distribution of a vessel would argue that the development of the process depends upon the condition of the vessel or of the "noxa" circulating within it.

To the alterations in the vessel walls in sclerotic areas numerous writers have, therefore, ascribed an essential significance, while others have regarded them as accessory and subordinate. Few writers have noted their entire absence; TAYLOR, in eight cases, could find no trace of vessel change, and ERBEN, in a careful investigation of five cases, found none that were not common to the whole central nervous system. Variations in the findings have been explained by the different stages in the development of the sclerotic process. In early stages engorgement and dilatation, cell infiltration of the walls, dilatation of the lymphatic sheaths, and capillary hæmorrhages have all been noted; at a later stage, marked nuclear increase in the adventitia and, in the actual sclerotic areas, condensation and hyaline change of the vessel walls. Probably none of the histological changes have been so variously interpreted as those related to the vessels.

The sequence of the changes in the blood-vessels seems to me to be the following: at an early stage the blood-vessels in an involved area become dilated and engorged with blood. It is not a question so much of one central vessel as of all the branches of one small vessel, and even the finest capillaries, are recognised; the vessels are in no way altered, and have no nuclear increase either in the intima or adventitia. During the stage of marked glia cell proliferation and commencing fat granule cell formation, in very numerous areas it has been impossible to recognise any structural alteration. The impression of a new formation of blood-vessels, both at this stage and at a much later one, is probably due to the engorgement making each fine vessel stand out distinctly, especially when stained with picro-fuchsin. Nowhere at this stage is the relation of individual parts of the tissues altered. In a few cases there have been noted a proliferation of the capillary endothelium and the possible passage outwards of the proliferated endothelial cells into the tissues. At the stage of abundant fat granule cell formation, when these cell elements are passing into the lymph spaces of the adventitia, every vessel in the affected zone is mapped out by a ring or rings of such cells (figs. 10, 13). The smallest capillaries show a single row of cells (fig. 433), often with an outer limiting membrane, stained pink with fuchsin or blue with Mallory's connective-tissue stain: the presence of this outer limiting membrane to such a row of cells seems a strong argument in favour of the existence of a thin adventitia in the capillaries. If such an area, with fat granule cells crowding the vessel sheaths and tissue spaces (fig. 434), be looked at, with low power, and especially in celloidin sections, where it is more difficult to analyse the constituent elements, the impression is given of a softened area with cell-infiltrated walls. The possibility that areas at such a stage of development have been taken as illustrating cell-infiltrated areas may explain the great significance that has been ascribed to the vessels and to the inflammatory character of the process. This is still more evident at a slightly later stage, when there is a reaction to the presence of these fat granule cells in the adventitial spaces and a proliferation of their cell elements. The cell proliferation is of a secondary nature, and is evident in uncomplicated cases, we think, only at this stage. It is evident that there is a marked increase in the nuclear content of the vessel walls, an increase in which the endothelium of the capillaries shares. As the resorption processes advance there is a gradual removal of the fat granule cell element in the adventitial spaces, but the cell body of many of these cells has gradually disappeared *in situ*, leaving a deeply-stained, crenated nucleus (fig. 14), and during this stage we get a further nuclear element added to the nuclear increase in the vessel wall. The adventitia has had its fibrils dissociated and its lymph spaces filled by the fat granule cells; as these disappear the lymph spaces, which remain distended for a considerable time during the advancing sclerosis, are to a certain extent now occupied by a cell infiltration of another kind—these are the small, round, lymphocyte-like cells common to all chronic processes.

These, with the elements distinctly recognisable as proliferated from the endothelium of the adventitial spaces and from the adventitial connective-tissue cells, together with a few remaining fat granule cells or their nuclei, form the cellular content of the vessel walls at this stage. Figs. 14 and 439 show beautifully the varieties of the cells found in such a vessel. I have never seen any marked grouping of small round cells analogous to the so-called "round cell infiltrations." As the sclerosis advances the dissociated fibres of the adventitia gradually come together, and proportionate to this is a gradual diminution in the contained cell elements (figs. 15 and 440). For a long time the outer adventitial fibres form a recticulum which can scarcely be distinguished from the peri-vascular glia reticulum, and in the meshes are still found various cell elements. At a still later stage the sclerosis affects all the parts of the vessel wall, and the dissociated fibrils form a fused, homogeneous, almost hyaline layer. As the vessel becomes hyaline, the elastica becomes broken up and lost, so that nothing can be recognised of specific muscle, connective tissue, or elastic elements (figs. 440, 441). The relation of the proliferating glia cells to the small vessels has already been emphasised, and at the later sclerotic stage the proliferating fibrils, perpendicular to the vessel wall, form almost a radiating ring around the vessel; but very frequently, especially in cerebral areas, the new-formed glia fibrils are laid down in concentric rings around the vessels (fig. 437). It has also been mentioned, but may here be emphasised, that it is frequently the peri-capillary glious zone in which the first traces of glia proliferation are noted.

In the majority of the sclerotic areas all the vessels are condensed—arteries, veins, and capillaries,—and it is not possible to draw any distinction between arteries and veins, arterioles and venules (figs. 442–444). Similar condensation of the vessels is found in all chronic sclerotic conditions in the nervous tissues, and LUGARO has pointed out that this is in keeping with the small claims of their nutritive function, for the sclerotic tissue requires less nourishing material.

(*b*) *Lymphatics.*

The increasing recognition of the importance of the lymphatic circulation in the central nervous system has led to numerous researches upon the precise nature of the lymph paths and the direction of the flow of the lymph within them. It cannot be said, however, that any exact knowledge on either of these points has yet been revealed. The present section of this paper is confined to the indications of changes in the lymphatic vessel system in disseminated sclerosis. The lymph apparatus shares in the changes in the blood-vessels, and BORST has strongly urged the view that a disturbance in the lymphatic circulation is the essential factor in the process underlying disseminated sclerosis. He points out that the factors which bring about this disturbed circulation are alterations in the vessel walls and in the meninges. Even slight affections of the former involve changes in the transudation of the lymph and lead to pathological exudations, and even slight adhesion of the

pia to the marginal glia zone would involve occlusion of the epi-spinal or epi-cerebral spaces, an occlusion which would be extended to the peri-vascular spaces at the periphery, and therefore cause a hindrance to the outflow of the lymph by these channels. In a recent paper the late Dr BRUCE and I indicated our agreement with NISSL'S contention that the adventitial lymph spaces of the blood-vessels, which open into the spaces of the inner layers of the pia, are the only true lymph spaces of the central nervous system. It has seemed, therefore, that this assumption of epi-spinal, epi-cerebral, and peri-vascular spaces is an error which invalidates greatly BORST'S views, and causes him to overestimate the part played by these adhesive changes. The fundamental importance of an increased transudation of toxic lymph cannot be overestimated, but the evidence of a hyperlymphosis is not by any means clear except in isolated cases, and its explanation when present cannot always be traced to be secondary to a closure of adventitial spaces. BORST thought that together with the change in the vessel wall, which allowed increased transudation, there was a closure of these adventitial lymph spaces, so that the lymph, unable to get back, dilates the tissue interstices, especially the peri-vascular glia and the peri-vascular space. In these dilated glia meshes the first changes of the nerve fibres occurred, and later, secondary to the degeneration, there was a substitutive proliferation in the glia. Such areas with dilated meshes he termed "Lichtungsbezirke."

In the course of this study attention has been directed to the fact that the adventitial lymph spaces showed in the early stages only a slight degree of dilatation, that, later, they were distended by the presence of fat granule cells, and that they remained dilated and filled with cell elements of various kinds till a late stage of sclerosis. In the early stages there was no question of a primary proliferation such as might be induced by a toxic lymph flowing in them—the cell elements of the adventitia are, firstly, the fat granule cells, secondly, these, together with proliferated cells of the adventitial walls—a result of the reaction to the foreign elements in the spaces—and, finally, a cell infiltration of lymphocyte-like cells. In an actual sclerotic area the adventitial lymph spaces were closed in the general condensation of the vessel wall, but here the relations of the lymph in the narrow interstices of the dense glia tissue must be very different from those in the normal tissue. The areolar zone which is sometimes found around areas of dense sclerosis may be due in part to the obstruction of the lymph flow from normal tissue into sclerotic tissue.

Very numerous peri-vascular sieve-like areas (figs. 448–450) were found, but these were frequently related to normally myelinated tissue. The change consisted in an extreme dissociation of all the fibres in the adventitia, so that the space between media and the peri-vascular glious zone was occupied by a connective-tissue reticulum with widened meshes which contained cell elements and frequently a granular deposit. There were frequently also found indications of a lymph congestion which extended over the whole transverse section of the cord and which found

expression in dilated adventitial lymph spaces, distended glia meshes, and a swelling of the contained myelin sheath and axis cylinder. In uncomplicated cases only occasional and insignificant variations in the soft meninges were present, yet it must be admitted that changes, if minute, might readily escape observation.

(*c*) *Cell Elements in the Vessel Walls.*

The statement is frequently made that infiltrations are met with in recent areas, and such cell infiltrations of the adventitial sheath are considered characteristic of the inflammatory process in the nervous tissue. In numerous references to the cell elements of the adventitia, an endeavour has been made to show that the first cell infiltration is one associated with resorption processes (fig. 13); that this is followed by a cell proliferation in the adventitia, which is probably a secondary reaction process to the presence of the first cells in the lymph spaces (fig. 437); and that, finally, we have a more or less marked degree of cell infiltration which is characteristic of a chronic inflammatory process in any tissue (fig. 14).

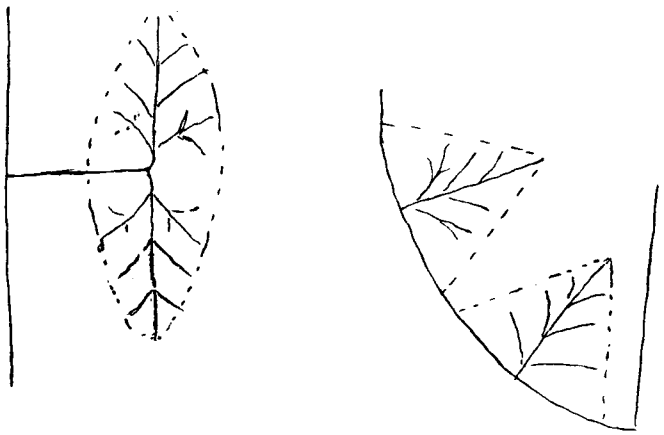
In the earliest stage, as a rule, there is no evident increase of the nuclei in the vessel wall, but sometimes a slight proliferation of capillary endothelial nuclei and adventitial nuclei is found, which may be related to the production of fat granule cells. In the stage of secondary reaction to the presence of the fat granule cells, the resultant cells in the adventitia are of two kinds: the one, with large nucleus and clear chromatin framework, have probably arisen from the endothelial nuclei of the lymph spaces, the other, with darker-stained nuclei, from the proliferation of the connective-tissue elements of the adventitia. In the third stage, in which the cell infiltration partakes of the characters of a chronic process, we have mostly lymphocyte-like cells, with a darker nucleus than any of those mentioned above, a few plasma cells and mast cells, together with pigment accumulations, either free in the spaces or within cells, and granular debris of various kinds (figs. 14 and 439). The subsequent fibrous thickening of the vessel wall in the advancing sclerosis has been traced by LHERMITTE and GUCCIONE to the transformation of plasma cells into fibroblasts. In this investigation quite characteristic plasma cells were present in extremely few sections. SCHOB, OPPENHEIM, and SIEMERLING and RAECKE found them in numerous instances and look upon them as the expression of a more or less chronic process. VOLSCH and FLATAU and KOELICHEN think most of the cells in late stages belong to the lymphocytes, and that plasma cells are rarely found in the vessel walls or in the meninges.

(5) OTHER HISTOLOGICAL FEATURES.

1. *Form, Symmetry, and Distribution.*

ROSSOLIMO first drew attention to the dependence of the sclerosed areas upon the topographical distribution of the blood-vessels. As the causal agent spreads itself by the blood channel, or the lymph channel accompanying the vessels, it was

asserted that the areas assumed certain well-defined forms. This apparent dependence upon the vessel regions was seen specially clearly in small wedge-like sclerosis situated at the periphery of the spinal cord, in which there was always found a condensed or even obliterated vessel radiating from the pia. When the area in the white matter was separated from the periphery by a zone of normal fibres it was usually round or oval. These basal forms were in agreement with KADYI'S experimental observations on the arterial distribution in the cord, to which we have already alluded. The lateral vessel passed transversely into the cord substance and its first branches were given off transversely, but the transitional vessels ran upwards and downwards in the long axis of the cord. The accompanying figures clearly show that the area of distribution of the transverse branches is wedge-shaped and that of the perpendicular branches is an elongated oval. Such vessels were looked upon by



KADYI and MAGER as end-arteries, but there is no doubt that there is a considerable amount of overlapping, and that, in consequence of this, the areas supplied by them are not sharply defined. The blood-supply, likewise, of the groups of ganglion cells is not from one individual branch of the commissural vessels, but from several. The sulco-commissural arteries form in the substance of the anterior horn a rich and intimate network which holds the cell groups enweaved in its meshes.

In the course of this study several small areas have been followed up, serially, throughout their whole extent, and I have come to the conviction that the changes appear within, but do not coincide with, the area of distribution of the arteries, and that it must be extremely difficult to determine the territory of an artery. In literature numerous statements are made to the effect that the position and the definition of the areas corresponded completely to the distribution of individual vessels, but neither in the white nor the grey matter could this be definitely traced.

In the cord (Pl. LXII) the prevailing form of the area at the periphery was wedge-shaped to a certain degree, but in the smaller isolated areas, in which one, or at most two, small lateral vessels were present, the definition was irregular and the shape was ampulla-like, with the neck of the ampulla (fig. 254) at the periphery of

the cord, or bowl-shaped (fig. 257). When a large part of the peripheral portion of the cord was affected, perhaps through fusion of contiguous lateral areas, the sclerosis frequently mapped out the triangular portion between anterior and posterior root entry zones and extended inwards to involve the grey matter—the base of this triangle being sub-pial (fig. 246). The areas within the white matter of the lateral columns were frequently round or oval (figs. 256, 258) and often occupied the region of the crossed pyramidal tracts. In the posterior columns the areas assume specially an elongated oval shape (figs. 194, 261), the long diameter of which is pointed sagittally. The centre line of this oval may be either the posterior median septum or the paramedian septum: in its extension the involvement of the columns is often uniform, but occasionally more on one side than another (fig. 259). When the ventral portion of the posterior columns is affected by a small, isolated area, it has usually a more or less triangular form, with the base to the posterior commissure (fig. 260). In its extension such an area involves both posterior horns, and may pass backwards on both sides of the median septum—the apex gradually approaching the periphery, but often leaving symmetrical islets of normal tissue in the angles near the posterior root entry zones on either side.

Isolated areas may occur in the grey matter of the cord, especially in the anterior horns. Such areas may apparently involve one group of nerve cells (figs. 234, 243), or may, rarely, map out the whole of one horn as a demyelinated area before it extends into the white matter (fig. 199). The most frequent involvement, however, of the grey matter is a peri-central sclerosis (figs. 197–199), which may be very marked at almost every level of the cord. In its extension this may pass anteriorly or laterally into the grey matter or directly anterior or posterior along both sides of the anterior and posterior fissures, or both or all combined, so that in its further extension it involves almost the whole transverse section of the cord. The symmetry of such involvement is often very marked (fig. 247), and is never more clearly brought out than where isolated islets of myelinated fibres are left at corresponding marginal parts of an otherwise demyelinated transection (fig. 210). Similar marginal areas in the region of the cerebellar tracts are also frequently left after an apparently symmetrical involvement of the lateral columns and adjoining portions of the grey matter.

The longitudinal extension of areas within the white matter is very varied, but sometimes reaches over several segments. Their form is usually an elongated oval, or a series of elongated oval areas have seemed to join on to one another at their adjacent ends (figs. 30–31). In the frontal longitudinal section of an isolated area in the posterior columns, it is possible to recognise how the numerous vertical branches of a vessel system are all involved and not one primary vessel stem. Very numerous segments were cut in serial longitudinal sections, both in frontal and sagittal direction. In some of these only traces of myelinated fibres could be found along the margins throughout the whole segment: in others, the primary oval area

was densely sclerosed and was surrounded by a broad, early transitional zone which above and below had a narrow wedge shape; and in others, as the area in the posterior columns was left behind, further serial sections showed the involvement of the posterior horns, the commissures and lateral tracts in one extensive area. The innumerable variations can thus only be hinted at, but one further feature must be mentioned. Such long stretches—extending sometimes over two upper dorsal segments for instance—showed that definite areas in the same columns were united by faintly-staining tissue, which sometimes showed Marchi degeneration, or such an appearance was continued onwards, ascending or descending, from definite sclerotic tissue. The illustrations sufficiently indicate that the cervical cord and dorsal cord were more frequently and more extensively involved than the lumbar and sacral cords.

In the medulla oblongata, pons, cerebral peduncles and cerebellum, the same two primary forms were present with numerous variations. Sub-pial areas were frequently wedge-shaped, and these within the substance of the tissue round or oval, with the long diameter in frontal or sagittal section. Here, too, the confluence of the areas was marked. The cranial nuclei shared in the general extension from the floor of the IVth ventricle—an extension which usually took place in isolated broad processes which subsequently fused with one another. The almost complete symmetry of the involvement is apparent in figs. 143 and 144, and in these areas again the islets of normal fibres left showed a remarkable parallelism. The extension of the sclerosis on the floor of the IVth ventricle passed laterally and, from the angles of the ventricle, inwards to involve the structures which at various levels are found in this region. The figures and the detailed topographical description sufficiently indicate the distribution. The lateral extension to the roof of the IVth ventricle involved the white matter of the cerebellum, the hilum of the dentate nucleus, the nuclei of the roof, and often the whole of the folia forming the vermis and nodules (*cf.* figs. 76–82).

The peri-ventricular areas showed also numerous primary, wedge-shaped areas with broad base to the ventricle, and extensions into the adjoining tissue in the form of finger-like processes or ampullæ, in each of which a central vessel could usually be found. All these areas were often united by tissue staining faintly in Weigert sections. Around the posterior and anterior horns of the lateral ventricle the sclerosis assumed the form of a hood, the apex of which was continued in the direction of the frontal and occipital poles by a series of rounded or oval small areas.

In the medullary rays numerous submiliary foci were present, round or oval, with the long diameter parallel to the course of the fibres. The areas in the medullary rays were often united by tissue in an earlier stage of degeneration. This gave a striped appearance even macroscopically. The peri-ventricular sclerosis of the descending horn of the lateral ventricle in almost every instance extended

from the adjoining white matter in radiating lines into each medullary ray. In the transition zone between cortex and white matter the affected area often assumed the form of an elongated spindle, and when this zone lay in the cup of a convolution the spindle curved on itself, with the concavity to the fissure. In the extension of either flat or curved spindle, the poles often passed to involve the transition zone between two or more adjoining convolutions, and in this extension the whole of the white matter from which the individual medullary rays arose was often cut across.

In the large basal ganglia, isolated areas were often quite round (fig. 266), but the fusion of primary areas in the optic thalamus, internal capsule, and lenticular nucleus produced large irregular areas in which might be traced the original forms. Symmetrical involvement of the basal ganglia and especially of the external capsule and claustrum, with an extension to the grey matter of the convolutions of the island of Reil, formed a prominent feature in several of the sections, especially in Case II. The distribution of the areas in the basal ganglia in individual cases has been given elsewhere, but here it may be noted that such areas seemed often to start in a peri-vascular zone around the lenticulo-striate and strio-thalamic vessels (fig. 267), and that the peri-vascular sieve-like areas were nowhere so marked as in this region, around the larger of these branches.

In the cerebral cortex the variation in the form of the areas is even more marked than elsewhere. These may be grouped into three divisions according to whether the demyelination (1) spreads from white matter into grey and is arrested within the radiations of the nerve fibres, or (2) is wholly within the cortex with a zone of intact nerve fibres forming a fine network superficial to it, or (3) spreads from the surface and extends for a variable distance inwards. The shape of those extending from the white matter is usually dependent upon the subcortical portion, and the extension may be simply a gradual one which involves the radiations in a sinuous or curved or even pointed outline. The definition of the cortical portion within the radial fibres is often very sharp, even under a high power, but frequently individual fibres or even the groups of fibres forming a single radiation may pass in from the white matter into the area for a considerable distance. In the areas, situated as far as could be made out by numerous serial sections, entirely within the cortex, no special shape could be noted. It was possible to trace small areas entirely within the tangential fibres (fig. 300), or involving the fine fibres forming the supraradial network or cutting across the Baillarger's or Genari stripe, but more often these small isolated areas were found limited to the intra-radial and radiating fibres, which pass, with a fan-like arrangement, from the tips of the medullary rays. In many such areas a small vessel, which seemed to be the centre of the demyelination, was certainly found, but others bore no relation to any of the numerous capillary vessels found within them. The shape of the areas, passing in from the surface of the convolutions, was often that of a modified wedge, or of an

arch with its convexity either on the surface or within the radiating fibres, and the outline of these areas which seemed to pass definitely over into the sub-cortical white matter was, as a rule, much sharper than that of those confined to the cortex (*cf.* Pls. LXIII–LXIV).

The close disposition of the numerous areas in certain convolutions gave place often to a coalescence, with a complete demyelination of cortical tissue extending over the whole of one convolution and sometimes round the cups of the adjoining convolutions. This demyelination in some cases affected the cortex irregularly, and the resultant line might further be broken into by wedge-shaped or bow-shaped areas extending further inwards (fig. 276). Short of complete coalescence of the areas, there were found stretches of the cortex which presented a moth-eaten appearance, in which only islets of the normal radiations or intra- or supraradial network of fibres were retained. Such a moth-eaten appearance was specially well brought out when the section was cut in a plane at right angles to the radiations (fig. 295). It is perhaps necessary to emphasise that such descriptions are taken from specimens in which it could be stated almost definitely that the demyelination was not due to over-differentiation. The limits of such areas are quite defined; the adjoining convolutions have their tangential fibres and the fine fibres of the supra-radial network well brought out; and the demyelination often corresponded exactly to the area of supply of the superficial vessel plexus of the cortex (*cf.* figs. 271–272), although no single larger vessel could be brought into relation to it. Such an extensive affection of the cortex, too, is often limited to certain convolutions. SIEMERLING and RAECKE, SANDERS, SCHOB, and others have pointed out similar extensive involvement of the cortex, and ALZHEIMER and SPIELMEYER in general paralysis have noted the existence of demyelinated areas involving the cortex extensively, in which none of the cellular changes of general paralysis were present.

The remarkable symmetry of the cortical areas is again sufficiently indicated in figs. 271–273, in one of which symmetrical areas on either side of an individual sulcus may be noted (fig. 273).

In the cerebellum the cortex often shares in the extensive involvement of the cerebral cortex. Here the medullary cores of individual folia may be simply cut across, or the fine reticulum of nerve fibres in the granular layer may be also affected: at other times, especially in the flocculus, the trunk of numerous medullary cores is cut across, and this involvement spreads to affect individual branches and the corresponding reticulum of fibres, while immediately adjoining cores, with the pertaining cortical reticulum, are unaffected. A striking parallelism may be presented in the two flocculi (figs. 27–28)—the peduncles of which may also be involved in an extension from the angles of the IVth ventricle.

It is thus seen that the areas are apparently distributed over the whole central nervous system, that their form can be related only in a modified way to two basal

types—wedge-shaped and round; and that a remarkable symmetry can be recognised in their localisation—a symmetry which can easily be underestimated when the areas are at different stages of development.

2. *Secondary Degeneration.*

The absence of secondary degeneration has been, till recently, accepted as one of the cardinal characteristics of the histological picture. CHARCOT related this feature to the preservation of the axis cylinders in the sclerotic tissue, and SCHULTZE has shown that complete demyelination of the nerve fibre at a circumscribed level occasions no secondary degeneration even in the myelin sheath itself, and that this follows only a considerable alteration of the axis cylinder itself.

The question of secondary degeneration is one not easily decided. A glance over the numerous illustrations of the spinal cord at successive levels will suffice to show that the zones of sclerosis are not followed in the usual sense of the term by secondary degeneration. It is probably frequently present, however, especially in late stages, but the ordinary difficulties of proving or recognising it in cases where numerous islets of sclerosis are present are increased by numerous factors. We have already referred to the frequent presence of diffuse changes which unite sclerotic areas or, on longitudinal section of the cord, are continued upwards or downwards as "Markschattenherde": it is probable that some at least of these changes must be related to a commencing secondary degeneration. The destruction of the axis cylinders is, again, only relative in any one area, and in consequence, the secondary degeneration will affect only a certain percentage of the nerve fibres of one column or even of one bundle: its recognition as a secondary degeneration is thus rendered more difficult. Further, the sclerosis below or above any one level passes over the boundaries of a system degeneration and may even affect the whole transverse section of the cord—the element in this change due to secondary degeneration would be impossible to trace. And, finally, more acute processes arising in the affected columns, without any loss of axis cylinders in areas above or below, may be explained by an analogous process in the area under consideration. It may also be noted that numerous, though only microscopically evident, areas may frequently be found in the course of one and the same conducting tract.

Changes outside the areas, such as the diffuse alterations of the myelin sheath, diffuse commencing alterations of the glia cells, similar dilatation and engorgement of blood-vessels and sieve-like dilatations of the adventitial lymph spaces and of the peri-vascular glia meshes, as the single expression of a not otherwise provable change, have all been referred to in the previous study. In late stages the blood-vessels throughout the whole central nervous system, and especially in the convolutions, showed varying slight changes, similar to those within the areas. ANTON and WOHLWILL have found the vessel infiltration sharply limited to the areas, but dilatation and engorgement throughout the whole cerebral white matter.

(6) Conclusion.

1. *General Features and Distribution of Areas in Case I.*

The number of areas was very large and their distribution throughout the central nervous system was very extensive. The parts most involved were the cervical enlargement of the spinal cord, the medulla oblongata, the pons, and the periventricular tissue. The most striking histological feature was that almost every area showed evidence of an advancing process (figs. 64–69). The areas were thus wholly in an "early" stage or showed a peripheral advancing zone around a central condensed zone, and the impression the latter areas left was that the primary affection had never died down, but had gradually extended peripherally, while the central sclerosis had also extended eccentrically. A further striking feature was the presence of very extensive areas of "shadow" sclerosis, which united the areas of demyelinated tissue. It is unnecessary to enter into the structure of the areas, as this has been fully given in the earlier part of the study: the great majority were at the height of the fat granule formation and had not reached the stage of commencing glia fibril formation.

In the spinal cord the cervical enlargement was very markedly affected: the dorsal cord much less so, except at the level of D 10, which showed a complete transection (fig. 58): the lumbar cord was also comparatively slightly affected, but almost the whole sacral cord showed a demyelination (fig. 63). The most striking feature of the cord affection was that with one or two exceptions no isolated areas could be traced. The exceptions were in the dorsal cord, and one of these (fig. 66), cut in serial sections, extended about one-third centimetre in longitudinal extent, and at each end gradually passed into normally staining fibres. The central portions of the posterior and lateral columns were the most densely sclerosed, but round the periphery of even these parts there was a zone more or less wide of fat granule cells; and radiating vessels, with their lymphatic sheaths filled with similar cells, passed from this zone to the circumference of the cord. The frequent symmetry is well brought out in figs. 49 and 59. Bielschowsky preparations showed a marked diminution in the number of axis cylinders, and those persisting were swollen and stained faintly. The ganglion cells showed all stages of degeneration and at no level were they normal: numerous atrophic forms with central chromatolysis and absence of processes could be found in the demyelinated tissue at almost every level, where the grey matter was affected (fig. 410). The membranes of the lumbo-sacral cord were slightly thickened and infiltrated with cell elements.

The areas in the medulla oblongata and pons were much more sharply defined, as a rule, than those in the cord. Their most striking feature was the large number that showed a zone of "shadow" sclerosis around them. This was specially evident in the areas occurring amongst the transverse fibres of the pons and grey nuclei, and such shadow sclerosis had here the same defined outline as the central area. The

nuclear areas on the floor of the IVth ventricle were markedly involved and many of the cells filled with a dark brown pigment. Nearly all the cranial nerve roots, on both sides, entered into demyelinated tissue. The areas have characters similar to those of the cord, only a few showing any definite central condensation. On the other hand, large irregular areas were found which showed a complete demyelination without any marked glia cell proliferation or blood-vessel change or alteration in the axis cylinders either in number or calibre. A very beautiful illustration of such an area is seen in figs. 16, 17, and 421, in which can be seen the sharp, irregular outline of the demyelinated tissue and the continuation onwards of the axis cylinders, which intersect in the median raphé. These axis cylinders are tortuous and delicate, and their density, in Bielschowsky preparations, is the same as in normal conditions. The blood-vessels here are dilated and their walls also impregnated by the silver. The distribution of the areas in relation to the floor and walls of the IVth ventricle and to the hilum of the dentate nucleus will later be referred to, but attention must here be drawn to the prominent involvement of numerous foliæ in the cerebellum and of the almost symmetrical affection of the flocculi (figs. 27 and 28) and of their peduncles.

The peri-ventricular sclerosis gave the impression of being the result of the fusion of sub-ependymal areas, and in individual sections such primary, wedge-shaped areas, with base to the ventricle, could be recognised. Around the lateral ventricles and their horns, on all sides, large isolated areas could be traced in the white matter: their connection with the peri-ventricular sclerosis, especially in the areas above the roof of the lateral ventricles, could frequently be definitely proved. Numerous fat granule cells were found distributed throughout the whole peri-ventricular tissue, and in the walls of the sub-ependymal veins. The ventricles were not dilated, their walls were smooth, and there was no change in the ependymal epithelium.

The cortical areas were not very numerous compared to those found in one or two other cases, and there was an almost complete absence of the irregular demyelination of the superficial layers of the cortex. The contrast between the fat granule cells of the grey matter and those of the white matter was often well brought out (*cf.* figs. 69 and 396). Bielschowsky preparations of the cortical areas showed numerous axis cylinders.

The optic nerves were extensively involved: the right was wholly demyelinated and showed a marked thickening of the connective tissue and glia trabeculæ (fig. 444). In the left nerve only one narrow strand of myelinated fibres could be found, but its whole length showed rows of fat granule cells (fig. 65).

2. *Topographical Distribution in Weigert Sections.*

Spinal Cord.

Cervical region (figs. 48–54).—At the upper part of the cervical cord only a deficient staining of the myelin was found, involving the antero-lateral column of

white matter with the adjacent anterior and lateral horns but sparing the area occupied by the direct pyramidal tract. A few sections lower this area increased in size and extended mesialwards to the anterior median fissure. A second area, of more complete sclerosis, is now present, involving the columns of Goll along their anterior two-thirds. This area increases very rapidly and soon forms a broad band along each side of the mesial line, both anteriorly and posteriorly, involving grey and white matter indiscriminately. The symmetrical distribution of the sclerosis is here very marked. Slightly lower, the early "shadow" area has almost disappeared, the large mesial area now extends laterally to involve the greater part of the posterior horn and column on one side and the corresponding third of the other side, and a third area has appeared on the opposite side in the crossed pyramidal tract.

In the third segment four well-marked areas are visible: the largest involves the whole of the right lateral column with the exception of the fibres of Lissauer's tract: on the same side a small triangular area extends outwards from the tip of the anterior horn. On the left side an irregular patch is present in the antero-lateral region, separated from the anterior horn by a narrow zone of normal fibres, while the fourth patch, roughly quadrilateral in outline, is found in the posterior columns and involves the centre of the posterior columns, extending slightly beyond the mesial line on each side. At a slightly lower level, each of these patches extends and leaves the normal tissue in the form of the letter H, while only a few sections lower there is almost a complete transection of the cord.

A section across the upper part of the cervical enlargement exhibits only a small area, along the periphery of the left antero-lateral region of the cord, where the fibres were unaffected, and even this area had a small patch of sclerosis about the middle. On the opposite side small isolated groups of normal fibres are present near the internal margin of the anterior horn and at the posterior root entry zone. In C6 the previous groups of uninvolved fibres have almost disappeared. On the right side, however, the direct pyramidal tract and the greater portion of the posterior columns are unaffected, and in C7 the normal tissue is increased—the greater part of the posterior columns on both sides being normal, as well as a portion of the right lateral and left anterior columns. In C8, the normal tissue is again much diminished and consists of fibres on either side of the anterior median fissure and a portion of the posterior columns. At a slightly lower level the posterior columns become involved, only a few scattered fibres here and there escaping—the lateral column on one side, and the antero-lateral on the other also escape. In the lowest part of C8, the only lesion is one large patch on one side, limited by the posterior horn of grey matter, extending over the whole antero-lateral portion, but allowing the direct cerebellar tract to escape.

Dorsal region (figs. 55–58).—In D1, this patch of sclerosis has spread across to the opposite side, leaving only a small area on the lateral part unaffected. In the third segment only two early areas are found: one on the right side, involving the

crossed pyramidal tract, the posterior horn, and the adjoining fibres of the column of Burdach; the other on the left side, extending lateralwards from the anterior horn. In the fifth segment there is one small oval patch in the region of the septo-marginal tract, and in the next segment two small patches appear, one in the centre of the left crossed pyramidal tract and the other towards the outer part of the column of Burdach. Still lower the whole of the anterior and antero-lateral columns with the anterior horn are completely sclerosed, with the exception of a few fibres along the direct cerebellar tract. In the eighth segment the sclerosis, which forms a quadrilateral around the central canal, involves each anterior horn completely and the anterior fourth of the posterior columns. At the junction of D10 and D11 there is a complete transection of the cord, except a few fibres along the outer border of the anterior columns.

Lumbar region (figs. 59–60).—At the level of the second segment one lateral patch involves the crossed pyramidal and ascending cerebellar tracts; in L 3 this area shows an early "shadow" sclerosis, and another patch, circular, around the central canal, extends forwards along both sides of the anterior median fissure. Here also the sclerotic tissue shows a marked symmetry, which is slightly masked by the shadow sclerosis in the lateral region. At the junction of L4 and L5, both these areas are normal and three other, isolated, patches are present—one in the left antero-lateral column, one in the right lateral column, and one along the two sides of the posterior fissure.

Sacral region (figs. 61–63).—In the upper part one small patch passes forwards from the tip of the anterior horn to the periphery, and on the left side three smaller areas are present related to lateral vessels. At the third segment one large area involves almost the whole of one side of the cord, with the exception of a small portion near the median line. This area increases as we pass downwards, until it involves the whole of the lower sacral region and conus. The nerve roots of the cauda are normal.

Medulla Oblongata.

Just above the decussation of the pyramids one small patch is found at the tip of the right substantia gelatinosa Rolandi—a patch which increases in size as it is traced upwards, when a symmetrical area develops on the opposite side (fig. 32). At the level of the middle of the inferior olive (fig. 35) there is a large area in the interior of the left olive and a second smaller area at the margin of the opposite restiform body. Still higher, these patches become larger and more prominent, and involve almost the whole of one inferior olive and extend from it along the side of the medulla to the restiform body, which is also sclerosed. The opposite olive and restiform body also show small areas (fig. 36), and another small triangular area is present between these structures, in the position of the tract of Gowers.

At the upper level of the medulla (fig. 38) both lateral margins are involved by

irregularly-shaped patches. On the one side the outer half of the pyramid and of the inferior olive, together with the whole of the restiform body and the intermediate structures, are affected. On the opposite side the posterior outer quadrant of the inferior olive is involved in an area which sends a small prolongation into the formatio reticularis, and extends upwards to involve the outer parts of the restiform body—leaving the fibres in the middle intact and connected with the formatio reticularis by a narrow band of normal fibres. The entering VIIIth nerve on each side passes directly into sclerosed tissue; the fibres in their extra-medullary course stain normally. The vermis and the accompanying nodules are also involved, and the sclerosed area extends on each side of the roof of the IVth ventricle, and passes into the hilum of the dentate nucleus—involving on one side the grey matter of the nucleus. Several of the medullary cores of the folia of the flocculus are demyelinated (figs. 27, 28, 39).

Pons Varolii.

As we ascend the brain stem the sclerosis becomes still more marked; the structures lining the floor of the IVth ventricle are particularly affected, and in the lower part of the pons both lateral angles are profoundly altered (fig. 39).

At the level of the lower third of the middle peduncles (fig. 40) patches are found reaching from the ventricle to the surface. The sclerosed area involves nearly the whole of one side of the pons, and extends over the median raphe to affect all the fibres of the mesial fillet: on this side the middle two-thirds of the pyramid escape together with a small tongue-like projection of normal fibres passing upwards into the inferior olive. The sclerosis here extends backwards along the floor of the ventricle and the lateral angle to the roof, and also laterally to involve the centre of the corresponding flocculus. On the opposite side a small area is present external to the inferior olive. The sclerosed tissue cutting across the middle peduncle is constricted in the middle, and thus is divided into two areas—one at the corner of the ventricle, and the other, at the zone of entry of the VIIIth nerve, extends into the white matter of the cerebellum and the corresponding flocculus. In the cerebellar white matter two small isolated patches are found, while in the folia several separate areas are present—one of which involves the vermis, two the junctions of the white matter and the folia, and others cut across the medullary cores of individual foliæ. The cranial nuclei in this region, which was cut serially, are all involved, the nuclei of the VIth nerve, the cochlear nuclei, and the nuclei of Bechterew and Deiters.

Slightly higher (fig. 41) the only normal tissue is in the middle line, both middle peduncles being obliterated. The normal tissue is intersected by several small areas in different stages of sclerosis, and is separated from the IVth ventricle by a broad band. On the one side the sclerosis of the middle peduncle involves the whole of the restiform body, the emerging root-entry zone of the VIIIth nerve and the associated nuclei, and extends round the angle of the ventricle to the roof. Laterally

the sclerosis extends into the white matter of the cerebellum, the remaining white matter of which also shows numerous irregular patches in early stages. Several of the cores of the foliæ are also cut across by other small areas.

Middle of the pons (fig. 41).—At this level the one middle peduncle is still involved by a large irregular area, which extends from ventricle to surface and involves most of the pyramidal fibres, the transverse fibres, the trapezoid fibres, the superior olive and associated nuclei, together with the nuclei around the IVth ventricle. On the opposite side the sclerosis of the middle peduncle is not so complete: one patch extends inwards from the surface and affects the outer pyramidal fibres, but does not extend further than the inner border of the trapezium. The floor, angle, and roof of the ventricle are also involved, and on this side two further areas occur — one destroying the superior olive, the other the trapezoidal and middle peduncle fibres; while a central area involves the trapezium again and the adjoining portions of the formatio reticularis.

Upper part of middle peduncles (fig. 42).—Here the aqueduct of Sylvius is surrounded by a well-marked ring of sclerosis, which extends to the surface, allowing only a few fibres of the superior cerebellar peduncles on each side to escape. On the one side this area extends laterally into the middle peduncle, almost completely obliterating it and sending a tongue-like projection into the fibres of the trapezium. On the other side the anterior third of the middle peduncle is affected, and the sclerosis extends postero-mesially and involves the grey matter of the pons, the corresponding fibres, and the middle of the pyramids.

Upper pons (fig. 43).—The ring round the aqueduct of Sylvius is now slightly altered; the greater part of one superior cerebellar peduncle escapes, while the anterior part of the opposite peduncle is also free. The sclerosis extends laterally, and is continuous on the one side with a large area involving the middle peduncle. Three further sclerosed areas are found: one in the middle line involving the pontine grey matter and fibres, and irregularly-shaped, almost symmetrical areas which extend postero-mesially from the lateral side of the pyramidal fibres on each side and involve two-thirds of their fibres with the corresponding connections.

At a slightly higher level the central oval area increases in size, while the sclerosis round the aqueduct diminishes, and is localised to one side.

Junction of Pons and Mid-Brain (fig. 44).

Three irregular areas here extend backwards from the surface of the pons. One, in the mesial line, reaches almost to the mesial fillet. This area cuts across, in irregularly-shaped, sharply-defined lines, the intersecting fibres of the raphe and the adjoining fibres on each side. The other areas, also irregular in outline, pass backwards on each side of the pyramidal bundles, which are also partly involved. A fourth patch extends forwards, from the aqueduct of Sylvius, in the middle line and involves the posterior longitudinal bundle and the cells in the adjoining grey matter.

At a slightly higher level (fig. 45) the mesial patch is found to extend inwards only a short distance from the surface, while another patch, commencing close to it, passes round the periphery of the pons on one side. Numerous other patches are present on the transverse section: three small areas towards the middle line; one, which reaches forwards from the aqueduct of Sylvius and extends laterally to involve the posterior part of one superior cerebellar peduncle; and another small area at the anterior level of this peduncle.

Still higher (fig. 46) sclerosed areas are present on the surface of the pons—on one side extending inwards to involve the mesial fillet. The sclerosis round the aqueduct of Sylvius involves it completely and sends a small projection forwards. In the centre of one pyramid a round "shadow" patch can be clearly identified, a second similar area is present in the middle line at the level of the mesial fillet, and a third at the lateral border of the mesial fillet.

Mid-Brain (fig. 47).

The aqueduct of Sylvius is now free, but an area occupies the mesial line in front of the commencing decussation of the superior cerebellar peduncles and another is found laterally and slightly posterior. A triangular area of sclerosis in the middle line extends inwards from the anterior surface, and two smaller lateral areas are present, one on the surface and one slightly internal. These areas are all sharply marked off from the surrounding tissue and bear no relation to any of the structures through which they pass.

Sub-thalamic Region.

In sections at this level an irregular patch is found in the anterior half of the mesial plane. The sclerosis extends outwards on each side into the red nucleus, and there are several small but well-defined areas in the ansa lenticularis on both sides. The aqueduct of Sylvius is surrounded by an oval patch, which extends outwards slightly beyond the grey matter.

Cerebral Hemispheres.

(1) Horizontal sections through the cerebral hemispheres at the lower part of the basal ganglia (figs. 23, 24).

Peri-ventricular sclerosis.—The most prominent lesion is that found at the posterior cornua of the lateral ventricles. These are both surrounded by large irregular areas of sclerosis, which extend at several points through the white matter to reach the surface of the brain. This is well marked on the inner side of both posterior horns, where the sclerosis cuts across the tapetum, the inferior longitudinal bundle, and the splenium, and reaches the surface at the parieto-occipital fissure. On the right side this area is continuous with another which extends from the

angle of the ventricle to the foot of the calcarine fissure. Several small isolated areas are found in the splenium itself. The anterior cornua of the lateral ventricles also show small patches of sclerosis at their tip, both very small in size however. The remainder of the ventricular surface is unaffected on the left side; and on the right side three isolated patches are found: a small oval area close to its anterior surface, a narrow band in the middle line, and a larger oval patch on the surface opposite the splenium. These are all related to the ventricular surface of the optic thalamus.

Basal ganglia.—A small oval area of sclerosis is present in the centre of the left optic thalamus, but the right, except for its ventricular surface, is unaffected. A number of minute areas occur in the anterior and the posterior limbs of both internal capsules, while a larger area is found on the posterior surface of the mesial border of the right putamen. The left putamen contains two early patches. One area, in the right claustrum, extends to involve two of the convolutions of the island of Reil. In the left claustrum there are six small round or oval areas, each of which extends into the white matter on each side, and one reaches as far as the putamen.

Convolutions.—The left frontal lobe appears normal with the exception of one strongly-marked oval area in the medullary ray and grey matter of the anterior part of the frontal operculum. An equally well-marked area is found at the posterior part of the calcarine region—extending from white matter directly to the surface. In the right hemisphere small areas occur in the white matter of the frontal lobe; a slightly larger one is present towards its anterior margin, extending into the medullary ray and grey matter of the gyrus. Two minute early areas are present in the middle of the white matter of the frontal operculum, and a number of narrow, irregular areas—some extending for a distance of over a centimetre—are found limited to the cortical grey matter of this operculum, both on its outer and inner aspects, and on the surface of the island of Reil itself. Similar patches occur in the greater part of the parietal region, together with a large number of minute patches and one larger one at the junction of the white and grey matter in the cuneus. In the occipital lobe, a large number of minute patches, at all stages of development, are present both in the white and grey matter. These are grouped mostly towards the mesial surface and especially around the calcarine fissure. A few early areas occur also extending posteriorly from the peri-ventricular area already described.

(2) At the level of the roof of the lateral ventricle (fig. 26).

The most striking feature at this level is the large irregular area occupying the whole of the outer wall and posterior tip of the ventricle. This sclerosis extends irregularly into the adjacent white matter and completely cuts across the superior longitudinal fasciculus. A number of isolated areas, in different stages of development, are found along the mesial wall of the ventricle: these extend into the corpus callosum. Several large round and oval well-defined areas are found in the

white matter, especially towards the occipital lobe—the largest of these measuring $1 \times \frac{3}{4}$ centimetre.

In the convolutions one small area is present at the tip of the frontal lobe; another occupies completely the medullary ray of the post-Rolandic gyrus; another is at the junction of the white and grey matter of the pre-cuneus, and two others, both circular in outline, occur in the grey matter of the calcarine region—one on the outer and one on the mesial surface.

The opposite surface of the cerebral hemisphere at this level shows a very similar affection and distribution.

(3) Above the ventricles (fig. 25).

Numerous areas occur in the white and grey matter of both hemispheres. In the frontal lobe on the right side one large irregular patch occupies the centre of the white matter; several smaller areas are found on either side; and three early patches extend from the white matter into the medullary rays of the convolutions at the tip of the lobe. A small oval area is present in the post-Rolandic convolution at the junction of white and grey matter, while a smaller one is present in the white matter adjoining it. Another very well-marked area is present in the calcarine fissure: this extends from fissure to fissure, undermining completely the upper portion of the arcus parieto-occipitalis. Two or three small areas, confined to the grey matter, are also present in this region.

(4) Horizontal sections through the temporo-sphenoidal lobe (fig. 29).

Sections just below the floor of the descending and posterior horns of the lateral ventricle show on both sides large irregular areas of sclerosis, which represent the downward continuation of the peri-ventricular sclerosis which has affected both these horns. The areas extend from the white matter almost to the surface of the convolutions, and the anterior margins of the descending horns are similarly affected. The sclerosis involves the greater part of the course of the occipito-temporal bundle of fibres; the convolutions in the region of the calcarine fissure are extensively involved—especially in the more superficial fibres of the grey matter; similar but more defined areas are present in almost all of the convolutions at the tip of the temporo-sphenoidal lobes; and the fibres of the hippocampal convolutions are also markedly affected.

3. *Note on the Pathological Physiology.*

There is no disease of the nervous system in which the symptoms may be more varied, in origin and in succession, than in disseminated sclerosis, a fact which can be well understood when one considers the wide range and irregular distribution of the areas of sclerosis. These, as we have seen, may occur in almost any part of the nervous system, producing peculiar symptoms and combinations of symptoms, which

may be of short duration and are usually followed by periods of remission, after which a new series of symptoms may appear. Once definitely established, the disease is almost invariably fatal. The great variation in the nervous symptoms has resulted in a tendency, on the one hand, for any disease of nervous origin of which the symptoms are unusual or difficult to interpret to be classified as "disseminated sclerosis"; while, on the other hand, the way in which the symptoms of a case of true disseminated sclerosis may simulate other nervous diseases has often led to errors in diagnosis. On account of the long duration of the disease in most cases, and the unsatisfactory results of treatment, patients are not kept in hospital for long periods of time, and thus the number of cases which come to autopsy is not large.

The earliest symptoms of the disease are extremely variable, and depend solely upon the particular part of the nervous system affected by a patch. There is, however, a tendency for these patches to occur more frequently in certain regions, and thus certain clinical symptoms appear more commonly than others, and as a result are considered more or less pathognomonic of this condition.

Of these symptoms one of the commonest is weakness of the legs. This is met with in a very large number of cases, and is associated in most with involvement of the spinal cord. It usually is progressive, and a spastic paraplegia develops. It is often accompanied by a number of more or less well-defined sensory changes. Such symptoms may result from one or more patches in the cervical or dorsal regions of the cord, involving the descending motor and adjacent sensory fibres. If the area involved be still lower, *e.g.* in the sacral region, then the only symptom may be a sphincter involvement. These spinal symptoms may be the only ones present, or they may be accompanied or followed by others due to involvement of the higher centres. Of these, the principal ones most commonly found are nystagmus, alteration in speech, and volitional tremor. These are largely due to want of co-ordination, and are the result of sclerosis spreading in from the ventricles.

The eye symptoms are of special importance, and are very often the first sign of the disease. They often disappear quickly or may ultimately proceed to total blindness. They are the result of patches in different places in the optic path, the optic radiations as they pass near the descending horn of the lateral ventricle being commonly involved in the peri-ventricular sclerosis. The later and more serious symptoms, however, result from involvement of the more peripheral part of the optic path, namely, the optic tracts and chiasma. The affection of the eye muscles occurs so frequently from the close relationship of the structures innervating them to the ventricular spaces, the peri-aqueductal sclerosis found in the mid-brain involving the third nucleus in many cases. The nucleus of Deiters and other vestibular nuclei situated at the angles of the IVth ventricle are also specially liable to involvement, and there is no doubt that it is the proximity of these structures to the ventricles which accounts for their frequent involvement and the special diagnostic importance of nystagmus and visual symptoms.

The "volitional" tremor and scanning speech are also symptoms of the very greatest importance. They are both the result of defects of co-ordination. The tremor occurs only on voluntary movement and is absent during rest. In attempting to carry out any movement the arm jerks about in an irregular manner, the tremor becoming quicker towards the end of the voluntary act. This form of involuntary movement, we know now, results from affection of the cerebello-rubro-thalamo-cortical path. Injury to this path allows involuntary movements to occur by removing the steadying influence which it normally exerts upon the Betz cells in the motor area. If this influence be removed, steady innervation of the anterior horn cells is impaired, and the more the pyramidal path is innervated, the more obvious does the tremor become. Involvement of the cerebello-rubro-thalamo-cortical path may occur, thus, at many different levels, and any of these lesions may result in this volitionary tremor. That this path is specially liable to be affected is well seen in these cases here described, as in most of them patches were found at many different levels. They occur very frequently in the superior cerebellar peduncles, in the red nucleus, and in the optic thalamus.

The relation of the symptoms to the areas of sclerosis found after death is well seen in Case I (L. W.). The symptoms in this case began with weakness of the legs, which passed off, recurred, grew rapidly worse, and terminated in a spastic paraplegia. This is obviously the clinical manifestation of the dense areas of sclerosis which were found throughout the spinal cord. These were obviously of long duration, and seem to have been the earliest manifestation of the disease. The patches which were found in the sacral region were also of an early date, and were responsible for the affection of the sphincters from which she suffered. The spinal cord lesions in this case were thus very extensive and appeared at an early stage of the disease.

The next symptom of importance to appear was the volition tremor, with which we associate the patches in the superior cerebellar peduncle, red nucleus, and optic thalamus. These appeared also at a fairly early stage. The nystagmus was also an early symptom, and was undoubtedly associated with the peri-ventricular and peri-aqueductal sclerosis, only parts of the oculo-motor nucleus being involved.

After a short time the symptoms followed each other rapidly. An extension of the patches in the cervical region caused sudden numbness in the left arm. This was followed by a rapid development of large patches in the pons, one of which, involving the VIIIth nerve, produced deafness in the right ear, and another, catching the facial nucleus, produced a right facial paralysis. These patches were found in an early stage and thus appeared late in the course of the disease. An extension still later of a patch involved the sixth nucleus, and led to diplopia from paralysis of the external rectus muscle. This was soon followed by the medullary patches which involved the XIIth nerve and nucleus, and led to a protrusion of the tongue to one side and slight difficulty in speech and swallowing. Later the vision suddenly became dim, and next morning she became totally blind. This was obviously the

result of the development of patches in the optic tracts and chiasma. Later the areas in the spinal cord became still more extensive, and the effects of a lower neurone lesion became evident, resulting in muscular wasting and emaciation.

V.

PATHOGENESIS AND ETIOLOGY.

INTRODUCTION.

To record these observations is the chief object of this paper: the secondary, but more difficult, task is to try to interpret them and to correlate the various conceptions which emerge in the process. It may be stated at the outset that no satisfactory explanation of the pathological process in all its bearings has yet been put forward, and that all that can be done here is roughly to estimate the factors which have been at work. It has been already pointed out that different investigators have given a different meaning to the same histological picture, while others, working solely or largely with individual elective staining methods, have laid stress on the feature of the process which that staining method rendered prominent. One important group, working with glia methods, considers that all the changes are subordinate to the primary glia proliferation. Another group, working with medullated sheath methods, equally forcibly maintains the primary parenchymatous origin of the process; and still others, working with diffuse stains, see in the changes in the blood-vessels the key to the whole process. From the histological point of view, therefore, the most important problems centre round the question of the rôle which falls to the various tissue elements in the origin of the process. From a clinical point of view, on the other hand, the question of the nature of the process is of more interest.

In the introduction it was briefly noted that it was necessary to discriminate between the nature of the process underlying disseminated sclerosis and its origin. In its nature it is due either to developmental causes, *i.e.* those inherent in the individual, or to inflammatory causes, *i.e.* those due to infections, intoxications, circulatory disturbances, etc.,—these two groups not being necessarily exclusive, as will be pointed out later. In its origin the primary change may arise in any of the

constituent elements of the nervous tissue—the neuroglia, the true nervous elements, or the blood-vessels. The views as to the developmental nature of the process are usually related to defects in the glia tissue, though a few writers refer to a "congenital degenerescence" of the true nervous elements. The views as to the inflammatory nature of the process are related again to primary changes in any of the tissue elements, and the factor or factors which bring the inflammatory changes into operation are admitted to circulate in the blood-vessels or lymph channels, and to exert their action primarily on the glia, the myelin sheath of the nerve fibres, or on the blood-vessel wall itself.

The two views as to its nature strike at the very root of the chief difficulties met with in explaining the evolution of the morbid changes. The inflammatory nature of the process, in some form, was admitted by most of the earlier observers, who traced it chiefly to a primary change in the glia. This theory was later upheld, especially by French writers, who, however, traced the process chiefly to inflammatory changes in the vessel walls, but such an explanation has appeared less certain since the works of STRÜMPELL and MÜLLER. These writers stated that the special evolution of the disease, with its frequent marked remissions followed by aggravations without apparent cause, was difficult to reconcile with the view of a toxic or infectious cause alone having engendered the condition. They also point out that inflammation as a rule alters rapidly the axis cylinders and ganglion cells, which in disseminated sclerosis are frequently preserved, and, further, that inflammatory phenomena are often very difficult to trace. Recent research has greatly diminished the importance of these arguments by showing both that the long duration of the affection takes from the negative finding of inflammatory phenomena much of its significance, and that, even in disseminated sclerosis, the ganglion cells and axis cylinders frequently perish.

For more than a quarter of a century after CHARCOT gave the first clinical and anatomical picture of the disease, it was looked upon as a distinct morbid entity, a chronic disease in which certain characteristic clinical and anatomical features were always present. Many later writers, however, have related it to a disseminated form of myelitis. They assert that previously only the final stages of the disease have been considered, and that, by suitable staining methods, areas may frequently be observed in the same case in all stages of development, from an area of inflammation into an area of sclerosis, from which all traces of inflammation have disappeared.

To this argument it is replied that there exist two forms of the disease: a primary chronic form due to a malformation of the glia, and a secondary myelitic form *en rapport* with infection and intoxication. It is admitted, however, that in primary disseminated sclerosis the development of the focus may begin under the reaction of external factors as *agents provocateurs*, but the disease is in no sense dependent upon these. In opposition to this, it is asserted that the separation into primary and secondary disseminated sclerosis is an artificial and arbitrary one, and

that no clinical or anatomical distinction exists between the two. An intermediate position is taken up by those writers who reconcile the inflammatory theory with the developmental one. They admit that congenital anomalies of the glia may become the point of origin of primary proliferations of the glia, but they believe that the blood-vessels distribute some toxi-infectious agent which settles there where the glia is abnormal, and thus calls this glia proliferation into being.

Turning now to the histological observations, it is necessary to ask: Do these throw any light:

(1) *Upon the Nature of the Process?*—Do the areas arise solely upon the basis of a gradually increasing glia hyperplasia, or on the basis of an inflammatory reaction, or on both? Further, are there sufficient grounds for distinguishing between the two?

(2) *Upon the Origin of the Process?*—If we admit a primary form of disseminated sclerosis of developmental nature, we have answered the question of its origin in the glia; but if we say that the underlying process is of an inflammatory nature, we thereby also say that the blood-vessels or lymph channels carry the ultimate causal factor to the tissues, but must further decide on which tissue element there is the first evidence of its action.

(3) *Upon the Etiological Factors postulated*—chill, trauma, psychic shock, intoxications, infectious diseases, etc.?

(4) *Upon the Mode of Action of the Causal Agent*, and the other questions which this consideration involves?

For the purposes of our argument it is assumed that the cases investigated were cases of disseminated sclerosis. This follows (1) from the clinical notes submitted; (2) from the macroscopic findings of disseminated areas in spinal cord and brain, with the characters usually ascribed to this disease; (3) from the recognised microscopic characters of these isolated or confluent areas in which were found absence of the myelin sheath of the nerve fibres, and varying degrees of glia proliferation, blood-vessel changes, and persistence of axis cylinders.

(1) Nature of the Pathological Process.

1. *Developmental.*

Müller has strongly upheld the view of the developmental nature of disseminated sclerosis, and has emphasised the distinction between the primary and secondary forms of the disease. Weigert's work showed that both from the morphological and biological points of view the neuroglia reacts as a true connective tissue. Müller's wider conception of this idea leads him to see that the ultimate product of processes entirely different in their pathogenesis, but presumably all giving rise to focal disease of the parenchyma, may show disseminated sclerotic patches. He divides them, on the one hand, into those processes which always occur as the direct result of exogenous factors and lead to multiple focal degenera-

tions and inflammations, and, on the other hand, into a morbid condition which has one uniform circumscribed pathogenesis, being due not to any known external cause but to a congenital abnormal disposition of the glia. Among the former, he states, are those "comparatively rare" processes which have resulted in injury to the nervous tissue due to some apparently primary blood-vessel condition, *e.g.* syphilitic or arterio-sclerotic disease of the vessels, or to a toxi-infective inflammation in the form of a disseminated myelitis or encéphalitis. In all these cases the histogenetic terminal product is a secondary disseminated sclerosis in the sense of SCHMAUS and ZIEGLER. In contrast to these is the "comparatively common" disease caused by congenital disturbances of development, and termed by SCHMAUS and ZIEGLER primary disseminated sclerosis. This form, which presents distinct clinical and anatomical signs and may be looked upon as a multiple gliosis (STRÜMPELL), is the only true disseminated sclerosis.

The essential anatomical signs of this condition are the following: (1) the foci are situated only in those parts of the nervous system which normally contain much glia; they tend to develop symmetrically and are often of considerable size, *e.g.* in the cord they may occupy the whole transverse section; their relation to the blood-vessel can be explained by the layer of glia—the glia limitans perivascularis—normally around the vessels. (2) Microscopically the foci consist of an excessive proliferation of glia, leading to a dense tissue which is never areolar: there is comparative integrity of the ganglion cells and axis cylinders in the area and a marked degeneration of the myelin sheath, with no secondary degeneration; and there is never evidence of a primary disease of the blood-vessels within the area. The foci, stained by means of Weigert's myelin sheath stain, appear clearly defined and as if punched out, but, stained by Weigert's glia method, the areas have not the same abrupt transition to the normal tissue—the proliferated glia becoming gradually lost in the periphery. In this circumstance MÜLLER found an argument for the primary glia origin of the process. He bases much of his description of the areas on sections, stained by Weigert's glia method, lent to him by WEIGERT himself. Sections so stained bring out very forcibly the enormous proliferation of the glia, and give the impression of a primary glia growth so out of proportion to the relative integrity of the ganglion cells and axis cylinders as to contradict any mere substitution proliferation. MÜLLER thinks it very striking that this colossal glia proliferation—the maximum found in pathological conditions (WEIGERT)—should be met with in a disease in which there is relative integrity of the true nervous tissue.

The clinical signs are also typical, and MÜLLER thinks that secondary disseminated sclerosis can never successfully simulate CHARCOT'S classical picture in the marked distinctness of each symptom and the peculiarly characteristic course. In spite of the great variableness in the symptoms, which may simulate widely-differing diseases of the brain or cord, the diagnosis can always be established by a study of certain individual symptoms and groups of symptoms, and of the course of the

disease. This study will reveal the fact—at first sight paradoxical—that the fundamental features of the clinical condition are in the great majority of cases absolutely the same. There is usually no real exciting cause: it may commence suddenly, but more commonly has a subacute or chronic onset; and it shows sudden exacerbations with marked remissions, but is, on the whole, a progressive and chronic disease.

MÜLLER holds that the relationship between infectious diseases and disseminated sclerosis has apparent justification only in cases where the one disease immediately precedes the other, or where there is a direct transition of the one into the other. True disseminated sclerosis shows a marked preference for youth, and the fully-developed syndrome is very rare in childhood during the years when infectious diseases are most common. Cases showing a close time-relationship are very numerous, and clinical experience shows that external factors are quite insignificant in the etiology of disseminated sclerosis. Further, the idea of a direct causal relationship appears incompatible with a satisfactory explanation of many of the characteristic features of the course of the disease. Disseminated sclerosis runs a chronic course, and MÜLLER asks if the typical exacerbations in its course are to be explained by inferring that the various exciting agents of scarlet fever, diphtheria, etc., circulate for months or years and become deposited in the foci to give rise later to fresh infection. On the same grounds, MÜLLER thinks it unlikely that disseminated sclerosis is caused by the action of metabolic products derived from bacteria (toxins), as in post-diphtheritic nephritis or polyneuritis. For this we would have to suppose that the products of metabolism from absolutely different bacteria and of entirely different chemical composition could give rise to absolutely similar foci, and also that a paroxysmal increase and decrease in the action of the toxin accounts for the exacerbations and remissions. He further thinks that such meta-infectious diseases are more likely to produce diffuse and system diseases than focal processes. True disseminated sclerosis, just as Friedreich's ataxia and psychoses due to congenital disposition, may develop at the conclusion of an acute infective disease, but all recognisable exogenous factors, which in a small minority of cases have a definite time-relationship with the commencement of the clinical symptoms, are capable only of acting as *agents provocateurs*—given an existing predisposition to the disease—making manifest or aggravating the condition. Infectious diseases may, however, give rise to a disseminated disease of the central nervous system, which may develop into a secondary disseminated sclerosis, but its pathogenesis, course, and histological details differ from true disseminated sclerosis. So-called acute disseminated sclerosis is to MÜLLER simply a disseminated affection of the central nervous system, which really belongs to disseminated myelo-encephalitis. In the rare cases in which it is difficult to make a pathological diagnosis between true disseminated sclerosis and the secondary forms, a consideration of the whole clinical condition and especially of the course of the disease will decide.

MÜLLER points to the fact that, so far as we are aware, there are no exogenous

factors which seem to produce in any other organ the development of a process comparable in any way to disseminated sclerosis as a strong argument in favour of its endogenous or developmental origin. By tracing true disseminated sclerosis to "abnormal congenital conditions," he simply differentiates it from forms due to recognised exogenous factors. He is in no way satisfied with this explanation, and states that further investigation must seek to discover the organic basis of such abnormal congenital conditions.

It is thus seen that the explanation of a "multiple gliosis" in STRÜMPELL'S and MÜLLER'S sense is very similar to that given for certain groups of tumours, which must be related to embryonal defects. RITCHIE, discussing the etiology of tumours, states that the soundest ground for assigning congenital defect exists when the tumour arises in some part of the body where at some stage of fœtal life the cells of one tissue must push aside those derived from another in order to attain their ultimate natural position: the sequence being that during the building up of the body the cells thus detached or pushed aside, after being embedded for a longer or shorter period, take on a vegetative activity and assume the characters of a tumour. MÜLLER claims that the favourite sites for the development of this gliosis are those which in the embryonal period show specially active processes of growth, or where two surfaces come together and fuse in later development ("Kielstreifen"), or where the marginal zone of the embryonic nervous system is pushed inwards by the ingrowing vessels. At such sites developmental disorders, such as germ invagination or detachment, might set in very readily. The ventricular surfaces and the peri-central tissue normally contain much glia, the postero-median septum and the optic chiasma are formed by such "Kielstreifen," and the marginal glia zone and the peri-vascular glia zone represent tissue carried inwards during development. Areas are, therefore, not necessarily related to blood-vessels, and when so related it is in virtue of the peri-vascular glia layer which surrounds their adventitial sheath. The frequent symmetry of the areas is related similarly to the glia and not to the distribution of a toxin by the blood-vessels.

The sequence of the process, as has already been pointed out, is a gradually increasing hyperplasia of the abnormal glia in these sites of predilection. This results in a disappearance of the myelin sheath of the nerve fibres, partly through direct compression, and perhaps indirectly by derangement of the circulation. No fat granule cells need necessarily appear at first, but in the zone surrounding the compact area there may be a secondary reaction to the products of degeneration, leading to a combination of primary and secondary proliferation with peripheral progress of the process. Here fat granule cells would appear as indications of a more recent process but by no means of an exogenous inflammatory one. The blood-vessels within the sclerosed area also show changes which are entirely secondary to the sclerotic process, which, in consequence of the peri-vascular glia layer, is specially marked immediately around the vessel.

Areas in secondary disseminated sclerosis, on the other hand, are stated to be of an "areolar" type: there is much greater involvement of the axis cylinders and ganglion cells: there is seldom any sign of real sclerosis—only the remaining glia network is present or a slight consolidation of it, which sets in concentrically from the normal tissue, not excentrically from the abnormal glia predisposed to proliferation: the blood-vessel changes are marked, and the dependence of the areas on the altered vessels is striking; and the foci are, as a rule, smaller in size, are frequently followed by secondary degeneration, and are often limited to the cord. Clinically, also, the disease occurs in definite relation to varied toxi-infective processes: after a shorter or longer period the symptoms either steadily progress or gradually recede to more or less complete recovery; and there is an absence either of any striking fluctuations during its course or of any further relapses.

In all the six cases examined by him, MÜLLER found, histologically, a complete absence of the undoubted components of inflammation, and, clinically, in eighty cases, an absence of toxi-infective processes in the anamnesis. He therefore felt justified in excluding exogenous factors and falling back upon developmental causes. It is difficult to criticise so important and careful a work as MÜLLER has given in his monograph—the chapter on the diagnosis and differential diagnosis alone extends to a hundred pages. It is there stated that more than twenty different diseases of the nervous system may be simulated by disseminated sclerosis, that a typical case is one of the most readily recognised diseases of the nervous system, but that atypical forms constitute by far the greatest proportion. We are here more concerned with the histological data, and these, as given in the monograph, are very slight. Several staining methods are briefly mentioned, but reliance has been placed chiefly on specimens lent to him and stained by Weigert's glia method, and also on Weigert's myelin sheath and Marchi-stained sections. The latter showed at the periphery of the areas an extending process, but all the areas examined in each case showed a dense, compact glia structure, and nowhere was there any indication of soft, *i.e.* early areas.

In all the nine cases examined by me there have been present side by side with dense areas, or forming an outer zone to such, very numerous foci in which transitions could be traced from "early" areas with numerous fat granule cells—the criterion taken by many writers for the existence of an inflammatory reaction, and which for the present I accept—to areas of almost complete sclerosis in which there was no indication even at the periphery of an advancing process. But such complete sclerosis was comparatively rare: even in the most advanced case, many of the areas showed the presence of fat granule cells in the walls of the vessels both within the area and leading from it: and the great majority of the dense areas showed a central sclerosis, gradually becoming less as it passed into the normal tissue, and this transition zone gave the impression that had time been given it would have under-

gone an excentric spread comparable to the central gliosis. The end result, then, of all such areas would probably have been a compact gliosis in which were very fine meshes not in the least similar to those of the areolar areas described by MÜLLER as characteristic of secondary disseminated sclerosis. The examination of many hundreds of areas has satisfied me that "early" areas—so-called areas of fat granule cell myelitis—can develop into areas of compact gliosis with all the characteristics of those described by MÜLLER as typical of true, primary disseminated sclerosis. None of the cases could be described as "acute multiple sclerosis," taking this term in the sense MARBURG and DINKLER have used it. In Case I, which has the shortest clinical course in the series, the illness had lasted fifteen months and death had resulted from diarrhœa and exhaustion. In this case no fewer than fifty different areas were examined by the Marchi method alone, and four-fifths of these showed fat granule cells distributed throughout the whole affected tissue. In the other areas these cells were limited to the periphery and to the vessel walls, while the centre of the area was composed of a dense glia feltwork with numerous axis cylinders in the fine meshes. In only two areas was there a complete absence of any such signs of inflammatory reaction. In the very numerous areas examined by other staining methods, a similar structure could be demonstrated and in similar proportions, for the areas chosen for the Marchi method were taken irrespective of their macroscopic soft or hard consistence.

I am in agreement with MÜLLER'S statement that the glia tissue had frequently not the same abrupt definition as the demyelinated tissue. Though not using Weigert's glia stain, it was often quite evident that the myelin sheaths at the margins of the area, in longitudinal sections, were thrust asunder by proliferated glia tissue. This, however, need not necessarily be explained on the ground of a primary glia proliferation (see p. 666). I am further in agreement with MÜLLER that the most frequent sites are the peri-ventricular and peri-central tissue, around the postero-median septum, in the lateral columns, and with the marginal glia zone as a base. Why certain parts are predisposed it is difficult to say, and this question must be discussed later. More easy to understand is the frequent remarkable symmetry emphasised by MÜLLER. This has been entirely confirmed, especially in cases where there was an almost complete transection of the cord, when the symmetry was perceptible in the marginal portions of preserved fibres, and again when both the lateral columns were affected and marginal zones were left corresponding to the dorsal cerebellar tracts. MÜLLER'S explanation of this symmetry has been referred to, but it may also be explained by the possibility of the two halves of the cord being exposed at the same time to a diffusely acting agent in the blood-vessels.

MÜLLER'S essential arguments are (1) that the participation of the blood-vessels within the area is only a secondary one, and (2) that the glia proliferation is far more than reparatory. In discussing the origin of the process we must refer to

both of these points and also to STRÜMPELL'S view that the vessels throughout the body, not solely in the central nervous system, would be affected were it an inflammatory process. But it may be stated here that STRÜMPELL and MÜLLER'S view of a "multiple gliosis" is scarcely tenable for the cortical areas, which have been proved not to consist of proliferated glia fibrils, and for areas in the peripheral nerves. The latter, however, if their existence can be demonstrated, might well be analogous formations—consisting of a proliferated, interstitial tissue whose origin is in the Schwann's sheath, in virtue of its ectodermal derivation from the neural crest.

From a comparison of the histological study with the above statements, it will be seen that I am not in agreement with MÜLLER'S view that the areas in disseminated sclerosis arise solely on the basis of an increasing glia hyperplasia, and that they can be always separated from those arising on the basis of an inflammatory reaction. In this study there is overwhelming evidence that the great majority of the areas have arisen on an inflammatory basis and that a small minority have arisen on the former basis. The end result of both is a tangle of glia fibres. During the process of the gradually increasing glia hyperplasia it is possible, especially in the lateral columns of the cord, to differentiate this mode of formation of a sclerosed area, and I relate such not to a developmental defect of the glia, as MÜLLER and STRÜMPELL have done, but to a special reaction in the glia, according to the nature and intensity of the causal factor (see p. 666). We have therefore not two affections, or necessarily different stages of the same process, but one causal factor which probably acts with varying intensity.

2. *Inflammatory.*

Having therefore given adherence, on the grounds of an exhaustive study of nine cases of disseminated sclerosis, to the inflammatory nature of the process underlying this condition, it must now be considered briefly what is meant by inflammation in the central nervous system.

It is usual to classify the varying histological pictures in the processes termed "inflammatory" in the central nervous system into parenchymatous and interstitial, analogous to the processes in the glandular organs of the body. But the conception of a purely parenchymatous inflammation in the central nervous system has little anatomical support, for the evidence of changes of a regressive nature in the nerve cells, axis cylinders, and myelin sheaths is accompanied by evidence of progressive phenomena in the other tissue elements. It is not possible, therefore, to draw any clear distinction between simple tissue degeneration and inflammation, and it is usual to designate as "myelitis" both the processes, which are from the beginning distinguished by inflammatory exudations and cell infiltration, and those which begin as degenerations and only in their further course are connected with pathological exudation or proliferative processes.

When, therefore, the inflammatory nature of the process is referred to, it is as a reaction process and one not necessarily associated with exudation of fluid and cell infiltration of the vessel walls. All changes which reveal any kind of progressive phenomena in any of the tissue elements are therefore included in this view of inflammation. Later the relations of disseminated sclerosis to acute and chronic myelitis must be referred to, but the widely varying views regarding the true nature of "acute myelitis" may here be touched upon. Many clinicians have given this name to all diseases of the spinal cord, the symptoms of which cannot be traced to an isolated affection of individual portions of the cord or systems of the cord. Others, before applying the term, make the additional condition that an inflammatory process should really be present. The conditions under which it is justifiable to entitle a disease "myelitis" are not yet defined either clinically or anatomically, and it is the anatomical substratum of the disease, when known, that usually defines the idea of the disease. BASTIAN, arguing largely from the similarity of the morbid changes to those occurring in the brain, which are due to thrombosis, has long maintained that the great majority of cases are really "thrombotic softening of the cord" rather than an infiltrative myelitis. An ischæmic softened area in the brain, in which great numbers of phagocytic cells, associated later with proliferation of the supporting tissue, are present, is not usually looked upon as an encephalitis. It is the custom to identify this finding by the name of "softening," and yet it is much rather a reactive condition that has set in secondarily, and is a secondary inflammatory reaction—secondary to the presence of the degenerated products. A similar condition may occur in the spinal cord as a result of thrombosis of the spinal vessels, and the reactive phenomena are here again not due to the primary cause which produced the tissue necrosis. On the other hand, as a result of toxi-infective agents, it is possible to get (1) typical cell infiltrations of the vessels and surrounding tissue; (2) simple degenerations of the tissue, in which the so-called inflammatory vascular changes may be absent; or, further (3), actual inflammatory softenings of the tissue. In the latter two forms we again get later reactive changes in the tissue elements, and these may be secondary to the tissue degeneration, or simultaneously called forth by the primary causal stimulus. Are such conditions to be termed inflammatory only when the primary blood-vessel wall changes are inflammatory? or is it not possible to recognise the complicated inter-reaction as an inflammatory process? Clinically, we cannot yet distinguish parenchymatous and infiltrative myelitis, nor these from acute inflammatory softening and acute thrombotic softening. Pathologically, it is sufficient to distinguish two main types in which myelitis may show itself: (1) Infiltration—a form to which some would limit the term "acute" myelitis; (2) softening—to which the term "myelomalacia" has been recently applied—a form which may be very varied in degree from the degeneration of a limited number of nerve fibres, in which the process is more probably subacute, to the necrosis of a large area, in which the process is more likely to be acute in onset.

(2) Its Origin.

It is necessary now to discuss the question of the structural element of the nervous tissue in which this inflammatory process has its origin. In the fully developed sclerotic area changes are evident in relation to the myelin sheath of the nerve fibre, the glia, and the blood-vessels. It is important to recognise on which tissue element the causal agent, circulating presumably in the blood-vessels or lymph sheath of the blood-vessels, first produces its effect.

1. *Changes in the Neuroglia Tissue.*

Charcot defined the histological picture of disseminated sclerosis as a chronic interstitial inflammation leading to a gradually increasing glia hyperplasia. This view is so frequently confused with that formulated by Strümpell, Ziegler, and Müller, in which there is also a gradually increasing glia hyperplasia, that at the risk of a too frequent repetition the distinction between the two must be emphasised. Strümpell's view is that abnormally placed glia cells take on a latent vegetative activity, and produce a multiple gliosis, while Charcot holds that an exogenous causal factor stimulates the glia anywhere within its range to a marked glia fibril formation. The sequence of the process appeared to him to be the following: the multiplication of the glia nuclei and concomitant hyperplasia of the reticulated fibrils of the glia constitute the initial fundamental fact and necessary antecedent; the degenerative atrophy of the nerve elements is consecutive and secondary, and the hyperplasia of the vessel walls plays merely an accessory part. Disseminated sclerosis is, therefore, looked upon as a primary and multilocular chronic interstitial myelitis and encephalitis. The contention of a primary glia change is based on the presence of glia hyperplasia, while as yet there is little or no evidence of either an alteration of nerve fibres or changes in the blood-vessels, and also on the fact that at the periphery of the areas, where presumably the morbid process is still active, there is a marked increase of glia cells; here, also, are the evidences of the strangling of the nerve fibres by the glia fibril formation. The substance of the argument of those who support this view seems to lie in the acknowledged fact that in many areas the glia proliferation is far in excess of that required as a mere reparatory or substitution process, and that it must therefore be looked upon as a productive primary stimulation. Weigert, whose views on such a subject necessarily carry great weight, believes that the maximum of pathological glia fibril formation is seen in this disease.

The presence of areas, especially in the lateral columns of the cord, of a gradually increasing glia hyperplasia, has already been indicated, and their comparative rarity in this study emphasised. I am, therefore, not in general agreement with this view, seeing it applies to so few of the areas, but in isomorphous sclerosis it is probable that the reaction phenomena may be all the more marked when the tissue is not greatly altered, and this would account for the colossal glia proliferation.

In the changes in the optic nerve also, there were evidences of a primary change both in the connective-tissue elements of the endoneurium and in the glia septa. Similar changes are described by FLEMING in retrobulbar neuritis in cases of intracranial tumour, and are ascribed by him to a toxic condition of the cerebro-spinal fluid. In other areas, especially where there was a gradual atrophy of the myelin sheath, an indirect action of the sclerosis on the nerve fibres could be traced, possibly by the sclerosis limiting the expansion of the blood-vessels, and interfering with the nutrition of the nerve fibres, but it is far from this to the direct compression causing destruction.

In referring to the histological study it will be noted that I seem to be in further agreement with the supporters of this view in looking upon the first change as being evidenced in the glia tissue. There it has been stated that an enlargement of the protoplasm and protoplasmic processes of the normally existing spider cells was the first change visible, but this must be referred rather to the difficulty of recognising, by such staining methods, an early change in the nerve fibre, and a change in isolated glia cells must be looked upon as being in the great majority of cases simultaneous with or possibly later than that in the myelin sheath. It has also been repeatedly stated in the histological study that the enlargement and proliferation of the glia cells can be traced amongst the normal fibres at the margins of the demyelinated tissue. This change and the presence of the nucleated peripheral zone of glia cells seem to us to be not necessarily a proof of the primary and essential change being related to the glia elements. Its possible significance will be referred to later in relation to the varying factors which may influence the development of the process, for it is important to recognise that the areas do not always develop proportionately.

A brief allusion may be made to the various functions attributed to the neuroglia. It is no longer held that the glia cells and their processes conduct the nutritive substance from the vessels to the nerve cells and fibres, and it is also probable that the neuroglia must be looked upon as more than a supporting structure or as a tissue element which serves to isolate the ramifications of the neurones. LUGARO has put forward the interesting and suggestive view that the glia serves to transform the products of metabolism of the nervous tissues and to render them inoffensive—the peri-vascular glia thus acting as a filter. NAGEOTTE and BABES have both ascribed to the glia cells a secretory action in virtue of their derivation from epithelial cells.

2. *Changes in the Nerve Elements—Nerve Fibres and Ganglion Cells.*

REDLICH, HUBER, STORCH, and others have contended that the "noxa" acts directly and primarily upon the nerve fibre before there is any trace of glia proliferation or vessel alteration. This change may be purely degenerative or an actual inflammatory degeneration. The interstitial changes in the glia may be,

therefore, on the one hand, secondary to the parenchymatous degeneration, or, on the other, also productive—passing beyond the bounds of a substitution process. The view that the toxic agent has an affinity for myelin has been supported by numerous recent writers: *e.g.* MARBURG speaks of the process as essentially a "lecitholysis," and MOTT thinks it might be explained by the slow, limited, and localised action of some "lipolytic" ferment which attacks the myelin covering of the nerve fibres.

In our histological study it has been pointed out that numerous small areas occur in which there is no appreciable change but a demyelination of the affected tissue. This is well brought out in Weigert myelin sheath sections, but in normally-evolving areas it is more apparent than real, for sections stained by Heidenhain's iron-hæmatoxylin almost invariably show that in such small areas the slightest demyelination is accompanied by a commencing glia cell proliferation, which continued parallel to, or even exceeded in proportion, the destruction of the myelin sheath. On the other hand, numerous areas are present in which there is a complete absence not only of the myelin sheath but of all signs, in the presence of fat granule cells and proliferating glia cells, either within the area or at its periphery, of an extending process, and in such areas the abundance of the glia does not justify the name of sclerosis. Here, again, it is probable that varying factors have been at work to alter what may be looked upon as the normal evolution of a sclerotic area. Arguing, however, from the presence of such areas, I am in entire agreement with the view that the most constant and uniform change is the absence of the myelin sheath: this usually commences as an early swelling, varicosity, and faint staining, which passes into a finely granular degeneration.

The glia proliferation, in the great majority of the areas, is, therefore, called forth by two factors: it is immediately occasioned by the stimulant action of the "noxa" which caused the degeneration of the nerve fibre, and it is secondarily brought about by the degenerated products of the parenchyma. The latter effect is explained in part by the irritant action of these products and in part by the well-known conception of WEIGERT ("Wegall von Wachstumhindernisse") that the constituent tissues of an organ are usually in a state of equilibrium, so correlated to one another that no cell can disappear without its place being taken by hyperplasia of the surrounding tissue. THOMA has suggestively applied this conception to explain the comparative absence of glia in the cortical areas. He points out the importance of considering two factors in the sclerosis: (1) the proved resisting power that the ganglion cells and axis cylinders show, and (2) the non-resistance of the myelin sheath, and he thinks that these two opposing factors account for the proportionate development of a sclerosis. In the medullary rays and at the base of the radiations in the cortex, where the myelinated fibres lie close together, their extensive degeneration brings about a marked sclerosis, but in the actual cortical layers two unfavourable factors—few myelin sheaths and a trifling glia

content—meet with a resistant factor in the numerous ganglion cells and axis cylinders, so that there results a sclerosis so limited that numerous authors state that it does not exist in the cortex.

CAJAL and MARINESCO, in relation to the satellite cells of the grey matter, have also developed WEIGERT'S conception. It is maintained that the nerve cells and the glia cells develop parallel to one another, and that in the normal state there is established a nutritive equilibrium between these two elements. This equilibrium probably is maintained by the secretion of certain substances—elaborated by the nerve cell—which hinders the excessive development of the glia cells. The nerve cells and satellite cells, therefore, constitute a kind of symbiosis, but MOTT thinks that the proliferation of satellite cells seen in acute toxic conditions is due to a failure of assimilative metabolic processes in the nerve cells as a result of the poison. There is, therefore, more nutriment at the disposal of the satellite cells, and they are thereby stimulated to proliferation.

In the description of areas in the grey matter, it has been shown that the involved ganglion cells in the cortex were frequently surrounded by proliferating satellite cells of various forms with numerous fine black granules in their protoplasm and branching processes (osmic acid), and at other times almost replaced by nests of proliferated satellite cells. In the grey matter of the spinal cord, on the other hand, no such satellite cells were ever found, and the ganglion cells seem there to undergo simply a gradual atrophy.

3. *Blood-vessels and Lymphatics.*

The general agreement of the areas, especially of isolated cerebral areas, with the topographical distribution of the blood-vessels has long led to the belief that these were primarily affected in the diseased process. The changes in the vessels may be expressed, however, in very various ways: a chronic inflammation of the walls of the vessel may affect the nutrition of the area supplied by it: primary thrombosis or thrombosis secondary to irritation of the intimal lining, by toxins circulating in the blood, might lead to similar malnutrition: some effect, toxic or mechanical, on the intimal lining may lead to minute capillary hæmorrhages: a primary acute vascular change with peri-vascular cell infiltration — a true inflammation in the generally accepted sense of the term—might extend to involve the adjoining tissue: or, finally, the vessel wall changes might lead to adhesion and closure of the lymphatic sheaths with a subsequent lymph stasis in the tissues. Each of these views has its adherents, and it is necessary briefly to indicate the sequence of the changes.

RINDFLEISCH thought that the chronic changes in the vessel walls (the cause of which appeared to him quite unknown) was followed by an atrophy of the nerve elements from malnutrition and a secondary glia proliferation. It is evident that the areas in which such chronic vessel changes were found must have been old

sclerotic areas, in which the changes may be the effect of the sclerotic process and not its cause.

RIBBERT thought that the exciting cause of the inflammation circulates in the blood: that owing to its presence a clot is formed at some part of a small blood-vessel; and that at this point an irritation of the vessel wall is set up with a peri-vascular inflammation, which extends to involve the surrounding tissue—causing degeneration of the nerve fibres and an active proliferation of the glia. The liability to thrombosis after the acute specific infections is well recognised, and French writers especially have suggested that multiple thrombi form owing to an altered condition of the blood or of the vessel wall. In the area of supply of such vessels there would appear ischæmic degeneration, followed by phagocytic cells, and a substitution glia proliferation. It is pointed out that such areas, unless examined shortly after the thrombus formation, would reveal no trace in the vessel of the cause of the focal degeneration. Amongst recent writers SIEMERLING and RAECKE have attached considerable importance to the presence of capillary hæmorrhages. In all the areas examined by them, and especially marked in the cortical areas, were minute hæmorrhages which were looked upon as the first evidence of the inflammatory process, and the cause of the initial fibre degeneration.

During the course of this investigation, a large number of small isolated areas, both in the brain and spinal cord, have been cut in serial section with the object of tracing the possible presence of thrombosis or of capillary hæmorrhages. In a few instances, especially in the lateral vessels of the cord and medulla, there have been found aggregations of white cells and the presence of fibrin, which have been taken as indications of intra-vital thrombosis, but nowhere has evidence been present of organisation of such thrombi nor of alterations in the vessel walls in relation to them, nor have these been always in relation to sclerotic areas. Again, in close relation to the engorgement of the blood-vessels, both within and without the areas, small hæmorrhages have been found. These, however, show no changes, and were looked upon as probably the result of the respiratory difficulties before death. The vessel walls also showed no changes which would explain the hæmorrhages, nor were there any signs of inflammation around them. Keeping in mind the difficulties in recognising small thromboses after actual sclerosis has set in, and also the admitted long time that extravasated blood may remain unchanged in the nervous tissues, it is difficult to account for the origin of sclerotic areas in such primary changes. The absence of any histological evidence of changes in the vessel walls associated with thrombosis or hæmorrhages is quite incompatible with a primary vascular lesion in this sense.

To true inflammatory changes in the walls of the blood-vessels a primary significance has been ascribed by a very large number of writers. "In the early stages inflammatory alterations, with small-celled infiltrations, can be recognised in the vessel walls." "The primary vascular inflammation determines a peri-

vascular embryonic infiltration." "In recent areas the reactionary vascular phenomena are entirely out of proportion to the myelin degeneration." Such statements, asserting the primary inflammatory character of the lesion in the vessels, can be found extensively throughout the literature of this subject, together with statements which show that the "granular cell myelitis" is also taken as a proof of the presence of an acute inflammation in the vessel walls. The sequence of the process is either that the primary affection of the vessel wall is transmitted direct, by a progressive diffusion, to the surrounding tissues, causing a solution of the myelin and a reactive interstitial inflammation, or the agent causing the inflammation is restricted to the vessels and causes in these first of all alterations, through which are produced changes in the nutrition of the surrounding tissue, which are no longer inflammatory but purely degenerative.

It would *a priori* be thought natural that an irritative substance circulating in the blood would, in its filtration and diffusion into the tissues, stimulate the capillary endothelium and cells of the adventitia to proliferate, and that its first effect would thus be on the vessel wall through which it passed. In this investigation special importance was attached to this point, and a reference to the histological study will show that it was impossible to trace, except in rare instances, a primary proliferation of the capillary endothelium, or a primary increase in the nuclear content of the adventitia. The first cell infiltration of the vessel wall was one of fat granule cells in the adventitial lymph spaces, secondary to the resorptive processes: this called forth a secondary proliferation in the endothelial and other cellular elements of the adventitia, and at a later stage there was a cell infiltration of lymphocyte-like cells analogous to those found in all chronic processes. In the event, therefore, of a disease-producing agent, either bacterial or toxic, being carried with the blood or circulating in the lymph sheaths, it must be assumed that this poison leaves the blood channels in so slight an amount or in such weak concentration that a recognisable injury of the vessel wall does not result. The only part played by the blood-vessels would thus be the bringing of the "noxa" to the tissues. BIELSCHOWSKY, who looks upon the vessel changes as entirely secondary, has come to the conclusion that only a "noxa" that has penetrated by the vessel into the tissue but has left the vessel wall intact has occasioned the process. TAYLOR, who was unable to find any trace of vessel changes in the examination of eight cases of disseminated sclerosis, thinks that it is perfectly conceivable that the manifestation of the toxic agent may occur without evidence of local inflammation in the vessel wall. MARBURG and other writers, who have described cases of "acute multiple sclerosis," have given this designation instead of "acute myelitis," "in virtue of the absence of any marked signs of actual inflammation in the vessel walls." The explanation of the numerous findings of such inflammation by other writers must be found either in the presence of areas of an acuter type than were observed by me, or in the possibility that areas were described

at a stage when the secondary infiltration of fat granule cells and the cellular reaction to their presence had occurred.

Alongside of the vessel lesions and dependent on them, BORST, SCHMAUS, and other writers have described disturbances of the lymph circulation. The sequence of the process is a little difficult to follow, for the change may be evidenced by a slight œdema and rarefaction of the tissue around a vessel with a dilatation of its adventitial lymph spaces, or it may be marked by a closure of the lymph spaces and a lymph stasis in the tissues from obstruction to the return flow of the lymph. BORST thought that a chronic inflammatory meningitic change initiates the process, leading to a closure of the epi-cerebral and epi-spinal spaces of His; the blood-vessel changes, especially around the para-central vessels, cause a closure of the adventitial lymph spaces, leading to a dilatation of the peri-vascular lymph spaces, and, with increased distension, the formation of cysts. As the congested lymph passes into the surrounding tissue, there comes about a hyperlymphosis with the formation of "Lichtungsbezirke." The obstruction to the outflow of the cerebral-spinal fluid by the obliteration of the adventitial lymph spaces and the closure of the epi-cerebral and epi-spinal spaces are therefore the causes of the disturbed lymph circulation. The acute infection which precedes the disease is stated to give rise to chronic inflammatory and proliferative processes in the meninges and vessel walls. In dependence on the lymph stasis a swelling and degeneration of the nerve fibres in the "Lichtungsbezirke" is brought about, and a later compensatory growth of neuroglia. The present writer's views in regard to the changes in the lymphatics and meninges have been stated elsewhere, and it is necessary here only to note that in these observations, in uncomplicated cases, no alteration in the meninges to which any significance could be attached could be found. The chronic inflammation in the vessel walls, with a closure of the lymph spaces, is to be regarded as entirely a late change, so that while I agree with BORST that the fundamental basis of the process underlying disseminated sclerosis may probably be a flooding of the tissues with toxic lymph, I disagree with him regarding the mechanism by which this is brought about in the early stages. In late stages the condensed vessel wall, with adhesion of the adventitial spaces, on its side may contribute to the production of a vicious circle in which hyperlymphosis plays a part.

It is thus seen that I am in more or less disagreement with all the views related to the primary nature of the vascular lesions.

(3) THE ETIOLOGICAL FACTORS.

In turning now from the nature and origin of the process to its determining cause, we find that there is no positive knowledge of the nature of the agent causing this disease. The etiological factors postulated may be discussed under two groups: developmental and external.

1. *Developmental.*

In the discussion of the pathogenesis it was shown that MÜLLER based his view overwhelmingly on the presence of an endogenous (developmental) process, under which naturally lay endogenous factors—inborn defects. One weak point in his arguments, however, lies in the fact that the evidence of congenital anomalies in the anamnesis is hard to find, or completely absent. Groups of cases occurring in families also have only been reported in one or two rare instances, and in this connection it must be remembered how great is the difficulty in the differential diagnosis between disseminated sclerosis and certain atypical forms of hereditary disease, and, further, that such cases might be family diseases with a symptom-complex like that of disseminated sclerosis. Again, cases of congenital multiple sclerosis are even more isolated. A neuropathic disposition has been alleged as an important etiological factor, but this association has not been substantiated, and where present no causal significance has usually been ascribed to it. Most observers note that patients were normal both physically and mentally.

MÜLLER, in answering this argument of the absence of family forms and neuropathic stigmata, points out that syringomyelia and glioma, attributed by numerous writers to congenital disturbances of development, have also no hereditary forms, and that heredity in nervous disease is seen chiefly in disease of the true nervous elements rather than in congenital anomalies of the glia. NONNE, who has examined the phenomena of inhibition of cobra poison hæmolysis in organic diseases of the central nervous system, states that this cobra reaction is specially frequent in the psychoses which are claimed as types of endogenous etiology. As he has found it present in disseminated sclerosis more frequently than in any other organic disease of the central nervous system, he claims that this reaction supports the view of the endogenous nature of the disease. NONNE himself, however, gives indications in his paper that this result must be accepted with great reserve, for the reaction is found in general paralysis, admittedly an acquired disease.

FÜRSTNER and others speak of "an early invalidity of the central nervous system," which is unloosed by later accidental factors. It is evident that such views do not bring the solution of the problem much nearer, yet it must be admitted that in some cases "congenital anomalies of development may be present in the sense that they lay the foundation of the constitutional tendency which renders the individual more susceptible to the injurious influences of later life" (MOTT). Such anomalies may be insufficient to give rise to any symptoms till the onset of these later factors, but they indicate a diminished resistance or a diminished vitality of the nerve elements such as GOWERS postulated for Friedreich's ataxia ("abiotrophy").

2. *External Factors.*

Among the more immediate factors must be considered the following: trauma (physical shock), psychical shocks, chills, infections, and intoxications. Modern

conceptions of disease do not admit of primary importance being attached to the influence of cold, injury, strain, and emotion in the production of diseases of the nervous system, but such influences, recent or remote, are repeatedly brought into relation to the onset of such diseases. As a rule we cannot go beyond the "post hoc ergo propter hoc" argument, for there are no other data available, yet it is necessary to consider briefly whether the histological data throw any light upon the mode of action of such influences, which are at least admitted to bring about a lowered resistance of the nervous system to the causal agent.

(*a*) *Trauma.*—Slight degrees of dystocic lesions of the infantile spinal cord may lead frequently to slight degrees of hæmorrhage, and it is thought not improbable that these may be the basis of the diseases of the spinal cord which are related to the formation of multiple areas of sclerosis, or to the formation of cavities and later syringomyelia. MENDEL is one of the principal advocates of the traumatic etiology of disseminated sclerosis. He believes that as a result of the trauma an impulse of movement is transmitted to the cerebro-spinal fluid, that this leads to pressure effects in the most delicate channels of both brain and spinal cord, and that through these alterations of pressure there may occur minute ruptures (of capillaries) and hæmorrhages. From the assumption that small hæmorrhages are sufficient to evoke symptoms of disease, there justifiably follows, therefore, the view that in the case of cerebral and spinal "commotio," intra-medullary hæmorrhages are responsible for the symptoms. That the symptoms frequently pass away rapidly must be ascribed to a rapid resorption of the poured out blood, but SCHMAUS argues from the fact that, since permanent disturbances frequently remain after shock, processes of degeneration in the nerve elements, which are beyond our present methods of recognition, have occurred. Hence his expression "molecular alteration of the nerve elements." The slighter degrees, he thinks, lead to transient symptoms, the severer to focal areas of degeneration, which thus have their rise in a molecular alteration resulting from "commotio."

The assumption of a molecular alteration of the nerve elements is hypothetical, since it does not rest on demonstrated microscopic findings at the time, but in the opinion of many writers intra-medullary hæmorrhages or outpourings of lymph into the tissue, of traumatic origin, may be followed by swelling and degeneration which lay the foundation of a "locus minoris resistentiæ" for toxic infective agents. It is also thought possible that in such damaged areas, still capable of functioning, the damage may be completed by any other factors which lower the resistance of the tissue. In relation to multiple hæmorrhages, it is relevant to mention the view put forward by TAYLOR and others, that at least a portion of the spinal cord degeneration found in some cases of pernicious anæmia is due to primary focal degenerations caused by hæmorrhages similar to those which occur in the retina and elsewhere in this disease. In the literature on disseminated sclerosis there are several cases reported in which the association between trauma and the onset of the disease was

a very close and striking one, but, as a rule, the association was questionable, and frequently some slight disturbance, such as giddiness, the symptom of an already-existing disease, was the cause of the accident. WOHLWILL requires the following conditions before there is proof of a causal connection between disseminated sclerosis and trauma: (1) that the individual was previously healthy; (2) a not too short and not too long interval between the accident and the first symptoms; and (3) a somewhat severe trauma from which one might expect injury of the brain or cord.

It has been already noted that in this investigation there was no evidence for the existence of capillary hæmorrhages, except those probably pre-agonal ones, due to respiratory difficulties. There are few positive data for the further fate of spinal hæmorrhages, and from those which we have as to the length of time taken in the absorption of cerebral hæmorrhages it is necessary to be cautious as to the conditions in the cord. The remains of such may continue to be evident for a very long time—often with no sign of degeneration or softening around them.

(*b*) *Psychical Shock.*—The influence of severe terror and other marked emotions has often been related not only to the onset ot the disease, but to a relapse or the aggravation of a present condition. A possible explanation may be found in the sudden changes of the circulatory conditions in the nervous system occasioned by such influences as act specially on the vaso-motor system. The profound influence of the vaso-motor system in the production of disease has scarcely been recognised, and in a later section its possible mode of action in disseminated sclerosis will be considered.

(*c*) *Chills.*—KRAFFT-EBING has attributed considerable etiological significance to chills. In forty out of a hundred cases he traced this factor, and represents the relationship between the two in the contraction of the vessels favouring ischæmic degeneration of nerve fibres in localised areas—especially if collateral anastomoses were absent.

In regard to cold, fatigue, and psychical influences, it is probable that these act as immediate factors by lowering the vitality or the resistance of the individual or in allowing, through vaso-motor influences, the emergence of a toxin already circulating in the blood. In the case of trauma, the possibility of the actual rupture of capillaries or of lymphatics must be admitted, and the consequent hæmorrhages or the toxic lymph thus admitted in sufficient concentration into the tissues will effect the primary degeneration of the nerve fibres and a secondary proliferation of glia.

(*d*) *Exogenous Intoxications.*—OPPENHEIM has laid special stress on the influence of lead, copper, and zinc, also of alcohol and carbonic oxide, and has met with such causes in eleven out of twenty-eight cases of disseminated sclerosis. He speaks also of a toxi-pathic tendency inherited by the children of workers in lead and other metallic poisons. HOFFMANN, however, in an analysis of a hundred cases, found lead present as a factor in only one patient. It is evident that some more general causal

agent must be at work, although such intoxications may be important as predisposing factors in the production of a toxic arteritis.

(*e*) *Infections and Endogenous Intoxications.*—Toxi-infective agents have long been held of primary importance. PIERRE MARIE has urged the recognition of acute infective disease as the actual final cause of disseminated sclerosis, which he believes arises on the basis of multiple inflammatory vessel alterations brought about by the infective agents of scarlet fever, measles, diphtheria, small-pox, puerperal fever, pneumonia, erysipelas, typhoid fever, cholera, etc., in combination with the organisms which produce a mixed infection. Many other writers have favoured the view of the relation of acute infectious disease to disseminated sclerosis, but HOFFMANN has strongly opposed it, and KRAFFT-EBING in an analysis of a hundred cases found this factor in the anamnesis only six times, and no organisms that can have any causal relationship to the disease have ever been identified, either in the blood, the cerebro-spinal fluid, or the tissues.

Malaria.—Several cases of disseminated affection of the central nervous system in consequence of malarial infection have been reported, chiefly by SPILLER and by Italian writers. These arise probably on the basis of a mechanical closure of the cerebral and spinal vessels by the parasites which form solid thrombi. This merely shows that malaria may be followed by a disseminated disease of the central nervous system, and such cases tend to recover more surely than cases of true disseminated sclerosis.

Tubercle and syphilis are both generally admitted to have no significance in the etiology. Syphilis may produce disseminated areas in the central nervous system, but the histological characters of these have, as a rule, nothing in common with those of disseminated sclerosis, in which disease also the reactions in the serum and in the cerebro-spinal fluid and the cytological examination of the latter are all negative.

Endogenous intoxications are of a very varied nature, and include not only the toxins engendered within the body by bacteria, but also auto-toxins caused through abnormal metabolic or assimilative processes and those the result of deficient or abnormal secretions. Systematic investigation of metabolic changes in disseminated sclerosis have not yet been undertaken, nor has any toxin of any nature been isolated either from the blood or the cerebro-spinal fluid. Investigations of the bio-chemical changes, analogous to those found in para-syphilitic affections, have thrown little light on the disease, but investigations along this line have not been extensive.

It is the unsatisfactory and contradictory result of each of the above-mentioned factors that has led numerous writers to seek for one common cause which will explain the real nature of the disease. KLAUSNER, in a careful analysis of a hundred and twenty-six cases of disseminated sclerosis, has come to the conclusion that few of the alleged causal factors are of any importance. MÜLLER, from the large number of causes postulated, has drawn the inference that none of these can be the essential

one, and therefore feels justified in falling back on his view of a developmental cause to which any of the other factors may be an exciting agent. FRANÇOIS, also, believes that only this congenital degenerescence of the central nervous system can explain the characteristics of disseminated sclerosis, and that infectious disease, chill, trauma, etc., allows this to come into play. It has already been pointed out that the assumption of the developmental genesis of the disease is insufficiently founded, and such a conception must appear, in the light of modern pathological knowledge, untenable, and justifiable only when every other factor has been eliminated.

The essential problem, then, lies still before us: What is the nature of the special stimulus which originates this process? In the attempt to answer this question it is important to remember that the causal factor must be in operation over long stretches of years, allowing remissions of the disease and relapses. It would, therefore, appear necessary to exclude those agents which actually attack the organism and then disappear rapidly. It is admitted by all, except the supporters of the developmental nature of the process, that the topographical distribution of the areas points to the blood-vessels or their lymphatic sheaths as the route of conveyance of this agent, and the assumption of an infection or intoxication harmonises with this relation to the blood-vessels.

In spite of the absence of any positive evidence for the presence of bacteria the organismal cause of disseminated sclerosis cannot be excluded, especially in view of the conditions existing in syphilitic and para-syphilitic affections on the one hand and poliomyelitis on the other. It has just been stated that the clinical and anatomical picture requires that the agent must be one whose influence extends over many years. We know that in syphilis we have an actual living organism remaining present in the body for years, therefore the chronic and variable course of the disease in disseminated sclerosis is not against the assumption of an infectious genesis. But with none of the acute infectious diseases which have been considered by PIERRE MARIE as etiological factors can we assume that the organism is preserved in activity in the central nervous system, and the supposition that in consequence of these infective diseases mixed infections, with persistent micro-organisms, establish themselves rests on no sufficient proof.

In acute poliomyelitis the earliest changes described in the nervous system are hyperæmia, and a collection of small round cells in the peri-vascular spaces of the blood-vessels of the soft membranes: this peri-vascular cell infiltration flows along the vessels as they enter the cord and reaches its height in the grey matter around the branches of the central vessels. Together with this cell infiltration there is marked œdema and the presence of minute or extensive hæmorrhages. These three features are all dependent on inflammatory vascular changes, and may be regarded as the primary reaction of the nervous system to the virus of poliomyelitis. Again, as a result of the acute infective diseases, we may get an acute infective myelitis, and probably one portion of the cases ascribed to disseminated sclerosis, following such

conditions, must be ascribed to true acute myelitic conditions, for PIERRE MARIE regarded the primary participation of the blood-vessels as an anatomical proof of his clinical theory of the relationship. Cases of acute infective infiltrative myelitis, with organisms present in the foci, have been described by PURVES STEWART and others, and there are also other cases in which it is impossible to state the exact nature of the infection. Further, the experimental investigations of MARINESCO, HOCHE, HOMEN, SALLE, and others have corroborated the organismal cause of certain forms of myelitis by the production of focal areas of infiltrative myelitis as a result of the infection of micro-organisms. These writers believe that organisms exert their action primarily upon the wall of the blood-vessel.

The forms of myelitis have been classified by TAYLOR and BUZZARD as infective, toxic, and syphilitic. The last-named variety shows changes which we have already noted as being readily recognised, and as quite distinct from the changes in disseminated sclerosis, so that it need not be further considered. The experimental work we have above referred to has shown that areas of infective and toxic myelitis may be produced by a number of bacteria and bacterial toxins, and a comparison of the histological changes in the two forms with those of similar conditions in man gives the following as the general differential histological characteristics. In infective myelitis we have dilated and engorged vessels, with an excess of nuclear elements in the adventitial sheath, probably derived from the proliferation of the structural elements of the adventitia rather than from the blood (TAYLOR and BUZZARD). Later there is proliferation of the glia elements and changes in the nerve cells and fibres, partly due to œdema and to the vascular changes, and partly to the toxic products of the invading organisms. In toxic myelitis, on the other hand, the changes are much less marked: the patchy areas of degeneration are unaccompanied at first by any cell infiltration of the vessel-adventitia or of the tissue, and there is, as a rule, marked swelling and varicosity of the axis cylinder and myelin sheath. The later reactive changes in the glia depend on the intensity of the primary change.

From the evidence of an infiltrative poliomyelitis, caused by the virus of poliomyelitis; from the recorded cases of acute infiltrative myelitis in man; and from the experimental production of infiltrative myelitis by bacterial injection into animals, it is natural to assume that organismal infection is more often associated with primary inflammatory (proliferative) changes in the blood-vessel walls. TAYLOR and BUZZARD, however, point out that some organisms may at one time and under certain circumstances determine an infiltrative form of myelitis and at other times a toxic, and that we are not fully acquainted with the laws which govern such different results. It must also not be forgotten that toxins circulating in the blood or lymphatics may also produce lesions first in the vessel walls; the work of ORR and ROWS has definitely proved that a cellular reaction in the adventitia may be due to a chronic lymphatic intoxication—the presence of numerous plasma cells in this reaction is the expression probably of a chronic inflammatory process. The balance

of evidence, however, goes to prove that an infiltrative myelitis is usually due to an organismal cause, and most workers conclude that areas of necrosis, without cell infiltration and independent of vascular thrombosis, must be ascribed to toxic influences. The toxic myelitis of pregnancy may be given as an evidence of the result of an auto-intoxication which is often responsible at the same time for serious trouble in connection with the cardiac and renal functions.

Turning now to the histological data previously given, it will be recalled that the conviction has been expressed that nowhere was there evidence of a primary vascular inflammation, but that the first evidence of cell increase in the adventitia was an infiltration of fat granule cells consequent to resorptive processes, that the subsequent proliferation of adventitial cell elements was secondary to and probably caused by this infiltration, and that only at a still later stage was there an infiltration of small lymphocyte-like cells analogous to those found in all chronic processes. It has been further stated that the histological observations lead to the conclusion that the stimulus acts primarily on the myelin, and almost simultaneously on the glia cells, surrounding the blood-vessels. The changes which have been outlined in a normally developing "early" area are thus much more nearly allied to those of a toxic myelitis than those of an infective myelitis, and differ from the former only in degree.

In the absence, however, of any definite proof of such a toxin either in the blood or cerebro-spinal fluid, other evidence must be submitted with great reserve. The example of general paralysis, in which disease NOGUCHI has demonstrated the presence of the spirochæta pallida in the cortex, but which formerly was ascribed to a chronic toxic encephalitis of lymphatic origin, must serve to show how quickly views regarding the pathogenesis and etiology of a disease may require to be modified. In this instance, however, it may be stated that the most recent writers on this subject, M'INTOSH and FILDES, look upon the inflammatory reactions—peri-vascular infiltration of lymphocytes and plasma cells involving the vessels of the pia and those that penetrate the cerebral substance; "primary degeneration" of the neurons; and proliferation of the glia—as all due to a primary reaction to the spirochæta pallida and not primary or secondary to one another: while NONNE (quoted by those writers) looks upon the lesions not as the direct result of the activity of the spirochæta pallida but as due to the action of the toxins, derived from them, which have a special affinity for nerve areas.

The important point, however, in relation to disseminated sclerosis is that experimental work has proved that circumscribed areas may be attacked by toxic materials, and that in such areas the first effect is on the nerve fibres and interstitial tissue surrounding the blood-vessels and only secondarily on the vessel walls themselves. The causal agent must be a weak one compared to the usual agents which produce toxic myelitis, for there is evidence of a slow, often limited and localised action, and the subacute onset in the relapses again argues for its slight intensity. For such a chronic course as disseminated sclerosis usually runs, with

many remissions, the "noxa" responsible must remain constant in the body, lead at certain periods to relapse, or even remain latent for a long period. The assumption of an auto-toxin agrees with this demand, and the example of pernicious anæmia in which the remissions may probably be traced to the result of absorption into the portal tract of some poisonous substances may serve as a possible analogy. The assumption of an organismal stimulus moving about in the body or malignantly stored in depôts such as the spleen or bone-marrow, or of the elaboration products of such organisms continually reforming and leading to new symptoms, would also agree with this demand. It is impossible to say that this is improbable, for the relapses in malaria and relapsing fever coincide with the reappearance in the circulating blood of free sporocytes of the malarial organism or of the spirillum of OBERMEYER, respectively: such relapse is therefore a re-infection from within (AINLEY WALKER). In para-syphilis, also, it must be supposed that the specific organism in some form enters the central nervous system, remaining latent for years either in the lymph vessels or in the brain tissues proper, and exerting its effect either by its direct action or by its toxins. The influence of such factors as infectious diseases, cold, trauma, etc., would thus be to produce an impairment of the nervous tissues, and so predispose them to degeneration from auto-toxins and other causes: or the lowered body resistance would allow of sufficient concentration of the toxin, through deficient elimination: or a combination of both factors, impairment of the tissues and an increasing intensity of the "noxa," probably acts in varying degrees in every case.

The views that have been put forward as to the source of the possible "auto-toxin" can be only briefly touched upon. MCCORMAC suggests that disseminated sclerosis is due to physico-chemical causes, which may be in operation for a long time, and thinks that as indol, skatol, and phenol—toxic products of intestinal putrefaction—might produce structural changes in the liver which are followed by nervous symptoms, it is possible that actual structural changes might occur in the nervous system itself. BRAMWELL suggests several possibilities: the toxic agent may be the result of deranged metabolism, possibly in the liver or some other organ, or it may be generated in and absorbed from the gastro-intestinal tract, as is probable in pernicious anæmia. The effect of exposure to cold in the production of hæmoglobinuria is explained by the probable rapid production of some toxic substance, the result of deranged metabolism. It is thought that the exposure to cold acts reflexly through the nervous system on some central organ—perhaps the liver—and produces a poison which is the cause of the rapid destruction of red blood cells, and that disseminated sclerosis might be the result of a chemical poison similarly formed. Another possibility is that the agent may not be a toxin properly so-called, but that the composition of the blood is so altered that some substance or substances necessary for the nutrition of the nervous tissues, especially the nerve fibres, is absent, or that the blood contains some substance

which acts injuriously on the nutrition of the nerve fibres. DIXON MANN thinks that disseminated sclerosis is due to an unknown autogenous toxin, which probably acts by setting up changes in the ultimate vascular supply of the part affected.

(4) THE MODE OF ACTION OF THE CAUSAL AGENT.

It must have been noted that as this chapter has progressed we have got deeper into the realm of theory. In discussing the nature and the origin of the process there were certain definite, though restricted, data to go upon: in regard to the final causal factor there were few data, but the hypothesis of a latent organism or a circulating toxin rested on certain analogies: and when we come to discuss the mode of action of this causal agent, and the further questions which this consideration presents, it is seen that in relation to some at least of these questions recourse has been taken still more to analogy. Yet it is necessary, at least, to state what these questions are, and, at most, to indicate briefly any reasonable explanation that has been put forward to answer them.

The principal questions which present themselves in this section may be stated thus:

1. Why and how is the process so irregularly distributed and at first circumscribed?
2. What is the cause of its further advance?
3. What factors cause modifications in its mode of action?
4. By what route, blood or lymph channels, is it conveyed to the nervous tissues?

1. *Its Irregular Distribution and Circumscription.*

If we could trace the disease to the entry of corpuscular elements, such as bacteria, or, thrombi infected by such, or emboli, there would be no further difficulty in accounting for circumscribed vascular areas being irregularly attacked. If it is not, however, a question of the immediate action of bacteria at an identical point, but probably of toxins circulating in the blood, how is it that these agents in solution in the blood choose such irregularly distributed spots?

From the frequent presence of a central larger vessel in the area it has been assumed that this vessel, by some alteration in its walls, limited to a certain definite stretch of its longitudinal course, was responsible for the sclerotic area. STRÜMPELL and MÜLLER, who opposed the view of the rôle ascribed to the vessels in the process, naturally found in this an argument in their favour, for they found it difficult to perceive how toxins could diffuse from such a large vessel instead of following the capillary area of ramification. It seems to me that MÜLLER has missed the significance of the vessels largely because he has preferred the cord areas, which do not allow these relations to be so readily recognised; but, on the other hand, it is probable, as has been frequently shown in the histological study, that it is not a question of one central vessel but of many transverse and oblique vessels, giving

the impression that not one single vessel but the branches of a blood-vessel stem are the starting-point of the process. Serial sections have frequently given definite proof, as the area was followed up, that it broke up into individually distinct smaller areas, which were related to the component branches of the previous central vessel. These sections, again, showed the gradual fusion of such areas around the ramifications of a vessel, and marginal strands of myelinated fibres still left between each primary focus. It must not be forgotten, however, that the whole vessel territory need not be attacked, and, on the other hand, that the area of ramification of non end-arteries has no sharp definition. The peri-ventricular areas, which we trace to the involvement of the terminal branches of the central arteries, which spread out on the ventricular surface, are a striking illustration of the implication of the area of ramification of end-arteries, and an instance equally marked is the demyelination of the surface layers of the cortex corresponding to the area of supply of the smaller cortical vessels.

The difficulty of understanding how a "noxa," *e.g.* a circulating toxin, in the circulation could assert itself in the immediate area of a large vessel, for a limited distance—so far as it had not to do with an actual disease of the vessel wall itself—rather than in the region of the capillaries which are distributed everywhere, has led numerous writers to fall back upon the assumption of a special predisposition of these areas either in the form of congenital defects or acquired "loci minoris resistantiæ." Such a predisposition was also held to explain the frequent symmetry of the areas, but this is again more readily understood if we admit, as the histological evidence favours, that it is the area of distribution of the vessels, which may naturally be of very varying extent, that is affected. Such a view, however, removes only a portion of the difficulty. If certain areas of distribution, large or small, are affected, what factors determine the exact areas chosen? For this no satisfactory explanation has been suggested, but certain analogies may be given.

In peri-axial neuritis in man, the result of chronic lead-poisoning, not only is the radial nerve picked out, but certain discontinuous areas are primarily affected in a manner very closely resembling the discontinuous myelin sheath degeneration in disseminated sclerosis. GOMBAULT and STRANSKY have also experimentally produced similar discontinuous areas in subacute lead-poisoning in animals. In these cases the toxin circulating in the blood is known to affect only certain irregularly distributed areas. The selective action of toxi-infective agents on particular parts of the nervous system may be further illustrated by the action of the virus of syphilis and that of rabies; by the effect of arsenic and that of the neurotoxin formed by the diphtheria bacillus, on certain nerves; and further, by the tetanus toxin, which like strychnine, acts mainly on the synapses of the reflex arcs of the brain stem and spinal cord, reducing their resistance.

Further, the combined degenerations found in pernicious anæmia, cancerous cachexia, diabetes, and the sclerosis found in chronic ergot poisoning, pellagra,

beri-beri, and other conditions, pick out the posterior columns, or both posterior columns and the posterior part of the lateral columns. In pernicious anæmia, at least, MINNICH and NONNE have traced such degenerations to primary focal areas in the posterior or lateral columns: such areas, later, either from the cumulative effect of several foci at different levels in relation to the same strands of fibres, or from the later involvement of the axis cylinders, are succeeded by secondary degeneration. In such conditions the toxin postulated must choose out certain definite vessel territories, and the symmetry is explained by the two halves of the cord being exposed to the same diffusely acting agent. Numerous writers, however, suggest that prolonged toxæmic states lead to primary degeneration of those parts of the cord which are apparently more sensitive to trophic disturbances, and either that the posterior and lateral columns have a poorer vascular supply or that, as the parts most affected are the neuraxons of the posterior spinal ganglia and those of the cortical motor cells, therefore the long terminal filaments of the cervical and dorsal cord, they are far removed from the influence of their trophic cells. When it is urged that certain areas of the nervous system may have a "general non-resisting power," it can be understood how such functional factors as overstrain may affect definite strands and areas, related to definite functions, but this view, however unsatisfactory and unconvincing even for such conditions as cause combined column degeneration, carries no weight when related to areas with the haphazard distribution found in disseminated sclerosis, for one of the characteristics of the disease is that the areas bear no relation to any functioning tract or group of cells.

The sequence of events in disseminated sclerosis is probably that in the circulating blood the "noxa" escapes from the capillaries and transition vessels, and acts upon the tissues in the sense that the area of supply of the vessel is affected, *i.e.* it passes over into the tissues with the nutritive fluid. Numerous recent experiments on man and animals tend to prove that, in general, drugs administered by the mouth or subcutaneously do not pass into the cerebro-spinal fluid, and MOTT has pointed out the significance of LEWANDOWSKY'S observations, which show that very much smaller quantities of these same drugs and bacterial toxins injected into the cerebro-spinal fluid of the sub-arachnoid space produce much more marked and a more rapid onset of symptoms. These and other observations are taken to prove that toxic substances are unable to pass from the capillaries into the lymph spaces of the nervous tissue. GOLDMANN'S investigations on the central nervous system by vital staining show that vital stains, if introduced by means of subcutaneous or intravenous injection, are kept back by the choroid plexus: that from the plexus the cerebro-spinal fluid receives important metabolic products which are carried to the nervous tissues by the fluid; and that the plexus possesses the power of protecting the fluid, and in this way the nervous substance, from the penetration of toxic substances. The rôle of toxins in the production of

nervous disorders has long been recognised, and also the rôle ascribed to the secretions of the protective organs of the body—amongst which must now be enrolled the choroid plexus—in neutralising the products of auto-intoxication. A defective function of these organs will cause an accumulation of such toxins in the body, which will immediately react on the nervous system. ORR has shown how such a primary intoxication may so lower the resisting power that micro-organisms and their toxins may gain access to the blood-stream.

Unless we admit, however, that such substances circulating in the blood can pass from the capillaries, how can we explain the action of poisons on the nervous system? WILLIAMSON attributes considerable importance to the cell walls of the capillaries and lymphatics of the central nervous system in reference to the pathology of disseminated sclerosis. He believes that the cells of the capillary walls act as true secreting cells, and when they are stimulated there is an increased flow of lymph into the surrounding tissue. Certain substances, such as toxins produced by micro-organisms, have the power of stimulating the endothelial walls, and as the endothelial walls of the central nervous system of capillaries and lymphatics are extremely delicate and active, the lymph flow is great. Numerous writers suggest that the toxins produce an unrecognisable injury of the vessel wall by which it becomes more permeable, and thus allows of the increased transudation of the lymph. Others think it possible that a transient paralytic dilatation of the vessels permits an exudation, which in other conditions does not pass through the vessel wall or is arrested by the glia filter. The conditions of the cerebral circulation are so little understood, and the vaso-motor mechanism so complicated, that such an irregular and localised vaso-motor action may be quite possible. The presence of large areas of demyelination, such as those seen in Case II, in which every level of the cord showed an almost complete transection, gave the impression, however, that such an extensive demyelination is preceded by acute vascular dilatation, and that the tissues are flooded with toxic lymph which has caused a rapid solution of the myelin. The dilated vessels found in all the "early" areas might also argue in favour of a persistent paralytic dilatation from want of vascular tone in the area.

None of these suggestions explain why certain areas are chosen while adjoining areas of distribution are, at least primarily, unaffected, and it may be that its causation has appeared unnecessarily mysterious and that it is quite analogous to the irregular distribution of other processes, *e.g.* the haphazard distribution of areas in experimental toxic myelitis or the atheromatous patches on vessel walls. It cannot be supposed that the tissues are in a state of proportionate equilibrium or equal resistance, and that there are not varying degrees of oscillation and pressure and permeability in the vessels. The filtration from the vessels, including whatever part secretory processes may play in the passage of the lymph through the vessel walls, may thus be related to alterations, the nature of which are as yet little understood, but which have a place in the normal mechanism of the body.

The frequent sharp delimitation of the primary isolated areas gives the impression that the spread of the process is in the nature of the diffusion of a toxic substance which spreads from a central focus till it exhausts itself. WILLIAMSON puts forward a very suggestive view of the causation of this characteristic. The margin or outline of an area is noted as passing through the structure of the brain or cord substance regardless of fibre tracts, nerve cells, or vessels. He suggests that this is due to the infiltration of the nerve tissue with a fluid of destructive character, the shape and margins of the area being determined by physical conditions, since patches of similar form can be produced when stained fluid is allowed to infiltrate the cord (post-mortem) from various points.

2. *Further Advance of the Process.*

The ebb and flow of the symptoms are, clinically, amongst the most characteristic features of the disease, and, anatomically, "early" areas are the expression of this recurrence of a long-standing disease. When the primary direct effect of the causal agent has become exhausted the areas become sclerosed, and in such cases there may be a true remission, but frequently in addition to "early" areas there are found at the periphery of the old areas indications of an advancing process. This may be due to the persistence of the action of the primary agent, or to the fact that the products of degeneration had caused a secondary reaction after the infective or toxic agent had ceased to work, or, possibly, to a new process surrounding the older one. Such recent areas show that the morbid agent persists in the organism. MÜLLER has urged that the similarity of the basal features of the clinical and anatomical pictures points to one common cause of the disease: he thinks that we cannot assume that, for example, the toxi-infective agents of the acute infectious diseases, *i.e.* of so different a nature, will always lead to one and the same definitely characteristic disease-picture. A similar view has been upheld by numerous writers, and, in the absence of any specific organismal or toxic cause, an explanation has been sought for along very varied lines. REDLICH thinks it possible that the characteristic symptom-complex is caused by the "general functional injury" to the nervous system: that the acute infectious disease, whose cause we otherwise look upon as specific, may yet produce a definite metabolic disturbance, which, in its action upon the central nervous system, is specific. MARBURG also looks upon disseminated sclerosis as a "meta-infectious" disease in this sense. Such a term seems justifiable in view of the use of the term meta- or para-syphilis in which it was believed that the syphilitic virus induced in the body profound metabolic changes. MOTT has pointed out that these resulted in a large amount of lipoids occurring in the serum and in the cerebro-spinal fluid: that these same lipoids are found in the normal body fluids, so that the specific character is thus manifested by quantity rather than by quality. The relations of syphilis to the para-syphilitic affections are of special interest in relation to the possibility that a latent organism

may be the cause of disseminated sclerosis. Before NOGUCHI'S discovery of the spirochæta pallida in the cortex, MOTT and SEWELL had defined these relations thus: (1) the syphilitic organism is in itself the causal organism; (2) there is produced within the body as the result of syphilis a toxin, and this post-syphilitic toxin is the cause; or (3) syphilis produces an impairment of the nervous system and so predisposes it to degeneration from auto-toxins and other causes. It is in this final sense we look upon REDLICH'S and MARBURG'S conception—that acute infectious diseases of very varied etiology may produce once for all a specific impairment of the nervous system, and so predispose it to degeneration from auto-toxins. It has also been suggested that the original agent may cause, in addition to the evident areas of degeneration, alterations in other portions, and that these later, not from a persistence in the organism of the causal agent, but from excess of function, strain, or circulatory disturbances, may degenerate. Again, that the presence of degenerative processes in the central nervous system may suffice in themselves for the production of further areas of degeneration. For either of these views there is no foundation nor analogy. In the absence, therefore, of any positive evidence as to the determining factor, it can only be presumed that relapses are due either to the intermittent evolution of a toxin, or to an unknown organism which, in the interval between a remission and a relapse, lies latent and inactive. The causation of pernicious anæmia, as we have seen, is thought to be due to the similar intermittent evolution of a toxin, and the discovery of the spirochæta pallida in the cortex in general paralysis is a sufficient analogy for the latter alternative. MOTT has suggested that this organism may exist in a latent, granular, or intracellular form in the parenchyma of the nervous system, where it cannot be reached by drugs such as arsenic, mercury, and antimony.

3. *The Factors which cause a Modification in the Action of the Causal Agent and the Relation of the Process to Acute and Chronic Myelitis.*

The variations in the histological picture have been ascribed by different writers to two main causes: the fact that the process was observed at different stages, and to the different nature of the etiological factor in individual cases. Apart from such basal differences and from the variations due to the influence of complications, there are modifications in the development of the process which can be attributed only to the fact that its progress, assuming one common causal factor, is not always typical, uniform, and progressive.

AINLEY WALKER, in discussing the relative changes in the tissue elements in inflamed areas, points out that stimulation and injurious irritation differ only in degree, and that whatever is capable of causing injury will, if sufficiently diminished in intensity, exert a stimulant action. On the other hand, stimulation, if sufficiently intensified or long maintained, becomes irritation and produces injury. He further points out that one and the same agency may have a different effect on different types

of cells, or even on different cells of the same type. The changes which occur in the tissues of inflamed areas are, therefore, of two types, degenerative and regenerative respectively. Both of these occur simultaneously in different orders of cells, *e.g.* the parenchyma of an organ may undergo degenerative change while its connective-tissue basis is proliferating. If we apply this to the changes in disseminated sclerosis, we can conclude that "there are certain principles underlying the inflammatory process which enable us to recognise in it different degrees of one process rather than several independent series of reactions." This shows that a common cause, according to the intensity and duration of its action, may produce a very varying picture.

If we assume as the causal agent in disseminated sclerosis a circulating toxin, it has been stated previously that this toxin must be in such weak concentration that it produces no recognisable injury on the vessel wall in passing through it. This weak toxin is further assumed to have an affinity for myelin, and it produces, in the immediate neighbourhood of the vessel from which it has passed out, a simple primary degeneration or solution of the myelin, with a proportionate reaction on the glia—thus its injurious action is exercised on the myelin sheath, its stimulant action on the glia. As this diffusion extends and the toxin mixes with the tissue fluid and becomes more dilute, its stimulant action would be more in evidence, and when the toxin tends to exhaust itself, *i.e.* at the peripheral zone of the primary area, there would be a solely stimulant action on the glia, an action which extends, therefore, beyond the area of degeneration of the myelin. This stimulant action of the toxin seems to us to account for two of the histological data brought forward by MÜLLER in evidence of a primary glia change: (1) that at the periphery of the area we have a glia nuclear proliferation; and (2) that this extends between the normal myelinated fibres at the margin of the area. These two data may possibly be partly explained by the secondary glia proliferation occasioned by the degeneration of the nerve fibres, but for our present purpose it is necessary to emphasise the stimulant action of the primary causal factor on the glia—a stimulus which increases according to its dilution. The development of such an area is that pointed out in tracing the evolution of an area through a stage of fat granule cell myelitis.

If we assume, further, that the concentration of the toxin is still more dilute from the commencement, the degenerative action on the myelin would be almost in abeyance, and the stimulant action on the glia would be its sole effect. A slowly-increasing glia hyperplasia could then result, which would lead secondarily to a myelin degeneration partly by direct compression and chiefly by the alterations in the blood and lymph circulation in the area. Such a stimulus would thus lead to an area of sclerosis through stages of a "gradually increasing glia hyperplasia," which we have previously outlined. If such an assumption is justifiable, the two types of areas are not two individually distinct processes, the latter developmental

and the former inflammatory, but both are occasioned by the same causal agent acting with different intensity and over a longer time. Such a slowly increasing interstitial change is, therefore, an illustration in the central nervous system of the fact that the first evidence of reaction, when the action of an irritant is slow enough for us to follow clearly its results, is a proliferative change.

If we assume still further that the toxin is in greater concentration and acting more quickly, the first effect would be solely on the myelin sheath, which would degenerate rapidly. If this were not followed by a compensatory glia proliferation, there would result the type of area described by numerous writers as "areolierte" areas, in which the myelin sheath is dissolved away, leaving the original network of the glia and the axis cylinders persisting. If there were an attempt at a substitution glia proliferation, the glia nuclei would form the nodal points of a brush-like formation of fibrils, but this fibril formation would yet be insufficient to fill up all the meshes of the tissue, and the resultant area would be midway in its sclerosis between an "areolierte" area and a dense sclerotic area. Both of these latter types of areas are very numerous, and give the justification for looking upon the change in the myelin sheath as the most constant and uniform one.

It is possible to go a stage further and assume that the toxin is so concentrated, or acts so rapidly, that it attacks not only the myelin sheath, but destroys the axis cylinders and goes on to destroy the meshes of the glia, which thus break into one another, giving the appearance of the so-called "Luckenfelder." We would thus get true myelitic areas, and this is the present writer's view of the relation of disseminated sclerosis to acute myelitis. The areas in disseminated sclerosis are areas of lesser degeneration, and the difference in the pathological process is one only of degree. I assume, therefore, that the changes are not so intense in degree as in acute myelitis, and I regard disseminated sclerosis as a localised disseminated subacute inflammation, which gradually tends to sclerosis. In such subacute processes the general architecture of the tissue is retained. Chronic myelitis is a term which is becoming obsolete. It can represent the remaining stage of a previous acute myelitis, of a process which has begun chronically, or is healing slowly. TAYLOR and BUZZARD state that disseminated sclerosis has some claim to be regarded as a chronic inflammatory disease of the spinal cord, and is sometimes held to be the only true instance of chronic myelitis.

It is difficult to answer the question whether an acute encephalo-myelitis can pass over into a disseminated sclerosis. The pathological conceptions of the disease, as have been indicated, pass over into one another, and with this conception is admitted the inflammatory nature of the process. Whether it can be regarded as inflammation, as degenerative inflammation, or as purely degenerative, depends fundamentally upon different definitions of the same process. It seems defensible to regard certain forms of disseminated sclerosis, especially those occurring in close relation to the acute infectious diseases, as having their origin in an acute dis-

seminated encephalo-myelitis, but, in spite of the seeming inconstancy of the symptoms and the irregular incidence in the position of the areas, it seems justifiable to regard disseminated sclerosis as an inflammatory process with a subacute onset and slow progressive course—often distinguished by remissions and acute or subacute relapses which depend upon the development of new areas, and to regard the final cause as a true specific "noxa," which may be either a metabolic disturbance or a special infective stimulus.

4. *Route of Conveyance of the Causal Agent to the Tissues.*

Writers admit two paths of infection of the central nervous system—the one, which has been looked on as the more constant,—the blood stream, and the other the lymph stream. The possibility of lymphogenous infection of the nervous system has received much attention since experimental evidence was established in favour of the spread of rabies and tetanus by the lymph channels of the nerves. Its increasing recognition in this country is largely due to the work of ORR and ROWS, who have taken as the principle of their research the fact, demonstrated by numerous experiments with organisms and coloured fluids, that the lymph stream in peripheral nerves is an ascending one and capable of conveying infection to the central nervous system. The main current of this ascending lymph stream is said to lie in the inner meshes of the peri-neural sheaths, and when it reaches the cord, chiefly by the posterior roots, it for the most part passes along the entering posterior nerve roots into the substance of the cord, and the remainder is distributed in the inner meshes of the arachnoid around the whole surface of the cord. The lymphatic path within the cord has, in the main, an outward direction, as is demonstrated by the presence of fat granule cells, containing the degenerated products of the nervous tissue within the adventitial spaces, but the experiments of HOMEN, SALLE, and MARINESCO, together with numerous histological observations, leave no doubt that it admits of a current inwards—thus admitting an invasion by cellular elements, micro-organisms, and toxic substances.

In the experiments of ORR and ROWS, celloidin capsules containing a broth culture of an organism were placed in contact with the sciatic nerve. The path of the toxic lymph could be traced by the inflammatory reaction in the sciatic nerve, posterior root ganglia, and along the spinal roots. If the capsules were placed near to the spinal cord, in order to lessen the distance along which the infection had to be conveyed, this reaction was evidenced within the cord substance itself, and its characteristics depend entirely on the potency of the irritant. When the capsules had not burst and the tissues were attacked by toxins only, the reaction was of a plasma-cell type, but when the capsules had burst and the organisms had grown in the tissues, there was an intense proliferation of cells of polyblast type. As the same animal was used and the same organism, the differing reaction must be attributed to the difference in quantity and potency of the irritant. The reaction

in the spinal cord was produced in both instances by injected lymph which spread by the same path—along the adventitial lymph spaces of the vessels entering from the pia, and therefore attacked the same cells, those of the adventitial sheath of the vessels. The plasma cell is looked upon as the type of cell characteristic of subacute inflammation, and the polyblast as characteristic of an acute inflammation in the central nervous system. If the toxin or organism gaining entrance to the central nervous system by this source be weak, or penetrate the tissues slowly, no other phenomena but that of adventitial proliferation need occur for some time, and the changes in the cord diminish in degree from without inwards.

These experiments tend to prove that infection passing into the cord by the lymphatic system takes a definite course, that the structures of the cord and the nerves react to infection by this path in a definite manner, and that the inflammation can be propagated by the toxic lymph to parts distant from the focus of greatest intensity. It is recognised that when once the inflammatory condition has been established within the spinal cord, the toxic lymph spreads by direct continuity, and this continuity of extension is looked upon as characteristic of lymphogenous infections. Numerous clinical data, from cases in which peripheral inflammatory foci existed, have been brought forward by ORR and ROWS, in support of their experimental work, to demonstrate the facility with which infection spreads along the lymph sheaths of nerves to the spinal cord. Here also the histological changes in the membranes and nervous tissues showed that the reaction varies with the potency of the irritant, and that the degree of reaction in the nervous tissues diminishes from without inwards. In connection with these changes the cord infection which sometimes follows inflammation of the urinary bladder is referred to and is of interest in relation to the evidences of inflammatory changes in the membranes and in the peripheral vessels of the cord found in some of our cases. ORR and ROWS further apply this principle of lymphogenous infection to acute polio-myelitis and general paralysis. They look upon the histological changes in the former disease as showing no essential differences to those found in their acute cases—in both the preponderating cell type is the polyblast. The changes in general paralysis also appear explicable only by the presence of toxins of organisms gaining access to the lymph which bathes the brain and membranes and circulates in the adventitial lymph spaces of the cortical vessels, calling forth a chronic periarteritis of a plasma-cell type.

In relation to acute polio-myelitis it may be stated that experimental evidence proves without doubt that it can be produced by lymphogenous infection, and the view that the virus may enter by means of the lymphatics and thus exert its first effect upon the meninges is strengthened by the anatomical findings (PEABODY, DRAPER, and DOCHEZ). The earliest change described in the nervous system is hyperæmia and the collection of numbers of small mono-nucleated cells in the perivascular lymph spaces of the blood-vessels of the lepto-meninges. The lymph spaces

surrounding the vessels of the cord are, anatomically, processes of the arachnoid space, and the lymph in them is in connection with the cerebro-spinal fluid. With the advance of the pathological process this peri-vascular infiltration follows along the vessels as they enter from the meninges and is most marked around the central vessels. The evidence, first pointed out by FLEXNER, that the respiratory mucous membrane provides for both the ingress and egress of the virus has much to support it. ROMER and WICKMAN, on the other hand, on clinical and experimental grounds, think that the virus has its habitat in the intestinal tract and thence finds its way along the lymphatic sheaths of the sympathetic nerves to the central nervous system. Once this is reached an infection of the lymph spaces in the adventitial sheath of the veins in the pia mater and spinal cord immediately follows. WICKMAN supports his view of the lymphogenous origin of acute polio-myelitis on the following histological grounds: that in many parts the chief and only change consisted in an infiltration of the larger vessels, while the capillary region of such vessels was quite free; that the changes in the longitudinal axis were continuous—a continuity which reaches its maximum intensity in Landry's paralysis, and that the infiltration of the adventitial sheath of the vessels argued for the causal agent circulating in the lymphatic spaces.

It has been assumed by most writers that the causal agent in disseminated sclerosis circulates in the blood, but the possible lymphogenous source of the infection has been supported on the following grounds: (1) the endo-vascular changes are much less marked than the peri-vascular; and (2) the pathogenic significance of the peri-ventricular sclerosis. With reference to the former argument, it is again necessary to point to the fact that in this investigation peri-arteritic changes, in the sense of adventitial nuclear proliferation, were completely absent in the early areas before the onset of a secondary cell infiltration due to resorptive processes had occurred. There was thus no evidence in the cell proliferation of the adventitial sheath that a "noxa" was circulating in the adventitial spaces. In view, however, of the findings of ORR and ROWS, that in infection of the cord by the passage of toxins along the sympathetic nerves no adventitial proliferation was found, such a possible source of lymphogenous infection cannot be denied.

The peri-ventricular localisation was such a striking feature in several of the cases that early in the investigation it was recognised that ependymal and peri-ependymal lesions lead to important considerations in reference to the toxicity of the cerebro-spinal fluid. BULLOCK'S recent experiments point to this toxicity, and LHERMITTE and GUCCIONE found that when carmine was injected into the lateral ventricles of a dog, it was found, ten days later, almost wholly in the sheath of the sub-ependymal veins and in the sub-ependymal tissue. It is logical, therefore, to assume that toxi-infective agents in the cerebro-spinal fluid might follow the same route. The absence, however, of any change in the ependymal epithelium seemed to contra-indicate the possibility of a simple soakage of the cerebro-spinal fluid into the peri-ventricular tissue and also to contra-indicate the irritating character of the fluid, for a granular condition of the ven-

tricular walls is usually associated with such a change in the fluid. BORST has pointed out that the terminal branches of the central arteries ramify on the ventricular walls, and this localisation of the areas might equally be related to the vascular richness of this region. The cell infiltration and proliferation around the sub-ependymal veins, which constitute the path of return of the peri-ventricular circulation, would then again be simply an indication of the resorptive processes consequent on myelin degeneration and not a result of a peri-ependymitis. LHERMITTE and GUCCIONE come to the conclusion that the toxic agent in disseminated sclerosis is carried mainly by the blood-stream, but that a part in the process must also be ascribed to the cerebro-spinal fluid.

Extra Note.

The wide-reaching possibilities of lymphogenous infection in connection with the elucidation of the etiology of some nervous lesions is well illustrated in the recent work of ORR and ROWS. These writers have kindly given the following account of this yet unpublished work. They consider that the lymphogenous infections are characterised by phenomena varying from a polymorpho-nuclear or polyblast cell exudation in the acute processes to a plasma-cell reaction in the chronic, and that peri-arteritis is an essential feature. On the other hand, when bacteria-laden capsules are placed in the abdominal cavity—a position least likely to lead to infection of the lymph sheath of the peripheral nerves—it is found that no peri-arteritic plasma-cell formation occurs in the spinal cord. The changes so far observed have been as follows: (1) hyaline degeneration of the vessel walls with hyaline thrombosis; (2) neuroglia proliferation around the vessels; (3) the nerve cells are practically normal; (4) there is no evidence of peri-arteritis; (5) small areas of disseminated sclerosis; (6) a slight degree of myelin degeneration which varies in distribution in the different levels of the cord; (7) the sympathetic nerve cells in the abdominal chain show chromatolysis. They are of opinion that the influence of the sympathetic cannot be excluded, and that the view of a general intoxication cannot be sustained as an explanation of these lesions owing to their patchy character. They incline to the view that the involvement of the sympathetic mechanism here and there causes dilatation and stasis in certain parts of the cord vessels, favours the formation of hyaline thrombosis, and hence myeline atrophy and sclerotic areas. The work on which these guarded conclusions is based is as yet far from complete, and I am deeply indebted to Drs ORR and ROWS for allowing me to refer to this view: its possible significance in relation to the determining cause of disseminated sclerosis cannot be overestimated.

VI.

CONCLUSION.

The three divisions of this study have now been completed: in the first an analysis and classification were given of the more important writings on this subject; in the second part the essential features of the histological process were set forth and an endeavour was made to avoid the needless repetition of examples and details by the selection of such examples as were necessary to a complete view of the subject; and, finally, it was attempted to bring out in order the nature of the questions that come into consideration in a study of the pathological process underlying disseminated sclerosis. In the critical discussion which this involved it was clear that no general and complete interpretation of the subject could be given, and that imperfectly known factors had to be suggested for the solution of several of the problems. It may have seemed, on the one hand, that difficulties have been suggested where everything was clear: if this be so it is because it was difficult, sufficiently clearly, to define the real point at issue; on the other hand, in one or two cases, it has been noted that the difficulties are there, undeniably, but that their importance may easily be overestimated. The tentative nature, therefore, of the attempted explanations on many points, and the fact that no uniform conception of the process can be offered, make it difficult, in these closing pages, to summarise the foregoing study. Nevertheless, it is customary and desirable to formulate certain conclusions, and the extent both of the histological examination and the critical examination of the available literature seems to justify such an attempt. The first group of these conclusions is related to those problems which are far from being completely solved; the second group rests on more definite histological data.

As the initial conclusion, that related to the nature of the pathological process may be selected. Its sequence, as it has presented itself to me in the normal evolution of an area of sclerosis, is distinguished by several stages, which may be briefly stated in terms of their dominant feature: (1) a commencing degeneration of the myelin sheath and a simultaneous reaction of the glia in the immediately peri-vascular tissue; (2) an increasing glia cell proliferation and a commencing fat granule cell formation; (3) the stage of so-called "fat granule cell myelitis"; (4) a commencing glia fibril formation; (5) an advancing and (6) a complete sclerosis. It is possible, and the possibility has been allowed for in the interpretation, that complications, *e.g.* septic fever, extreme decubitus, etc., may modify the presentation of the picture at any stage. The histological study has given overwhelming evidence that the great majority of the areas in these cases, both in the brain and spinal cord, have arisen on the basis of this evolution through a stage of fat granule cell formation. On the ground, therefore, (1) of the nature of this evolution,

(2) that acutely-inflamed areas are rarely present, and (3) that in subacute processes the general architecture of the tissue is retained, it is concluded that:

(i) The process underlying disseminated sclerosis is a subacute disseminated encephalo-myelitis, which terminates in disseminated areas of actual and complete sclerosis.

It has been contended, however, by SCHMAUS, ZIEGLER, STRÜMPELL, and MÜLLER that there are two forms of disseminated sclerosis: the one, true primary disseminated sclerosis, which develops on the basis of an increasing glia hyperplasia —with developmental factors as its determining cause; the other, secondary disseminated sclerosis, which develops on the basis of an inflammatory process; and further, that the two forms can be clinically and anatomically distinguished from each other. This point of view is admirably simple, and I admit not only that certain areas in individual cases arise on the basis of an increasing glia hyperplasia—for such in small numbers are present in my cases—but also that, in certain cases of disseminated sclerosis in which the symptoms evolve very gradually, the areas might altogether develop on such a basis—discounting, however, the developmental factor. But when MÜLLER, who is the most strenuous upholder of this position, further contends that disseminated sclerosis, developing on such a basis, is a "comparatively common disease" in contrast to secondary disseminated sclerosis, and further states that the essential histological characteristic of the areas in the latter forms is "areolar," it is at once obvious that this study prevents the acceptance of such a uniform conception of the process—a conception which would rule out each of the nine cases. MÜLLER defends his position by arguments based on clinical and anatomical data, and the objections to his contentions may be put from these two points of view—clinical and anatomical. The question whether this is a position compatible with clinical experience lies outside the scope of this paper, and can be only briefly alluded to. My position is, naturally, determined by the cases that have come under histological observation. In these, two things stand out clearly: the one that the clinical notes, though admittedly meagre, point to a subacute onset of the symptoms, with no apparent immediate cause (see later), to periods of quiescence and betterment followed by relapses, again with subacute onset, and to the circumstance that these symptoms are quite compatible with the variability of the symptoms found in disseminated sclerosis. The second and more decisive fact, however, is related to the character of the areas. On pages 638–644 have been given MÜLLER'S criteria of the anatomical characteristics of the areas of primary and secondary sclerosis: it has also been stated above that the great majority of the areas in these cases develop on the basis of an inflammatory process, in MÜLLER'S sense, and that in the end-result they bear all the characteristics ascribed by MÜLLER to areas in primary disseminated sclerosis, *i.e.* with dense glia meshes in which persistent axis cylinders may frequently be found, and altogether different from the

"areolierte" areas ascribed to secondary disseminated sclerosis. It seems, therefore, justifiable to assume that cases of true disseminated sclerosis clinically have as their basal histological features areas of actual sclerosis, which have evolved through a stage of fat granule cell formation, and areas which are in process of a similar evolution.

It might, however, further be contended that areas arising on the basis of an increasing glia hyperplasia and those arising on an inflammatory basis are present in the same case. MÜLLER's explanation of this finding is that, to the primary true disseminated sclerosis, due to developmental factors, a secondary form, due to toxi-infective influences, is superadded. I have already admitted the presence in the same case of areas arising in both ways, and also the presence of "areolierte" areas, and in the foregoing section the possibility, that a uniform explanation of the development of these three types of areas can be found, has been put forward. In view of the essential importance of the difficulty of accounting for such types of areas, a brief summary of the argument there presented will be given. The essential point in this argument is related to the well-known fact that a common cause, according to the intensity and duration of its action, may produce a very varying picture, and therefore several factors, which cannot be strictly separated, are acting in concert.

It is probable that when the causal agent diffuses through the blood-vessel walls with average concentration and intensity, areas arise on the basis of (1) a primary solution of the myelin—a result of the irritant action of the "noxa"; and (2) a simultaneous glia reaction—the result of the stimulant action of the "noxa," and that such areas pass through stages of fat granule cell formation, glia fibril formation, to a complete sclerosis with very fine, dense glia meshes. On the other hand, if the causal agent be of weaker concentration and intensity and acting over a longer time, its stimulant action on the glia is solely in exercise: areas would then arise on the basis of a gradually increasing glia hyperplasia. The comparative picture presented by the end-result of each could be differentiated only by the possibly more isomorphous character of the resultant sclerosis in the latter case. Further, the "noxa" may be of stronger intensity and its irritant action predominate, so that areas of a more acute myelitic character arise, in which the rapid degeneration of the myelin sheath is accompanied by a destruction, not a mere swelling, of the axis cylinder. Such areas, followed by a certain amount of secondary degeneration and later by a reparatory sclerosis, are also found in disseminated sclerosis, but this is not the normal evolution of an area. At the same time it is clear that a varying intensity of the "noxa" might cause areas to arise, in which the resultant sclerosis shows all transitions from a simple retention of the glia network—the so-called "areolierte" areas of MÜLLER, through areas with a certain but not complete degree of fibril formation—in which the proliferated glia nuclei are the nodal points of radiating fibrils to areas of complete sclerosis in which the glia meshes are very close. This varying picture, seen best with glia stains, depends, therefore, not on different under-

lying processes, but more probably on the varying intensity of one causal agent and the varying factors which modify its action in individual cases and at individual times. It is concluded therefore that:

(ii) Disseminated sclerosis is probably not due to a developmental process, and there are no sufficient grounds for distinguishing between primary and secondary disseminated sclerosis in the sense used by ZIEGLER, STRÜMPELL, and MÜLLER.

It is important to observe that this conclusion has been qualified by the addition of the words "in the sense used by ZIEGLER, STRÜMPELL, and MÜLLER." I differ fundamentally from those writers in their grouping of the forms of disseminated sclerosis into true, primary disseminated sclerosis—a developmental disease, with characteristic clinical and anatomical features—and secondary disseminated sclerosis, one of a group of allied diseases, without such. Yet it is considered that the clinical and anatomical picture of disseminated sclerosis stands out clearly and well defined, that it is probably due to a specific but unknown morbid agent, and that it is probably quite distinct from other diseases of the central nervous system, which, in virtue of the disseminated distribution of their lesions, call forth clinical symptoms resembling disseminated sclerosis. Two of the chief of such disseminated affections are those due to multiple arterio-sclerotic and multiple syphilitic endarteritic processes, in both of which, however, a careful clinical and anatomical examination makes the differential diagnosis possible. Rarer forms are those due, *e.g.* to thrombi in the cerebral vessels, formed by malarial parasites, and to multiple tumour-formations, *e.g.* multiple neuromata of the central nervous system. The most important form, however, is that due to toxi-infective conditions, which may give rise to disseminated areas of myelo-encephalitis. From what has already been said about the varying intensity of the "noxa" and from the assumption that when this was stronger in its intensity areas might arise of an acute myelitic type, it may legitimately be assumed that such disseminated areas may arise in immediate relation, *e.g.* to the acute infective diseases, and produce symptoms impossible to distinguish clinically from disseminated sclerosis except in the acuteness of their onset and their severity. It is further probable that the clinical course of such cases, if they become chronic, would not be characterised by definite remissions and relapses, and, anatomically, the end-result of such areas would be characterised by a reparatory sclerosis or, the opposite extreme, an absence of evidence of glia reaction and the so-called "areolierte" areas of MÜLLER. It seems unlikely that the specific toxi-infective agents of the different acute infective diseases can each produce a clinical and pathological condition so characteristic as that of disseminated sclerosis, while it is conceivable, and we know from experimental and other evidence that it is possible, that the various toxi-infective agents can call forth an acute disseminated myelitis which runs its course and remains stationary. The clinical symptoms would resemble disseminated sclerosis, but the characteristic remissions and relapses would

be wanting. The grounds for such a view are based largely upon an increasing knowledge of the selective character of toxins. Several instances of such have been given in an earlier section, and here allusion may be made to progressive lenticular degeneration—a symmetrical degeneration of the lenticular nuclei—which WILSON traces to the selective action of the morbid agent on these collections of grey matter; and also to the secondary neuroses (psychoses) following the various fevers, *e.g.* pneumonia and typhoid fever, which KRAEPELIN has differentiated from one another. Analogies can never be conclusive, but they at least mark the possible direction in which we may look for a solution and allow of the suggestion that a characteristic anatomical and clinical picture is called forth by a specific morbid agent.

It is probable, however, that the significance of acute infectious diseases, when they occur in the anamnesis in definite time relationship to the onset of symptoms, is that which has been attributed also to chill, trauma, psychical shock, and all the recognised external factors: that they are capable of acting only as exciting factors manifesting or aggravating the condition. In four of the nine cases from which the material of this study has been drawn the symptoms came on without apparent cause, and in the other cases the chill, trauma, shock, influenza, and miscarriage cannot be regarded as in immediate causal relationship. The duration of the series of cases is as follows: fifteen months, four years, five years, in three cases ten years, fifteen years, and seventeen years. Eight of the nine patients were young women, whose ages averaged slightly over twenty years at the time of the first appearance of the symptoms.

The essential points of difference between the standpoint of ZIEGLER, STRÜMPELL, and MÜLLER and my own are very few, but they are basal. These writers confine true disseminated sclerosis to a disease with a characteristic clinical course, *i.e.* with remissions and relapses. So far we agree, but this condition has, as its anatomical expression, an increasing glia hyperplasia (for the present the developmental factor at its basis may be left out of account), and from this pathological conception all the nine cases must be excluded. Further, these writers look upon secondary disseminated sclerosis as chiefly due to toxi-infective agents, and these forms have as their anatomical expression "areolierte" areas, and again, from this pathological conception all the nine cases are ruled out. It may be argued that the notes in some of the cases do not justify our looking upon them as cases of true disseminated sclerosis, but if these are omitted and those only included which sufficiently point to their inclusion in MÜLLER'S clinical picture of true disseminated sclerosis, there still remains overwhelming evidence that the great majority of the areas arise on the basis of an inflammatory process, and lead to areas of actual sclerosis in MÜLLER'S sense. In five out of the nine cases areas in all stages of development were found in both brain and cord; in three, the areas in the cord were mostly of an older date, and those in the brain at all stages; while in one case the spinal cord areas were all of an early type, and those in the brain of a more sclerotic type. It is,

therefore, legitimate to assume that the varying picture is dependent upon certain principles which enable us to recognise different degrees of one process rather than several independent reactions.

It is necessary, at the risk of complicating this argument, to mention one further point. The anatomical expression of a "remission" must naturally be the gradual clearing up of the cell exudation, and a sclerosing of the tissue with a retention of the axis cylinders. The anatomical expression of a relapse is the presence of "early" areas, so that the presence of areas in different stages of development is characteristic of the anatomical picture of disseminated sclerosis. Now it is conceivable that a disseminated myelo-encephalitis due, for example, to the direct toxi-infective agents of the acute infectious diseases might run a slow course—healing slowly, and if death resulted at this stage, the anatomical picture would show some areas actually sclerosed, or at least with no trace of an existing process, and others in which such traces were still left. It is evident that such an anatomical picture would be difficult to separate from that of disseminated sclerosis, and that the long clinical course would simulate a case of disseminated sclerosis with no true remissions. It is still further necessary to refer to cases of so-called "acute multiple sclerosis." Such cases are very difficult to classify: up to a certain point they resemble disseminated sclerosis in virtue of their being disseminated affections of the central nervous system; but the criteria which give its characteristic course to disseminated sclerosis have not had time to evolve. As the pathological data, however, resemble those of a subacute process, with retention of axis cylinders, it might reasonably be admitted that such cases are true disseminated sclerosis, which, from the importance of the position of the earlier areas involved or other causes, have led to an acute course of the disease and death.

I therefore divide disseminated affections of the central nervous system into (1) disseminated sclerosis—a subacute encephalo-myelitis, a condition which runs a characteristic course with remissions and relapses, and (2) other disseminated affections. The only member of this group which presents real difficulties in clinical and anatomical diagnosis is that due to acute disseminated myelo-encephalitis. In this case the pathological and clinical concepts of the two diseases pass into each other: the differential diagnosis must rest, clinically, on the further course of the disease, and anatomically on data which differ only in degree.

(iii) It is concluded, therefore, that there is much to favour the view that true disseminated sclerosis is due to a specific morbid agent which calls forth a clearly-defined clinical and anatomical picture: that other disseminated affections of the central nervous system, such as disseminated arterio-sclerotic, syphilitic endarteritic, and acute encephalo-myelitic processes may all produce a symptom-complex very similar to that of disseminated sclerosis, but that they, in their further course, differ from the latter in the characteristic remissions and relapses; and further, that acute infective diseases, trauma, chill, shock, and all known exogenous factors may act as

exciting factors in lowering the resistance of the organism, and thus allowing the final determining factor to operate.

The most important question yet remains: What is the nature of this postulated specific morbid agent which is the final and determining factor in the process? It has already been frequently stated that this is quite uncertain, and that there is not sufficient evidence to show whether it is microbial or of the nature of a toxin. There is much in favour of the view that the disease is toxic in origin; the histological evidence, which is far from conclusive, is related to the absence of cell infiltration of the vessel walls, for it is admitted by most writers that areas of degeneration without cell infiltration are more usually due to toxic influences, while infective agents more uniformly call forth an infiltrative form of myelitis. More decisive, however, is the clinical evidence: many of the early symptoms, symptoms which sometimes last for years, are slight motor palsies and transient psychical symptoms, which pass off readily under treatment with faradism or suggestion—such transient symptoms are very suggestive of the persistence in the body of some toxin which exercises its action on the nervous system. The variability of the early symptoms, which has so frequently led to the diagnosis of hysteria, suggests that at this stage areas may be affected by a "nutritional" rather than a structural change. The possibility of dynamic modification of function is now well recognised, in diseases of the nervous system, while as yet structural change is slight, and this being so, it is therefore more likely that the agent producing this varying disturbance of function is some form of toxin. The importance of determining the relation of the so-called Westphal-Strümpell pseudo-sclerosis to disseminated sclerosis is very great, for in this affection the symptoms of disseminated sclerosis are present with negative pathological findings.

If we assume the presence of a toxin as the essential stimulus, we must further decide the route of its conveyance to the nervous tissues. The histological evidence in favour of hæmatogenous and lymphogenous spread has been given in a previous section: it was there stated that although certain circumstances, such as the frequent marked peri-ventricular sclerosis, and recent experimental evidence in favour of the toxicity of the cerebro-spinal fluid, point to a lymphogenous spread, there is no histological evidence to support this view.

(iv) The causal agent is, therefore, probably of the nature of a soluble toxin, and it is conveyed to the nervous tissues probably by the blood channel.

We have still to explain the restriction of the action of this circulating toxin to certain areas. The difficulty of explaining how the degeneration connects itself with special vascular tracts, and avoids others, has led many writers to fall back upon the assumption of developmental defects or minimal tissue injuries, which form "loci minoris resistentiæ" where the circulating toxin might settle. In the

histological study it has been pointed out that it is not a question of one central vessel, a portion of the longitudinal course of which is affected, but rather of a blood-vessel stem with its terminal branches or a division of its branches. It is probable that the circulating toxin escapes from the capillaries and transition vessels in the sense that the area of supply of the ramifications is affected. It has been suggested that the toxin may have a chemiotactic influence on certain portions of brain tissue, but it is difficult to conceive of such an irregularly and widely distributed chemiotaxis unrelated to definite functional nuclei or fibre-systems. The toxin may, however, conceivably select certain areas of blood supply, for it is known experimentally that certain substances can influence the blood supply of regional parts of the brain, and MEYNERT has suggested that this may be the explanation of the maniac depressive psychoses, which he looks upon as neuroses of the vaso-motor system limited to certain cerebral areas. The recent experiments of ORR and ROWS also point to the possibility of a localised affection of the vaso-motor system due to the action of toxins on the sympathetic nerves. In the present state of our knowledge, as it is impossible to determine the final causal agent, it is equally impossible to determine the factor which allows of its diffusion through certain terminal areas of the ramification of a blood-vessel.

(v) It is suggested, however, that the restriction and distribution of the pathological process is in some way related to the selective action of the toxin on certain areas of the blood supply, or that unknown factors determine an irregularly distributed paralytic dilatation, with an increased filtration through the vessel walls.

It is, further, necessary to explain not only the presence of this morbid agent in the blood-vessels, the restriction and distribution of its effect, but also its continued presence in the body through a series of years, during which its action is apparently exhausted, remains quiescent, and again breaks out. Clinically the remissions and relapses are the outcome of this peculiar action, and anatomically it finds expression in the areas in different stages of development in the same cases. Allowing that it is microbial in origin, we may find an analogy in cerebro-spinal syphilis, in which there are also the same exacerbations and remissions. If we admit, rather, its toxic origin, the closest analogy is probably found in pernicious anæmia, where it is thought likely that both the hæmolysis and the cord changes are due to the same toxin. The source of the toxin is here also uncertain, but the fact that gastro-intestinal disturbances are so common in this disease lends support to the view that it is of intestinal origin, and that its intermittent evolution or its insufficient elimination lead to the remissions. Such analogies can again not be final, and in the latter case the parallel breaks down from its incompleteness. There is no known association of disseminated sclerosis with any changes in the gastro-intestinal tract or elsewhere: the connection, if any, with glands of internal secretion has never been worked out: the general metabolic changes occurring in the body have not been

investigated; and the cerebro-spinal fluid is known not to exhibit the cytological and bio-chemical changes which are so marked in para-syphilitic affections. The investigations of the cerebro-spinal fluid have as yet been very incomplete, and the evidence which tends to prove that it is toxic does not decide whether it is so as a result of the process or whether this toxicity is its cause.

(vi) The remissions and relapses, therefore, necessitate the assumption of the latent presence of the morbid agent in the body, or, if this is an autogenous toxin, either its intermittent evolution, or its accumulation from deficient elimination.

Variability of the symptoms. It is a little difficult to explain the mechanism of the fleeting early palsies and psychical symptoms. The possibility of an early dynamic modification of function has already been noted, but the period now referred to is one when presumably structural changes have set in. I consider that the involvement of the psychic areas at such a stage is to be explained in the same way as the affection of the motor areas. In such cases it is possible that the motor area or tract involvement is insignificant, for, if it were the essential lesion, the recovery could never be so rapid. Every movement requires the integrity of a large number of association areas, but we realise this only when we watch a child trying to walk, or a paralysed person trying to move. It is possible, therefore, that in these transient palsies the disturbance is in one of the association paths: with each recurrence of an area in such paths, motor images and memories would be progressively blotted out till the motor area is so cut off from its usual associations that progressive paralysis occurs. So long as an axis cylinder remains, a stimulus is capable of passing. The destruction of the myelin sheath probably results in the increase of the resistance to the passage of any stimulus. If a sufficient number of association areas can be linked up around a particular function, in order to elicit from it a discharge sufficient to overcome this resistance, then remission is possible. By stimulation through suggestion, faradisation, etc., these remissions may be brought about with a success dependent upon the degree to which the paralysis is psychic or motor. In this the extra stimulus is probably gained by the linking up of distantly connected association areas and thus utilising or deviating their energy to the desired process. It is also possible that when one path is blocked by disease, others, perhaps not so direct, or possibly new paths, may be opened up.

The lesions are disseminated through the cerebro-spinal axis and disturbances are, therefore, especially liable to affect systems which are extensive. Thus the pyramidal fibres, in their long course from the cerebral cortex to the anterior horn cells in the cord, are invariably and usually early affected: this affection may at first be so slight as to be evidenced only in a unilateral loss or diminution of the abdominal reflexes, or it may be so severe as to give a spasticity great enough to abolish the deep reflexes. As the co-ordinating system has peripheral,

spinal, vestibular, cerebellar, and cerebral components, it is co-extensive with the nervous system: some part of this extensive system is almost invariably implicated. Nystagmus, tremor, — both static and intentional — and ataxia all occur: the spasticity to a certain extent masks the inco-ordination in the gait and gives rise to a spastic cerebellar type of progression. In spite of the length of the afferent paths of common sensation, loss of common sensibility is rare: the cause of this anomaly is uncertain, but it is possible that a considerable degree of involvement of the sensory columns may occur without a marked loss of sensibility, and that afferent sensory stimuli survive when weaker efferent stimuli fail.

It has been already pointed out that many of the symptoms are due to loss of cerebral inhibition, and this loss of cerebral control is a source of great confusion in interpreting the symptoms. Just as the interception of the volitional motor impulses permits increased irritation of the reflex mechanism, so does the loss of the unconscious cerebral control permit increased irritation of the automatic, the sympathetic, and the reflex mechanism.

The frequent presence of daily variations in the symptoms after the disease has become established emphasises the importance of the mental factor in the symptomatology. Structural lesions do not thus vary, but the external evidences of them—the patient's reaction to them—may vary. This variation probably depends upon environmental stress, upon nutritive factors, and probably chiefly upon the intermittent evolution of endogenous toxins.

(vii) It is suggested, therefore, that fleeting early motor paralyses and psychic symptoms may be related to the presence of areas in association paths: that remission of these symptoms is possibly due to the linking up of other association paths, or their compensation by the opening up of new paths; and, further, that the variation of the symptoms in all stages of the disease emphasises the importance of the mental factor in the symptomatology.

We are now in a position to turn to the conclusions based on definite histological data. An explanation has already been offered for the formation of certain types of areas, but one or two changes related to these areas still require to be mentioned.

(viii) The "areolar" zones, the true "areolar" areas, and the peri-vascular sieve-like areas must probably be referred to an œdema of the peri-focal and peri-vascular tissue, due to alterations in the blood and lymph circulation, firstly within the area, and then in the general tissue—through the presence of numerous foci. This is a secondary process, and is the result and not the cause of the sclerotic areas.

Areas of "shadow" sclerosis which have a definite outline or surround, with such an outline, true sclerotic areas must be ascribed to a diffusion of the toxic lymph in concentration insufficient to cause a complete demyelination. Such areas are often accompanied by a diffuse glia hyperplasia.

Further, areas of diffuse and lighter staining, which connect true sclerotic areas

—sometimes over long stretches of tissue—may be caused by several factors, among which may be mentioned: (1) a diffuse spread of the toxic lymph in the lymph spaces, (2) circulatory derangements in consequence of numerous foci, (3) considerable participation of the axis cylinders causing a certain degree of secondary degeneration.

Finally, especially in the cord, there are frequent evidences of an early degeneration of the myelin sheath (Marchi staining), over the whole myelinated tissue and the nerve roots. This must be referred to the general somatic disturbances.

(ix) Sites of predilection are probably related (1) to the vessels: to the terminal ramifications of end-arteries, *e.g.* on the ventricular surfaces, and to the points where vessels break up, *e.g.* in the transition zone between grey and white matter—both in the central and cortical grey matter; and (2) to areas where much glia is normally present: again, therefore, to the peri-ventricular and to the peri-central tissue, to the optic chiasma, to the postero-median and para-median septa, to the marginal glia zone, and to the peri-vascular glia layer. The peri-ventricular affection was very marked in six of the cases, slight in other two, and scarcely noticeable in one. The optic chiasma and one or both optic nerves were affected in seven out of the eight cases in which they were examined, and in six cases there was an extensive involvement of the optic radiations on both sides—an involvement which seemed to extend laterally and posteriorly from the sclerosis around the posterior horn of the lateral ventricle.

The frequent marked symmetry of the areas may be related to both of these circumstances.

(x) Cortical areas. The essential change is a demyelination, and the cyto-architecture of the cortex is frequently retained. On the other hand, the ganglion cells may show a marked increase of their satellite cells or all stages of degeneration, but these changes are not strictly limited to the area of demyelination. The glia cells in the deepest layers are markedly proliferated and show all stages of glia fibril formation: in the layer of the deep pyramids there is an hypertrophy of the normal glia cell content with formation of fibrils—insufficient to lead to sclerosis: in the upper layers the glia cell changes diminish in intensity, but fine glia cell forms with long processes of uniform calibre are present, especially around the ganglion cells and capillaries; and in the sub-pial marginal layer there is again an increase of both cells and fibrils. Cortical and subcortical areas were numerous in six of the cases, few in two, and in the ninth case not evident—but this brain was the only one not examined microscopically in large sections.

The changes in the cortex have been held to account for the psychical symptoms, often so marked a feature in the clinical picture. Such symptoms, however, have been present in cases which anatomically showed little cortical change, and, again, marked involvement of the cortex has been noted in cases which clinically presented no

change in the intellectual or psychical functions. That the cortical areas share in the production of such symptoms cannot be doubted, but probably when these are defined they are dependent upon the inhibition of the action of those cortical cells which control the thalamic centres—the latter being intimately related to the emotions and forming part of Langley's autonomic system. Such inhibition would take place by the presence of sub-cortical areas in relation to the cortico-petal fibres and to the presence of areas in the optic thalamus itself. Reference has already been made to the possibility that early psychical symptoms, such as restlessness, emotionalism, involuntary fits of laughter, may, together with the early transient palsies, be referred to a functional change which precedes an anatomical, structural change.

(xi) Ganglion cells. The ganglion cells in the grey matter of the spinal cord, and in the analogous nuclei in the medulla oblongata and pons, retain for a long time, even in the advancing sclerosis, their nucleus and chromophile granules. There is considerable histological evidence to show that this accounts for the absence of secondary degeneration in the anterior nerve roots, and, in part, for the remission of the symptoms—for there is no reason to suppose that such cells do not function.

The later varied changes in the ganglion cells must be ascribed to (1) the increasing condensation of the sclerotic process; (2) the absence of function; and (3) the associated somatic disturbances—the latter two factors will also influence the cells throughout the non-sclerotic tissue. I have never seen in the cord an increase of the satellite cells such as has just been described around the cortical ganglion cells.

(xii) Axis cylinders. The persistence of numerous axis cylinders in the sclerotic areas has been accepted as an axiom by most writers, and with this view I am in entire agreement. Secondary degeneration is therefore not well defined, but it affects a certain number of fibres.

In the early areas the axis cylinders undergo a swelling, which may go on to a granular disintegration, but those that survive the swelling, or have not shared it, persist, in the advancing sclerosis, for a long time. This circumstance has been held to explain (1) the absence of secondary degeneration; (2) the remissions: the gradual retrogression of the symptoms must be related to the resorption of the fat granule cells, the swollen axis cylinders then diminish in volume, and impulses would thus be able to proceed by means of the denuded axis cylinders—giving, therefore, a remission of the symptoms; and (3) the intention tremor—it is thought that this impulse would be carried on irregularly in a broken or jerky manner and would thus produce the oscillations which disturb the due execution of the voluntary movements. It is supposed that this is effected in part by the absence of the insulating myelin sheath, which allows of the diffusion of the impulse to neighbouring axis cylinders and also by the pressure of the increasing glia. It must be remembered, however, that though function is related in development to

the presence of the myelin sheath, there is, as far as we know, no evidence that non-medullated axis cylinders do not transmit impulses as regularly as medullated fibres. Again, fibres lying adjacent to each other in an area do not end necessarily at the same level or in adjacent cells. The leakage, then, if it existed, would take place from the entire circumference, and the result would be not an incoordinated act, but a very feeble one, or none at all. Further, the glia meshes in which the naked axis cylinders lie must themselves insulate the fibre.

The distribution of the areas in all the cases lends support to the view which associates tremor with disturbances of the afferent and efferent extra-pyramidal paths. These, according to WILSON, are respectively the cerebello-rubro-thalamo-cortical path from the nucleus dentatus of the cerebellum, by the superior cerebellar peduncle to the red nucleus of the opposite side, and thence to the inferior and external divisions of the optic thalamus and so to the sensory and motor cortex. The efferent path is the lenticulo-rubro-spinal system, by the ansa lenticularis and sub-thalamic region to the red nucleus, and thence by the rubro-spinal tract of Monakow to the anterior horns of the spinal cord. Lesions of the former path probably remove the inhibitory function of the cortico-petal fibres which pass to the cortical cells, and lesions of the latter remove the normal inhibiting or steadying influence which the corpus striatum exercises on the anterior horn cell. Reference must again be made to the possibility that in the early stages functional changes may be present, and that the so-called dynamic modification of function may account for many of the early symptoms indicative of defect of cortical control.

(xiii) Myelin sheath of the nerve fibre. It is held by many writers that the morbid agent has a special affinity for the myelin sheath and for the myelo-axostroma, a constituent element of the axis cylinder, related to the myelin. The question, which is the primary structural element of the nervous tissues attacked by the causal agent, constantly recurs throughout the literature, and from this histological study it will be seen that the change in the myelin sheath must be looked upon as the most constant, the most uniform, and in many cases the primary one. This has all the characters of a primary degeneration in contrast to those of a secondary degeneration, and is due to the destructive or irritant action of the stimulus. The myelin sheath is presumed to have an insulating action: it probably also facilitates the transit of nervous impulses.

(xiv) Neuroglia. The glia changes set in, as a rule, simultaneously with those in the myelin sheath: the earlier reaction is due to the stimulant action of the morbid agent; and the later reaction is secondary also to the degenerative processes.

The glia changes correspond to the age of the process and its intensity: on the one hand glia cell proliferation with the formation of large protoplasmic, potential

fibril-forming cells, and, later, glia fibril formation at the expense of this protoplasm: glia cells which have produced fibrils undergo slow, regressive changes, the glia nuclei subsequently atrophy and disappear, and to such a disappearance is due the fact that the old sclerotic areas have fewer nuclei than the normal tissue: the course and direction of the glia fibrils is, as a rule, in the direction of the normal longitudinal course of the nerve fibres, especially in the posterior columns of the cord, but frequent whorls are found or a dense tangle with very fine meshes.

In the progressive alteration in the glia all its component parts share—nucleus, protoplasm, and specific fibres: the "glia limitans peri-vascularis" is the first to show signs of reaction: the abundance of the glia in an area justifies the name "sclerosis," but the process may stop short of complete sclerosis and so areas are present showing all degrees of density of the glia meshes: the sclerotic tissue is more loosely constructed in the grey matter of the cord and the analogous nuclei.

The glia changes in the cortex lend support to the view that the adult glia consists of (1) cells—with nuclei, cell bodies, and protoplasmic processes; (2) differentiated fibrils — whether anatomically independent or not; (3) intercellular fibreless glia.

It seems unnecessary to postulate areas of glia abnormality and that the blood-vessels carry the morbid agent to such points: but this can neither be proved nor disproved.

(xv) Blood-vessels. The topographical relation of the areas points to the blood-vessels, or their lymphatic sheaths, as the route by which the "noxa" is conveyed to the tissues: in its diffusion through the vessel walls the morbid agent causes no recognisable primary alteration, but probably there is an abnormal permeability and diminished resistance to the oscillations of the blood-pressure by which an increased transudation of (toxic) lymph is made possible — the only anatomical expression of this is dilatation and engorgement.

On the ground of numerous serial sections of areas it has been concluded that it is the branches of one vessel stem which are affected, and that the primary minute areas, related to each branch, subsequently coalesce.

There is no evidence of a primary nuclear increase in the endothelium or in the adventitia: the first cellular increase is secondary to the resorptive processes —an infiltration of fat granule cells: this is followed by a proliferation in all the cell elements of the adventitia and, at a later stage, by a modified infiltration of lymphocyte-like cells and a few plasma cells. The derivation of the nuclear content of the adventitia at a later stage is, therefore, a very varied one. The later changes in the vessel walls are related to a condensation of its adventitia, such as is found in all chronic conditions: the separate layers of the adventitia gradually blend, its nuclear contents break up, and are carried away in the lymph spaces or fuse with the adventitia; and finally, both adventitia and media show a

homogeneous "hyaline" change in which nothing can be recognised of specific muscle, connective tissue, and elastic elements.

(xvi) Fat granule cells ("Fettkörnchenzellen"). The first fat granule cells probably arise from the proliferation of the small round glia cells, and at a later stage, also from a proliferation of the endothelial elements of the adventitia. They absorb the degenerated myelin in the form possibly of a solution, which is precipitated as granules in the protoplasmic substance of the cell: they pass, or are drawn in by suction and the pressure of the increasing glia fibrils, into the lymphatic sheaths of the capillaries and transition vessels, and thence by the larger vessels to the inner layers of the pia. On their way large numbers are broken up *in situ*, and their crenated nuclei can for a long time be recognised as one of the nuclear elements of the adventitia.

(xvii) The cranial and spinal nerve roots are frequently involved in the glious portion of their extra-medullary course. Such changes, in the posterior spinal and analogous nerve roots, may account for the existence of the sensory changes, which are almost always present to a slight extent, and especially for the trigeminal neuralgia.

(xviii) The meninges. The occasional variations in the meninges are related to complications and are probably of no significance in the pathogenesis of the disease.

Approximately final answers can, therefore, be given to the questions relating to the nature of the process underlying disseminated sclerosis, to its origin, to the relation of several secondary etiological factors, and to certain aspects of the mode of action of the final causal agent. We are, however, still quite in the dark concerning the nature of this final cause, which determines, anatomically, a process, so well defined, and one without any close analogy; and, clinically, a disease which, however variable the early symptoms, conceals its characteristic course only temporarily. The frequent presence of the cardinal symptoms, in spite of the seeming irregularity and incidence in the position of the areas and their restriction, seems to point to a certain constancy in the changes, the nature of which is not yet fully known, but which may be dependent on the production of a specific metabolic disturbance, due to a latent organism or an auto-toxin. All that is most important, therefore, still remains for future investigations along bacteriological, serological, and experimental lines, which have recently done so much to clear up the etiology of other affections of the central nervous system.

APPENDIX.

It has already been stated that the foregoing histological study is based on the observations made in nine cases of disseminated sclerosis, and that, as it had been possible to follow one of these cases, clinically and anatomically, that case has been taken, more or less, as the basis on which the study was built up. The other cases, however, were almost as minutely studied, and were freely drawn upon in the descriptions already given. It has, therefore, seemed desirable to give an account of each under the following headings :—

1. The available clinical notes.
2. The post-mortem report.
3. Brief summary of the general characters of the areas.
4. A more or less detailed description of the topographical distribution of the areas in Weigert sections. In reference to these descriptions it is necessary to note that in some, individual sections were taken, while at other levels such descriptions are given from several successive sections of a series, so that the latter do not completely correspond to individual illustrations.

CASE II.

Clinical Notes.

C. S.—This patient was admitted to the late Dr ALEXANDER BRUCE's wards in the Royal Infirmary, Edinburgh, on the 13th of July 1906. At this time she was twenty-two years of age, and complained of weakness in the legs and arms, and difficulty of speaking, of about five years' duration. She had had measles and typhoid fever as a child, and scarlet fever at the age of ten. She had also had two attacks of influenza—the first about six months before the present illness began, and the second about eighteen months previous to admission. She was a total abstainer, and had one child, one year old. Her father and mother were both aged fifty-two, and were alive and healthy. Four brothers and three sisters are all alive and well. One brother died in infancy.

The present illness began when she was a kitchenmaid five years ago. She noticed then that frequently, especially when she was laughing, her legs gave way under her and she fell to the ground. She also noticed that she let dishes fall and had curious fits of drowsiness, especially about midday. This continued for over two years without compelling her to leave work. After this she suddenly got quite well and was married. About six months previous to admission she began to be troubled with giddiness and developed a staggering gait. This grew steadily worse, until she had to remain in bed. The eyesight became poor, and diplopia was present for about eight weeks previous to admission. She noticed that her speech had become more deliberate, and that there was some trouble with the sphincters.

Condition on Admission.—She could neither walk nor stand, and cannot sit up in bed without help. There is no weakness of the hands or arms, but on making any movement her head always begins to nod. Co-ordination of the upper limbs is slightly interfered with. Sensation is impaired in the legs. The speech is staccato, and coarse nystagmus is seen in looking to the right, left, and upwards. A curious vertical movement of the upper eyelid was also noticed. The knee-jerks were much exaggerated, both plantar reflexes were extensor, and patellar and ankle clonus was well marked. The other organs showed nothing of note, except some involvement of the left apex of the lung.

The nodding of the head became worse and the speech more slurring. From being happy and contented, she became depressed. She remained for over a year in Dr BRUCE'S ward, the condition steadily progressing. She became quite unable to feed herself, and slept during a great part of the day. Incontinence of urine developed, and she was re-

moved to the Longmore Hospital, where she remained four and a half years, death being preceded by a curious state of coma which lasted for about a fortnight.

Post-mortem Report.

Post-mortem rigidity present. Marked contracture of the right leg at the hip, the thigh being flexed and drawn across the left thigh.

Brain.—The dura mater was adherent both to the brain and to the skull. The brain itself felt soft and œdematous. On cutting through the pons, numerous grey gelatinous patches were seen, especially developed round the aqueduct of Sylvius.

Spinal Cord.—The dura and pia showed no large adhesions. The surface presented an almost uniform flaky appearance. On section very advanced sclerotic areas were found at all levels, in some occupying the whole of the section. At other levels small patches occurred on the surface of the cord.

Heart.—Small; considerable epicardial fat. Chambers normal in size, the valves healthy, as were also the muscle fibres.

Lung.—Left upper lobe was somewhat congested. The lower lobe, with the exception of the extreme base, is completely solidified, at a stage of grey hepatisation. The right lobes were congested and œdematous, but there was no consolidation.

Liver.—Small; vessels prominent, and marked cloudy swelling.

Spleen.—Large, soft and almost diffluent on section.

Kidneys.—Marked cloudy swelling. Capsule strips freely.

Skull-cap.—Thick and solid, with some little nodular new bone formation on the inner surface of the frontal bone.

General Characters of the Areas.

The extent of the affection, both of the brain and cord, was greater than in that of any of the other cases that came under our observation. The histological changes also, in the affected tissue, presented features which distinguished this case as compared with the others. Not only were those, characteristic of the diseased process in disseminated sclerosis, more marked in degree, but there were also present the maximum of the changes which have been related to the chronicity of the process and to complications. We have, therefore, (1) an extensive demyelination; (2) a more advanced degree of sclerosis; (3) a more constant persistence of the axis cylinders; (4) changes in the ganglion cells associated with a chronic process; and (5) thickening of the cerebral and spinal meninges and a nuclear infiltration of the walls of their blood-vessels and of the peripheral vessels of the nervous tissues.

The spinal cord, from its highest to its lowest level, showed an almost complete demyelination (figs. 83–88): at a few levels isolated groups or bands of peripheral fibres were left, which, on closer examination, were found to be related to the marginal tissue through which the anterior and posterior roots passed, and to these nerve roots themselves. Frontal longitudinal sections through the base of the anterior fissure showed on either side the demyelinated anterior pyramidal tracts, grey matter of anterior horns, and a myelinated peripheral zone, with obliquely-coursing nerve roots (fig. 90): in Marchi sections those remaining fibres were found to be in an early stage of degeneration. Glia-stained sections showed that an advanced, but not complete, degree of sclerosis was present, and that this was most marked in the more central parts of the posterior and lateral columns. In this sclerosis many still large nuclei were left—nuclei forming the nodal points of radiating fibrils—showing that the tissue had not yet reached its more complete degree of sclerosis. Even in the lateral columns there was no evidence of the sclerosis having developed through stages of an increasing glia hyperplasia. Axis cylinder stains, both Cajal's and

Bielschowsky's, at every level gave a striking illustration of the extensive persistence of the axis cylinder in not only demyelinated, but in far advanced sclerotic tissue (fig. 427). At not a single level of the many examined were these wanting: they also retained their normal arrangement, calibre, and numbers to a remarkable degree. It must be remembered, however, that the cross-section of the cord was much smaller than normal. Further, the ganglion cells in the demyelinated and sclerotic tissue showed all degrees of pigmentation, atrophy, and disappearance, but very many rounded forms were present, with an otherwise normal structure and chromatophile granule content and arrangement (*cf.* fig. 410). In Marchi sections, it was possible to recognise a few fat granule cells at almost every level: these were, in most of the segments, confined to the walls of the vessels, and longitudinal sections showed beautifully long stretches of capillaries and transition vessels with a single outer layer of these cells along their whole course or at isolated stretches. Marchi sections thus gave a picture almost as completely negative as the Weigert sections, but there were also present a few isolated areas still in a stage of fat granule cell myelitis. Such areas, as a rule, immediately adjoined the grey matter, especially mesialwards from the posterior horns.

In the medulla oblongata, pons, and mid-brain, the extensive peri-ventricular and peri-aqueductal sclerosis is well brought out in figs. 76–82. The cranial nuclei, without exception, were involved, and their cells showed marked pigmentation and a degree of atrophy not nearly so marked as those in the anterior horn of the cord. Most of the areas also showed not so advanced a degree of sclerosis, and several areas were present in a stage of fat granule cell myelitis.

In the brain the areas were present in all stages of fat granule cell formation, and in all degrees of sclerosis, but the majority examined still showed fat granule cells distributed throughout the tissue as well as in the walls of the blood-vessels. The ganglion cells of the cortex throughout not only the areas but in adjoining convolutions, which showed no patch, were found to be surrounded or replaced by satellite cells (fig. 393). Cortical and subcortical areas presented a marked persistence of the axis cylinders. The degree of peri-ventricular sclerosis, the affection of the basal ganglia, the demyelination of long stretches of medullary rays, and the frequent involvement of the cortex, all of which were more marked than in any other case, is well brought out in figs. 70–75.

The optic nerves, chiasma, and tracts were completely gelatinous to the naked eye, and as it was evident that they were demyelinated, the tissue was fixed in alcohol for Cajal's stain. It was found that there was an apparently complete persistence of even the finest axis cylinders, and that these were almost unchanged in calibre. Figs. 431 and 432 are taken from one optic nerve and the chiasma respectively.

The soft cerebral and spinal membranes were thickened and the vessels, both of the meninges and of the nervous tissues, were infiltrated with cells of a lymphocyte type.

Topographical Distribution of Areas in Weigert Sections.

Spinal Cord (figs. 83–90).—Areas of sclerosis caused almost a complete transection of the cord at every level, and in no section were more than a few normal fibres present. These, as a rule, occupied the marginal areas and frequently exhibited a marked symmetrical arrangement (fig. 87). The whole cord from the upper cervical region to the lowest sacral segment seemed to be involved in the sclerosis, and the margins between white and grey matter were invisible. The normal peripheral fibres sometimes formed a continuous band, occupying the region of the posterior or lateral circumference of the cord, or individual small groups of fibres were scattered irregularly along the circumference. The fibres frequently stain faintly, and are obviously involved in an early stage of sclerosis. In the eighth cervical segment a larger triangular band of darkly-staining fibres is present on each

side of the anterior median fissure, and this area of normal tissue on one side includes a portion of the grey matter. This triangular area on both sides extends into D1, but is diminished in size and is soon lost. Small symmetrical groups of normal fibres are here found at the tip of both posterior horns. In the upper dorsal region the normal fibres are found in three isolated triangular groups. Such small triangular groups of normal but faintly-staining fibres are found at numerous levels of both the lower dorsal and lumbar cord. The sacral region shows the same extreme involvement.

Medulla Oblongata.—Absent in Weigert sections.

Pons Varolii.—Lower Third (fig. 76).—The distribution of the sclerosis is most irregular and is especially developed around the floor and roof of the IVth ventricle. The whole of the floor of the ventricle is affected, with the exception of a small band at the median raphe, which includes the posterior longitudinal fasciculus. On the one side the sclerosed tissue forms a large triangular area, the base of which extends from the median raphe to the angle of the ventricle, and the apex reaches as far forwards as the tranverse fibres of the pons. It thus completely blocks out the whole of the corresponding restiform body, and as it extends around the angle of the ventricle, the nuclei of Deiters and of Bechterew cannot be distinguished. The VIIIth nerve passes into this area of sclerosis: the nucleus of the VIth nerve and part of the VIIth are also involved in this area. Close to this larger area are three smaller ones, one of which exactly picks out the superior olive, the second lies between this and the lateral fillet, and the third lies in the formatio reticularis. Several small or oval areas are present amongst the transverse fibres of the pons. On the opposite side a tongue-like projection is seen extending from the floor of the IVth ventricle along the mesial side of the restiform body; this involves the spinal root of the Vth nerve, and a part of the ventral cochlear nucleus. A small dense area and several early areas are present in the restiform body. Two further small areas lie on the surface of the pons, one just mesial to the entering fibres of the VIIIth nerve, and one at the level of the anterior margin of the pyramids. The lateral walls and roof of the IVth ventricle are extensively affected, and a sharply-outlined area obliterates the posterior portion of the dentate nucleus on the right side. In front of this nucleus, in the white matter of the cerebellum, lies a small area surrounded by a zone of faintly-staining tissue, also with a sharp outline. A large diffuse early area is also found in the opposite central white matter of the cerebellum.

Middle Third of Pons (fig. 77).—The peri-ventricular involvement on all sides is very striking. The whole of the floor of the ventricle is sclerosed, and six irregular sclerotic projections pass ventrally from this base line. The sclerosis extends laterally around the angles of the ventricle: on the right side the dentate nucleus escapes, but the white matter adjoining contains two rounded areas, each with a zone of shadow sclerosis: on the left side the dentate nucleus contains two early areas, the anterior of which is continuous with the sclerosis of the angle of the ventricle. Several large and small early areas are found in the central white matter of the cerebellum, and the white matter of the flocculi is also affected. In a section at a higher level (fig. 78) the peri-ventricular sclerosis forms a broad zone so extensive as to involve the whole of the floor, sides, and roof of the ventricle and the complete vermis: from this zone projections of sclerotic tissue pass anteriorly into the middle peduncle, cutting it across on one side and reaching to the surface of the pons, and laterally and posteriorly into the white matter of the cerebellum. In the remaining portion of the pons several dense and early irregular areas are found. Two lie to one side of the median raphe and are united by a narrow band: they involve the pyramidal fibres, the transverse middle peduncle fibres, and the grey nuclei of the pons. Other three lie just in front of the trapezium and involve very much the same fibres as the last. The zone of sclerosis along the lateral sides of the ventricle extends into the hilum of the dentate nucleus on both sides. Several other areas are found, affecting the lamellæ of the dentate nuclei, and the white matter of the cerebellum. On the right side the patches are oval, sharply defined

and fairly large : on the left there is one very large dense area surrounded by a more diffuse shadow sclerosis, which extends to the margin of the foliæ of the cerebellum.

Upper Pons (figs. 79–80).—The peri-ventricular tissue is again very involved on all sides. A few fibres stain darkly in the anterior medullary velum, which is otherwise involved. The posterior third of one superior cerebellar peduncle is sclerosed, together with a narrow band on the surface. Both superior longitudinal fasciculi are demyelinated and a bulb-shaped projection passes laterally from them into one formatio reticularis. The opposite superior cerebellar peduncle shows a broad band of sclerosis which extends forwards to the anterior margin of the middle peduncle, thus involving some of the deep fibres of the Vth nerve, the lateral fillet, the tract of Gowers, and adjoining fibres of the formatio reticularis and middle pontine fibres. On the opposite side a broader and more irregular band completely cuts across the middle peduncles and some of the fibres of the Vth nerve, and continuous with this broad zone a projection passes into the formatio reticularis. On the anterior surface of the pons three smaller, flattened, oval areas are present, one close to the middle line and the other two on either side of it. A large number of very minute areas are to be found involving individual bundles of the transverse fibres and the associated nuclei, or bundles of the pyramidal tracts.

At the level of the decussation of the superior cerebellar peduncles (fig. 81) the sclerosis around the aqueduct of Sylvius is very well developed, but one of the posterior longitudinal fasciculi has completely escaped and stands out clearly in the sclerotic tissue. From the peri-central sclerosis a narrow band passes forwards in the middle line expanding suddenly to a large bulbous extremity which obliterates the decussating fibres of the superior cerebellar peduncles. Small areas are found on both sides lateral to the superior cerebellar peduncles, and several small areas are found on the surface just posterior to the transverse fibres of the pons.

Mid-Brain (fig. 82).—Around the aqueduct of Sylvius a broad zone of sclerosis extends into the surrounding tissue on all sides, involving most of the structure of the tegmentum. The lateral margins of the corpora quadrigemina stain normally, but both third nuclei are lost. The adjacent fibres of the IIIrd nerves and adjacent parts of both red nuclei are also affected, and in addition several small, round areas are present in the substance of the red nucleus on both sides. Early shadow sclerosis is seen in both substantia nigra, but both crura are unaffected except for a slight early sclerosis close to the lateral sulcus.

Cerebral Hemispheres.—(1) Section through the middle of the basal ganglia (figs. 70–71): at this level the peri-ventricular sclerosis is the dominant feature. This is most marked around the posterior horns of the lateral ventricle and along the sides of the optic thalamus.

On the right side a dense irregular zone of sclerosis is present along the whole lateral wall of the ventricle, and at the apex of the posterior horn this extends as a roughly quadrilateral area into the adjacent white matter, cutting across the tapetum, the optic radiations, and inferior longitudinal bundle. The involvement of the anterior horn is limited to a few small areas in the immediate white matter : this sclerosis is separated from the ventricle by a narrow band of normal tissue. The surface of the right optic thalamus is irregularly attacked. Dense areas occur at its anterior and posterior borders, with earlier areas between them, and from the middle areas sclerotic tissue extends into the substance of the thalamus. One large defined patch, roughly triangular, occurs just between the optic thalamus and the lenticular nucleus, involving part of the genu of the internal capsule. A smaller round area involves the retro-lenticular portion of the internal capsule. Two small areas are present in the claustrum, and sclerotic tissue extends from these areas into the medullary rays of the convolutions of the island of Reil. The convolutions of the parietal operculum show extensive involvement both of the medullary rays and grey matter, and similar areas occur in the white matter of the frontal operculum. The parietal and occipital lobes both show numerous areas : some of these are limited to the white matter, others occupy the

transition zone between white and grey matter, and a few small areas are limited to the grey matter.

On the left side an even broader band of sclerosis extends along the margin of the lateral ventricle from the caudate nucleus to the posterior horn. A few minute areas are found on the ventricular surface and in the substance of the splenium, and from the posterior horn irregular projections of sclerotic tissue pass into the adjoining white matter, again cutting across the tapetum, the optic radiations, and the inferior longitudinal fasciculus. Along the course of these bundles of fibres small round or oval areas are found in the substance of the white matter of the occipital lobe : some of these reach to the medullary rays of the convolutions of the calcarine fissure. The anterior horn shows a patch more or less triangular, near its tip, and another area extends inwards just anterior to the caudate nucleus. The genu of the corpus callosum at this level is normal. The optic thalamus is very extensively affected, the irregular surface zone extending inwards into its substance for about one-third of its transverse diameter, leaving here and there a few bundles of less affected fibres. Two isolated early areas are seen in the substance of the optic thalamus itself, one circular, and the other, elongated, involves the internal capsule. Numerous minute elongated areas are present in the claustrum and on either side of it, and one of these extends for some distance into the putamen. From the claustrum the sclerosis extends into the apices of several of the convolutions of the island of Reil. Several small areas are present in the frontal and parietal and occipital white matter, and an extensive demyelination affects the medullary rays, especially of the parietal convolutions.

(2) Sections through the upper part of the basal ganglia (figs. 72–73) show a still greater degree of peri-ventricular involvement : the lateral walls of the lateral ventricles throughout their whole extent on both sides presenting broad, irregular bands of sclerosis which cut into the substance of the optic thalamus and white matter.

On the right side the posterior horn sclerosis forms a wide band, the apex of which extends for a long distance into the occipital white matter, along the course of and involving the tapetum, optic radiation, and inferior longitudinal fasciculus. The splenium along its whole ventricular surface is also irregularly affected. The anterior horn presents a crescentic zone of sclerosis, which again extends into the white matter of the frontal lobe along several lines. The genu of the corpus callosum presents a narrow band of sclerosis along its ventricular surface. From the ventricular surface of the caudate nucleus and the lateral part of the optic thalamus, irregular areas of sclerosis project into their substance. Very numerous small circular areas are found in the anterior portion of the optic thalamus, and larger areas extend from it across the internal capsule into the lenticular nucleus. Two areas cut across the anterior limb of the internal capsule, cutting across the fibres passing between the caudate nucleus and the lenticular nucleus. A narrow band of sclerosis extends along the greater part of the claustrum : this is continuous posteriorly with the lateral portion of the posterior horn sclerosis, and laterally it sends projections into the medullary rays and grey matter of the island of Reil. Two well-defined areas are present in the frontal operculum, one limited to the cortex, the other reaching from the white matter to the surface. The parietal lobe shows numerous early and late areas in its white matter and an extensive and continuous affection of the medullary rays and cortex. In the occipital lobe very numerous small areas lie posterior to the splenium, while the tissue from posterior horn to the base of the calcarine fissure presents one long stretch of sclerosis, with smaller detached areas in the adjoining medullary rays.

On the left side the sclerosis resembles very closely that of the opposite side. The extensive involvement of the optic radiations ; the very numerous areas in the substance of the optic thalamus, internal capsule, lenticular nucleus and claustrum ; the continuous demyelination of numerous medullary rays and convolutions—especially of the parietal lobe ; and the areas in the corpus callosum, are all present in an equally marked degree.

(3) Section above the level of the lateral ventricles (fig. 74). A section through the cerebral hemispheres at this level shows over twenty isolated areas in varying stages of development. These are distributed through the grey and white matter, and more than half of them lie in the frontal lobe and are of very varying shape and size. They are described more fully in the histological study under " cortical and subcortical areas," as most of them involve the medullary rays and adjoining grey matter : a few are limited to the cortex.

(4) Sections of both hemispheres above this level (fig. 75) show an only slightly less involvement. Their distribution corresponds closely to that just described, but more are limited entirely to the white matter, and one or two are limited to the cortex. Sections still higher show that numerous areas are present up to the extreme vertex of the hemispheres, and that they are slightly more numerous at the frontal end.

Case III.

Clinical Notes.

Mrs G., aged thirty.—Patient was admitted to Professor Greenfield's ward, Royal Infirmary, Edinburgh, on the 13th September 1911, suffering from weakness of both legs and the right arm. Three years previously she had a miscarriage at the seventh month, and three months later began gradually to lose the power of the right arm and leg. This increased, until in three or four months she could use only the left leg and walk by holding on to things. Since that time she has become gradually more helpless and her general health feebler. On 12th September 1911 she had a shivering fit during the night, and on trying to get up her legs became rigid, and she fell back on the floor : she has little recollection of anything that has passed till her admission to the Infirmary on the day following.

Previous Health, etc.—Patient had inflammation of the bladder nine years ago. She has had four children, two of whom are alive and well. Her family history is negative. Her home surroundings are poor.

Condition on Admission.—Patient looked very ill and was half dazed. There is no œdema of the legs. Nervous system : the pupils react equally to light and accommodation, and the ocular movements are normal. The arms can be moved very slightly, and the grip on both sides is very feeble : there is a tendency to drop-wrist on both sides. Flexion and extension are very feeble. Very slight tendon jerks can be elicited in both arms. The legs can hardly be moved : the right leg cannot be drawn up at all, and the left only to a slight extent, and with great difficulty. Both feet can be flexed to a slight extent. The patellar reflex and the knee-jerks are absent on both sides. There is no ankle clonus, apparently from the tendency to a spastic extended condition. The abdominal reflexes are absent. There is no paralysis of the face. The urine had to be drawn off. There is no anæsthesia anywhere, as far as can be made out in the patient's half-dazed condition. There is not much of note in the other systems. Staphylococci and bacillus coli are present in the vaginal discharge. On ophthalmoscopic examination on 16th September the discs appeared normal.

Progress.—The symptoms varied much : at times the knee-jerks were exaggerated and at times were absent. The plantar reflex was extensor ; ankle clonus was present on the right and occasionally on the left side. Sensation was affected. Pus was present in the urine since admission, with swinging temperature and symptoms of pyelitis. Death occurred on the 24th November from toxæmia and exhaustion.

Post-mortem Report.

The body is that of a young, slightly built female. Rigor mortis general. No adhesions or excess of fluid in pleura, pericardium, or peritoneum.

Brain.—Skull-cap heavy and dense ; somewhat nodular appearance on the inner table,

especially in the frontal region; diplœ practically absent. Dura somewhat thickened but not unduly adherent. Pia arachnoid shows slight, patchy thickenings and is œdematous. Convolutions somewhat flattened over both temporal regions, especially the left. Slight thickening of the arachnoid at base. Vessels at base not altered.

Spinal Cord.—Thickening of dura in the cervical region. In the cervical, upper dorsal, mid-dorsal, and lumbo-sacral regions there are slightly depressed, firm, silver-grey areas varying from 2 cm. to 1 mm. in length. On section these have a grey gelatinous appearance, and extend from 1 mm. in diameter to the whole thickness of the cord. The cord has elsewhere a shrivelled appearance and is firm.

Lungs.—Slight emphysema of upper lobes and margins. On section there is congestion throughout.

The *liver* shows engorgement of larger vessels and cloudy swelling.

The *kidneys* are both enlarged: both ureters are dilated and slightly tortuous: on section there are found numerous small abscesses along the lines of the vessels in the cortex and in the pyramids; and the vessels and pelvis are much congested.

General Histological Characters.

There were no outstanding features in this case such as were noted in Case II, with the possible exception of the extensive diffuse and faint staining referred to as occurring frequently over the whole transverse section of the cord. This affected chiefly the lower dorsal and the lumbar segments. In marked contrast also to the widespread sclerosis of the cord in the previous case were the numerous isolated areas found, especially in the dorsal cord (fig. 109). Several of these were followed in serial section, and some were found to extend over not more than from twenty to thirty celloidin sections. Such areas were found most frequently around the dorsal portion of the posterior median fissure and in the lateral columns. The sclerosis of the cervical enlargement of the cord was, however, very marked, especially at C6 (fig. 105). Marchi sections proved the existence of very numerous areas in all stages of fat granule cell formation: some of these areas were very minute, corresponding to those cut in serial section; others extended over the whole antero-lateral column and the adjoining grey matter. Glia sections showed that the sclerosis was again more advanced in the central portions of the posterior and lateral columns. Bielschowsky preparations gave very unsatisfactory pictures in this case, but faintly-staining, swollen axis cylinders could be recognised in large numbers in most of the areas and in one or two of the minute areas in almost normal numbers. The ganglion cells showed changes which could be related to a slow sclerotic process and also to the toxæmia from which the patient suffered: at many levels the ganglion cells were deficient in number, having undergone a slow atrophy and disappearance, and other cells were found with marked condensation of the whole cell structure and deep staining.

The very numerous central areas showed beautifully the three types of areas met with in Marchi preparations: (1) that giving a negative picture, in which the process had become stationary; (2) that in which a peripheral zone gave evidence of an advancing process or one not yet exhausted (fig. 311); and (3) that in which the fat granule cell formation was at its height (fig. 301). All transitions between these types could be found, and sometimes an old area was found in which fusion with a more recent area had occurred along one margin. The glia stains likewise showed areas in all stages corresponding to the above, but also gave examples of the different degrees of sclerosis which an area may reach after the active process has apparently come to a standstill (figs. 367–369). The degree of peri-ventricular sclerosis is sufficiently indicated in figs. 93–96: it was found that this sclerosis, to a large extent, showed a peripheral extending zone of fat granule cells. The cortical ganglion cells, not only within the areas but in the adjoining stretches of the convolutions, again were sur-

rounded by numerous satellite cells. The blood-vessels had, to a very striking extent, their adventitial sheaths dilated, and in areas passing over from the base of the radiations into the deeper cortical layers the short and long medullary vessels, with widened adventitia, could be traced passing out from the area at both limits. In the areas in the central white matter the vessels often showed clearly the gradual disappearance of the cell content of the vessel wall—after the removal of the fat granule cells—and the very slow fusion of the previously separated connective-tissue fibrils of the adventitia into a " hyaline " homogeneous layer (*cf.* figs. 14–15).

Topographical Distribution.

Spinal Cord.—Cervical Enlargement (figs. 104–108).—At C5 the two most marked areas occur in the form of triangles : the one has as its base a line drawn outwards from the posterior commissure and its apex is the tip of the anterior fissure. The other has a curved base in one postero-lateral periphery of the cord : its apex is continuous with the lateral angle of the other triangle in the centre of the grey matter ; and it blocks out the whole of the antero-lateral column, the posterior horn, and part of the adjacent posterior column. A bowl-shaped area is present in the posterior columns, with its base on the surface of the cord, and diffusely-staining fibres extend antero-laterally from it. A narrow zone clearly outlines the other posterior horn, and two smaller areas appear in the lateral column of this side. At C6 there is almost a complete transection of the cord : five separate groups of normally-staining fibres remain—two of these lie on one side at the anterior and posterior root zones ; a third, larger, area near the opposite posterior root zone and anterior from it ; and the others are isolated fibres near to the central canal and the para-median septum on the same side. At C7 one large area involves the whole of one-half of the cord, with the exception of the tissue anterior to an undulating line drawn outwards from the base of the anterior fissure : it passes into the grey matter and posterior columns of the opposite side—leaving a small isolated group of fibres close to the posterior root-entry zone. The borders of the anterior fissure are also involved, and this sclerosis is continuous with the larger area. On the opposite side a semicircular marginal area is present, opposite the lateral aspect of the anterior horn, together with a smaller patch directly anterior to the horn. At C8 the anterior half of the cord stains well : the postero-lateral columns on one side are completely sclerosed, with the exception of isolated fibres in the posterior root-entry zone and in the column of Goll : and on the other side the postero-lateral columns, with the exception of its anterior portion and a band of fibres in the column of Burdach—the anterior horn escapes on this side, while on the opposite side only the antero-mesial portion is free.

Dorsal Region (figs. 108–111).—In D1 the whole of one-half of the cord is again involved, with the exception of a triangular area which lies in the columns of Burdach, immediately adjoining, and including, part of the posterior horn. On the opposite side the sclerosis involves the cord posterior to a line drawn outwards from the central canal, but into this sclerotic tissue a pointed process of normally-myelinated grey matter passes, so that the normal antero-lateral portion has one sharply concave and one curved border, both clearly outlined. In D3 the sclerotic area is in the form of a right-angled triangle—one side being formed by a line in the opposite column of Goll parallel to the posterior median fissure, the other side by a line drawn outwards from the base of the anterior fissure, and the base being formed by the curved circumference of the cord. A number of smaller areas are also present : one lies on the surface in the centre of the anterior root zone ; a second, marginal, area in the opposite side, half-way down the anterior fissure ; a third in the apex of the posterior horn ; and a fourth in the fibres immediately ventral to this horn. At D4 this latter area has become an elongated oval, and is continued by faintly-staining fibres as far

as the posterior commissure: a further area involves one anterior quadrant of the cord, with the exception of a group of fibres in the angle of the anterior fissure—this area is posteriorly surrounded by a faintly-staining zone. At D8 the posterior column area has again diminished in size and is limited to an oval, with indistinct outlines, surrounding the dorsal portion of the posterior median fissure: in both posterior horns a narrow band of demyelinated tissue stretches from the surface to the peri-central tissue; and a small marginal triangular area lies ventral to one posterior horn. At D10 the section is normal except for a narrow band in one posterior horn and a small area continuous with it in the posterior root-entry zone. At D12 the section is also normal, except for a slight peri-central sclerosis and a diffuse and faint staining in the antero-lateral and posterior columns.

Lumbar Region (figs. 112–113).—With the exception of the outer two-thirds of the posterior columns, the whole section at L1 shows extensive diffuse staining: at L2 the whole transverse section is similarly involved—a triangular area in the one posterior column alone escaping. This faint diffuse staining of the whole cord is continued throughout L3 and L4.

Medulla Oblongata.—At its lower level (fig. 98) there is a large and dense area of sclerosis present in the region of the substantia gelatinosa Rolandi, which is completely obliterated, together with the descending root of the Vth nerve and the adjacent formatio reticularis fibres. At the middle of the inferior olive (fig. 99) five small areas are present: these lie around the central canal, in the substantia gelatinosa Rolandi, in the descending fibres of the Vth nerve, in the gracile nucleus, and on the surface of the pyramid all on the same side.

Pons Varolii.—A section through the lower portion of the pons shows no marked involvement of the peri-ventricular area. One large area, however, extends from the floor of the ventricle as far as the VIIth nucleus: it involves also part of the VIth nucleus, the fibres of the VIIth nerve during this part of their course, and a small projection reaches as far as the mesial side of the restiform body. A large number of diffuse areas is present in the white matter of the cerebellum: most of these show a central zone of dense sclerosis, and two of these are present in the right dentate nucleus. Several small areas are present in individual foliæ of the cerebellum.

Middle Pons.—Sections at this level show few areas: one small patch extends inwards from the surface into the right cerebellar white matter, an early band of sclerosis extends from the ventricular surface into the right dentate nucleus, and the nodule is demyelinated. At a higher level the motor nucleus of the Vth nerve on one side is picked out, and still higher a round dense area is present anterior to the end of the right superior cerebellar peduncle. This area extends inwards from the surface and involves part of the lateral fillet and a portion of the fibres of the superior cerebellar peduncle before their decussation.

Mid-Brain.—The peri-aqueductal tissue is here irregularly involved: on one side the sclerosis affects only the adjoining grey matter, but on the other it spreads out as a triangular-shaped area into the white matter and includes a small portion of the anterior IIIrd nucleus. The emerging oculo-motor fibres are also involved, and several small areas lie in the crura on one side. The optic chiasma is cut across by an oval-shaped band of sclerosis (fig. 101) not far from the middle line, and a smaller oval area is found in the remaining substance of the chiasma, an area which in serial section is found continuous with the larger one. The inner aspects of both optic nerves, near the chiasma, are also affected (fig. 100)—the zone of sclerosis being continuous with the anterior margin of the sclerotic band in the chiasma.

Cerebral Hemispheres.—(1) Horizontal section through the basal ganglia near the base of the optic thalamus (figs. 93–94). The peri-ventricular localisation is in this case again very marked, especially around both posterior horns. These are surrounded by irregular zones of sclerosis, which extend for a varying distance into the adjoining white matter: on the mesial side of both horns this extends into the grey matter at the base of the fissure:

on the outer side it involves the tapetum, the optic radiations, and the inferior longitudinal fasciculus ; and posteriorly it is continued in a series of round or oval areas along the line of these groups of fibres to the apex of the occipital lobe. Around the anterior horns the sclerosis is less extensive, but the ventricular surface of the corpus callosum is affected by a narrow zone, specially marked at the angle of one ventricle. A broad band of diffuse, faint staining is present on the ventricular surface of the right optic thalamus, and within this incomplete sclerosis lie denser areas—especially towards its posterior and outer portion. Two well-defined early areas are found in the retro-lenticular portion of the internal capsule, and narrow bands of demyelinated tissue lie in the claustrum. The optic thalamus on the left side is not so extensively affected, but several small areas lie near its anterior ventricular surface. A number of minute areas occur in the white and grey matter of the different lobes : some of these are limited to the cortical white matter or to the medullary rays, but most extend from the medullary ray into the cortex. The most clearly-defined of these areas lie in the convolutions of the right parietal operculum, and the left middle temporal convolution.

(2) Horizontal sections through the basal ganglia above the middle of the optic thalamus (figs. 95–96). The peri-ventricular affection around the posterior horns is now still more evident : the lateral walls of the ventricle show broad zones of sclerosis, which on the right side can be traced in the white matter from the retro-lenticular portion of the internal capsule almost to the tip of the occipital lobe. On the left side areas, apparently isolated from this zone, pass outwards almost to the base of several of the medullary rays of the parietal convolutions. The ventricular surface of the splenium of the corpus callosum, on both sides, is eaten through by dumb-bell shaped areas, which pass through the forceps major into the medullary rays of the convolutions of the gyrus fornicatus. The ventricular surface of the central part of the splenium is also extensively involved, and in addition several minute, oval, isolated areas occur in its substance. The long diameter of these areas is in the long axis of the fibres. The anterior horn on each side shows an almost symmetrical involvement, being surrounded by a deep bowl-shaped or cup-shaped area, which in other sections is found to be continued for some distance into the frontal white matter. The ventricular surfaces of the optic thalamus show an early change, and the zone of sclerosis along the lateral wall of the posterior horn is continuous with sclerotic tissue at the posterior border of the medial nucleus. The branches of the lenticulo-optic and lenticulo-striate vessels have dilated adventitial sheaths and are surrounded by lighter-stained zones. One of these, on the left side, extends to involve a part of the optic thalamus, the posterior limb of the internal capsule, and a portion of the lenticular nucleus. Numerous minute and larger areas are present in the white matter of the medullary rays, some of which reach over into the cortex. On the left side one of these sharply cuts off the fibres as they pass to two convolutions of the parietal lobe, and completely demyelinate the rays and radiations of these, with the exception of a few radiating fibres of one convolution.

(3) In the hemispheres at all the levels above the roof of the lateral ventricles (fig. 97) a very large number of areas were present. Some of these were large and affected the white matter at the base of several adjoining convolutions, and extended to involve grey and white matter indiscriminately : the cups of several of the convolutions were also involved. The more striking of the areas are well brought out in figs. 97 (*a*), 279, and 281.

Case IV.

Clinical Notes.

J. W., admitted to Longmore Hospital, 2nd December 1910; died 17th January 1911. Duration of illness—five years.

Post-mortem Report, 19th January 1911.

Spinal Cord.—The cord as a whole is small, especially in the dorsal region. There are one or two calcified plates in the arachnoid. On the surface of the cord a number of irregular, bluish, gelatinous spots could be seen. A particularly large one could be seen in the upper lumbar region. This was removed for experimental purposes.

On section of the cord there were seen exceedingly well-developed patches of disseminated sclerosis. On the surface of the pons one distinct patch was found, but the brain was not cut into. The membranes appeared healthy.

Heart.—Small; slight fatty change at aortic and mitral valves. Otherwise healthy.

Lungs.—Left healthy. Right: externally showed extensive consolidation of the greater part of the lower lobe and posterior parts of upper and middle lobes, a few unconsolidated portions standing out very clearly against the consolidated portions. On section: throughout the consolidated parts were abundant white tubercles, which on microscopic examination were found to be due to a septic staphylococcal broncho-pneumonia. The distribution of these patches was apparently bronchial, but the consolidation was so extensive as to be almost lobar. There were no enlarged bronchial glands.

Liver.—Small, especially the left lobe. Healthy appearance on section.

The *spleen* and *kidneys* were small and very pale: the suprarenals were apparently healthy, and the mesenteric glands not enlarged.

General Histological Characters.

The parts most extensively affected in this case are the cervical and dorsal cord: the numerous cranial nuclei and the intra-medullary course of their fibres, especially those of the IIIrd, IVth, Vth, VIIth, and VIIIth nerves; and the tissues around the lateral walls and roof of the IVth ventricle, especially marked in relation to the dentate nuclei (figs. 121–122). The sclerosis around the walls of the lateral ventricle, with the exception of the walls of the descending horn which were very strikingly changed, was much less noticeable than in the previous case, but both the genu and splenium of the corpus callosum showed numerous areas (figs. 114–115). The basal ganglia showed a few isolated areas, and numerous areas were present in the convolutions, especially those of the upper levels of the hemispheres. The meninges and cortical vessels showed a considerable degree of cell infiltration.

The areas in the brain gave the impression of being, as a rule, of older date than those in the spinal cord. No areas in the central white matter were found in which there was not a well-marked central sclerosis, and many were present in which there was no evidence of an existing process. Such areas showed all degrees of sclerosis from a loose neuroglia network to a fairly dense tissue with fine meshes. Many areas, however, showed the presence of fat granule cells both in their peripheral zone and around the vessels in the central denser zone. The peri-ventricular sclerosis was also of an older date than in the previous case, and few fat granule cells were found in the walls of the sub-ependymal veins. The structure of the more recent areas in the cerebral white matter and in the transition zones gave the impression of a slow excentric sclerotic process. One or two of the areas (fig. 286, and *cf.* figs. 391–392) in the deepest layers of the cortex showed beautifully the typical structure of such areas, composed of a fine network of delicate capillaries, in the meshes of which lie large protoplasmic glia cells with branching processes, many of which are attached to the capillary walls. In the finer meshes formed by the capillary network and the branching processes lie numerous fat granule cells and small round cells.

The areas in the pons, medulla oblongata, and spinal cord all showed numerous fat granule cells, except those in the posterior columns of the cord, which were very densely sclerosed. Bielschowsky preparations demonstrated the persistence of many axis cylinders

in many of the areas, but these were more markedly swollen and faintly stained than in any of the other cases. The areas in the cord, especially in the cervical enlargement, were, as a rule, sharply outlined and, though many areas of " shadow " sclerosis could be traced, these were also less numerous than in some of the other cases.

Topographical Distribution of Areas.

Spinal Cord.—Cervical Enlargement (figs. 125–129).—At its upper level several areas are present : one lies in the posterior columns, roughly triangular, with its apex near the central canal : the other patches involve the crossed pyramidal and direct cerebellar tracts on each side ; and a band of sclerotic tissue connects that on the left with the area in the posterior columns. Lighter staining is present in the white matter at the tips of both anterior horns. In the sixth segment the posterior column patch is now limited to an area on each side of the middle line ; the lateral patches are still present—the one extending to involve the whole lateral region of the cord, the other separated from the surface by a narrow zone of normal fibres. The early areas close to the anterior horns are present as before. In the seventh segment the posterior area is very irregular in shape and very extensive. The sclerotic tissue extends anteriorly along the two sides of the anterior median fissure, involving the tissue around the central canal : it then passes dorsally to involve the whole of one posterior horn with all the corresponding white column and the greater part of the opposite posterior columns : it also extends laterally to involve the lateral region on one side. The opposite crossed pyramidal and direct cerebellar tracts show an area commencing at the surface and extending inwards to involve the posterior horn, and an oval area lies in the white matter in front of the right anterior horn. In the eighth segment two areas are present : one in the posterior region, which extends into the lateral portion of the cord, and the area in the opposite crossed pyramidal tract, which is now smaller. At the first dorsal segment the posterior patch is extremely irregular and forms a band which arises in the middle of one posterior column and extends into the middle of the opposite posterior column. It also sends a tongue-like projection in the direction of the central canal, the posterior commissure of which is sclerosed. This area is connected with a large sclerosed area in the opposite side of the cord by a number of separate strands which pass through the grey matter at the root of the anterior horn.

Dorsal Region (figs. 130–134).—In the upper dorsal segments the whole of the centre of the cord is occupied by a patch which sends marked projections both dorsally and laterally. At a slightly lower level this becomes broken up into three areas : one on the lateral side of the anterior horn, one in the posterior columns close to the posterior commissure, and the third in the lateral columns, involving crossed pyramidal and direct cerebellar tracts. About the middle dorsal region the most extensive involvement is a patch on both sides of the anterior median fissure, which extends into each anterior and antero-lateral column, obliterating the anterior grey matter on one side and including part of the corresponding posterior horns. In the lower dorsal region four individual areas are present : one, around the central canal, which extends into the posterior columns ; another occupies the whole of the lateral region of the cord ; a third involves the lateral horn and the adjoining grey matter ; and the fourth reaches from the tip of the anterior horn to the periphery of the cord. In the last dorsal segment there is a dense patch in the posterior columns, extending from the central canal backwards : a second dense area is found between the lateral horn and the surface ; and a third, early, area in the crossed pyramidal tract of the opposite side.

Lumbar Region (figs. 135–138).—In the lumbar region the areas are very few, small, and isolated. In the first segment a narrow ring of sclerosis surrounds the central canal, and there is an indication of early involvement of one crossed pyramidal tract. In the second segment early areas occur in both crossed pyramidal tracts, at the inner anterior angle of

the anterior median fissure on both sides, and in the white matter between the tip of the right anterior horn and the periphery. In the third segment the pyramidal involvement is scarcely recognisable. The posterior columns, near to the central canal, show early change; and a dense area is found along the left side of the anterior median fissure—extending to meet the area around the central canal and sending a projection into the grey matter of the posterior horn. In the fifth segment the central canal shows a slight ring of sclerosis, and evidence of early involvement is found along each side of the anterior median fissure.

Sacral Region (figs. 139–142).—In the first and second segments the change is limited to slight involvement of the lateral column on one side, but the third segment shows an almost complete sclerosis of the cord at this level—the only fibres escaping being a few peripheral, symmetrically-situated, antero-lateral and posterior fibres. The fourth sacral segment shows again little change—a small area being present around the central canal and at the tip of the left posterior horn. The nerve roots of the cauda equina are normal.

Medulla.—Just above the decussation of the pyramids. A quadrilateral area extends round the central canal: from one corner of this a large irregular patch passes to the anterior surface along the middle line, cutting through the middle of the decussation. At a slightly higher level (fig. 118) the central canal sclerosis is still well marked, but it is separated from the adjoining area, which occupies now the position of the left pyramid—leaving only a few superficial fibres intact. This portion, as it is traced upwards, diminishes in size and disappears altogether (fig. 119). The patch around the central canal is still present, together with a small elongated area in the right mesial fillet parallel to the median raphe. Small symmetrical areas are found in the outer arm of the accessory inferior olive on each side—limited to the grey matter of the nucleus.

Middle Medulla.—An isolated area is present between the right pyramid and the adjoining part of the inferior olive. This affects slightly the right pyramid and intersects the fibres of the hypoglossal nerve. A smaller area is found in a similar position on the opposite side. At a slightly higher level these areas disappear and only one patch is present, involving the right restiform body. This area, when traced upwards, becomes much larger and extends forwards along the surface almost as far as the level of the inferior olive (fig. 120). A similar area appears in the opposite restiform body and this, when traced upwards, is found to reach the angle of the ventricle.

Upper Medulla.—The floor of the ventricle is here normal. A "shadow" area extends from the angle of the ventricle on one side to the surface of the medulla, and two older areas are found in the same position on the opposite side—separated from each other by normal fibres and unconnected with the ventricle. The left mesial fillet is almost completely obliterated by an area which extends across the raphe into the opposite olive and part of the pyramidal tract. The left olive contains two areas, one between the olive and the pyramid and the other immediately dorsal to the olive. Several smaller areas occur in the formatio reticularis.

At the extreme upper limit of the medulla (fig. 121) a dense irregular area extends from the ventricle to the surface, obliterating altogether the restiform body and extending into the white matter of the cerebellum, and surrounded more or less by diffuse "shadow" areas. On the opposite side a diffuse, irregular area extends from the angle of the ventricle into the white matter of the cerebellum. On both sides the peduncle of the flocculus and the intra-medullary portion of the VIIIth nerve are involved. An early area is found also in the hilum of the right dentate nucleus.

Pons Varolii.—Lower Third.—A dense area extends along the floor of the ventricle from the median raphe to the angles: this is surrounded by a more diffuse sclerosis. An area of dense sclerosis is found along the middle third of the raphe, and here also is found a surrounding zone of lighter staining. Both facial nuclei and part of the fibres of each facial

nerve are involved in the sclerosis. The white matter of the cerebellum on both sides shows irregular diffuse areas of " shadow " sclerosis. The dentate nucleus on both sides contains in its hilum early areas, with an additional area of older date on the left side. The medullary cores of the vermis are markedly altered.

Middle Third (fig. 122).—The patches here are mostly small in size and are related to the ventricle. One area of sclerosis extends from the median raphe to one angle of the ventricle, and in relation to it a more diffuse " shadow " sclerosis is present. Several other diffuse and dense areas are present in the formatio reticularis on both sides, and one very marked area is present in the intra-medullary root zone of the left Vth nerve. Numerous patches are found in relation to the dentate nuclei, several small ones in the middle peduncle, and several of the cores of the foliæ of the cerebellum are cut across by minute patches.

Upper Third.—Patches, around the aqueduct of Sylvius, pass into the posterior portion of each superior cerebellar peduncle. Numerous smaller areas occur on each side of the raphe, in the formatio reticularis, and a dense area, in front of the superior cerebellar peduncle, obliterates the lateral and part of the mesial fillet. On each side dense areas of sclerosis involve the emerging root zones of the Vth nerve—the one on the right side extending irregularly from it around the surface of the pons into the middle peduncle fibres. Another small area is found in the transverse fibres near the left margin, while several early areas appear in the pyramidal and other fibres, and the grey matter in this region.

At a higher level (fig. 123) the areas round the Vth root zones increase rapidly in size, especially on the right side. The area around the aqueduct extends forwards to involve the IVth nucleus and the motor fibres of the Vth nerve on each side.

Mid-Brain (fig. 124).—A dense triangular area is found around the aqueduct of Sylvius: this extends along the median raphe to the anterior surface. Two areas are found in the corpora quadrigemina on one side and several small ones in the formatio reticularis on the other. Sclerosis also occurs, on both sides, near the point of emergence of the IIIrd nerves, the fibres of which are involved. Several small areas are present in both substantia nigra, one of which extends into the red nucleus on one side and another into the middle third of the crus on the same side.

Optic Tract and Chiasma.—On each side patches are found at the junction of optic tract and chiasma. The remainder of both optic tracts is unaffected till near the point of its passage into the corpora geniculata interna, when both are again sclerosed. The optic nerves on both sides show an advanced sclerosis: this sclerosis extends on both sides up to the junction of the nerve with the chiasma, and on one side extends into it. The chiasma is thus less affected than optic nerves or optic tracts.

Cerebral Hemispheres.—(1) Horizontal sections at level of the middle of the basal ganglia (figs. 114–115).

Ventricles.—Narrow bands of sclerosis are found irregularly distributed around the posterior horns. On the left side one of these passes for a considerable distance into the adjoining white matter and cuts across the optic radiations; the tips of both anterior horns also show similar areas, extending diffusely into the surrounding white matter; the lateral surfaces of both optic thalami are also extensively affected—the areas extending, for a varying distance, into their substance. Numerous small areas are found in the substance of the genu of the corpus callosum: some of these have their long axis parallel to the direction of the fibres. More extensive areas are found in the splenium, and the ventricular margin of the forceps major is markedly affected. The fibres of the anterior pillars of the forceps also show early involvement.

Basal Ganglia.—On the left side a well-marked oval area is present in the anterior part of the substance of the thalamus: a small circular patch in the putamen of the lenticular nucleus; and three irregular areas in the white and grey matter of the island of Reil, involving to a slight extent the claustrum. On the right side two areas are present in the substance

of the thalamus, in addition to the irregular zone of sclerosis extending inwards from the ventricular surface.

Convolutions.—Left side. Numerous very minute areas are found in the white matter of the frontal, parietal, and occipital lobes. An oval area is present at the foot of the fissure of Rolando in the medullary ray, and several small areas are confined to the parietal grey matter. A long narrow patch is present in the white matter of the occipital lobe: this involves the tapetal fibres, the inferior longitudinal fasciculus, and the optic radiations, and projects into the grey matter of the calcarine fissure. On the right side also several small areas are found in the white substance of each lobe: a very defined area is present at the foot of the fissure of Rolando—in a position almost exactly corresponding to the area on the left side—and the optic radiation is here again extensively involved.

(2) Horizontal sections immediately above the roof of the lateral ventricles (fig. 117). On the left side seven isolated areas, in various stages of development, are present in the white matter: these cut across the superior longitudinal fasciculus and the corona radiata. Several of these areas are surrounded by a zone of lighter staining. On the mesial surface the grey matter, especially on the surface of the convolutions, is very definitely involved. On the left side the cups of several of the convolutions on the mesial surface of the frontal lobe are picked out by a well-marked sclerosis; other areas are found in the white matter of the frontal lobe, and one very well-defined patch involves both medullary ray and grey matter of the convolution at the tip of the lobe. Another well-defined area, involving both grey and white matter, is present at the foot of the fissure of Rolando, in its anterior wall, and a smaller patch in the white matter of the post-Rolandic convolution, together with two early areas in the white matter at the foot of this gyrus. The cups of two of the convolutions in the parieto-occipital fissure are also affected.

(3) Sections of the hemispheres 1 cm. above the roof of the ventricles. Here only two areas could be detected microscopically: one in a convolution of the internal parieto-occipital fissure: this was an elongated oval patch which involved the medullary ray and extended into the adjoining grey matter on one side; the other area is found on the mesial surface of the marginal convolution.

(4) Sections at a still higher level (fig. 116) also show few areas. One is found in the white matter of the post-Rolandic gyrus, and one in the white matter of the upper frontal convolution towards the mesial surface.

(5) Sections through the hemispheres at their highest level. These show a sudden increase in the number of the areas. On the left side at least twelve can be identified microscopically. A very large oval patch is present at the foot of the Rolandic fissure: this extends across the grey matter into the white matter and then into the grey matter of the marginal convolution. Another oval area, involving both grey and white matter, is present on the mesial surface of the frontal lobe, and on the outer surface of this lobe three areas are present; one in the grey matter alone, one involving both grey and white matter, and the third in the medullary ray alone. Behind the pre-central fissure two areas are present: one limited to the grey matter and one to the medullary ray; and at the foot of the intra-parietal fissure a clearly-marked area involves the cup of the convolution. Small areas occur in the posterior part of the section.

(6) Sagittal sections through the temporo-sphenoidal lobe. These show a well-marked peri-ventricular sclerosis around the descending horn of the lateral ventricle. This extends into the adjoining white matter, intersecting the inferior longitudinal fasciculus and spreading into the radiations. The white matter of the hippocampal convolution is also extensively affected.

Case V.

Clinical Notes.

S. S.—The patient was a trained nurse, aged forty-four, born at Kirkwall. Her father died at sixty-four from " dropsy," and her mother at fifty from decline. She had two brothers, sailors, who have been lost sight of, and two sisters alive and well, while a third died at twenty-six from psoas abscess, and a fourth at thirty from typhoid. She had always been healthy. When she was thirty-four years of age, she suddenly became blind for a week in the left eye, with acute pain on movement. Three months later the right eye was similarly affected. Shortly after, when nursing in Perthshire, " something came into the muscles of the legs nearly making her fall," and something of this kind occurred periodically. She was able to continue at work nursing for the next four years, when she gave it up and took a house and kept boarders. She was last able to walk about one year ago, but she fell down a stair and injured her knees, and has never been able to walk since. Sensation in the lower limbs is fairly good, except to heat and cold. Both legs are quite helpless, being flexed on the thighs, and the thighs on the abdomen, and quite immobile. Babinski's sign is present on both sides. The upper limbs were only affected very late. Pain and weakness developed in the right upper arm, but no inco-ordination could be detected. Nystagmus was absent. Admitted to Longmore Hospital, 28th March 1906; died 8th March 1910.

Post-mortem Report, 10th March 1910.

Great contracture of lower extremities, the hips and knees being flexed at an acute angle. Numerous small ulcers over the right buttock from $\frac{1}{8}$ in. to $\frac{1}{3}$ in. in diameter. A large abscess containing about one pint of pus was found in the left buttock.

Brain.—Great œdema of pia arachnoid: the substance was soft. The under surface of the pons and medulla oblongata showed patches of sclerosis. The left optic nerve was grey and gelatinous as far as the chiasma, the right optic nerve was only partially degenerated. The chiasma was of a cream colour, and the right optic tract of a mixed colour.

Cord.—The spinal cord showed no thickening of the dura mater or other membranes. Greyish-red gelatinous-looking patches were seen in the cervical and dorsal regions.

Lungs.—Pleura free from adhesions. Both lungs œdematous. Caseous mass at root of left lung about the size of a large walnut and firmly encapsulated. Lower lobe of left lung partly collapsed.

Heart.—Contained pale yellow thrombus in the right side extending into the pulmonary artery. Muscular walls somewhat flabby, valves normal.

Liver.—Large, engorged with fluid blood and considerable fatty infiltration.

Spleen.—Diffluent; not much increased in size.

Kidney.—Right: capsule thickened and slightly adherent, leaving a finely granular surface on stripping. Cortex slightly reduced in size. Some calcareous deposits in tubules. Left: as in right, with addition of a few small abscesses in cortex and medulla. Several small capillary hæmorrhages in pelvis. Condition is one of " commencing surgical kidney."

General Characters of the Areas.

Only a few features call for reference here. The most extensive affection was present in the cervical, dorsal, and upper lumbar cord, and at several levels, especially in the cervical cord, there was a marked symmetry in the position and form of the areas—a symmetry which was continued throughout several segments and gave the appearance of an ascending and descending secondary degeneration (figs. 148–149). The areas found were, again, in

different stages of development, but here, perhaps more than in any other case, these different stages gave the impression of having been quite independent in time and not, as was so frequently the case, an extension of an already-existing process or the addition of a new process to one not already exhausted. Further, even in the densest areas of sclerosis, longitudinal sections showed that even the finest capillaries were patent : such capillaries could be traced over long stretches with a single or double row of red blood cells within their lumen. The vessel walls were, therefore, not so condensed as was often the case. And still further, it may be noted that in the lateral columns there were indications of a slowly-increasing glia hyperplasia, and in the optic nerves, in keeping with this finding, there was a very marked chronic interstitial change affecting both the connective tissue and the glia elements. Cajal and Bielschowsky preparations allowed numerous axis cylinders to be recognised, and the ganglion cells showed changes, mostly of an atrophic nature. The meninges were not thickened, but in the lumbar cord there was found a slight cell infiltration.

The medulla and pons were comparatively slightly affected in comparison with the changes found in most of the cases, but the roof and angles of the IVth ventricle showed a slightly greater degree of involvement than the floor and lateral walls. The brain in this case was not examined in large sections.

Topographical Distribution.

Spinal Cord.—Cervical Region (figs. 148–149).—In sections at the level of the third cervical segment, the sclerotic areas are very symmetrically placed : one occupies the posterior region, and other two, almost triangular in outline, are in the antero-lateral columns, separated from the posterior horns by fibres which stain faintly. On both sides these areas reach almost to the periphery of the cord. The posterior area is large and oval and extends from the base of the anterior fissure, across the commissures, almost to the posterior margin of the cord. Two projections, which pass laterally from this area, almost map out the posterior horns. In C4 this arrangement of the sclerosis is continued, but both the antero-lateral areas have increased in size and reach to the periphery, and the posterior area is subdivided into four—one around the central canal, one in each posterior horn, and one V-shaped, with the apex of the V in the anterior third of the posterior columns. The tissue between these areas stains faintly. At C5 the areas have greatly diminished in size : the two antero-lateral ones are now small but still triangular in outline, and reach from the grey matter of the anterior horn to the surface—on one side involving the greater part of the postero-lateral group of nerve cells. The other, subdivided, areas are still present, but smaller in size, the posterior one being an almost equilateral triangle bisected by the posterior median fissure. At C6 the largest area occurs as a broad band stretching from the central canal to the surface along the posterior median fissure. Narrow bands are present along the two sides of the anterior fissure, and the glia border zone is considerably widened along the anterior surface of the cord. Several minute areas are present, distributed irregularly in the white matter and posterior horns. At C7 the symmetry of the sclerosis is again very marked and corresponds closely to that found in C4. From a peri-central sclerosis bands radiate posteriorly and laterally, widening considerably as they pass towards the surface. These areas thus involve large portions of the anterior and posterior grey matter on either side : they are separated from the surface of the cord by bands, varying in width, of normally-staining fibres. Zones of diffusely and faintly-staining fibres occur around all these areas.

Dorsal Region (figs. 150–152).—In the first dorsal segment the arrangement is a modification of C7, but the patches are much more defined in shape, involve more of the grey matter, and the symmetry is not quite so striking, for the posterior sclerosis extends on one side to involve the whole of the posterior horn, and it is united by a narrow band to the sclerosis

in the antero-lateral columns. In the mid-dorsal region the areas are very irregular in outline, and nearly all radiate as narrow or broad tongue-like projections from the central canal. The base of both anterior horns is thus involved, together with the whole of the lateral horns and the greater part of each posterior horn. The anterior half of both posterior columns is also affected, and from this sclerosis, on one side, a dense band runs across the posterior root-entry zone to the surface—extending forwards to involve the fibres of Lissauer's tract. A small isolated area is present also in the antero-lateral column of this side. In the lower dorsal cord one large area is present : it occupies the whole of one antero-lateral column, except a narrow marginal zone, together with the anterior, lateral, and posterior grey matter and part of the posterior columns on the same side. A small isolated area is present in the opposite antero-lateral column.

Lumbo-sacral Region (figs. 153–155).—In the second lumbo-sacral segment a large irregular area, with diffuse changes at its borders, extends from the central canal to the surface of the cord on one side. Its position is roughly that of the area in the segment just described, but it does not pass so far anteriorly and posteriorly. In L3 this area is still present with a wider extension and faintly-staining outlines. At L5 all the areas have disappeared, and the cord is normal till the second sacral segment is reached, when a peri-central sclerosis gradually enlarges to involve each crescent and extends forwards along each border of the anterior fissure. Areas of sclerosis, limited to the grey matter, also occur in the antero-lateral group of nerve cells on the one side, and in the postero-lateral group on the other. These areas in the grey matter extend for only a short distance in longitudinal extent, and at the fourth sacral segment the only recognisable change is a slight increase in the peri-central sclerosis.

Medulla Oblongata.—At the level of the decussation of the fillet the appearance of the sections is practically normal, but slightly higher an area of sclerosis, in the middle line anteriorly, gradually increases and forms an elongated oval lying between the two inferior olives (fig. 143). This area involves the mesial and ventral portion of the mesial fillet, and a small part of the pyramidal fibres on both sides. At a higher level this area becomes lozenge-shaped, and the lateral angles pass into the hilum of each inferior olive (fig. 144). As this area is traced upwards it gradually lessens in size, and at the upper level of the medulla other small areas appear, all on the same side : one in the restiform body, one behind, and one in front of the inferior olive : the last of these sends a small process which extends forwards to involve the arcuate nucleus.

Pons Variolii.—Lower Third.—The roof of the IVth ventricle is extensively involved, the vermis and nodules being completely demyelinated. An irregular area also extends from the one lateral angle of the ventricle and involves Deiters' and Bechterew's nuclei. In the centre of the fibres of the middle cerebellar peduncle on the opposite side, a narrow area is present, and in the same side a large irregularly outlined area extends inwards from the antero-lateral surface of the pons—involving both pyramidal and middle cerebellar peduncle fibres. On both sides small areas occur, in the white matter of the cerebellum, involving the peduncle of the flocculus.

Middle of the Pons (fig. 145).—Slight irregularly outlined bands of sclerosis pass round the floor, lateral walls, and roof of the IVth ventricle. Three denser round areas are present between one angle of the ventricle and the lateral surface of the pons : one near the angle, one involving the root-entry zone of the Vth nerve, and one midway between these two points, involving both trapezoid and pontine fibres. Smaller areas are found in the white matter of the cerebellum, especially in relation to the hilum of the dentate nuclei and its outer lamellæ. Slightly above this level the peri-ventricular sclerosis becomes more marked, especially at one angle : the area on the pons surface, at the entry zone of the Vth nerve, is increased in size, and several areas occur in the white matter of the cerebellum.

Upper Pons.—At the lower part of this level the peri-ventricular sclerosis lessens and

the only area present is an oval one found in front of one superior cerebellar peduncle: this extends forwards to involve trapezoid and middle peduncle fibres. At the upper limit of the pons (fig. 146) this area is still present, but is displaced lateralwards, while another, on the ventral aspect of the pons, extends amongst the superficial transverse fibres for a short distance. As these areas are traced upwards, the latter increases in size for a time, becomes divided into two by a narrow band of dark fibres, and finally both divisions disappear: the former becomes smaller and soon disappears, while a further patch develops in the posterior part of the superior cerebellar peduncle.

At the level of the corpora quadrigemina (fig. 147) a peri-aqueductal sclerosis is present, together with three other oval areas with indistinct outlines. These lie, one in the middle line in front of the decussation of the superior cerebellar peduncles, a second in front of one lateral fillet, and a third on the same side, on the lateral surface of the pons.

Case VI.

Clinical Notes.

C. G.—Patient was a baker's shopwoman, aged twenty-four, and was admitted to Longmore Hospital on 12th October 1910. She died on 28th March 1911.

No notes of this case could be found previous to her admission to hospital, and even these were very scanty. She looked pale but healthy, although both legs were powerless. On 24th March she suddenly had a convulsion, becoming rigid, cyanosed, and biting her tongue. The arms and legs twitched and nystagmus developed. She remained in an unconscious condition until death occurred four days later.

Post-mortem Report, 29th March 1911.

A large number of small superficial ulcerations of the skin was found on the buttocks and on the lower part of the back. No emaciation nor contractures, and the body was well nourished.

Spinal Cord.—Some adhesions in pia arachnoid. Lower part congested, but not atrophied. On section typical patches of disseminated sclerosis could be seen in various places.

Brain.—Dura mater normal. Surface œdematous. Cortex somewhat congested and post-mortem development of gas below pia. Marked injection of all small vessels over pons and medulla. The pons looked very small.

Lungs.—Left: lower lobe was deeply congested and there were a number of hæmorrhages both on the surface and in its substance. Upper lobe normal. Right: considerable area of consolidation near the root involving both upper and lower lobes in a condition of grey hepatisation.

Kidneys.—Both kidneys are small, show cloudy swelling; the capsules strip freely.

The *spleen* is somewhat large, of pale colour, and firm.

The *liver* shows marked cloudy swelling, with some wedge-shaped areas paler than the rest—so-called infarcts.

The *heart* is small: muscle good colour. Ante-mortem clot on both sides. Valves healthy.

General Characters of the Areas.

The outstanding feature in this case was the absence of any marked degree of sclerosis in any of the areas, either spinal or cerebral. The patches, almost without exception, were in a stage of fat granule cell formation (figs. 178–184), and the more advanced showed a moderate amount of glia fibril formation.

In the cord the extensive and diffuse character of the demyelination is brought out in

figs. 166–173. In the cervical and dorsal segments there is no clearly-defined outline to any of the areas in Weigert staining, and Marchi sections of the adjoining blocks, or Scharlach R. frozen sections, gave a picture of fat granule cell formation corresponding closely to the extent of the demyelination. Bielschowsky preparations showed that a very large number of the axis cylinders had disappeared and were in a granular condition. In the lower cervical and dorsal cord many normal axis cylinders were retained in the ventral portions of the posterior columns, and in the more isolated and smaller areas found at these levels. The ganglion cells were in all stages of chromatolysis, both in the less and more affected levels : they were not deficient in number, and showed no marked atrophy or pigmentation. The glia marginal zone was very widened : the nerve roots throughout the cord and of the cauda equina showed a certain rarefaction ; and the membranes a slight degree of cell infiltration.

Similar changes were found in the areas in the medulla oblongata, pons, and brain, and in the cerebellum. Areas in relation to the hilum of the dentate nucleus (fig. 177) showed beautifully in Marchi sections, the early involvement of the longitudinal fibres passing to the lamellæ.

In the brain no horizontal sections of the hemisphere were cut except at the lower level of the basal ganglia, in close relation to the sub-thalamic region. These sections and those through the mid-brain showed the involvement of the red nucleus on either side (figs. 161–162). Over one hundred blocks of tissue, containing isolated or confluent areas, were taken through, in celloidin and paraffin, from the hemispheres above this level, and these all showed that the areas were in the stage of so-called "fat granule cell myelitis." A few showed a central clearing up of these cells (fig. 182), and an advancing glia fibril formation (figs. 365–366). The peri-ventricular affection, which was very marked, was also at an early stage (fig. 181). Areas were found in every portion of the hemispheres, and especially numerous in relation to the central convolutions. In most of these areas the extension was from subcortical white matter to the deper layers of the cortex : the Betz cells were extensively involved (fig. 387) ; and the vessels in these layers surrounded with fat granule cells. The optic tracts were normal as far as they could be followed, but an early affection of the chiasma and both optic nerves was present (figs. 163–165). The soft membranes of the brain showed a moderate degree of cell infiltration.

Topographical Distribution.

Spinal Cord.—Cervical Enlargement (figs. 167–169).—At the upper part the whole of the posterior columns and the greater part of the left antero-lateral columns are involved in an early area of sclerosis. A few well-marked patches also appear at the two entering posterior root-entry zones and at the extreme lateral border of the cord. As we descend the cord the group of normal fibres in the antero-lateral columns is greatly increased—the principal fibres affected being in the position of, though not strictly limited to, the crossed pyramidal tract. An earlier area is found in the opposite antero-lateral columns—the peripheral cerebellar tracts escaping. At C5 the whole of the right antero-lateral and posterior columns are affected—only a few fibres at the base of the anterior median fissure and at the periphery of the posterior roots escaping. Signs of early involvement are also found at the base of the opposite direct and crossed pyramidal tracts.

In the segment lower one large area is present : this is mostly unilateral and involves posterior and antero-lateral columns. A zone around the periphery, especially wide anteriorly, escapes, while the outer two-thirds of the opposite posterior columns show only slight involvement. The opposite crossed pyramidal and direct cerebellar tracts show early involvement as before.

At the lower part of the cervical enlargement the greater portion of the cord is involved.

The posterior columns are occupied by an advanced patch : the anterior and antero-lateral by early sclerosis, but towards the lateral margins of the cord on both sides areas of more dense sclerosis are present in the centre of early diffuse areas. The only fibres unaffected are those at the tip of the posterior horns and at the lateral and anterior periphery of the cord.

Dorsal Region (figs. 170–173).—In the upper dorsal segments, the posterior columns are densely sclerosed. There is evidence of early involvement of the crossed pyramidal tract on both sides. The grey matter is almost unaffected ; and a few normal fibres are found at the periphery of the posterior columns. At the level of the third and fourth segments the areas have increased in size, and the normal fibres form a narrow zone round the antero-lateral margin. About the middle dorsal region the single area found above is again broken up, and three areas are present. One occupies the middle two-thirds of the posterior columns, and the other two are in the centre of the lateral columns. These patches are continued, without any very great change, throughout the whole middle dorsal region, the two lateral areas then diminish in size, while the posterior one increases, and in the lower dorsal segments occupies the greater portion of the posterior columns.

Lumbro-sacral Region (figs.174–176).—The upper lumbar segments show little involvement, but in the fourth segment five separate areas occur : one at the tip of the posterior horns on each side, one has picked out the postero-lateral group of cells in the anterior horn of the left side, another occupies a similar area on the opposite side, but has extended to involve the white matter lying between it and the surface of the cord, and the remaining area forms a circular ring around the central canal. The marginal glia zone varies considerably in thickness, and at the lateral margins shows extensive development. In the fifth lumbar segment diffuse early sclerosis is found towards the middle line in the posterior and antero-lateral columns. In the sacral cord the sections are normal, with the exception of a possible narrow ring of sclerosis around the central canal and an increase in width of the lateral marginal glia.

Medulla.—Just above the decussation of the pyramids (fig. 158), one large area is present on the antero-lateral portion of one-half of the medulla, extending inwards to involve the lateral nucleus, the emerging spinal accessory nerve, and the corresponding decussating pyramidal fibres. A smaller but earlier area is present in the same position on the opposite side, and a third, quadrilateral, area surrounds the central canal and extends on each side into the nucleus gracilis. At the lower level of the inferior olive (fig. 159) these three areas are still found—one of which involves the inferior olive and is continuous with the peri-central area. In the region of the middle medulla (fig. 160) the internal two-thirds of the left inferior olive is occupied by an area of sclerosis, which blocks up the hilum and extends across the middle line to involve the mesial third of the opposite fillet, and a portion of the posterior pyramidal fibres. A further area is found in the position of the substantia gelatinosa Rolandi : it involves all the descending root of the Vth nerve, but is separated from the periphery by normal fibres. There is also an area around the central canal and a small one in the formatio reticularis, through which the fibres of the mesial fillet pass previous to their decussation.

Lower Pons (fig. 156).—The patches here are found in two positions : firstly, around the floor and angles of the ventricle ; and secondly, at the lateral sides of the pons, close to the VIIIth root. The former areas are extremely irregular : they do not involve the dentate nucleus but send anteriorly a number of projections which involve the whole of one restiform body, the posterior portion of the other, and all the nuclei along the floor of the ventricle. A well-marked oval area is present in the right mesial fillet, and early diffuse patches in both pyramids. On the left side a dense area extends from the corresponding pyramid to the root of the VIIIth nerve, and on the opposite side of the VIIIth nerve a large patch is present extending from the angle of the ventricle to the surface of the middle peduncle, but intersected by two strands of normal fibres. Other areas are present in the middle of the formatio

reticularis, at the posterior part of the olivary nucleus, and around the entrance of the right VIIIth nerve.

At a slightly higher level the areas are still more numerous and more extensive. Those along the floor of the IVth ventricle now extend to the anterior end of the dentate nucleus. Deiters' and Bechterew's nuclei and the posterior longitudinal fasciculus on both sides are all involved. Both mesial fillets show large oval patches, and the whole of one pyramid with the adjacent grey matter and transverse fibres of the pons are sclerosed. A dense area, including three-quarters of the opposite pyramid, extends to the entry zone of the VIIIth nerve, and from both angles of the ventricle a broad area extends to the surface of the pons, practically isolating it from the cerebellum.

Pons at Level of the Vth Nerve Root (fig. 157).—Here the areas are again best developed at the angles of the ventricles. From this they spread along the floor of the ventricle to meet in the middle line and from the right angle upwards to the roof of the ventricle, and both inferior peduncles are involved as they pass to the dentate nuclei. A large early patch is present in the left pyramid and adjoining grey matter and transverse fibres, and on the opposite side the outer half of the pyramid is affected. The intra-medullary portion of the left Vth nerve, immediately in its entrance, is markedly affected, and a smaller area involves the opposite nerve fibres. A number of smaller areas are found in the formatio reticularis and just anterior to it.

Upper Pons.—Extensive sclerosis is present around the aqueduct. This reaches into the superior cerebellar peduncle on both sides, and on the left passes through the peduncle to the surface. These areas also extend anteriorly through the formatio reticularis to involve, on one side, the whole of the mesial fillet and adjoining pontine fibres. Amongst the latter a number of smaller patches are irregularly distributed. On the opposite side a single large area occupies the outer two-thirds of the pyramid and adjoining grey matter, reaching to the surface of the pons. The VIth and VIIth nuclei on both sides are affected, as well as both motor roots of the Vth nerve.

Mid-Brain (fig. 161).—A triangular area is found around the aqueduct: this extends to involve the third nucleus on both sides. Both red nuclei show irregular areas on their dorsal aspect: that on the right extends through the substantia nigra into the crus, where a circular patch extends about half-way to the surface in its middle third. Another large irregular area is found on the opposite side at the point of emergence of the IIIrd nerve: this area passes upwards into the ventricle part of the corresponding red nucleus. At a slightly higher level the red nucleus is not so extensively involved, but the patches in the crus become more extensive.

Cerebral Hemispheres.—At Level of Lower Border of Optic Thalamus.—The area around the aqueduct is considerably more extensive and spreads into the greater part of one anterior corpora quadrigemina, a portion of the other, and extends downwards in the middle line in a triangular process between the two red nuclei. A second large irregular area is found in the middle line at the point of emergence of the IIIrd nerve: this area stretches upwards into the ventricular portion of both red nuclei (fig. 162).

On both sides a thin irregular patch occupies the greater portion of the claustrum and extends into the grey matter of the convolutions of the island of Reil. Two small patches are present in the parietal operculum of one side, and similar but more extensive areas on the opposite side. The posterior horns of the lateral ventricle show a number of irregular patches, which extend outwards into the adjoining white matter. On the right side this area extends to involve the tapetum, inferior longitudinal fasciculus, and optic radiation —all of which are also involved in a well-marked round area at the base of the calcarine fissure. Within the calcarine fissure on this side two small areas are found extending from the surface of the grey matter directly into the medullary ray.

Optic Nerves and Chiasma (figs. 163–165).—Sections cut horizontally through the chiasma

and adjoining portions of the optic nerves and tracts show extensive early involvement of both optic nerves on the lower surface. This sclerosis stops short of the chiasma, but as we pass deeper into the chiasma the sclerosis passes as a narrow band along the anterior margin and at the deepest portion of the chiasma cuts it across from side to side.

Case VII.

Clinical History.

J. M'N.—The patient was a cabinetmaker, aged forty-two, born in Edinburgh. He was admitted into Longmore Hospital on 11th October 1905, and died on 30th May 1909. On admission he showed complete paralysis of both legs and of both arms.

His father died at the age of sixty-three from phthisis; his mother was still alive and well. He had two brothers and one sister who died in childhood, and five brothers and two sisters living, all of whom are in good health, with the exception of one sister, who has suffered from "nervous troubles" for ten to twelve years.

The disease was first noticed seventeen years previously, when he says he felt cold in his back after being at an entertainment. This was followed by some shakiness in the limbs on the left side, but this soon passed off, and he was able to continue at work for four years afterwards. About five years ago he finally lost the power of walking; before this he had gradually required increasing help, first from sticks, then from crutches.

His hearing had been very defective, especially in his right ear, since he had scarlet fever when six or seven years of age. His eyesight was defective, especially the left eye. There was nystagmus on looking upward or to the left; the movement to the right was defective. The speech was slurring. There was slight increase of myotatic irritability, and much unsteadiness in attempting to grasp anything. The grasp of the right hand was weak, that of the left hand extremely feeble. The lower limbs were completely paralysed, although sensation appeared to be normal. Both knee-jerks were exaggerated: there was well-marked ankle clonus on each side, and a double Babinski reflex. The control of the sphincters was retained. The thoracic and abdominal organs appeared normal.

Progress.—The patient remained in very much the same condition during the whole of his stay in hospital. He had at intervals severe attacks of hiccough lasting from six to nine days. For some weeks before his death he did not appear to be so well, but nothing definite could be made out. He died somewhat unexpectedly.

Post-mortem Report, 31st May 1909.

Both arms were atrophied, the fingers were flexed at all the three joints. The ankles were extended and the knees and hips were straight. Slight œdema of both feet; and the abdomen was slightly green.

Brain.—The vessels at the base were quite normal. Slight thickening of the fine membranes near the left IIIrd nerve. Slight milky opacity in membranes at posterior inferior part of the cerebellum. Slight atrophy of convolutions at vertex without material thickening of membranes. On section a large patch of sclerosis was found in the optic radiations of the right hemisphere. Other patches with a clearly-defined outline and a greyish-red gelatinous appearance were seen in front of the caudate nucleus. The grey matter round the aqueduct of Sylvius presented a similar gelatinous appearance. On one side there was a patch of the size of a threepenny piece near the red nucleus. The grey matter under the floor of the IVth ventricle in the medulla oblongata presented similar patches of sclerosis, with the same sharp margin.

Cord.—The spinal cord showed clearly-defined islands of sclerosis throughout its whole length. These were mostly separate from each other.

Lungs.—Both lungs were adherent to the chest wall, especially in the upper lobes. They were studded with broncho-pneumonic tubercles. The lower lobes of the right lung were in a state of grey hepatisation and very friable. The lower lobe of the other lung was congested, but not consolidated.

Heart.—There was some thickening and fusion of several chordæ tendineæ, but no narrowing of the orifice of the mitral valve. The cardiac muscle was fairly normal.

General Characters.

The areas in the spinal cord and those in the brain were here in marked contrast to one another. The former throughout the whole extent of the cord showed a more advanced and uniform degree of sclerosis than in any of the other cases—no "early" areas were found. In the brain, on the other hand, the areas showed all stages of a commencing and advancing sclerosis.

In the cord the sclerosis conformed closely to the typical anatomical picture given by CHARCOT: the areas (1) were, as a rule, insular; (2) had clearly-defined outline; (3) presented an advanced and in many cases complete degree of sclerosis; (4) showed a marked persistence of the axis cylinders; (5) atrophic changes in the ganglion cells; (6) chronic changes in the blood-vessels; and (7) the glia marginal zone throughout the whole cord was very widened. Marchi sections, both transverse and longitudinal, however, showed that at numerous levels a few fat granule cells were still present in the walls of the blood-vessels, and such areas had a peripheral zone of sclerosis, less dense than the central zone. In the still myelinated tissue there was no evidence of an increasing glia hyperplasia, and the impression was left that all the areas had arisen on the basis of a fat granule cell stage. Several patches were cut in serial section, and they were found to retain, throughout, their clearly-defined outline. The nerve roots were normal, and showed no rarefaction: the posterior root ganglia, examined at numerous levels, were entirely normal, and the membranes were not materially altered.

In the brain "early" areas were found in several medullary rays, and patches were present in the central white matter above the ventricles. The peri-ventricular sclerosis around all the horns of the lateral ventricles was very marked, especially around the descending horn on both sides. The tissue of the medulla oblongata, pons, and cerebral hemispheres, with the exception of a few levels, was removed for mounting (figs. 200–201). The ventricles were not dilated, and their walls showed zones of greyish-blue staining, which outlined the sub-ependymal veins (fig. 201).

Topographical Distribution of Areas.

Spinal Cord.—Cervical Cord (figs. 185–188).—In its upper segments the clerosis is limited to a narrow band along the outer half of the posterior median fissure and to a broad band which passes obliquely across the cord in the region of the central canal. Diffuse changes are also present in each crossed pyramidal tract. In C3 only one area is present: this is very irregular in outline and occupies one antero-lateral column with the whole of the corresponding anterior and posterior horns of grey matter. It then passes into the opposite anterior horn and also sends a broad band along the posterior median fissure. At C6 the sclerosis affects chiefly the posterior columns: this is a triangular area with its blunted apex at the posterior commissure and its base at the periphery of the cord: the lateral outlines are clearly defined and leave a considerable portion of the columns of Burdach, adjoining the posterior horns, unaffected. Several small dense areas are also present in the lateral column on one side. The glia border zone around the whole circumference of the cord is

markedly widened. In C7 the posterior column area has almost disappeared, except for a narrow oval zone along the median fissure. An irregular area is present in the anterior half of the cord ; this forms a square arranged along each side of the anterior fissure, with the posterior commissure as its limit. Irregularly-shaped dense areas also occur near the tip of each posterior horn : an oval area, larger on one side, in each antero-lateral column ; and a small area picks out the centre of the postero-lateral group of nerve cells in the anterior horn. The same widening of the glia border zone is again present. At the lower level of this segment the areas tend to fuse : the antero-lateral column on one side is occupied by a large triangular patch which leaves the fibres of the direct cerebellar tract untouched and is continuous, across the grey matter, with the anterior quadrilateral patch. A small isolated area is also present in the tip of the anterior group of nerve cells on this side, and two other areas, irregularly triangular, with base to the pia, are present in the lateral column of the opposite side. The area in the posterior columns is much larger and forms an elongated oval reaching almost from posterior commissure to surface. At C8 one-half of the cord is normal, with the exception of a narrow band which picks out the tip of the posterior horn. A portion of the column of Goll also is affected as part of the extension across the median fissure of a square area which occupies almost the whole of the opposite posterior columns. The whole antero-lateral portion of the cord on this side is affected—both grey and white matter, but in this sclerotic tissue bands of myelinated fibres stand out clearly—these roughly correspond to the emerging anterior root fibres with the intermediate tissue and to a zone of fibres occupying the extreme lateral periphery of the cord.

Dorsal Region (figs. 189–193).—In the first segment an area is present in the posterior columns : this occupies its mesial and one lateral portion, and its mesial border, parallel to the median fissure, is clearly defined from the posterior commissure to the periphery. Small surface bands of sclerosis are also found at the posterior root-entry zones on each side, and the rest of the fibres over almost the whole transverse section stain more diffusely and lightly than in the normal cord. In the mid-dorsal region the section is normal, except for a small area which extends inwards from the antero-lateral surface of the cord on one side and small areas at the tips of the posterior horns. In the lower dorsal region a triangular area again occupies almost the whole of the posterior columns, leaving symmetrical bands of fibres adjoining the posterior horns. The blunted apex of this triangle reaches as far forwards as the base of the anterior fissure. As this area is traced downwards it gradually diminishes in size, and in the upper part of D12 is present as a broad band, on the posterior periphery, which sends a narrow process forwards along each side of the median fissure : the whole of the rest of the posterior columns shows an early change. At the lower part of this segment the picture is again altered ; a dense area of sclerosis follows the line of one para-median vessel, and an early change involves the rest of the posterior columns and part of the lateral and anterior columns.

Lumbar Region (figs. 194–199).—At the upper level of this segment a peri-central sclerosis extends into each crescent, and the posterior median fissure is the central point of a narrow oval area. At the lower part of the second segment several minute areas occur : the peri-central sclerosis extends further into one crescent : in the opposite grey matter the antero-lateral group of nerve cells is involved : on the same side a narrow zone of sclerosis extends round the surface of the cord with the tip of the posterior horn as its centre, and a minute area is present immediately on one side of the posterior median fissure. In L3 an irregular area, with oblique borders, extends across the dorsal portion of the postero-median fissure —as this is traced downwards it diminishes rapidly and forms a small oval area immediately in the middle line. Minute areas are also present in each antero-lateral corner of grey matter, and the peri-central sclerosis extends into each crescent. In L4 a dense broad band passes along each side of the anterior fissure, and at its base these unite and expand into a large peri-central area, which extends into one anterior horn. At L5 the whole of this

anterior horn, with the exception of the antero-mesial corner, is involved in an area of sclerosis which surrounds the central canal and ceases at the base of the opposite crescent.

Medulla Oblongata.—At the lower level of the inferior olive two areas are present: one in the left olivary nucleus itself, the other chiefly in one postero-lateral region. This latter extends from the gracile nucleus on one side towards the central canal, passes into the opposite formatio reticularis, substantia gelatinosa Rolandi, Vth nerve, and the adjoining sensory fibres in the caudate nucleus. At the level of the middle of the inferior olive one large area occurs in the centre and inner portion of one restiform body, and spreads into the adjacent formatio reticularis. A large diffuse area is also present in the ventral half of the inferior olive and adjacent pyramid and fillet.

Case VIII.

Clinical History.

M. R.—The patient was a woman, aged thirty-three, born at Whithorn, a typist. She was admitted to Longmore Hospital on 2nd October 1903, and died 3rd September 1910.

Her father was alive and well: her mother died from heart disease at the age of sixty-six. She has three brothers all alive and well, and three sisters all in good health. Two sisters died in infancy.

Patient was always very strong and healthy as a girl. At the age of eighteen, she became weak and was very helpless for about a year. She does not know the nature of this attack, but it was called "a kind of rheumatism." She completely recovered, and learned short-hand and typewriting. She worked at this for about one year, when her health gave way owing to bleeding hæmorrhoids, and she again became very weak. She then went home and kept house and remained in fairly good health, except that she was "always tired," and the bleeding still continued. About six years ago she had an attack of influenza which she attempted to walk off; her legs again became very weak, and after about a fortnight she was unable to stand and had to remain in bed. She slowly recovered from this condition, until she was able to go about the house holding on to tables, etc., and even managed to go up and down stairs, except in very damp weather, which always made her worse. About three years ago she had a severe and widespread attack of eczema, from which she took nearly a year to recover. The condition has been liable to recur, especially in spring and autumn. It was about this time that her legs became drawn up. She was also liable to repeated attacks of influenza, which always depressed her.

On examination both legs were found to be drawn up beyond a right angle at the knee, but some slight passive movement was present. There was complete absence of all voluntary movement of the lower extremities. There was some dulling of sensibility in both hands and in both legs. All the muscles of the upper limbs were weak, especially on the right side. The knee-jerks could not be elicited, but there was marked ankle clonus and well-marked crossed adductor jerks on both sides. Babinski's sign was positive on both sides. The other systems appeared normal.

Post-mortem Report, 4th September 1910.

Body emaciated. Marked contracture of lower limbs.

Spinal Cord.—Showed usual appearances of sclerosis in many parts.

Abdomen.—Descending colon very friable—adherent to wall in left iliac region—with local signs of recent peritonitis. The whole colon, from hepatic flexure to rectum, is ulcerated, in some places down to the peritoneum. The liver and kidney show slight fatty changes, the suprarenals are large, and the pancreas shows no gross lesion.

General Characters of the Areas (Plate LIX).

The marked involvement of the spinal cord and the comparative integrity of the remaining portion of the central nervous system are the striking features of this case. Macroscopically it was evident that the cervical and dorsal cord were almost completely sclerosed, but no areas could be so recognised after a careful examination, even of mordanted blocks, of the medulla, pons, mid-brain, and hemispheres. Several levels of all of these portions were, however, cut in celloidin sections, and microscopic examination proved the presence of a few isolated areas throughout the brain stem and hemispheres. These were related to the pons, chiefly to the root-entry zones of the VIIIth nerve and to the superior cerebellar peduncles: in the hemispheres there was a very slight peri-ventricular sclerosis around the posterior horns, a very few subcortical and cortical areas, and an extensive demyelination of the superficial layers of the cortex over several convolutions.

The segments of the cervical enlargement showed an almost complete and advanced degree of sclerosis throughout their whole extent (figs. 209–211). A similar advanced sclerosis was present in the dorsal cord (figs. 212–214), and this was almost as extensive, especially in the upper and lower dorsal regions. The densest sclerosis was again present in the central portions of the posterior and lateral columns. Marchi sections of numerous levels showed that very few fat granule cells were present, and that these were almost restricted to the walls of the peripheral vessels; there were no "early" areas present at any level. Bielschowsky- and Cajal-stained sections proved that numerous axis cylinders were absent and that many of those persisting stained faintly. The ganglion cells were very atrophic, but amongst them were found rounded forms with chromophile granules almost normal in structure and arrangement. The nerve roots were normal at most levels (figs. 209–211), but a few showed slight rarefaction. The membranes were practically normal.

Topographical Distribution.

Spinal Cord.—Cervical Region (figs. 202–203 and 209–211).—In the first (fig. 203) and second segments there are traces of early involvement on each side of the anterior fissure, in the region of the crossed pyramidal tracts, and in the columns of Goll. At the third segment (fig. 202) three well-defined areas are present—each with a zone of lighter staining around it. These lie, one in the posterior, and the others in the antero-lateral columns. A small dense peri-central area is also present, and there is a marked widening of the glia border zone, especially over the anterior surface of the cord. At the sixth segment the whole transection shows a dense sclerosis, with the exception of a few symmetrically-placed fibres near the posterior root-entry zone and a group of lateral peripheral fibres on one side. At the seventh segment the sclerosis is almost as complete, but the preserved groups of fibres are larger and reach, on one side, diagonally into the substance of the cord from the anterior and posterior root zones. On the opposite side the areas are smaller but similar in position.

Dorsal Region (figs. 212–214).—At the first dorsal segment the sclerosis is still very complete: on one side anteriorly a broad band of peripherally-placed fibres and posteriorly a peripheral zone, lying between the tips of the posterior horns, escape. Between these four deeply-sclerosed segments of the cervical enlargement (C6–D1), the sections all show an almost complete demyelination with the exception of peripheral groups, varying slightly in size and position, but often placed symmetrically. The whole of the upper dorsal cord shows a marked degree of sclerosis, but in the mid-dorsal region the form of the areas becomes more irregular. A peri-central sclerosis forms the centre, from which radiate in all directions more or less marked areas: the largest of these cuts across the grey matter, and occupies almost the whole of one antero-lateral column, allowing peripheral anterior and direct cerebellar tract fibres to escape. A second area extends along the posterior

median fissure as a broad band, which is surrounded by a zone of lighter staining: and further areas involve the other anterior horn, part of the antero-lateral column, and the posterior horn on the same side. At a slightly lower level we find a complete transection posterior to a line drawn horizontally across the cord at the level of the base of the anterior fissure. At a lower level the sclerosis affects the whole of one-half of the cord, except the anterior third, part of the opposite posterior column, and then stretches as a broad band diagonally across the grey matter of the opposite side to involve the part of the corresponding antero-lateral column. At the next segment the whole of the former severely-affected half of the cord is involved—except a few peripheral anterior and lateral fibres—and the sclerosis advances on the opposite side uniformly as far as a line drawn antero-posteriorly at the outer margin of the anterior horn. At D8 one-half of the cord is again deeply sclerosed, and the opposite side shows evidence of early involvement. At D9 the sclerosis is now much less marked: one small peri-central area and an early degree of sclerosis in one antero-lateral column being alone present. At D10 the same picture is presented, but the antero-lateral area is more evident. At D11 there is again considerable involvement: one-half of the cord is more or less sclerosed, except a peripheral zone, and at D12 two dense areas occur: one in the posterior columns, the other an irregularly-outlined patch which involves a great part of the grey matter on one side and the base of the anterior horn on the opposite.

Lumbar Region (figs. 215–216).—The first lumbar segment is practically normal. L2, at its upper part, is also normal, but at the lower levels small areas lie peri-centrally and in the substantia gelatinosa Rolandi on both sides. In L3 these areas are all more definite and larger, and the posterior and lateral columns on one side show early involvement: at the lower levels of this segment minute areas appear also at the lateral margin of one anterior horn and along the posterior median fissure. In L4 the early involvement seen in the previous segment has become a large definitely demyelinated area, which occupies the whole of one-half of the section—with the exception of posterior and antero-lateral broad peripheral zones—and stretches across the middle line to involve the inner portions of the anterior and posterior horns and a corresponding portion of anterior and posterior column fibres.

Sacral Region (fig. 217).—As this area is traced downwards through L5, it becomes very irregular in outline, and in S1 it forms a broad band on each side of the mesial line: from one side of this band projections pass laterally through the posterior horn and crossed pyramidal tract to the surface and also anteriorly along the outer aspect of the anterior horn. Two early areas also occur on the opposite half of the cord. In S2 these areas have disappeared, and there is little abnormal except a possible lightening of the fibres in the antero-lateral region and a demyelination of the substantia gelatinosa Rolandi. S3 and S4 are normal, with a possibly increased peri-central sclerosis.

Medulla Oblongata.—In its lower part (fig. 204), about the level of the decussation of the fillet, an early area is present on both sides: this shows a diffuse and light staining, and stretches between the inferior olive and the substantia gelatinosa Rolandi. In the middle of the medulla (fig. 205) similar areas are found in the left restiform body—one towards its centre and one at its posterior surface.

Pons Varolii (figs. 206–208).—The areas lie mostly in the cerebellar portion. Only a slight involvement is found around the ventricle, but slightly internal to the angles small areas occur which involve the fibres of the VIIIth nerve on both sides. Sclerotic tissue is also closely related to the zone of entry of this nerve: on one side this area is situated immediately on its cerebellar side and is surrounded by a zone of lighter staining which involves the root-entry zone. On the opposite side a similar small early area also involves the fibres of the VIIIth nerve as they pass into the pons. In the upper part of the pons (fig. 207) the section is apparently normal, except for small areas which lie in the pontine grey matter and middle cerebellar peduncle. On the right side a small, dense, somewhat rectangular area is present, slightly internal to the surface: this is situated just at the point where

the transverse fibres of the pons begin to form the middle cerebellar peduncle. At the level of the decussation of the superior cerebellar peduncles (fig. 208) a large dense area is found at the anterior surface : this involves the superficial fibres, the adjacent grey matter, and the pyramidal fibres. A few small early patches can be traced amongst the transverse fibres of the pons, and a well-marked triangular area lies close to the left corner of the aqueduct of Sylvius.

Cerebral Hemispheres.—Horizontal sections at the level of the lower and upper parts of the optic thalamus show that only a very slight degree of peri-ventricular involvement is present. This is an area of shadow sclerosis related to the posterior horn, and is of very slight extent. No other definite areas can be found in these sections, but at higher levels two or three small cortical and subcortical areas can be found in each section. An extensive demyelination of the superficial layers of the cortex of several convolutions is also present.

Case IX.

Clinical Notes.

L. H.—The patient, aged thirty, was admitted to Longmore Hospital on 24th May 1911, dying on 13th July 1911.

As a school-girl she had always been healthy, although she has been late in walking. She used to take part in all games and gymnastics and was quite strong until she reached the age of twenty, when she began to notice a loss of power in her right foot. About this time she had an attack of chorea. For the last six years she has got decidedly worse, and has had to remain in bed. Only the lower limbs and the bladder were affected.

Post-mortem Report, 15th July 1911.

Marked contracture of both lower limbs. Bed-sores over both hips and left shoulder.

Brain.—No adhesions of the dura. Some excess of clear cerebro-spinal fluid. Some congestion of cortical vessels and pia mater and œdematous fluid under the pia. Convolutions somewhat atrophied. Gelatinous patch of disseminated sclerosis at junction of medulla and cord. The right VIIIth nerve appeared to be atrophied.

Spinal Cord.—Very small. On section numerous patches of typical disseminated sclerosis were seen.

Lungs.—Right : firm adhesion at the base. Pale in front, hypogastric congestion posteriorly. On section marked œdema in upper lobe, congestion in lower. Left : in a somewhat similar condition.

The *heart* was small and flabby ; no valvular disease.

The *liver* was enlarged and pale, with considerably fatty change.

The *spleen* was very small, and the post-mortem discoloration was marked.

The left *kidney* was a little enlarged, with the appearance of subacute parenchymatous nephritis : the capsule stripped freely.

General Characters of the Areas.

This case, also, presented a marked contrast between the areas in the spinal cord and those in the brain. The former were almost wholly in the stage of advanced sclerosis : the majority of the latter were in a stage of fat granule cell formation.

In the cord the only extensive affection was found in the lower sacral region (figs. 238–239). Throughout the lumbar cord there was a remarkable symmetry in the small areas found in this region—especially in those which involved groups of nerve cells in the anterior horns of grey matter. Few fat granule cells could be found at any level, and those present

were either in relation to vessels in the periphery of the areas or in narrow zones immediately mesial or lateral to the posterior horns. Bielschowsky preparations proved the persistence of a large number of axis cylinders. The ganglion cells were very atrophied, and some were wholly filled with pigment—the *jaune dégénération* of CHARCOT. Numerous cells of "fisch" type were present both in the anterior grey matter and in Clark's columns. The central portions of the posterior columns frequently presented a whorl arrangement of the glia, while, on the other hand, the sclerosis of the lateral columns at several levels appeared to be progressing on the basis of an increasing glia hyperplasia. The nerve roots, posterior root ganglia, and membranes presented few changes.

The areas in the lower medulla (figs. 218–220) were very extensive, but those in the upper medulla and pons (figs. 221–224) were very limited, and were specially related to the angles of the ventricles, the adjoining cerebellar white matter and folia, to the superior cerebellar peduncles, and to the motor and sensory Vth nuclei.

The peri-ventricular sclerosis of the lateral ventricles was very slight. A very large number of "early" areas were found in the medullary rays of the convolutions, and a few limited to the cortex. The former frequently presented in a striking degree an affection limited to the borders between the white matter and the cortex. Such an involvement could sometimes be traced for a considerable distance along both transition borders of the medullary ray in a narrow convolution, and sometimes along one border, into the cup of the fissure, and along the border of an adjoining convolution.

Topographical Distribution.

Spinal Cord.—Cervical Enlargement (figs. 228–230).—At its upper level the sclerosis affects chiefly the antero-lateral columns and is present in different stages: an early zone is also present along the sides of the posterior-median fissure, while a denser area occupies one posterior horn and extends into the adjacent fibres of the posterior column. At C5 one-half of the cord shows a diffuse change, and in the other more normally-staining half there is present a demyelination of the tip of the posterior horn and of the substantia gelatinosa Rolandi. At C6 the greater part of the cord shows an early involvement, while other areas are present in the lateral columns on one side and in the posterior columns. The more normal fibres are arranged around the grey matter both of the anterior and posterior horns, and in a part of the periphery of the cord. A very similar picture is continued through C7, but as C8 is reached the early extensive involvement of the previous segment gives place, in one lateral column, to a still fainter staining and in the other to a complete demyelination, with the exception of a peripheral zone. Diffuse staining is also found distributed irregularly through the rest of the section: the more normal fibres lie chiefly around the anterior horn, at the base of the anterior median fissure, and in the region of the direct cerebellar tract. The intra-medullary fibres of the anterior root stand out clearly on both sides.

Dorsal Region (figs. 230–232).—At D1 the condition does not essentially differ from that in the last cervical segments: the dense area in one side is more extensive and the darker staining in the posterior columns is more limited. Throughout the whole of the remaining dorsal region the areas present all show diffuse changes, with a lighter staining of the myelin. The majority of these are found in the posterior and lateral columns, but their outline is very undefined and in no way determined by fibre systems. The fibres along the periphery of the cord and in immediate relation to the grey matter, along all its borders, as a rule stain better than those in the more central parts of the white matter. The grey matter also shows a diffuse staining throughout its whole longitudinal extent: about the level of D6 both anterior horns are obliterated by denser areas, which extend anteriorly to reach the surface at the fissure and lateral surfaces. They are thus continuous with

one another across the base of the fissure, and involve both commissures, the base of the posterior horns, and the lateral horns.

Lumbar Region (figs. 233–236).—At the level of the first segment the picture is very similar to that found throughout the whole dorsal cord, but throughout the remainder of the lumbar and in the sacral cord the areas found are denser and more defined in outline. At L2 a peri-central sclerosis passes into the associated grey matter on either side and affects both commissures: a triangular area extends along the posterior median fissure: smaller areas occur in each substantia gelatinosa Rolandi, and on the surface of the cord, especially at the tips of the anterior fissure; and a small area is confined to the postero-lateral grey matter of the anterior horn on one side, with the immediately adjoining nerve fibres. At L3 little change has occurred: the posterior area is now limited to a narrow zone along the fissure, and the area in anterior grey matter is almost continuous with surface areas in the region of the root-emergent zones. At L4 these areas have fused laterally, and the portion within the grey matter involves both postero-lateral and antero-lateral groups of cells. Minute early areas are found along the antero-lateral surface of the opposite side, and the areas around the central canal in the substantia gelatinosa are more extensive.

At L5 the sclerosis is limited to these three latter areas: they are now still more extensive and involve almost the whole posterior horn on one side and, on the other, the area is continuous with a large glious zone in one extra-medullary posterior root. The sides of the anterior fissure and the posterior columns stain faintly.

Sacral Region (figs. 237–239).—At S1 the peri-central sclerosis extends into the bases of the anterior horns and along each side of the anterior fissure: the areas in the substantia gelatinosa Rolandi are small: a minute area is still present in the postero-lateral group of nerve cells in the anterior horn on each side; there is also a slight involvement of the fibres around the dorsal portion of the posterior median fissure. At S3 there is almost a complete transection of the cord: a few normal fibres are left around the postero-lateral and anterior margins of the cord. In S4 the normal fibres are limited to a crescentic band lying in the anterior and antero-lateral surfaces, and to a few individual fibres in the regions of the posterior horns. The nerve roots of the cauda equina stain almost normally: a few nerve roots, however, are faintly stained.

Medulla Oblongata.—At the level of the decussation of the pyramids (fig. 218), two areas of sclerosis are present: the smaller involves one substantia gelatinosa Rolandi; the larger affects nearly the opposite half of the medulla and extends obliquely from the substantia gelatinosa Rolandi across the central canal to the outer margin of the opposite pyramid. The area ventral to this oblique line is demyelinated, except a few peripheral fibres and pyramidal fibres after or during their decussation. A diffuse change is present throughout much of the remaining tissue. As the large area is traced upwards (fig. 219) it becomes more symmetrical and triangular in shape: its apex lies in the posterior median fissure, almost all the pyramidal fibres are involved, and from the lateral borders projections pass into each gelatinous Rolandic substance. At the level of the decussation of the fillet (fig. 220) two clearly-marked areas are present: the one, peri-central, resembles a maple-leaf in form, and includes at its margin the hypoglossal nuclei; the other is obviously a continuation upwards of the previously described triangular area. It now extends from the posterior longitudinal fasciculus and involves both mesial fillets, both pyramids, and the lower end of both inferior olives.

Middle Medulla.—Few areas are present at this level: the most marked is situated ventrally in the middle line just at the junction of the mesial fillet with the pyramids. It involves the mesial portion of each pyramid, with a few of the adjoining fillet fibres, and probably represents the continuation upwards of the triangular area. A slight involvement of the tissue along the floor of the IVth ventricle is also present.

Upper Medulla (fig. 221).—A broad band on one side passes diagonally backwards

towards the ventricle from the surface of the medulla : this cuts across the fibres passing from the inferior olive to the restiform body and involves the nucleus ambiguus and the adjacent portion of the formatio reticularis. From the angle of the ventricle on the opposite side a dense band also passes to the surface of the medulla : this involves the fibres of the VIIIth nerve, the acoustic tubercle, the outer portion of the restiform body, and a portion of the peduncle of the flocculus. Narrow zones of sclerosis are also present on this side between the pyramid and the mesial fillet, and between the pyramid and the inferior olive. A few minute areas occur in the hilum of each inferior olive and amongst the fibres of the mesial fillet. The lateral walls and roof of the ventricle are more involved than the floor, and large areas of an " early " type pass from the ventricular surface into the hilum of each dentate nucleus. Further areas are found in different stages of development in the cerebellar white matter, especially at its junction with the folia : the cores of the folia of both flocculi and of the vermis are markedly involved.

Pons Varolii.—Lower Third.—The angles of the ventricle and lateral walls are again more affected than the floor, and the sclerosis is continuous along the lateral walls to the hilum of each dentate nucleus : on one side the whole ventral half of the dentate nucleus is demyelinated. Several areas, mostly of early type, occur in the central white matter of the cerebellum and at its junction with the folia. Denser areas are present amongst the pyramidal fibres and early areas in the formatio reticularis on both sides.

Middle Third.—The most affected parts lie in relation to the angles of the IVth ventricle. From one a large area spreads outwards and forwards : it completely obliterates Deiters' and Bechterew's nuclei and the restiform body fibres, and extends for a considerable distance into the cerebellar white matter. From the opposite angle the sclerosis extends along the floor of the ventricle as far as the median raphe : it obliterates the VIth nerve nucleus and the genu of the VIIth nerve, extends for a short distance into the formatio reticularis, and from the angle a diffuse area extends into the cerebellar white matter and along the lateral wall to the roof of the ventricle.

Upper Third (fig. 222).—The same two areas, in relation to the angles of the ventricle, appear at this level : one of these passes into the middle peduncle, involving the motor and sensory Vth nuclei and several of the adjacent cerebellar foliæ : the opposite area is much smaller, but a diffuse zone extends around it to occupy a position similar to the affected tissue on the opposite side. Smaller patches occur among the transverse fibres of the pons, and larger areas towards the ventral aspect of the pyramidal bundles. At a higher level (fig. 223) both the areas in relation to the ventricle have disappeared—the peri-aqueductal tissue being normal. An irregularly wedge-shaped area is present on the ventral surface of the pons to one side of the middle line, a similar area passes inwards from the surface at a point just ventral to the superior cerebellar peduncle, and several early areas lie in the middle peduncle and in the formatio reticularis on both sides.

At the level of the inferior quadrigemina (fig. 224) a slight peri-aqueductal sclerosis occurs : this does not involve the posterior longitudinal fasciculus, but extends into the quadrigeminal bodies for a short distance. A small area is present in the middle line in front of the decussation of the superior cerebellar peduncles—an area which higher up extends to involve part of the mesial fillet and surrounding fibres. A larger area passes inwards for a short distance amongst the anterior superficial pontine fibres on one side, and at a slightly higher level several small areas are found in relation to the anterior and lateral surfaces.

Horizontal sections through the optic chiasma (fig. 225) show that the myelin stains faintly over the whole optic chiasma, both optic nerves, one optic tract, and part of the other. There is a narrow zone of complete demyelination in the anterior margin of the chiasma, which extends forward along the inner border of one optic nerve : the septal connective tissue and vessels of both optic nerves are very thickened.

Cerebral Hemispheres.—Horizontal sections through the basal ganglia: a very slight peri-ventricular sclerosis is present around the posterior horn of the lateral ventricle, and minute areas occur in the white matter immediately adjoining, but the basal ganglia are free.

Sagittal sections through the temporo-sphenoidal lobe, passing through the descending horn of the lateral ventricle, show a slight peri-ventricular sclerosis and diffuse areas in the adjoining white matter. Numerous minute peri-vascular areas are also present, especially at the base of the medullary rays.

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DESCRIPTION OF PLATES.

(Figs. 1–22 are from drawings; figs. 23–456 are micro-photographs.)

The illustrations are grouped together to follow as closely as possible the different sections of the histological study. Plates XLVIII–LX give various levels of the brain and spinal cord in the different cases and show the general topographical distribution of the areas (myelin sheath stain). In the remaining illustrations chief stress has been laid upon the evolution of the sclerotic areas and upon the sequence of the changes in the individual tissue elements.

PLATES XLV–XLVII:

Figs. 1–4. Evolution of a sclerotic area in the spinal cord through a stage of fat granule cell formation—longitudinal direction of the nerve fibres.
„ 5–7. Ditto. Cerebral area: transverse direction of nerve fibres.
„ 8–12. Ditto. Spinal cord: transverse direction of nerve fibres.
„ 13–15. Sequence in blood-vessel changes.
„ 16–17. Related to axis cylinders.
„ 18–20. „ evolution of the fat granule cells ("Fettkörnchenzellen").
„ 21–22. „ changes in the cerebral cortex.

PLATES XLVIII–LX. Topographical distribution of areas in Cases I–IX.
„ LXI–LXV. Special features of spinal cord and cerebral areas. Weigert stain.
„ LXVI–LXVII. Ditto. Marchi method.

FIGS. 325–342. Evolution of a sclerotic area—through a stage of fat granule cell formation: spinal cord—longitudinal direction of nerve fibres.
„ 349–360. Ditto. Spinal cord—transverse direction of the nerve fibres.
„ 361–369. Ditto. Cerebral white matter—transverse direction of the nerve fibres.
„ 370–378. Ditto. Cerebral white matter—longitudinal direction of the nerve fibres.
„ 343–348. Ditto. Through a stage of increasing glia hyperplasia.
„ 379–384. Types of glia cell changes and glia fibril development.
„ 385–396. Changes in cerebral cortical areas.
„ 397–402. Positive and negative pictures—meyelin sheath and neuroglia stains.
„ 403–408. Changes in the transition zones of areas.
„ 409–420. „ related to ganglion cells.
„ 421–432. „ „ axis cylinders.
„ 433–450. „ „ blood-vessels.
„ 451–456. „ „ nerve roots, etc.

PLATE XLV.

Figs. 1–4. Successive stages in the evolution of a sclerotic area in the posterior columns of the cervical spinal cord. Sections are cut in the longitudinal direction of the nerve fibres (p. 563) and show a gradually increasing glia fibril formation. *Cf.* figs. 325–336. Figs. 1 and 3, Ford-Robertson's methyl-violet stain; figs. 2 and 4, palladium methyl-violet. × 400. *a* = glia nuclei; *b* = glia fibrils; *c* = fat granule cells; *d* = persistent axis cylinders.

Fig. 5. An "early" area in the cerebral white matter (*cf.* fig. 361): shows a central blood-vessel (*b*), a peripheral nucleated zone (*d*), and is composed almost wholly of fat granule cells (*c*) and proliferated glia cells, seen only as nuclei (*a*) under this power. Heidenhain's iron-hæmatoxylin. × 26.

Fig. 6. Area in the cerebral white matter. Numerous fat granule cells in the upper part of the drawing with an already advanced degree of fibril formation: few fat granule cells in the lower part with a still more advanced fibril formation—the glia nuclei almost wholly isolated from the fibril. *a* = protoplasmic glia cells with processes differentiated into fibrils; *b* = glia fibrils; *c* = fat granule cells; *d* = glia nuclei isolated from the fibrils. Heidenhain's iron-hæmatoxylin. × 350. (P. 567.) *Cf.* figs. 361–369.

Fig. 7. Types of proliferated glia cells with varying degrees of fibril formation. *a* = fibrils recurring near nucleus; *b* = glia nucleus forming nodal point from which fibrils radiate. *Cf.* figs. 382–384. Heidenhain's iron-hæmatoxylin. × 400.

PLATE XLVI.

Figs. 8–12. Successive stages in the evolution of a sclerotic area in the posterior columns of the cervical spinal cord. Sections cut transversely to the direction of the nerve fibres (p. 565). *Cf.* figs. 349–360. Van Gieson's stain. × 350. *a* = glia nuclei; *b* = blood-vessel; *c* = fat granule cell; *d* = myelinated nerve fibre; *e* = finely granular glia tissue; *f* = naked axis cylinder; *g* = transition to normal tissue.

Fig. 8. Shows a commencing enlargement of the nucleus, cell body, and processes of the glia cells and a commencing change in the myelin.

Fig. 9. Stage of glia cell proliferation and fat granule cell formation. Note the multi-nucleated glia cells, the presence of numerous deeply-stained nuclei in the tissue, the swollen and faintly-staining axis cylinders, and the "Gitter" structure of the fat granule cells.

Fig. 10. Tissue is composed almost wholly of fat granule cells, many of which have accumulated within the adventitial sheath of the blood-vessels.

Fig. 11. Stage of advancing sclerosis: the glia fibrils, cut transversely, are represented as closely compressed fine dots; the persisting axis cylinders stain deeply; a few fat granule cells are still left in the tissue.

Fig. 12. Stage of advanced sclerosis. The tissue is dense and finally granular, contains numerous axis cylinders and a few fat granule cells—chiefly within the adventitial sheath of the capillaries. On the left transition to the normal tissue of the cord.

Figs. 13–15. Sequence of changes in the blood-vessels (p. 614). *Cf.* figs. 433–450. Van Gieson's

stain. × 350. *a* = glia nuclei; *b* = blood-vessel; *c* = fat granule cell; *d* = cell containing blood pigment; *e* = lymphocyte-like cells; *f* = plasma cell; *g* = glia tissue; *h* = connective-tissue cell.

Fig. 13. A transition vessel with its adventitial sheath filled with fat granule cells; numerous similar cells and enlarged glia cells in the surrounding tissue.

Fig. 14. A larger vessel (*cf.* fig. 439), during the stage of advancing sclerosis, to show the cell content of the adventitia after the removal of the fat granule cells.

Fig. 15. Small artery in an area of advanced sclerosis. Note the commencing "hyaline" fusion of the media and adventitia; the outer layers of the adventitia and the layers of the peri-vascular glia are still dilated and have an increased cell content. At a later stage the glia sclerosis immediately surrounds the dense, homogeneous vessel wall, which then shows few or no cell elements.

Plate XLVII.

Figs. 16–17. Persistence of axis cylinders across a demyelinated area in the pons. *Cf.* figs. 289 and 421. Bielschowsky-Williamson silver impregnation method. Fig. 16, × 20; fig. 17, × 90. *a* = line of transition between myelinated and demyelinated fibres; *b* = median raphe where axis cylinders intersect; *x* = shown in fig. 17, under high power.

Figs. 18–20. Stages in the demyelination of an area and in the evolution of the fat granule cell. Frozen sections cut in the longitudinal direction of the nerve fibres. Scharlach R. × 300. *a* = small glia nuclei; *c* = fat granule cell; *b* = transition forms between *a* and *b*; *d* = nerve fibre; *e* = blood-vessel; *f* = proliferated glia nuclei.

Fig. 18. Longitudinal nerve fibres immediately adjoining a demyelinated area. Note the cells containing fat granules.

Fig. 19. Structural elements in the transition zone of an early area. Note the longitudinal myelinated nerve fibres passing into the area, the rows of enlarged glia cells, and the numerous fat granule cells in all stages of their formation. The first fat granules are contained in the protoplasm adjoining the poles of the nucleus and as they increase in amount the cell becomes round.

Fig. 20. Capillary, in a demyelinated area, completely surrounded by a layer of fat granule cells. Adventitial sheath not brought out in this stain.

Figs. 21–22. Glia changes in a completely demyelinated area in the cortex (p. 595). *Cf.* figs. 301–396. Ford-Robertson's methyl-violet stain. × 500. *a* = proliferated glia cells with protoplasm and processes differentiated into fibrils; *b* = capillaries with glia fibrils attached to their outer membrane; *c* = ganglion cells; *d* = small glia cells forming nests around the remains of ganglion cells; *e* = degenerated ganglion cells; *f* = retained axis cylinders. Note that the normal cyto-architecture of the tissue is preserved.

Fig. 21. Deepest (polymorphous) layer of the cortex.

Fig. 22. Layer of the deep pyramids.

Plates XLVIII, XLIX, L (Case I).

Figs. 23–63. Sections of brain and spinal cord. Kulschitsky-Pal myelin sheath stain with picro-fuchsin. Figs. 64–69. Sections to show the prevailing type of area present. Marchi method.

Figs. 23–24. Complete horizontal sections through the cerebral hemispheres at the lower part of the basal ganglia (p. 631). *a* = peri-ventricular sclerosis around the posterior horns of the lateral ventricles, whence the sclerosis is continued backwards towards the calcarine fissure; *b* = the involvement of the splenium of the corpus callosum; *c* = area in the left optic thalamus; *d* = areas in the right and left claustrum extending to involve the convolutions of the island of Reil—small areas are present also in the anterior and posterior limbs of the internal capsules and in the right and left putamen; *e* = oval area in the medullary ray and grey matter of the anterior part of the left frontal operculum (*cf.* fig. 284); *f* = two small areas in the right frontal operculum; *g* = several areas in the convolutions of the occipital lobe in both sides, especially around the calcarine fissure.

Fig. 26. Level of the roof of the right lateral ventricle. *a* = involvement of the outer wall and posterior tip of the ventricle; *b* = large areas in the adjoining white matter, especially towards the occipital lobe; *c* = area in the medullary ray of the post-Rolandic gyrus in the precuneus.

Fig. 25. Above the left ventricle—numerous areas in the white and grey matter especially. a = in the centre of the white matter towards the frontal lobe; b = at junction of white and grey matter in the post-Rolandic gyrus; c = area in convolutions of the calcarine fissure.

Figs. 27 and 28, × 7. Almost symmetrical involvement of the white matter of the flocculus of the cerebellum—an involvement (a) which extends into the cores of numerous foliæ.

Fig. 29. Horizontal section through the temporo-sphenoidal lobe just below the floor of the descending horn of the lateral ventricle. a = extension of the peri-ventricular sclerosis to the region of the calcarine fissure; b = involvement of the convolutions at the tip of the lobe; and c = of the fibres of the hippocampal lobe.

Figs. 30 and 31, × 2½. Frontal longitudinal sections of the lower cervical cord from serial sections. In fig. 30 note the involvement of the anterior columns on either side of the anterior median fissure, with extension into the grey matter (a) and the lateral white matter (b). Fig. 31, through the central canal, with similar involvement of grey (a) and white (b) matter. Note the indication of the primary oval form of the areas.

Plate XLIX.

Figs. 32–47 taken from Weigert serial sections of medulla oblongata and pons. × 2. Note the distribution of the areas in relation to the floor and walls of the IVth ventricle; the involvement of the dentate nucleus; the frequent sharp definition of the areas; that several are surrounded by a zone of shadow sclerosis, which has also a sharp outline; and that nearly all the cranial roots enter into demyelinated tissue (pp. 628–631).

Fig. 32. Medulla oblongata above the decussation of the pyramids.

Fig. 33. At level of accessory olivary nucleus. a = peri-central sclerosis.

Fig. 34. At lower end of inferior olive.

Fig. 35. At middle of inferior olive.

Figs. 36 and 37. At the opening of the central canal into the IVth ventricle.

Fig. 38. Upper medulla continuous with the cerebellum. a = entering VIIIth nerve on each side; b = demyelination of vermis and accompanying nodules. c = involvement of the hilum of the dentate nucleus on both sides.

Fig. 39. Junction of medulla oblongata and pons. Note involvement of the fibres of the inferior and middle cerebellar peduncles on both sides, with extension to the centre of the corresponding flocculus. a = figs. 27 and 28; b = area in the cerebellar white matter.

Fig. 40. Pons Varolii at the level of the lower third of the middle cerebellar peduncle.

Fig. 41. Middle of pons. In figs. 38–41 note the involvement of all the cranial nuclei in this region—the nuclei of the VIth, the cochlear nuclei, and the nuclei of Bechterew and Deiters; also the complete involvement of both middle cerebellar peduncles.

Fig. 42. Pons at upper part of the middle peduncle. a = an area in the median raphe, which in higher sections (figs. 43–45) reaches the anterior surface.

Fig. 43. Upper pons. Note the symmetry of the involvement.

Fig. 44. Junction of pons and mid-brain. a = area in the middle line which reaches almost to the mesial fillet and cuts across, in sharply-defined lines, the intersecting fibres of the raphe and the adjoining fibres on each side. *Cf.* fig. 289 and figs. 16, 17, and 421, which show the complete retention of the axis cylinders across this demyelinated area.

Fig. 45. Slightly above (fifty serial sections) fig. 44. a = zone of "shadow" sclerosis around area.

Fig. 46. Fifty serial sections above fig. 45. Note three areas of "shadow" sclerosis. a = in centre of the pyramid; b = in middle line at level of mesial fillet; c = at lateral border of mesial fillet.

Fig. 47. Mid-brain. Aqueduct of Sylvius free. a = area in middle line anterior to the commencing decussation of the superior cerebellar peduncle.

Plate L.

Figs. 48–63. Various levels of the spinal cord. Myelin sheath stain. × 2. (Pp. 626–628.) Note that there are few isolated areas and that there is frequent almost complete symmetry of the involvement

(*cf.* figs. 49 and 59). Note further the complete demyelination at the lower dorsal (fig. 58) and lower sacral segments (fig. 63), and the complete myelination of the nerve roots of the cauda equina (figs. 62 and 63; *cf.* figs. 452 and 453).

Figs. 64–69. Marchi sections to show the prevailing type of areas present in optic tract and optic nerve (figs. 64 and 65, × 10); in spinal cord (figs. 66 and 67, × 6), and in the brain (fig. 68, × 75, and fig. 69, × 10).

Figs. 64 and 65. Showing "early" degeneration with rows of fat granule cells.

Fig. 66. Small "early" area in the posterior columns (*cf.* fig. 313).

Fig. 67. Posterior columns show a late stage of sclerosis with dense glia tissue staining darkly; both lateral columns show an "early" stage with rows of fat granule cells around the vessels.

Fig. 68. Typical small "early" area in the central white matter. The tissue around a central blood-vessel is permeated with fat granule cells.

Fig. 69. Demyelinated "early" area at the tip of a medullary ray, extending through the radiations almost to the superficial cortex—its medullary portion and the vessels radiating from it are permeated with fat granule cells.

PLATES LI AND LII (CASE II) (pp. 690–694).

Figs. 70–92. Various levels of brain and spinal cord. Kulschitsky-Pal with picro-fuchsin.

Figs. 70–73. Horizontal sections through the cerebral hemispheres at the level of the middle (figs. 70–71) and upper part (figs. 72–73) of the basal ganglia. Note *a* = the very marked peri-ventricular involvement, especially of the posterior horns and of the ventricular surfaces of the basal ganglia; *b* = the numerous areas within the basal ganglia—one of which, on the left side, occupies the genu of the internal capsule and involves both optic thalamus and lenticular nucleus; *c* = the demyelination of long stretches of the medullary rays, involving frequently several convolutions, especially of the parietal lobe and of the island of Reil, and extending into the grey matter; *d* = the continuation of the posterior horn sclerosis towards the calcarine fissure—involving the optic radiations, the tapetum, and the inferior longitudinal bundle.

Figs. 74 and 75, × 2. Above the level of the roof of the right lateral ventricle. Sections show very numerous isolated areas, most of which involve the medullary rays and the adjoining cortex. *a* = fig. 277; *b* = fig. 288; *c* = fig. 280; *d* = fig. 278.

Figs. 76–82. Sections of pons and mid-brain. Note the extensive peri-ventricular and peri-aqueductal sclerosis—the cranial nuclei, without exception, being involved. Note also the extensive involvement of the red nuclei (fig. 82).

Fig. 76. Lower third of pons. × 2½.

Fig. 77. Middle third of pons. × 2. Note *a* = the irregular areas of sclerosis passing as projections from the floor of the IVth ventricle; *b* = zone of "shadow" sclerosis around area in the cerebellar white matter.

Fig. 78. Slightly higher than previous figure. × 2½. *a* = involvement of the hilum of each dentate nucleus.

Figs. 79 and 80. Upper third of pons. × 2½.

Fig. 81. Level of decussation of the superior cerebellar peduncles. × 2½.

Fig. 82. Mid-brain. × 2. Peri-aqueductal sclerosis with involvement of most of the structure of the tegmentum, to the IIIrd nuclei, and adjoining parts of both red nuclei (*a*). Several additional small isolated areas in each red nucleus (*b*).

Figs. 83–88. Various levels of the spinal cord. Myelin sheath stain. × 2. The sections are typical of the almost complete demyelination of the whole spinal cord; the still preserved fibres occupied, as a rule, the marginal portions and showed a marked symmetry.

Fig. 89, × 10. Cervical cord showing complete demyelination, condensation of the vessel walls, and nerve roots staining almost normally.

Fig. 90, × 2. Frontal longitudinal section of the dorsal cord showing a similar demyelination.

Fig. 91, × 2. Nerve root and posterior root ganglion attached to the above segment.

Fig. 92, × 2. Conus medullaris and nerve roots of cauda equina in longitudinal section, showing normally staining nerve roots although the whole cord is demyelinated.

PLATE LIII (CASE III) (pp. 696–698).

Figs. 93–113. Sections through brain and spinal cord. Kulschitsky-Pal and picro-fuchsin.

Figs. 93 and 94. Through cerebral hemispheres near the base of the optic thalami. *a* = affection of the posterior horns; *b* = of the anterior horns; *c* = of the genu of the corpus callosum; *d* = areas in the path of the optic radiations; *e* = two early areas in the retro-lenticular portion of the internal capsule; *f* = in the right parietal operculum; *g* = in the left middle temporal convolution.

Figs. 95–96. Through basal ganglia above the middle of the optic thalamus. (*a*), (*b*), and (*d*) as in previous figures; *c* = areas in the splenium of the corpus callosum; *e* = in the medullary rays and grey matter of two parietal convolutions (fig. 285).

Fig. 97. Horizontal section through left hemisphere near vertex. ×2. Numerous large and small areas involving medullary rays and radiations. *a* = in the para-central lobule; *b* = in the pre-central lobule; *c* = in the superior frontal gyrus.

Figs. 98 and 99, × 3. Medulla oblongata above the decussation of the pyramids and at the middle of the inferior olive.

Figs. 100–101, × 3. Involvement of the optic chiasma and inner aspects of both optic nerves.

Figs. 102–113, × 2. Various levels of the spinal cord.

PLATES LIV AND LV, FIGS. 123–142 (CASE IV) (pp. 700–703).

Figs. 114–142. Sections through brain and spinal cord. Kulschitsky-Pal with picro-fuchsin.

Figs. 114–115. Horizontal sections through cerebral hemispheres at the level of the middle of the basal ganglia. *a* = affection of the posterior horns; *b* = of the anterior horns; *c* = of the genu, and *d* = of the splenium of the corpus callosum.

Fig. 117. Above the roof of the right lateral ventricles. *a* = areas in the central white matter—probably an extension of the peri-ventricular sclerosis of the roof of the ventricle.

Fig. 116. At a higher level, left side. *a* = area in a convolution of the intra-parietal sulcus; *b* = in the upper frontal gyrus.

Figs. 118–124. Levels of medulla oblongata and pons Varolii. × $2\frac{1}{2}$.

Fig. 118. Above the decussion of the pyramids.

Fig. 119. At lower level of the inferior olive.

Fig. 120. Middle third of medulla.

Fig. 121. Upper limit of the medulla with the cerebellum. *a* = affection of the hilum of the dentate nucleus on both sides.

Fig. 122. Middle third of pons with the cerebellum. *a* = areas in relation to the dentate nucleus; *b* = to the intra-medullary root of the Vth nerve.

Fig. 123. Upper third of pons. Note areas around the Vth root zones.

Fig. 124. Mid-brain. *a* = peri-aqueductal sclerosis. *b* = extension forwards along median raphe, involving the IIIrd nuclei and the red nuclei on both sides; *c* = area in the substance of the right red nucleus; *d* = in the middle third of the right crus.

Figs. 125–142. Various levels of the spinal cord. × 2. Note the marked involvement of the cervical enlargement, the dorsal cord, and the third sacral segment; that the areas in the lumbar cord are small and isolated, and are frequently confined to the grey matter; and the almost complete symmetry of the involvement in figs. 125, 126, 129, 130, and 138.

PLATE LV, FIGS. 143–155 (CASE V) (pp. 705–707).

Figs. 143–147. Levels of the medulla oblongata and pons Varolii. Kulschitsky-Pal with picro-fuchsin. × 2. Note that these regions were comparatively slightly affected in comparison with most of the cases.

Fig. 143. Medulla oblongata above the decussation of the fillet.

Fig. 144. Medulla oblongata through the middle of the inferior olive. Note the symmetry in both this and the previous figure.

Fig. 145. Middle third of the pons and the cerebellum. Note the very slight peri-ventricular sclerosis.

Fig. 146. Pons—at level of root zone of the trigeminal nerve.

Fig. 147. Upper limit of pons—at level of anterior corpora quadrigemina.

Figs. 148–155. Various levels of the spinal cord. Kulschitsky-Pal with picro-fuchsin. × 2. Note the symmetry of the involvement in fig. 148 (C4) and fig. 149 (C7)—a symmetry which was continued between these segments and gave the impression of an ascending and descending degeneration. Note in fig. 155 small, isolated areas in each anterior horn of grey matter.

Plates LVI and LVII (Case VI) (pp. 708–711).

Figs. 156–177. Sections of brain and spinal cord. Kulschitsky-Pal with picro-fuchsin. Figs. 178–184. Sections to show the prevailing type of area present. Marchi method.

Figs. 158–160, × 2. Medulla oblongata above decussation of the pyramids (fig. 158); at lower level of the inferior olive (fig. 159); and through middle medulla (fig. 160). Note the symmetry in the two lower levels.

Fig. 156, × 2½. Lower pons with cerebellum. Note *a* = the marked involvement of the floor and lateral walls of the IVth ventricle; *b* = the extensive distribution of early diffuse areas through the rest of the tissue; and *c* = the involvement of the intra-medullary portion of the VIIIth nerve roots.

Fig. 157, × 2½. Pons at level of Vth nerve root. Note *a* = involvement of both inferior peduncles as they pass to the dentate nuclei; and *b* = of the intra-medullary portions of the Vth nerve roots.

Fig. 161. Mid-brain. × 2½. Note (*a*) involvement of both red nuclei; (*b*) extension to the substantia nigra and point of emergence of the IIIrd nerve on both sides.

Fig. 162, × 2½. Subthalamic region. × 2½. *a* = Peri-aqueductal sclerosis extending between the red nuclei; *b* = ventricular portion of both red nuclei also involved.

Figs. 163–165, × 2. Optic tracts, chiasma, and optic nerves.

Figs. 166–176. Various levels of the spinal cord. Figs. 166–169, × 3; figs. 170–176, × 2. The cord at all levels was in a stage of early involvement (*cf.* figs. 178–180).

Fig. 177, × 2. "Early" area involving the hilum of the dentate nucleus of the cerebellum.

Figs. 178–184. Frozen and Marchi sections to show the prevailing "early" type of area present in this case.

Figs. 178–180. Spinal cord areas in cervical and dorsal segments: to show the extensive distribution of the areas containing fat granule cells—involving frequently the whole transverse section of the cord. Fig. 178, Scharlach R, × 6; figs. 179–180, Marchi, × 6.

Figs. 181–184. Typical cerebral areas. Marchi method. Fig. 181, × 15, peri-ventricular area; fig. 182, × 20, showing cone-shaped mode of extension; fig. 183, × 20, triangular area at the extreme tip of a medullary ray—extending to involve the radiations; fig. 184, × 20, area involving a medullary ray along its whole course, and passing into the radiations at the tip of the convolution.

Plate LVIII (Case VII) (pp. 712–714).

Figs. 185–199. Various levels of the spinal cord. Figs. 185–186, × 4; figs. 187–199, × 6. The areas showed a more complete degree of sclerosis than in any of the other cases, and numerous small, isolated areas were present—several of which picked out individual groups of anterior horn cells, *e.g.* figs. 187 and 195 (C7 and L2). Note also the widening of the glia marginal zone (*cf.* figs. 194–199 (*b*)) in all of the sections, and in the lumbar cord a peri-central sclerosis which extends into the grey matter on each side for a varying distance (*cf.* figs. 194–199 (*a*)).

Fig. 200. Horizontal section through cerebral hemispheres at the level of the middle of the basal ganglia—showing marked peri-ventricular sclerosis, especially around both the anterior (*b*) and posterior (*a*) horns of the lateral ventricles. Mounted specimen. × ½.

Fig. 201. Outer wall of lateral ventricle showing zones of greyish-blue staining, which outlines the sub-ependymal veins (*a*). Mounted specimen.

PLATE LIX (CASE VIII) (pp. 715–717).

Figs. 202–217. Levels of the pons, medulla oblongata, and spinal cord. Kulschitsky-Pal with picro-fuchsin. Note the marked involvement of the spinal cord from the cervical enlargement downwards, and the comparative integrity of the remaining portions of the central nervous system.

Figs. 202 and 203. Upper cervical cord (C3 and C1). × 2.

Fig. 204, × 2. Medulla oblongata above the decussation of the fillet; diffuse staining of the tissue between the inferior olive and the substantia gelatinosa Rolandi on each side.

Fig. 205, × 2½. Middle medulla with cerebellum. Early areas in both restiform bodies; section otherwise normal.

Fig. 206, × 2½. Lower pons; areas lie mostly in the cerebellar portion, and small areas are related to the zone of entry of the VIIIth nerve on both sides.

Fig. 207, × 2½. Upper pons; shows only two small areas which lie in the pontine grey matter and middle cerebellar peduncle.

Fig. 208, × 2½. Pons—level of decussation of the superior cerebellar peduncles; antero-lateral area involving superficial transverse fibres, pontine grey matter, and pyramidal fibres; also slight peri-aqueductal sclerosis.

Figs. 209–217. Various levels of the spinal cord. Note the advanced degree of sclerosis of the cervical enlargement and dorsal cord; few of the levels showed any fat granule cells. Note also that the remaining myelinated fibres (frequently peripheral) show a marked symmetry in their grouping and arrangement, and that the spinal nerve roots at most levels stain normally.

PLATE LX (CASE IX) (pp. 718–720).

Figs. 218–224. Levels of the medulla oblongata and pons. Kulschitsky-Pal with picro-fuchsin. × 2 (fig. 221, × 1). Note the extensive involvement of the lower medulla, but that the areas in the upper medulla and pons are few and are related specially to the angles of the ventricle, to the adjoining cerebellar white matter and foliæ, and to the superior cerebellar peduncles.

Figs. 218–220. Lower medulla. Note the symmetry of the involvement.

Fig. 221. Upper medulla with cerebellum.

Fig. 222. Pons Varolii—upper third—areas are specially related to the angles of the ventricle, pass on both sides into the middle peduncles, involve several of the adjoining cerebellar foliæ and the motor and sensory Vth nuclei.

Fig. 223. Upper limit of pons; peri-aqueductal tissue now normal.

Fig. 224. Pons—level of inferior corpora quadrigemina.

Fig. 225, × 2. Horizontal section through optic chiasma; narrow zone of complete demyelination in anterior margin of chiasma and along the inner border of one optic nerve—the rest of the tissue stains faintly.

Fig. 226, × 2. Frontal longitudinal section through segment of dorsal cord.

Fig. 227, × 2. Posterior root ganglion related to previous figure.

Figs. 228–239. Various levels of the spinal cord. Kulschitsky-Pal with picro-fuchsin. × 2. Note the extensive affection of the lower sacral segments (figs. 238, 239), and the symmetry present in the small areas found in the lumbar cord—especially in those which involve groups of anterior horn ganglion cells (figs. 236, 237).

PLATE LXI.

Figs. 240–249. Transverse sections of the cord from various cases to illustrate special features of individual areas. Kulschitsky-Pal with picro-fuchsin. Figs. 240–243, × 10; figs. 244–249, × 6.

Fig. 240. Sixth cervical segment. Note complete preservation of nerve roots.

Fig. 241. Fifth lumbar segment. Note lateral vessels (*a*) passing to the postero-lateral projection of the anterior horn (*cf.* fig. 253).

Fig. 242. Fifth lumbar segment. *a* = involvement of the glious, extra-medullary portion of posterior nerve root.

Fig. 243. Third lumbar segment at a low level. Note areas at the tip of the anterior fissure and around posterior median fissure. Also a = peri-central sclerosis, and b = area in lateral part of anterior grey matter.

Fig. 244. Third cervical segment. Note the tendency towards symmetry and the varying stages of the involvement.

Fig. 245. Junction of seventh and eighth cervical segments. a = small isolated areas.

Fig. 246. Eighth cervical segment near the junction with first dorsal. Note a = large triangular area with base to surface of the cord—extension to the grey matter which is still outlined.

Fig. 247. Third lumbar segment. a = symmetry of involvement of the tissue around central canal and adjoining anterior median fissure.

Fig. 248. Fourth lumbar segment—incomplete symmetry.

Fig. 249. First sacral segment. Large irregular area with distinct outline.

Fig. 250, × 10. Frontal longitudinal section of the cord showing complete demyelination. a = normal nerve roots; b = longitudinal small vessels with condensed walls.

Figs. 251–252. Upper and lower levels of first dorsal segment—from serial sections. Involvement simulates secondary degeneration.

Plate LXII.

Figs. 253–264. Special features of spinal cord areas. Kulschitsky-Pal with picro-fuchsin. Figs. 253–258 and 260–263, × 30; fig. 259, × 40; fig. 264, × 80

Fig. 253 (*cf.* fig. 241 (*a*)). Note a = lateral vessels passing to area which has picked out the postero-lateral group of anterior horn cells; b = wide glia marginal zone.

Fig. 254. Small oval area around an artero-lateral vessel.

Fig. 255. Larger area extending from the anterior surface of the cord to involve the anterior margin of grey matter (*a*).

Fig. 256. a = small oval area at junction of white and grey matter, around the terminal branches of a lateral vessel; b = smaller area near the surface around a lateral vessel.

Fig. 257. Wedge-shaped area with truncated apex.

Fig. 258. Small undefined area within the lateral column of white matter.

Fig. 259. Triangular area in posterior columns with apex near posterior commissure (*a*). This area extends posteriorly to the surface of the cord.

Figs. 260–262. Indistinctly outlined, small areas around the anterior, middle, and posterior thirds, respectively, of the posterior median fissure.

Fig. 263 (*cf.* fig. 242 (*a*)). Demyelinated glious area in the immediately extra-medullary portion (*a*) of the posterior root and continuous with large area in the postero-lateral region of the cord (L5).

Fig. 264. Similar demyelinated glious area (*a*) immediately external to the "Ablassung" zone (*b*); intra-medullary fibres normal (*c*).

Plate LXIII.

Figs. 265–276. Special features of cerebral areas: figs. 265–268, in the basal ganglia; figs. 269–276, chiefly involving the cortex. Kulschitsky-Pal with picro-fuchsin.

Fig. 265, × 5. Two areas (*a*) involving both internal capsule and globus pallidus; a third area (*b*) cutting across the internal medullary lamina of the lenticular nucleus and extending into both globus pallidus and putamen.

Fig. 266, × 13. Area around blood-vessel in the lenticular nucleus.

Fig. 267, × 6. Areas, around vessels, involving a = optic thalamus; b = internal capsule; and c = lenticular nucleus.

Fig. 268, × 7. Area in the white matter of the occipital lobe in the path of the optic radiations.

Fig. 269, × 6. Convolutions around the calcarine fissure, showing involvement of the optic radiations (*a*) and of the cortical grey matter (*b*).

Fig. 270, × 6. Convolutions around the opposite calcarine fissure of the same case as fig. 269, showing a large number of areas. a = small area confined to a medullary ray; b = areas involving both

medullary ray and radiations; c = confined to the deep cortex; d = extensive demyelination of the superficial cortex.

Fig. 271, × 7. Convolutions at the extremity of the occipital lobe; the medullary ray and radiations at the tip of both convolutions (a) all sharply cut off in an irregular line.

Fig. 272, × 7. Convolutions at the extremity of the opposite occipital lobe of the same case as previous figure. a = complete demyelination of the superficial cortex over an extensive surface; and b = invasion of the deep cortex.

Fig. 273, × 7. Superior frontal convolution. a = cutting off of the medullary radiations at the adjoining tips of two convolutions.

Fig. 274, × 7. Convolutions surrounding the central fissure at the extreme vertex of the hemisphere. a = irregular demyelination of the superficial and invasion of the deep cortex.

Fig. 275, × 7. Convolutions of the para-central lobule. a = area confined to the medullary radiations; b = wedge-shaped area involving whole depth of the cortex and extending with truncated apex into the transition zone of white matter.

Fig. 276, × 6. Convolution of the island of Reil. a = irregular demyelination of the cortical radiations and extension into the cups of the adjoining convolutions; b = small area in the white matter at base of the medullary ray.

Plate LXIV.

Figs. 277–288. Special features of cerebral areas, chiefly cortical. Kulschitsky-Pal with picro-fuchsin.

Fig. 277, × 6. Convolution of the para-central lobule. Note the sharp delimitation of the area both in the white matter and in the radiations of the cortex (*cf.* fig. 74 (*a*)).

Fig. 278, × 15. Convolution of the intra-parietal sulcus. Wedge-shaped area in the cortex extending with truncated apex into the white matter.

Fig. 279, × 13. Convolution of the marginal gyrus. Area surrounded by a zone of lighter staining both in the white matter and cortex.

Fig. 280, × 12. Convolution of the parieto-occipital fissure.

Fig. 281, × 10. Superior parietal convolution. Involvement of the cup of a convolution.

Fig. 282, × 7. Superior frontal convolution. Area extending from the medullary ray and sharply cutting off the radiations.

Fig. 283, × 5. Convolution of the para-central lobule. Two well-defined areas in the white matter and one extending from medullary ray to surface of the convolution.

Fig. 284, × 6. Convolution of the frontal operculum. Area cutting across the medullary ray and involving cortex on either side (*cf.* fig. 25 (*e*)).

Fig. 285, × 5. Area in a parietal convolution involving several medullary rays with their radiations, with the exception of the tip of one convolution (*cf.* fig. 95 (*e*)).

Fig. 286, × 28. Area at the lateral surface of a convolution—involving both transition zone and radiations, and showing the very abundant capillary plexus of the cortex.

Fig. 287, × 33. Small area situated within the radiations, with central longitudinal vessel.

Fig. 288, × 13. Convolution of the central fissure—well-defined area in the medullary ray and involving the transition zone (*cf.* fig. 74 (*b*)).

Plate LXV.

Figs. 289–300. Special features of individual areas, chiefly cerebral. Kulschitsky-Pal with picro-fuchsin. Fig. 291, Heidenhain's iron-hæmatoxylin stain.

Fig. 289, × 10. Area in the mesial line of upper pons—cutting across, in sharply-defined lines, the intersecting fibres of the raphe and the adjoining fibres on each side. *Cf.* fig. 44 (*a*); also figs. 16, 17, and 421, which show the complete retention of the axis cylinders across this demyelinated area.

Fig. 290, × 6. Showing a = involvement of the medullary cores of several cerebellar foliæ; b = areas in the cerebellar white matter; and c = in the peduncles.

Fig. 291, × 10. Medulla oblongata at level of middle of inferior olive, showing faint staining of the

pyramidal tracts. Section is given to illustrate the use of Heidenhain's iron-hæmatoxylin stain to bring out myelinated nerve fibres.

Figs. 292–294. Areas with central blood-vessels: fig. 292, × 30, in external capsule and claustrum; fig. 293, × 30, in central white matter; fig. 294, × 13, in central white matter.

Fig. 295, × 28. Multiple, minute, demyelinated areas in the superficial cortex: sections cut at right angles to the radiating fibres of the cortex.

Fig. 296, × 50. Radiating fibres passing for an irregular distance into an area.

Fig. 297, × 10. Bowl-shaped area in the superficial cortex.

Fig. 298, × 30. Demyelinated area (*a*) showing no change in the cyto-architecture of the cortex (*cf.* next figure).

Fig. 299, × 50. Demyelinated area (*a*) showing marked cell reaction in the cortex (*cf.* previous figure).

Fig. 300, × 30. Slight demyelination (*a*) of the tangential fibres of the cortex.

Plate LXVI.

Figs. 301–312. Special features of early cerebral areas, in which numerous fat granule cells are present, both scattered in the tissue and collected around the blood-vessels. Marchi method.

Fig. 301, × 20. Area in the central white matter.

Fig. 302, × 20. Area confined to a medullary ray.

Fig. 303, × 20. Area involving apex of a medullary ray and passing into the radiations.

Fig. 304, × 20. Similar area with central (older) portion clearing up. Note that the longitudinally-running vessels, passing from the area, are outlined by fat granule cells.

Fig. 305, × 20. Narrow area extending along the transition zone of a medullary ray.

Fig. 306, × 30. Area distinctly limited to the medullary ray in one convolution but passing in another into the radiations.

Fig. 307, × 20. Involvement of the genu of the corpus callosum.

Fig. 308, × 30. Peri-ventricular area around the descending horn of the lateral ventricle.

Fig. 309, × 20. Involvement of the hilum and lamellæ of the dentate nucleus of the cerebellum.

Fig. 310, × 33. Area in central white matter, showing clearing up of the central zone.

Fig. 311, × 20. Area on the path of the optic radiations (*cf.* fig. 268). Note that the fat granule cells are confined to the peripheral zone.

Fig. 312, × 50. Area, almost completely sclerosed, in which a few fat granule cells are present in both central and peripheral zones.

Plate LXVII.

Figs. 313–324. Special features of areas in the spinal cord: figs. 313–315, transverse section; figs. 316–323, longitudinal section. Marchi method.

Fig. 313, × 35. Small area around the vessels of the posterior median fissure (*cf.* fig. 66); fat granule cells, stained black with the osmic acid, permeate the tissue and surround the capillary and larger vessels.

Fig. 314, × 100. H.P. of previous figure.

Fig. 315, × 30. Margin of cord with pia, showing the lateral vessels, with fat granule cells in their adventitial lymphatic sheaths, passing towards the inner layers of the pia, within which they spread in all directions.

Fig. 316, × 5. Longitudinal interrupted lines of fat granule cells.

Fig. 317, × 7. Ditto. Paler appearance of part of the section is due to the removal of the fat granule cells in the adventitial lymphatics.

Fig. 318, × 35. H.P. of previous section, showing these cells in longitudinal rows.

Figs. 319–323. Evolution of the Marchi changes, in the nerve fibre, which lead to the formation of the fat granule cells; early change frequently a darkening of the myelin (fig. 319, × 50); early degeneration in the form of rows of small globules (figs. 320–322, × 30); gradual appearance of fat granule cells (fig. 323, × 200).

Fig. 324, × 40. Degeneration in the sciatic nerve in Case I.

Plate LXVIII.

Figs. 325–333. Evolution of an actual sclerotic area, in the posterior columns of the spinal cord, through a stage of fat granule cell formation (fig. 333); sections cut in the longitudinal direction of the nerve fibres (pp. 584–585). *Cf.* figs. 1–4. Figs. 325–331, × 200, Heidenhain's iron-hæmatoxylin; figs. 332–333, × 200, Palladium methyl-violet. *a* = glia nuclei; *b* = glia fibrils; *c* = fat granule cells; *d* = persistent axis cylinders; *e* = blood-vessels.

Fig. 325. Commencing reaction of all the tissue components.

Fig. 326. Fat granule cell formation with commencing glia fibril formation.

Figs. 327–328. Glia cell proliferation with glia fibril formation at the expense of the glia cell protoplasm and protoplasmic processes.

Figs. 329–330. Increasing glia fibril formation with gradual removal of fat granule cells.

Figs. 331–333. Advancing and complete sclerosis.

Figs. 334–336. Variations in the final glia picture. Fig. 334, retained axis cylinders (darker lines) surrounded by parallel coursing fine glia fibrils. Methyl-violet, × 200. Fig. 335, undulating lines of glia fibrils and thickened longitudinal vessels. Kulschitsky-Pal and picro-fuchsin, × 50. Fig. 336, sclerosed area with numerous glia nuclei. Hæmatoxylin and eosine. × 200.

Plate LXIX.

Figs. 337–342. Low-power view of the evolution of an actual sclerotic area through stages similar to those in previous plate. Longitudinal sections of the posterior columns of the spinal cord. Van Gieson's stain, × 70. Fig. 341, × 50. Letters *a–e*, as in previous plate; *f* = still myelinated nerve fibres; *g* = dense sclerotic tissue.

Fig. 337. Commencing glia proliferation and fat granule cell formation. Note the rows of large protoplasmic glia cells (fig. 379).

Fig. 338. Typical picture of "early" area in stage of so-called "fat granule cell myelitis."

Fig. 339. Increasing glia fibril formation.

Fig. 340. Gradual condensation and removal of fat granule cells.

Fig. 341. Advanced sclerosis with their complete removal.

Fig. 342. Complete sclerosis; tissue consists of longitudinally coursing glia fibrils, blood-vessels, and a few persistent axis cylinders.

Figs. 343–348. Evolution of an actual sclerotic area in the spinal cord through stages of increasing glia hyperplasia. Transverse sections of the lateral columns. Note no fat granule cells are seen in any of these sections. *a* = glia nuclei; *b* = glia trabeculæ; *c* = glia reticulum; *d* = naked axis cylinders; *e* = blood-vessel; *f* = myelinated nerve fibres.

Fig. 343, × 80, and fig. 346, × 500. Commencing thickening of the glia trabeculæ and of the fine glia reticulum. Van Gieson's stain.

Fig. 344, × 50, and fig. 347, × 150. Gradual condensation of this reticulum. Van Gieson's stain.

Fig. 345, × 150. Condensation and almost fusion of the glia reticulum. Note the still preserved axis cylinders and the enlarged glia cells. Cajal's silver method.

Fig. 348, × 200. Shows lesser and more advanced degrees of the increasing glia hyperplasia. *tz* = transition zone. Cajal's silver method.

Plate LXX.

Figs. 349–354. Evolution of an actual sclerotic area (fig. 354) in the posterior columns of the spinal cord, through a stage of fat granule cell formation; sections cut transversely to the direction of the nerve fibres (pp. 577–583). *Cf.* figs. 8–12. Heidenhain's iron-hæmatoxylin stain. Figs. 349–351, × 370; figs. 352–354, × 200. *a* = glia cells; *b* = glia fibrils; *c* = fat granule cells; *d* = axis cylinders; *e* = "Kielstreifen"; *f* = blood-vessels surrounded by layers of fat granule cells; *g* = central canal; *h* = dense glia tissue; *i* = glia fibrils forming whorls.

Fig. 349. Stage of glia cell proliferation and fat granule cell formation.

Fig. 350. Stage of so-called "fat granule cell myelitis."

Fig. 351. Advancing glia fibril formation.

Fig. 352. Fat granule cells collected in the adventitial sheaths of the vessels and gradually being drained away from the area.

Fig. 353. Stage of advanced sclerosis; no fat granule cells but finely granular glia and retained axis cylinders.

Figs. 355–356. Same evolution under low power. Small area in anterior third of posterior columns. Fig. 355, stage of advanced glia fibril formation. Van Gieson's stain. × 70. Fig. 356, stage of advanced sclerosis. Van Gieson's stain. × 50.

Fig. 357. H.P. of transition zone (*t*) of area similar to that in previous figure (*cf.* fig. 12).

Figs. 358–360. Variations in the final glia picture of the above evolution; transverse sections of the posterior columns of the cord.

Fig. 358. Dense sclerotic tissue containing a few fat granule cells and numerous enlarged glia cells. Van Gieson's stain. × 200.

Fig. 359. Showing glia whorls and irregular glia fibril formation. Van Gieson's stain. × 50.

Fig. 360. Central "Kielstreifen," with numerous large glia cells and swollen axis cylinders in the dense sclerotic tissue on either side.

Plate LXXI.

Figs. 361–366. Evolution of a sclerotic area (fig. 364) in the cerebral white matter, through a stage of fat granule cell formation; nerve fibres cut mostly transversely (pp. 586–588). *Cf.* figs. 5 and 6. *a* = glia cells; *b* = glia fibrils; *c* = fat granule cells; *d* = axis cylinders; *e* = blood-vessels. Heidenhain's iron-hæmatoxylin stain.

Fig. 361, × 40; *cf.* fig. 5. Small "early" area with *e* = central blood-vessel; *t* = transitional nucleated zone.

Fig. 362, × 60. Stage of commencing glia fibril formation and fat granule cell formation; *f* = fig. 365.

Fig. 363, × 60. Stage of advancing glia fibril formation; *f* = fig. 366.

Fig. 364, × 60. Stage of complete sclerosis—a dense tissue with very fine meshes.

Fig. 365, × 300. H.P. of fig. 362 (*f*).

Fig. 366, × 300. H.P. of fig. 363 (*f*).

Figs. 367–369. Variations in the density of the final glia network. Iron-hæmatoxylin. Figs. 367, × 150, open network with a few persistent axis cylinders; figs. 368, × 150, denser network, especially around the capillaries; fig. 369, × 80, numerous glia nuclei which form the nodal points from which radiate glia fibrils.

Figs. 370–372. Evolution of a sclerotic area (fig. 372) in the cerebral white matter (medullary ray); nerve fibres cut longitudinally (p. 588). Heidenhain's iron-hæmatoxylin. × 200. Note the persistence of the axis cylinders as swollen, homogeneous lines.

Plate LXXII.

Figs. 373–378. Sclerotic areas in special situations. Iron-hæmatoxylin. Fig. 373, × 70, in the middle cerebellar peduncle; fig. 374, × 150, ditto, showing a more advanced glia fibril formation; fig. 375, × 200, in the hilum of the dentate nucleus; fig. 376, × 38, "early" peri-ventricular area; fig. 377, × 200, H.P. of previous figure; fig. 378, × 150, area cutting across a medullary core of a cerebellar folia.

Figs. 379–384. Types of glia cell changes; *cf.* figs. 391–396. Iron-hæmatoxylin. Fig. 379, × 500, in the posterior column of the spinal cord; rows of large, frequently multi-nucleated, protoplasmic glia cells; fig. 380, × 600, in the cerebral white matter; protoplasmic potential fibril-forming cells; fig. 381, × 200, in the cortex; nests of small glia cells (*a*) surrounding the ghosts of ganglion cells; also (*b*) protoplasmic glia cells.

Figs. 382–384. Evolution of glia fibrils from large protoplasmic glia cells. × 600. Note the definition of the borders of the protoplasmic processes (fig. 382), which can be followed throughout the concave border of two adjoining processes (fig. 383), and that the general outline of the fibrils corresponds at first to the

general outline of the borders of these processes (fig. 384). Such cells are found very abundantly in the cerebral white matter and in the deepest layer of the cortex.

PLATE LXXIII.

Figs. 385–396. Changes in cortical areas.

Fig. 385, × 60. Demyelination of cortex without any change in the cyto-architecture.

Fig. 386, × 45. Demyelination of cortex with marked glia cell reaction in the transition zone and in the deep layers of the cortex.

Fig. 387, × 60. Ditto. Note the marked alteration in the Betz cells (*a*). Figs. 385–387, Van Gieson's stain.

Fig. 388, × 80. Cortical and subcortical area with glia cell reaction in the deep layers of the cortex.

Fig. 389, × 200. Transition zone. *a* = glia cells ; *c* = fat granule cells.

Fig. 390, × 200. Transition zone ; stage of advancing sclerosis. *a* = glia nuclei ; *b* = glia reticulum.

Figs. 391–396. Glia cell changes in the respective layers of the cortex ; *cf.* figs. 21 and 22. *a* = proliferated glia cells with numerous fibrils ; *b* = nests of small glia cells, around the ghosts of ganglion cells ; *c* = ganglion cells ; *d* = persistent axis cylinders ; *e* = blood-vessels. Note relation of the glia cell processes and fibrils to the capillary walls.

Fig. 391, × 200, and fig. 394, × 600. In the polymorphous (deepest) layer. Methyl-violet.

Fig. 392, × 200, and fig. 395, × 600. In the layer of the deep pyramids. Methyl-violet.

Fig. 393, × 200. In the granular layer ; nests of small glia cells around ganglion cells or replacing them. Hæmatoxylin and eosin.

Fig. 394, × 400. In the layer of the large pyramids. Note ganglion cells (*c*) surrounded by enlarging satellite cells (*f*), whose protoplasm is filled with black-stained granules. Marchi method. Similar cells are found around the capillary vessels in this layer.

PLATE LXXIV.

Figs. 397–442. Low-power view of areas in myelin sheath and glia stains to show comparative negative and positive pictures.

Fig. 397, × 40, and fig. 400, × 30. Areas in the central white matter showing absence of myelin.

Fig. 398, × 60, and fig. 401, × 30. Similar areas to show presence of glia in the demyelinated tissue.

Fig. 399, × 50. Very minute area in the central white matter showing slight demyelination.

Fig. 402, × 200. Similar minute area to show the commencing enlargement of the glia cells (*a*) in this area of slight demyelination.

Figs. 403–405. Transition peripheral zones in areas in the central white matter to show the glia nuclear proliferation. Van Gieson's stain. Fig. 403, × 40, an old area with zone of small glia cells (*b*) ; fig. 404, × 200, sclerosis still incomplete with large (*a*) and small (*b*) glia cells ; fig. 405, × 60, wedge-shaped zone of small glia cells (*b*).

Figs. 406–408. Transition zones of advancing areas in the spinal cord to show the mode of degeneration of the myelin. Frozen sections ; Heidenhain's iron-hæmatoxylin. Fig. 406, × 60, longitudinal myelinated fibres passing into an "early" area ; fig. 407, × 300, similar fibres under H.P. to show the fine globules and droplets of myelin which take the hæmatoxylin stain ; fig. 408, × 300, similar nerve fibres in transverse section.

PLATE LXXV.

Figs. 409–419. Ganglion cell changes in the anterior horn of the spinal cord (except fig. 418) (pp. 607, 608). Figs. 409–413, changes probably not related to the sclerotic process, but to the accompanying want of function, decubitus, etc. ; figs. 414–419, changes probably related to both processes.

Fig. 409, × 40. Ganglia cells very atrophic, but rounded forms present with nucleus and chromophile granules almost normal in structure and arrangement. Figs. 409–411, polychrome methylene blue.

Fig. 410, × 80. Similar cells occurring in a demyelinated area.

Fig. 411, × 200. Cells in a demyelinated area showing chromatolysis and excentric nuclei.

Figs. 412–413, × 75. Cells showing marked pigmentation both in myelinated and demyelinated tissue. Weigert's myelin sheath stain.

Fig. 414, × 275. Commencing reaction of the glia cells around a ganglion cell. Figs. 414–416, polychrome methylene blue.

Fig. 415, × 200. Atrophy and disappearance of ganglion cells with marked neuroglia cell reaction.

Fig. 416, × 200. Similar to previous figure—occurring in the opposite anterior horn.

Fig. 417, × 200. Ganglion cell, retaining its processes and chromophile structure, in the midst of sclerotic tissue. Figs. 417–419, Heidenhain's iron-hæmatoxylin.

Fig. 419, × 150. Disappearance, atrophy, and rounding of cells in the hypoglossal nucleus, with marked glia cell reaction.

Fig. 419, × 200. One rounded atrophic ganglion cell present in the midst of a dense glia network.

Fig. 420, × 200. Ganglion cells in one of the posterior root ganglia related to a completely demyelinated area. Polychrome methylene blue.

Plate LXXVI.

Figs. 421–432. Changes related to the axis cylinders.

Fig. 421, × 10. Intersection in the median raphe of the pons of persistent axis cylinders. Note the darker staining of the still myelinated tissue on both sides (*cf.* figs. 16, 17, 44, and 289).

Fig. 422, × 300. Persistent swollen axis cylinders in a medullary ray.

Fig. 423, × 200, and fig. 424, × 50. Persistent axis cylinders continued as shadowy lines into the dense sclerotic tissue; longitudinal sections of cord. Figs. 421–424, Bielschowsky-Williamson silver method.

Figs. 425 and 426, × 300. Granular disintegration of the axis cylinders in a sclerosing area. Hæmatoxylin and eosin.

Figs. 427 and 428, × 200. Persistent swollen axis cylinders in cross section; posterior columns of the cord. Bielschowsky-Williamson silver method.

Fig. 429. Complete retention of axis cylinders; longitudinal section of the cord. Figs. 429–432, Cajal's silver method. × 200.

Fig. 430. Small area in cerebral white matter; axis cylinder network.

Figs. 431 and 432. Axis cylinder contact in optic chiasma and nerves which were completely gelatinous.

Plate LXXVII.

Figs. 433–444. Sequence of changes in the blood-vessels (pp. 614–616); *cf.* figs. 13–15.

Fig. 433. Area in longitudinal section of the spinal cord showing capillary and transition vessels with rows of fat granule cells (*c*) in their adventitia. Van Gieson's stain. × 60.

Figs. 434–437. Blood-vessels in the cerebral white matter. Heidenhain's iron-hæmatoxylin. × 200. Fig. 434, vessel cut transversely (*b*) with fat granule cells (*c*) in its adventitial lymph spaces, and glia cell reaction (*a*) in the surrounding tissue; fig. 435, × 200, similar vessel cut longitudinally; fig. 436, × 400, H.P. of previous figure to show the relation of the glia "Fuss" to the outer layers of the adventitia; fig. 437, × 75, vessel surrounded by concentric layers of glia fibrils.

Fig. 438. Vessel in the posterior median fissure; adventitial lymph spaces filled by fat granule cells which have been drained from the surrounding sclerotic tissue. Van Gieson's stain, × 250.

Fig. 439 (*cf.* fig. 14). Transition vessel to show the cell content of the adventitia during the stage of advancing sclerosis. Van Gieson's stain, × 370.

Fig. 440. Condensed "hyaline" vessel (*a*) with the outer layers (*b*) of its adventitia still separated. Note lessening cell content of the vessel wall. Iron-hæmatoxylin. × 360.

Fig. 441. Similar vessels with the peri-vascular spaces (artefacts) filled with a coagulum (*a*). Van Gieson's stain. × 70.

Fig. 442, × 60. Lateral columns of the spinal cord; radiating longitudinal thickened vessels (*a*). Figs. 442–444, Kulschitsky-Pal with picro-fuchsin.

Fig. 443, × 50. Posterior columns of the spinal cord with similar vessels cut transversely (*a*) and longitudinally (*b*).

Fig. 444, × 250. Optic nerve; connective-tissue septa and thickened vessels in longitudinal section.

Plate LXXVIII.

Figs. 445–450. Special features of the changes in the blood-vessels.

Fig. 445. Cerebral white matter; small dilated capillary surrounded by a zone of shadow sclerosis. Kulschitsky-Pal with picro-fuchsin. × 25.

Fig. 446. Cerebral cortex; two dilated and thickened small cortical vessels passing into a demyelinated area. Van Gieson's stain. × 50.

Fig. 447. Dilated vessels at posterior horn of lateral ventricle. Van Gieson's stain. × 50.

Fig. 448. Groups of vessels in a sclerotic area with very dilated peri-vascular tissue. Kulschitsky-Pal with picro-fuchsin. × 10.

Fig. 449. Similar vessels in an area of more advanced sclerosis. Van Gieson's stain. × 30.

Fig. 450. Similar vessels both within the area and in the adjoining tissue. Van Gieson's stain. × 45.

Figs. 451–454 illustrate various features in the changes in the nerve roots. Kulschitsky-Pal with picro-fuchsin.

Fig. 451, × 75. Rarefaction of the anterior nerve roots.

Fig. 452, × 75. Normal nerve roots in the cauda equina. H.P. of next figure.

Fig. 453, × 6. Normal nerve roots surrounding a completely demyelinated fifth sacral segment of the cord.

Fig. 454, × 6. Normal sciatic nerve in same case as previous figure.

Fig. 455. Ependymal proliferation in wall of lateral ventricle. Heidenhain's iron-hæmatoxylin. × 300.

Fig. 456. Normal glandular portion of the pituitary body. Hæmatoxylin and eosin. × 300.

DR DAWSON—HISTOLOGY OF DISSEMINATED SCLEROSIS.

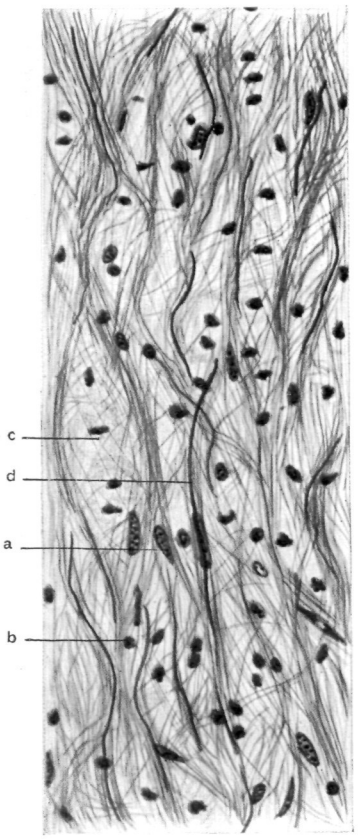

FIG. 1.

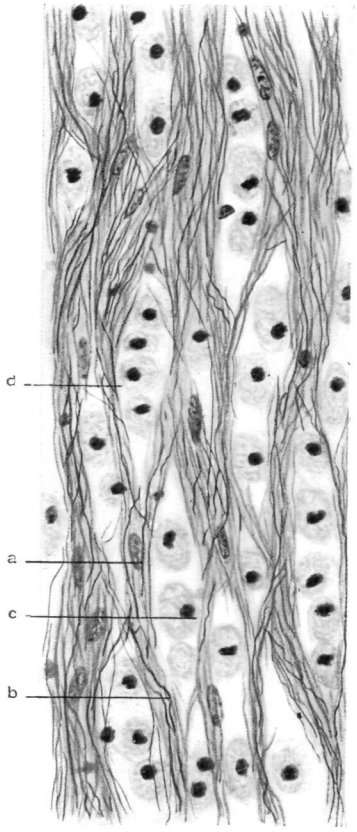

FIG. 2.

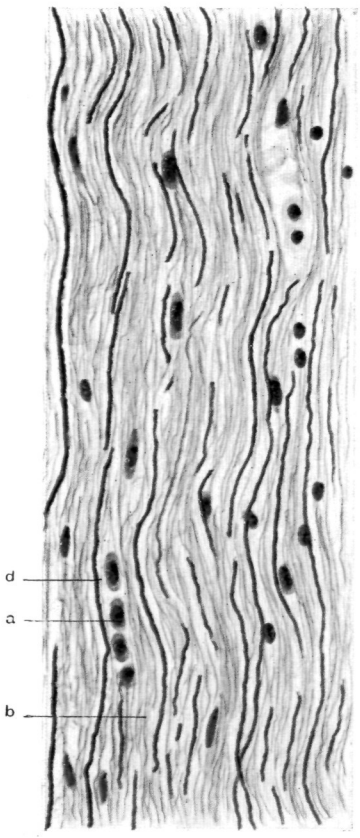

FIG. 3.

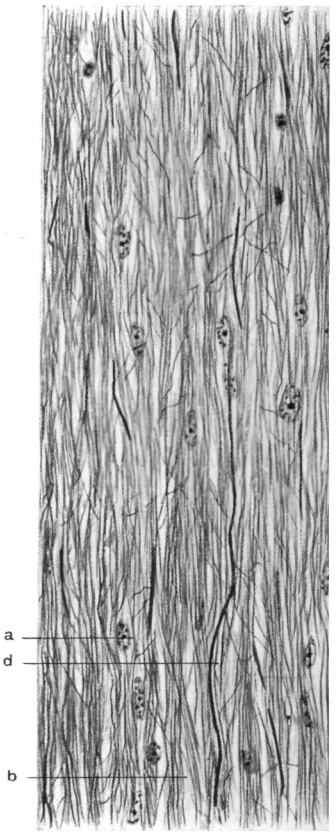

FIG. 4.

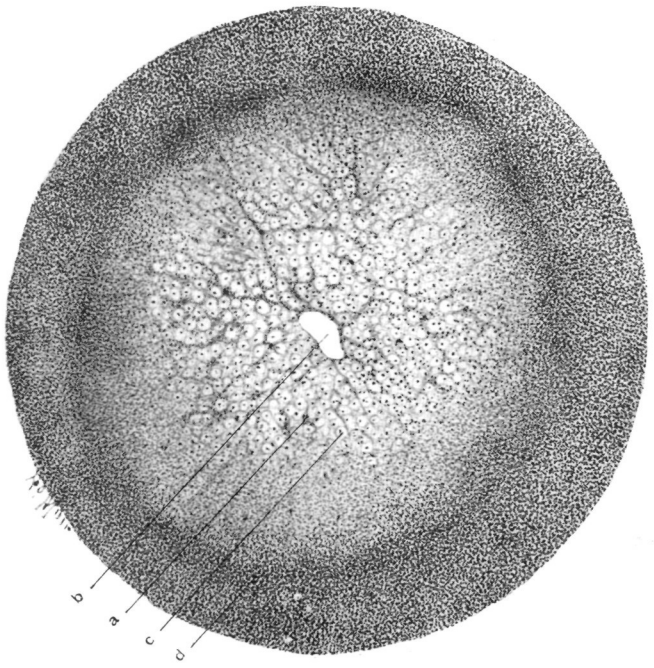

FIG. 5.

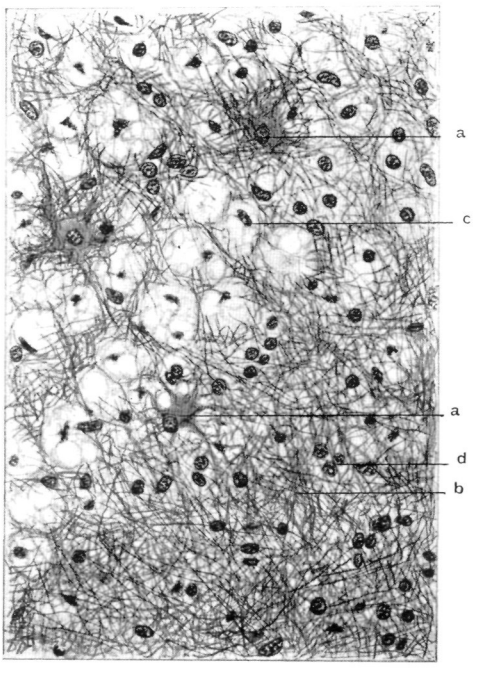

FIG. 6.

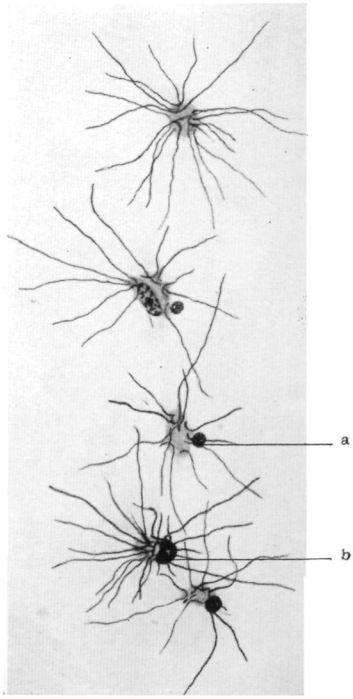

FIG. 7.

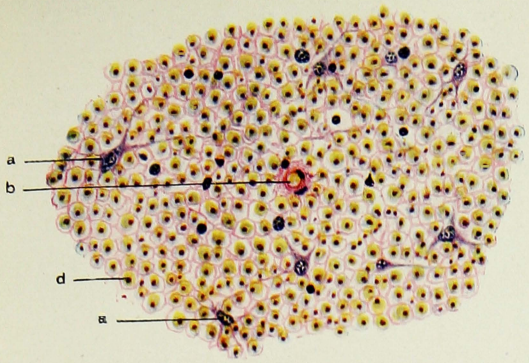

FIG. 8.

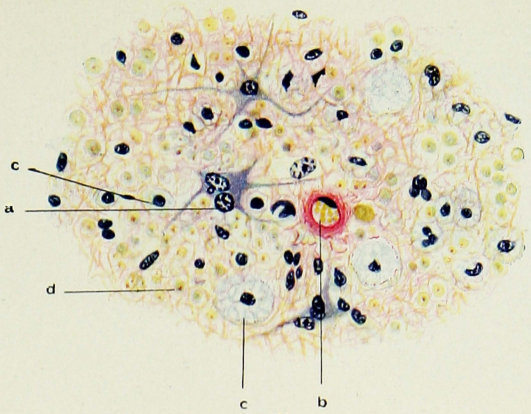

FIG. 9.

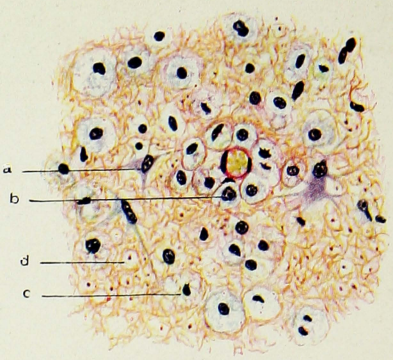

FIG. 10.

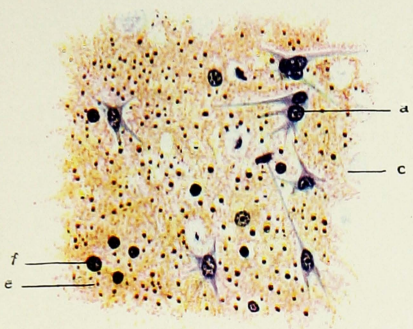

FIG. 11

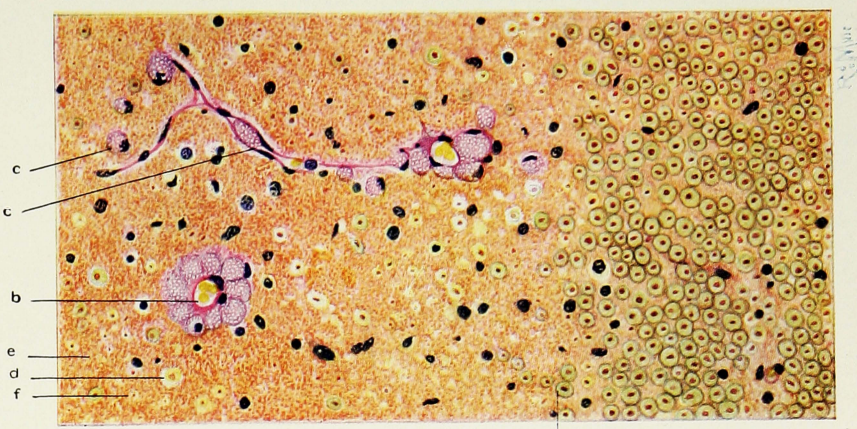

FIG 12.

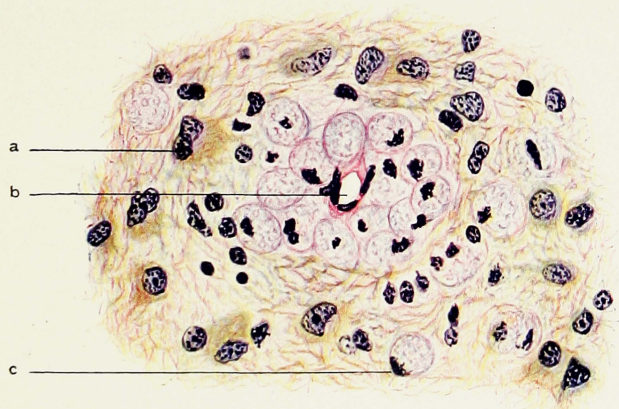

FIG. 13.

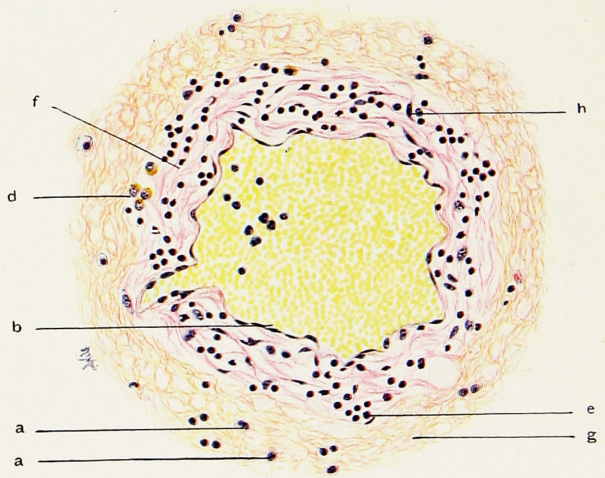

FIG. 14.

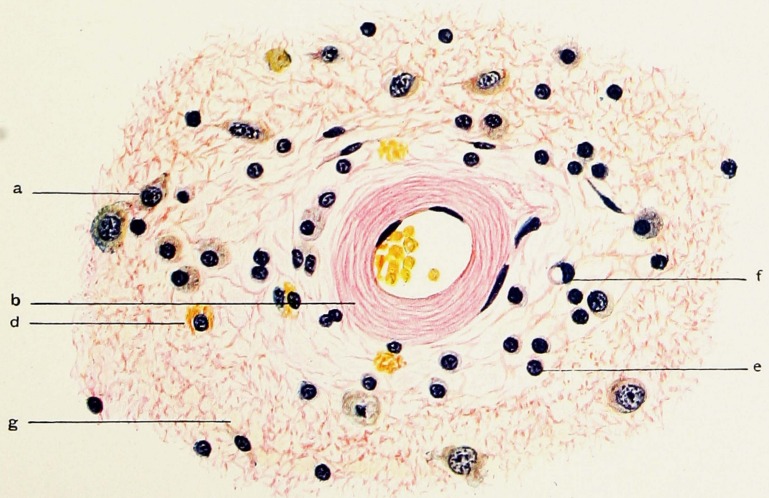

FIG. 15.

DR DAWSON—HISTOLOGY OF DISSEMINATED SCLEROSIS.

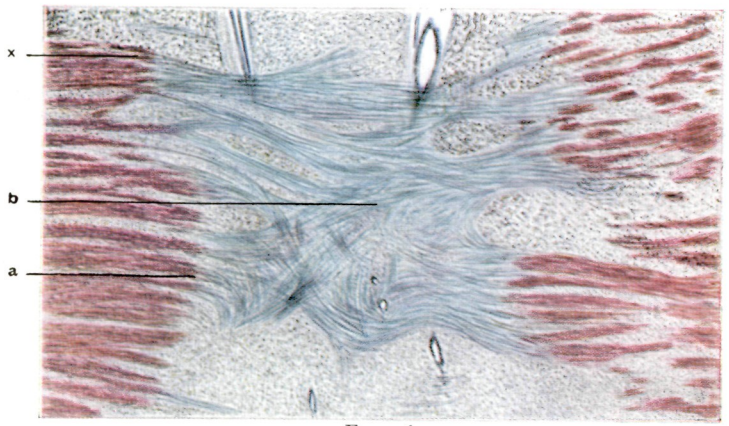

FIG. 16.

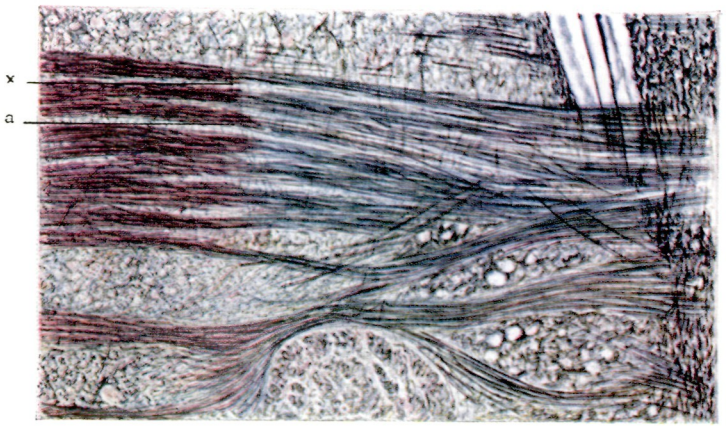

FIG. 17.

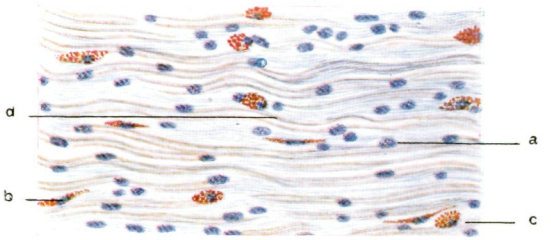

FIG. 18.

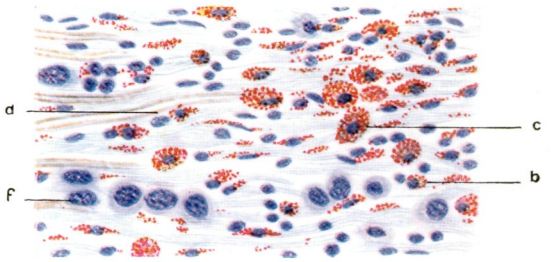

FIG. 19.

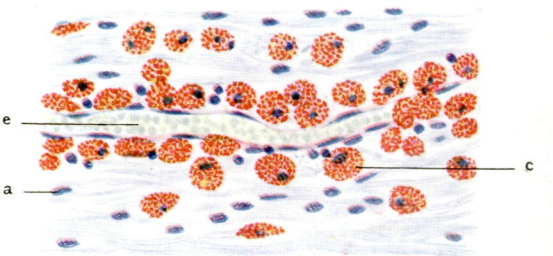

FIG. 20.

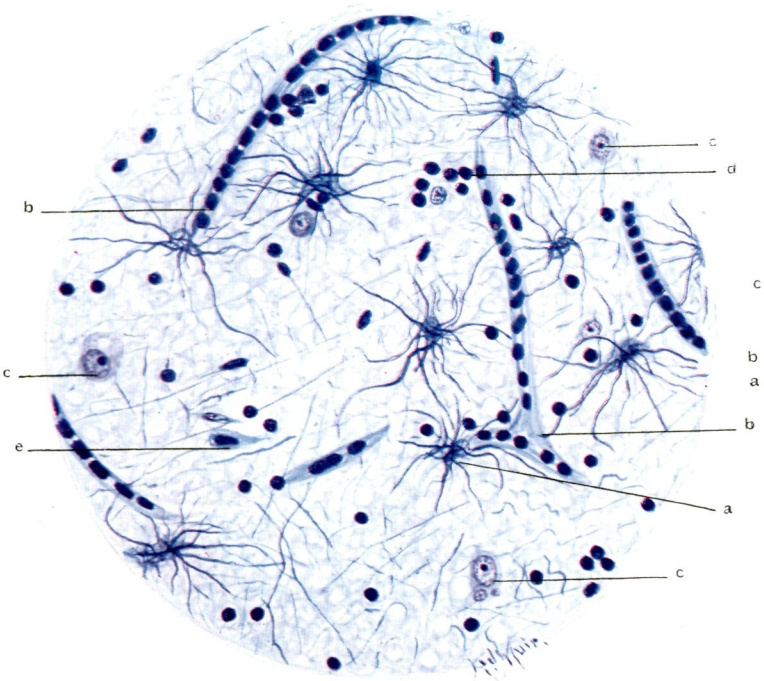

FIG. 21.

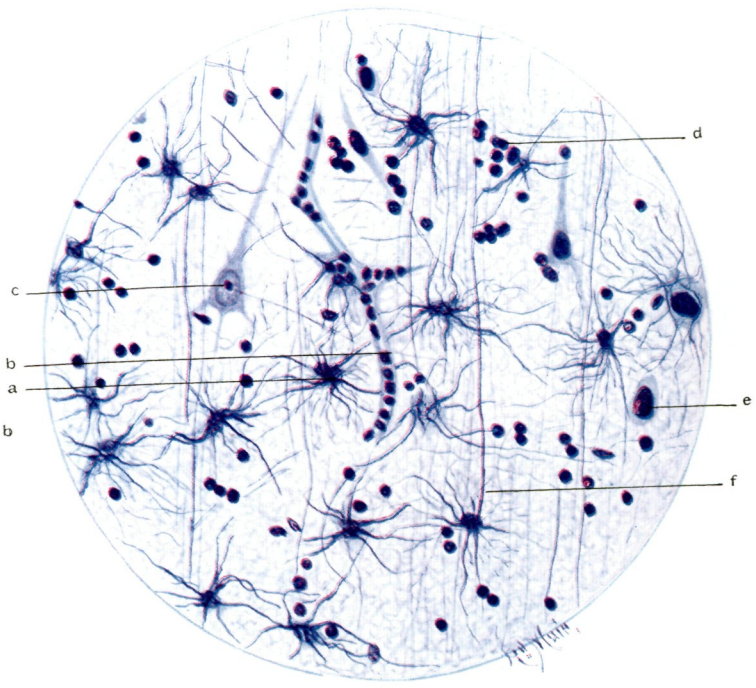

FIG. 22.

DR DAWSON—HISTOLOGY OF DISSEMINATED SCLEROSIS.

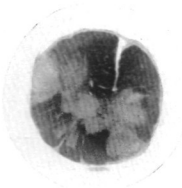

FIG. 32.

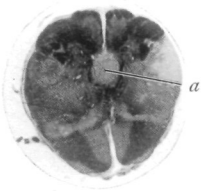

FIG. 33.

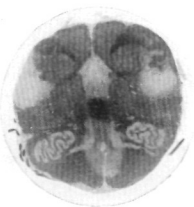

FIG. 34.

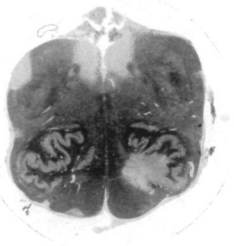

FIG. 35.

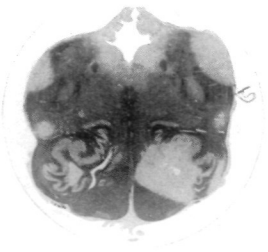

FIG. 36.

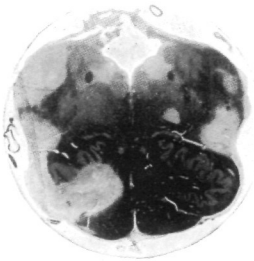

FIG. 37.

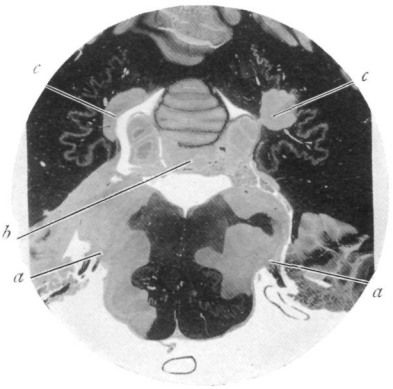

FIG. 38.

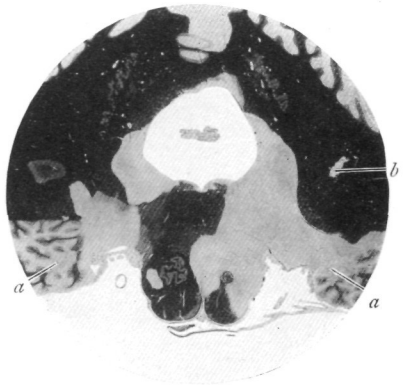

FIG. 39.

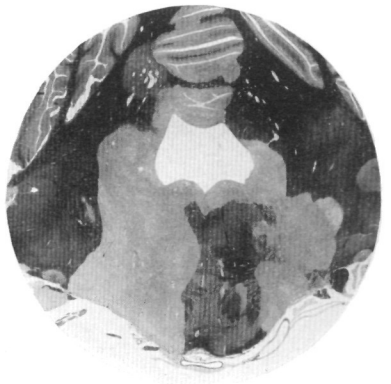

FIG. 40.

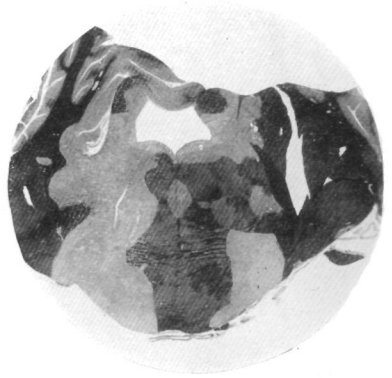

FIG. 41.

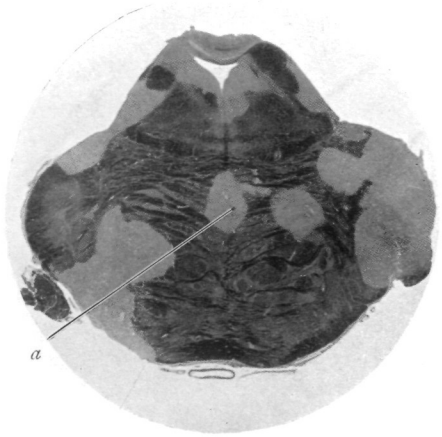

FIG. 42.

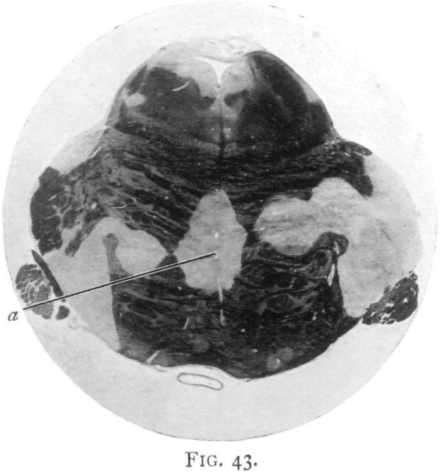

FIG. 43.

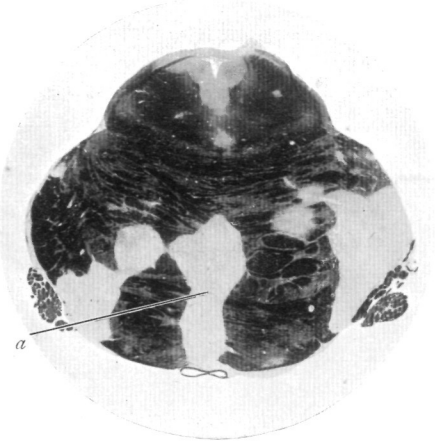

FIG. 44.

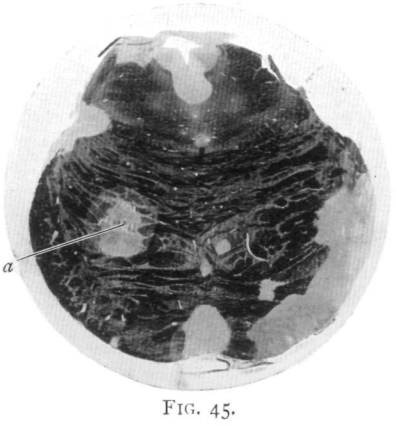

FIG. 45.

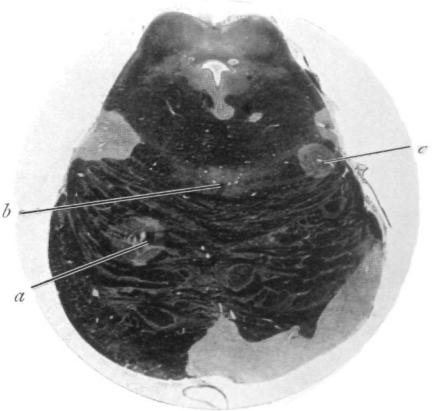

FIG. 46.

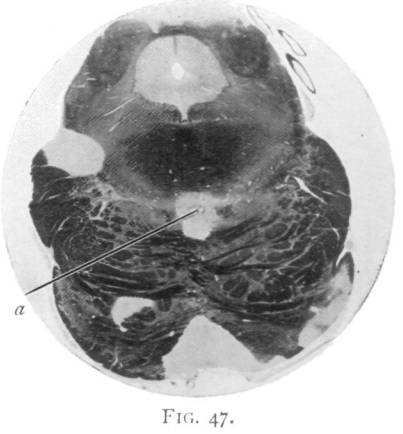

FIG. 47.

DR DAWSON—HISTOLOGY OF DISSEMINATED SCLEROSIS.

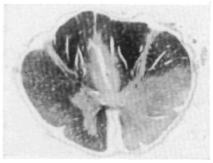

FIG. 48—Upper C_2

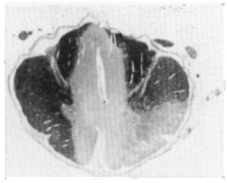

FIG. 49—Lower C_2

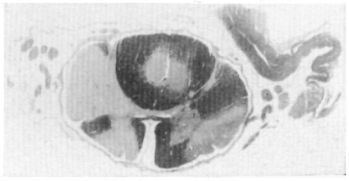

FIG. 50—Upper C_3

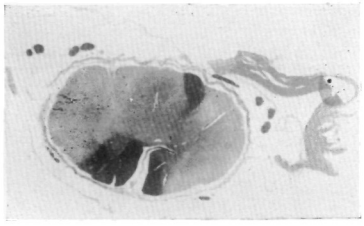

FIG. 51—Lower C_3

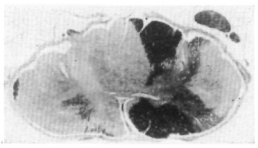

FIG. 52—C_5

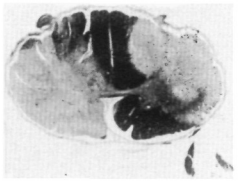

FIG. 53—C_6

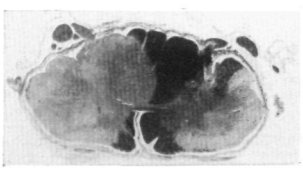

FIG. 54 - Upper C_8

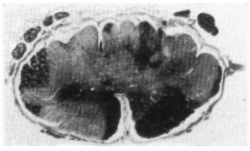

FIG. 55—D_1

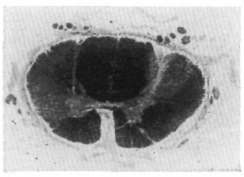

FIG. 56—D_4

FIG 57—D_6

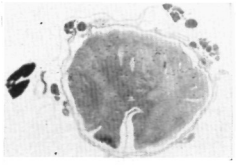

FIG. 58—D_{10}

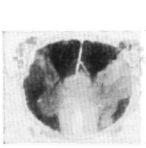

FIG. 59—L_3

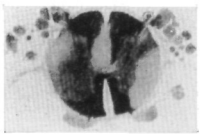

FIG. 60—L_4

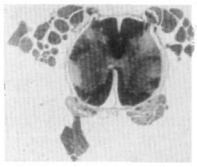

FIG. 61—S_1

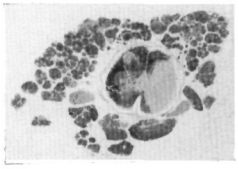

FIG. 62—S_2

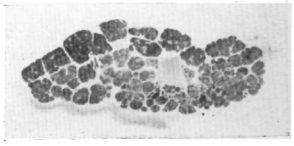

FIG. 63—S_5

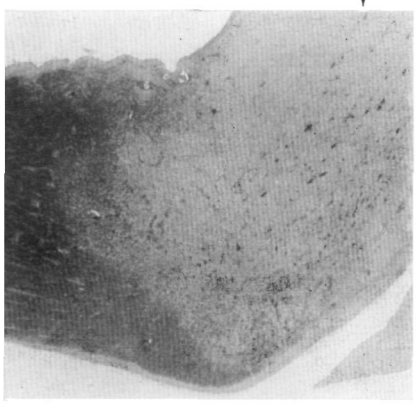

FIG. 64.

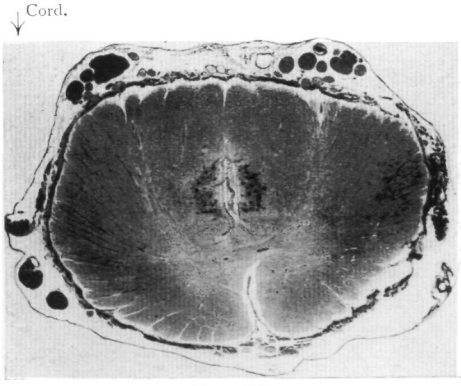

FIG. 66.

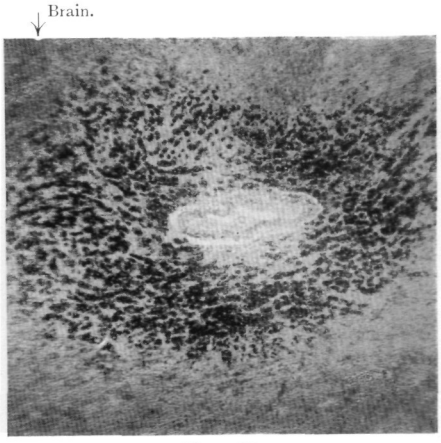

FIG. 68.

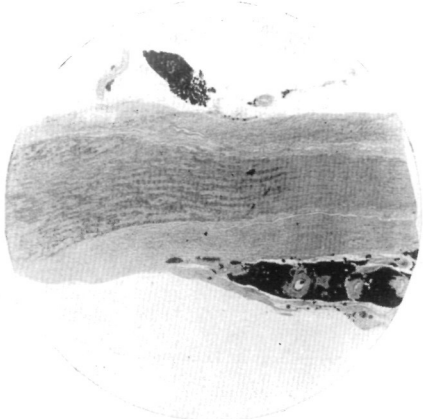

FIG. 65.

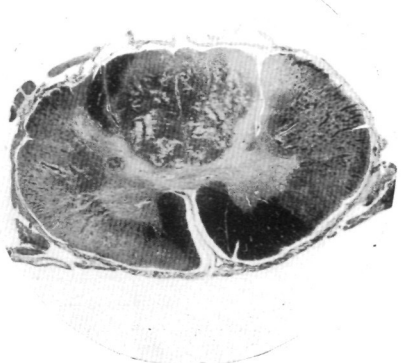

FIG. 67.

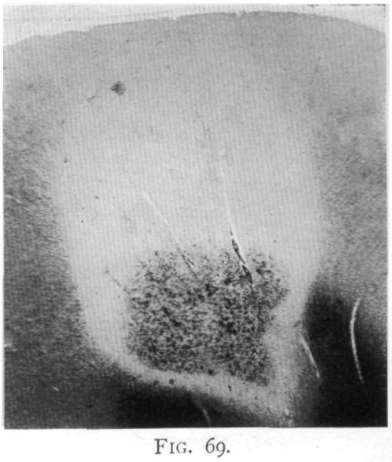

FIG. 69.

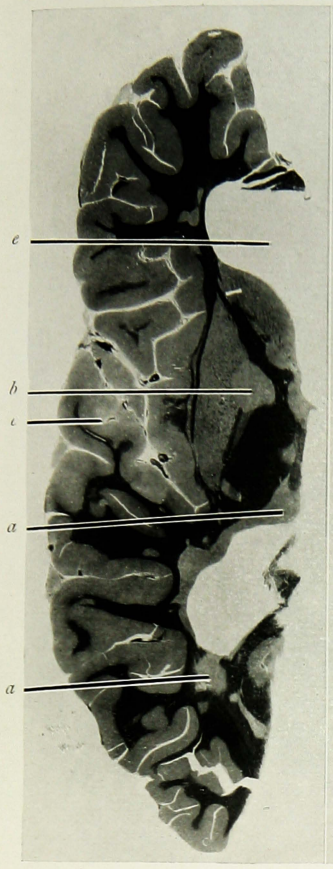

FIG. 70.

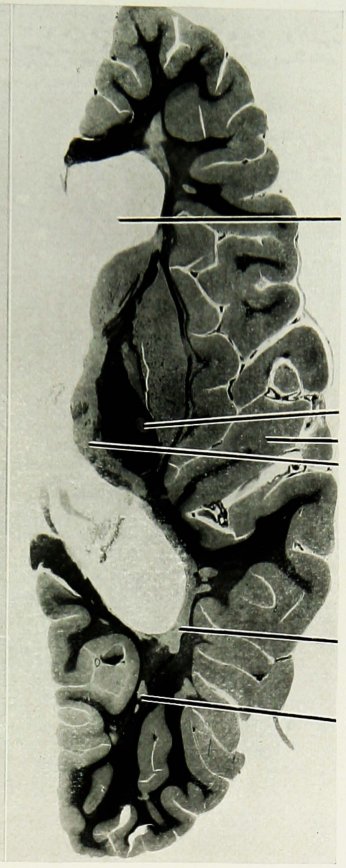

FIG. 71.

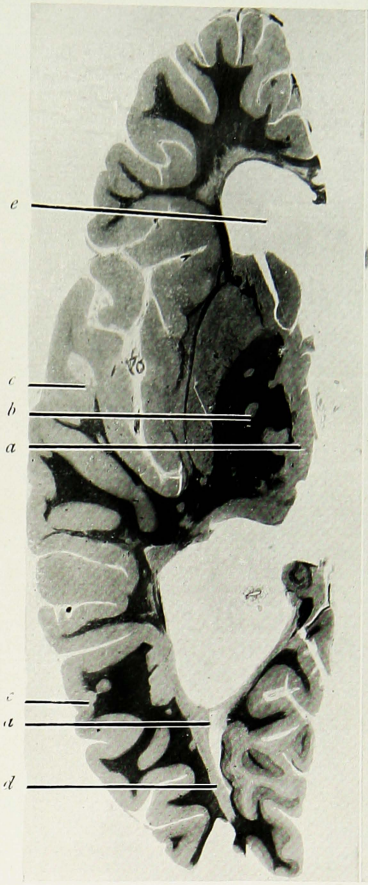

FIG. 72.

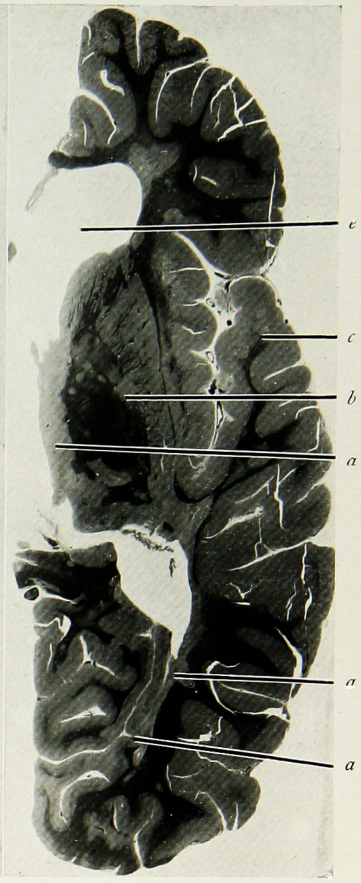

FIG. 73.

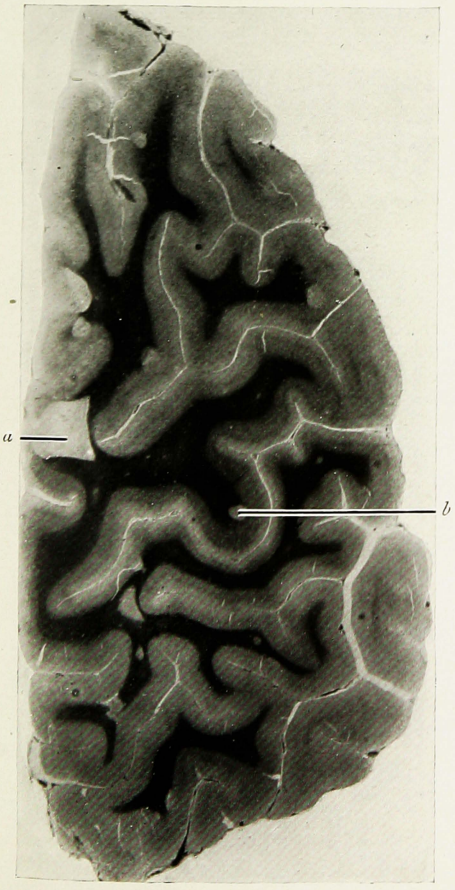

FIG. 74.

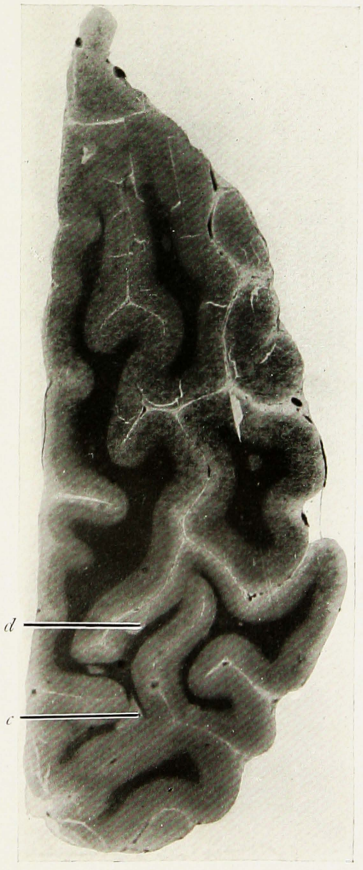

FIG. 75.

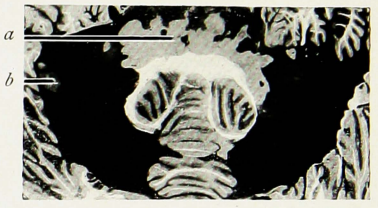

FIG. 76.

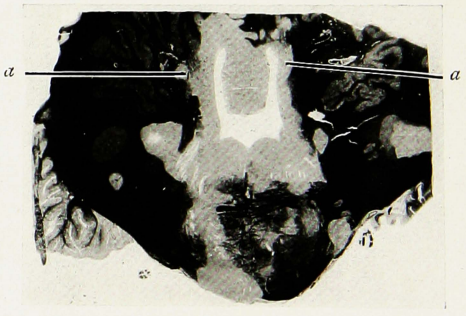

FIG. 77.

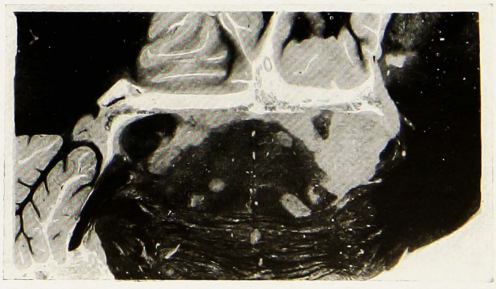

FIG. 78.

DR DAWSON.—HISTOLOGY OF DISSEMINATED SCLEROSIS.

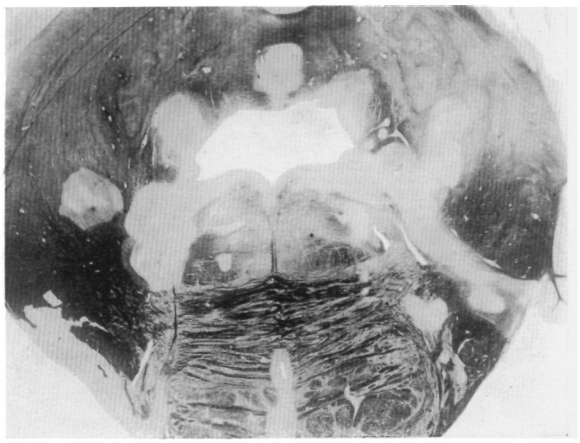

FIG. 79.

FIG. 81.

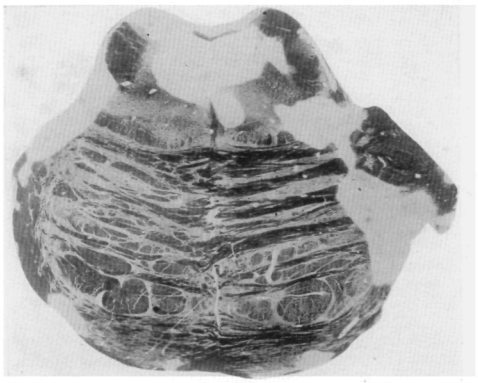

FIG. 80.

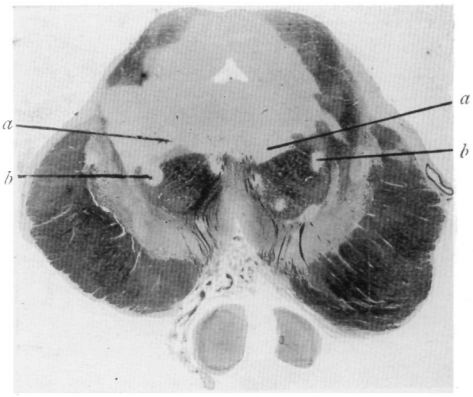

FIG. 82.

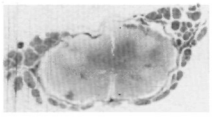

FIG. 83—C_7

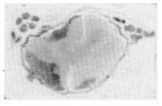

FIG. 86—Mid. D.

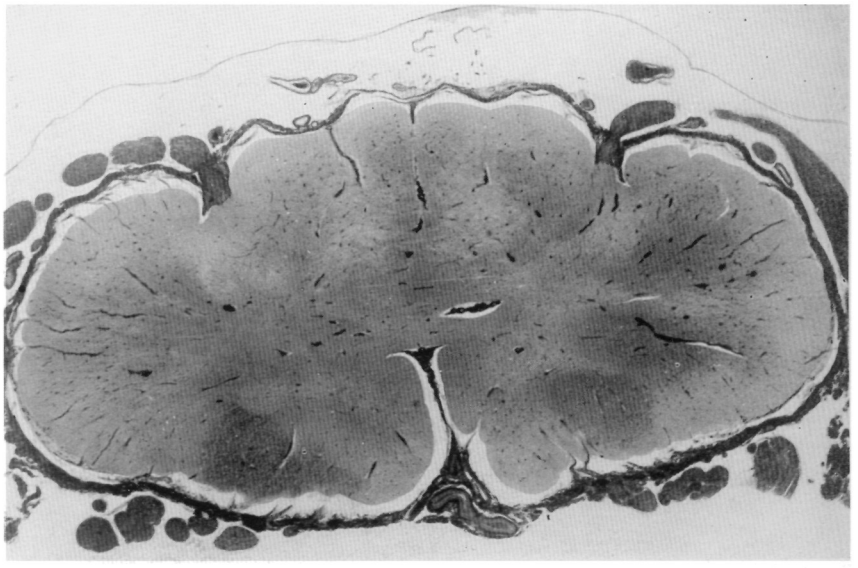

FIG. 89.

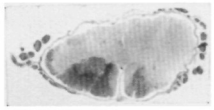

FIG. 84—C_8

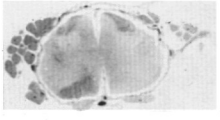

FIG. 87—L_4

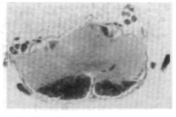

FIG. 85—D_1

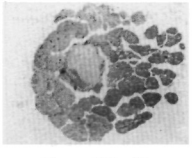

FIG. 88—S_4

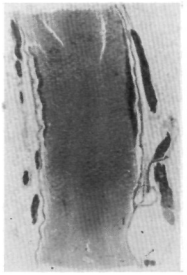

FIG. 90.

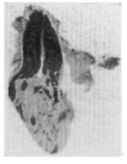

FIG. 91.

FIG. 92.

DR DAWSON.—HISTOLOGY OF DISSEMINATED SCLEROSIS.

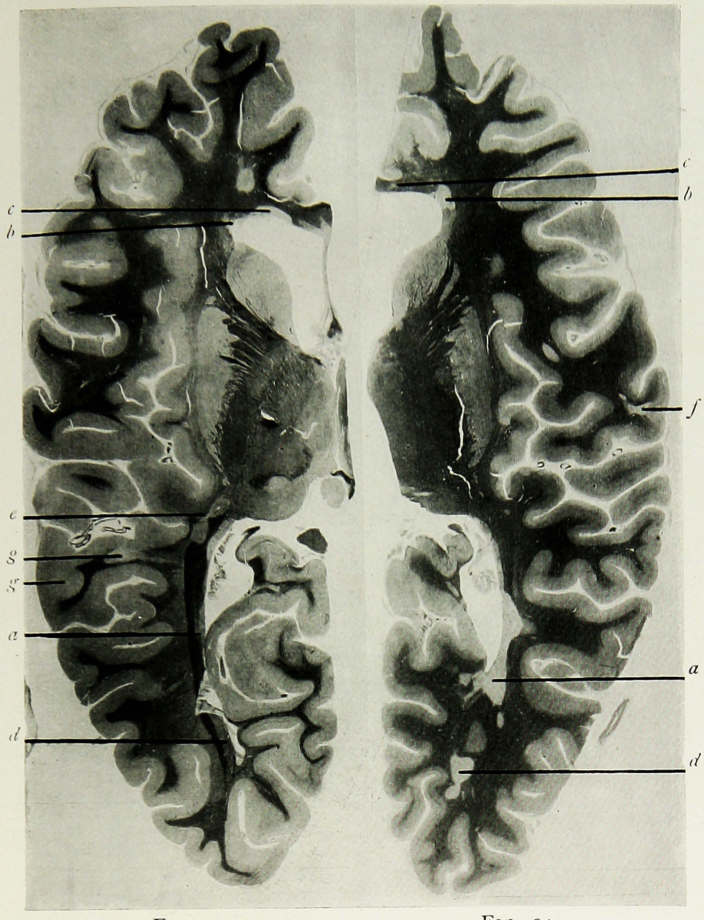

FIG. 93.

FIG. 94.

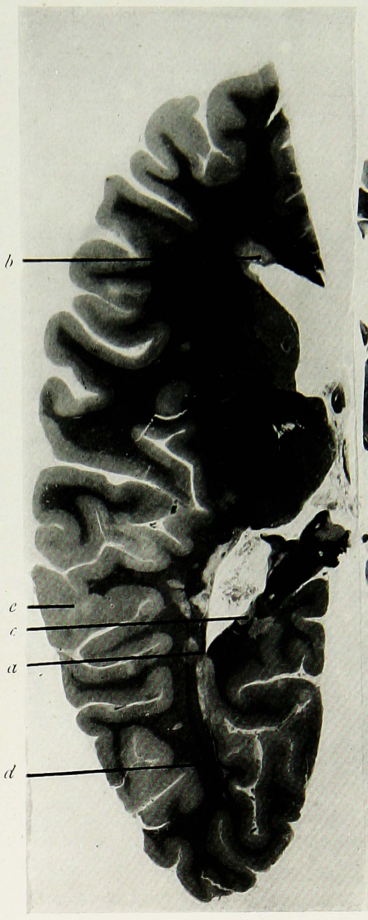

FIG. 95.

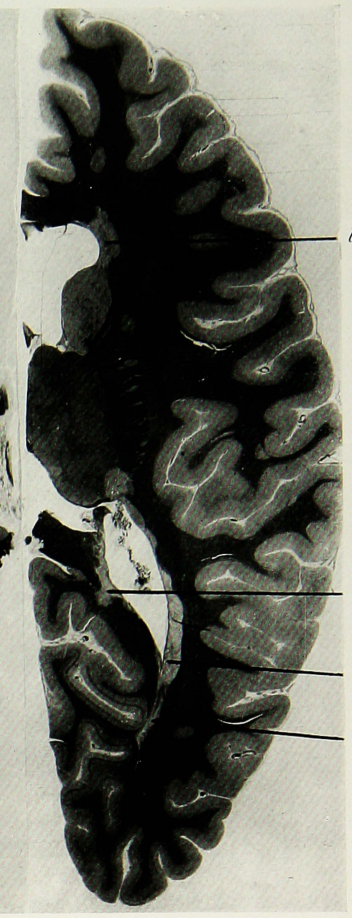

FIG. 96.

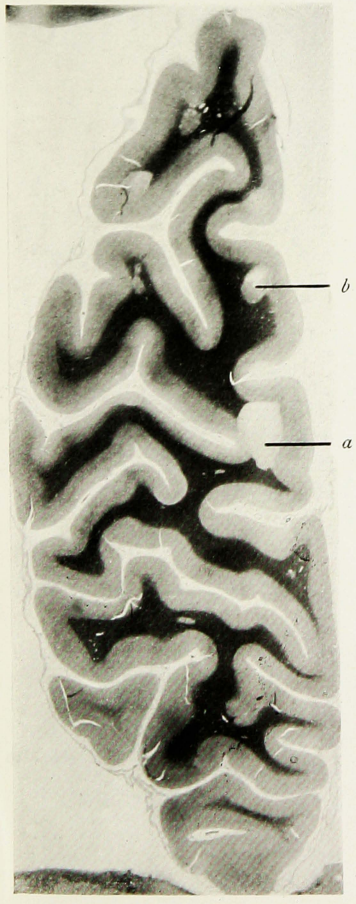

FIG. 97.

FIG. 98.

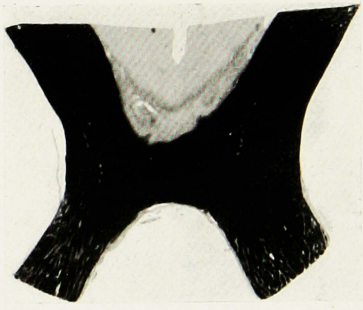

FIG. 100.

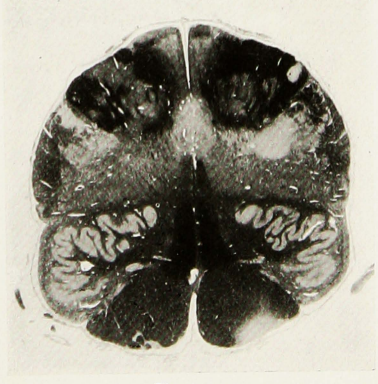

FIG. 99.

FIG. 101.

FIG. 102.—C_1

FIG. 108.—D_1

FIG. 103.—C_3

FIG. 109.—D_3

FIG. 104.—C_5

FIG. 110.—D_7

FIG. 105.—C_6

FIG. 111.—D_{10}

FIG. 106.—C_7

FIG. 112.—L_1

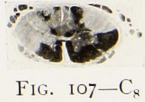

FIG. 107.—C_8

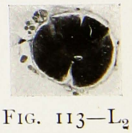

FIG. 113.—L_2

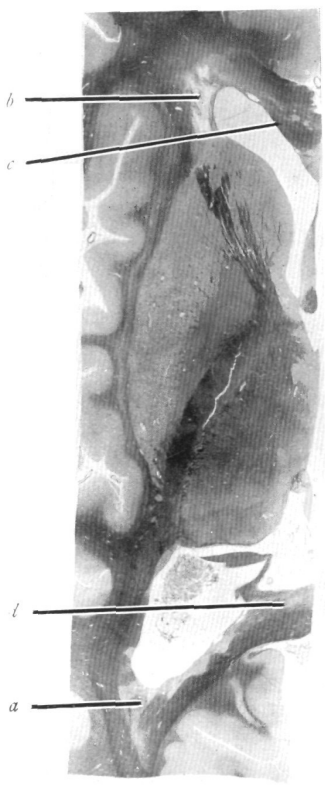

FIG. 114.

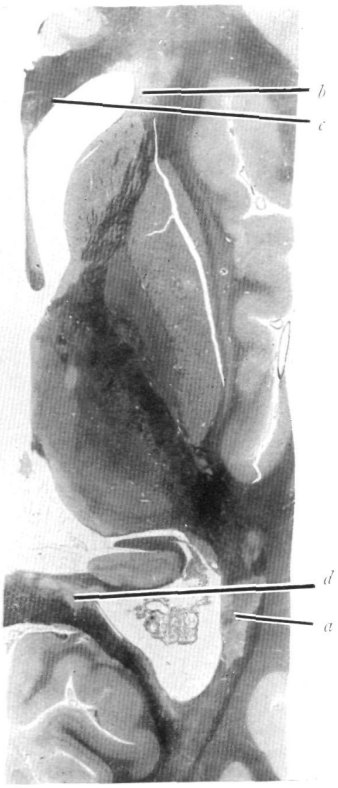

FIG. 115.

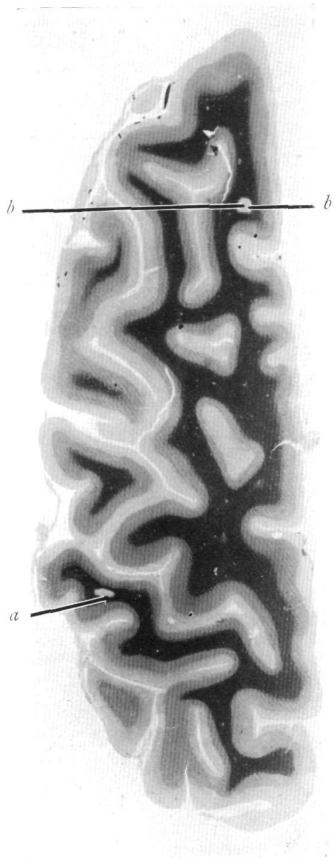

FIG. 116.

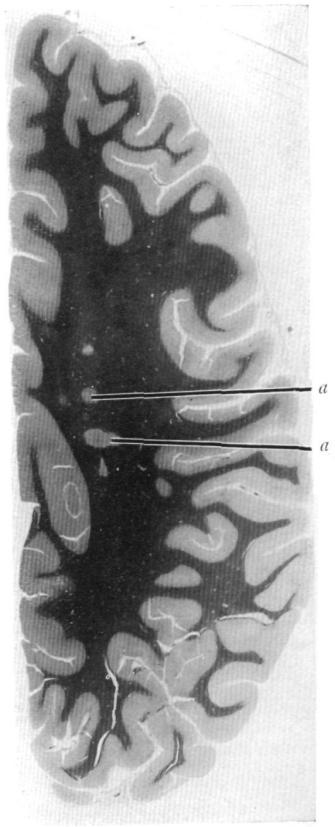

FIG. 117.

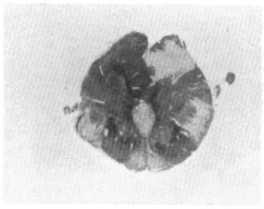

FIG. 118.

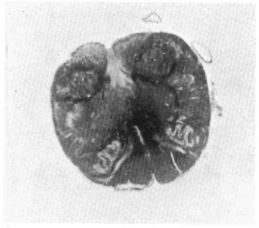

FIG. 119.

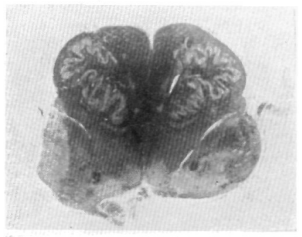

FIG. 120.

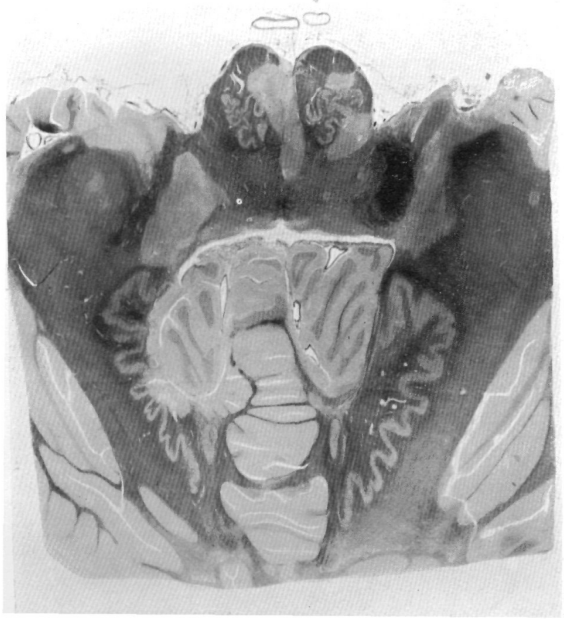

FIG. 121.

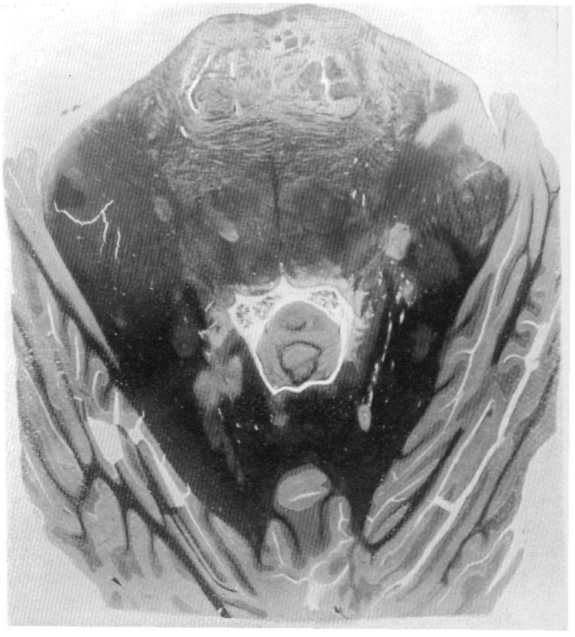

FIG. 122.

DR DAWSON—HISTOLOGY OF DISSEMINATED SCLEROSIS.

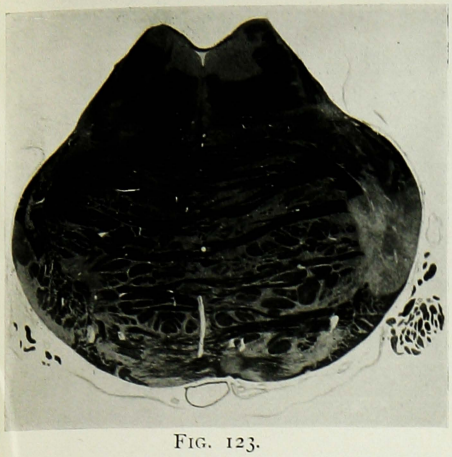

FIG. 123.

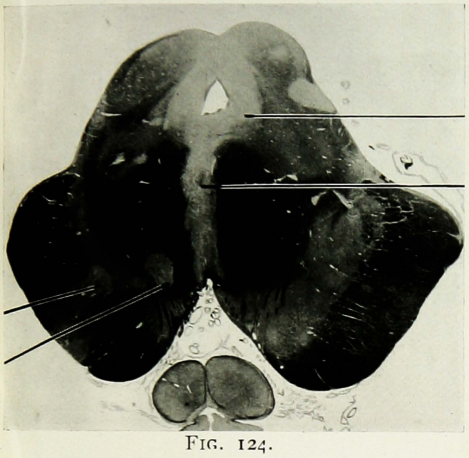

FIG. 124.

FIG. 125—C_5

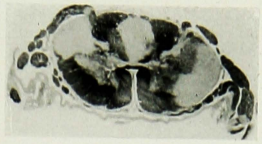

FIG. 126—C_6

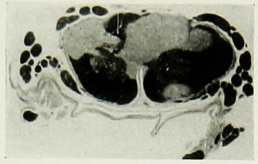

FIG. 127—C_7

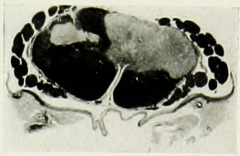

FIG. 128—C_8

FIG. 129—D_1

FIG. 130—D_3

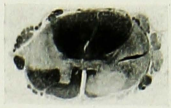

FIG. 131—D_5

FIG. 132—D_7

FIG. 133—D_{11}

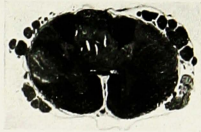

FIG. 134—D_{12}

FIG. 135—L_2

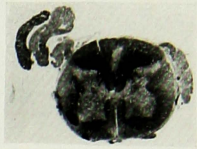

FIG. 136—L_3

FIG. 137—L_4

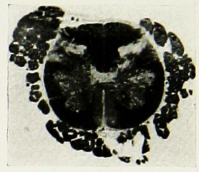

FIG. 138—L_5

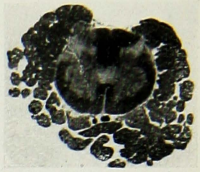

FIG. 139—S^1

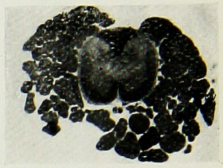

FIG. 140—S_2

FIG. 141—S_3

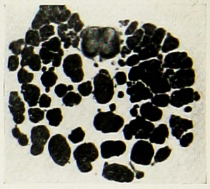

FIG. 142—S_4

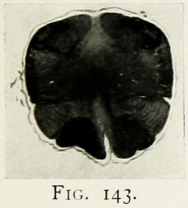

FIG. 143.

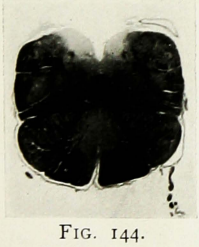

FIG. 144.

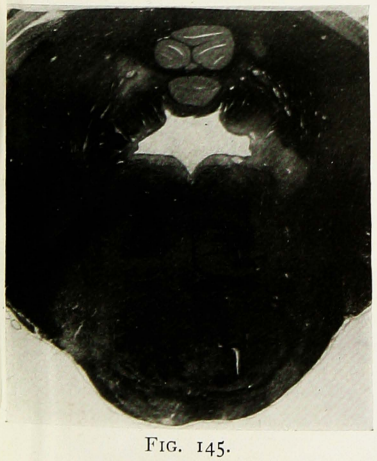

FIG. 145.

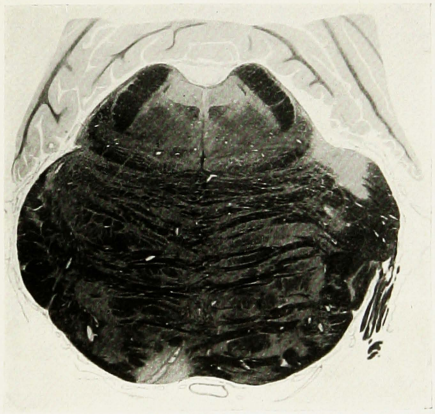

FIG. 146.

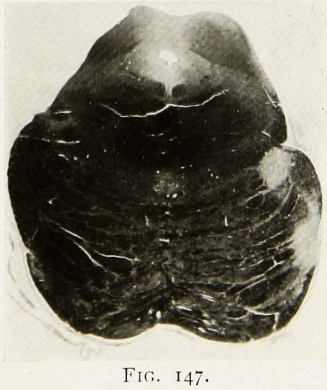

FIG. 147.

FIG. 148—C_4

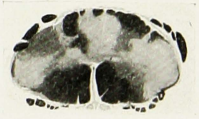

FIG. 149—C_7

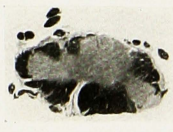

FIG. 150—D_1

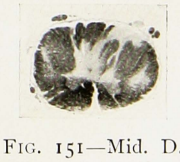

FIG. 151—Mid. D.

FIG. 152—Low D.

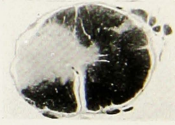

FIG. 153—L_3

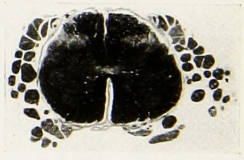

FIG. 154—L_5

FIG. 155—S_2

DR DAWSON—HISTOLOGY OF DISSEMINATED SCLEROSIS.

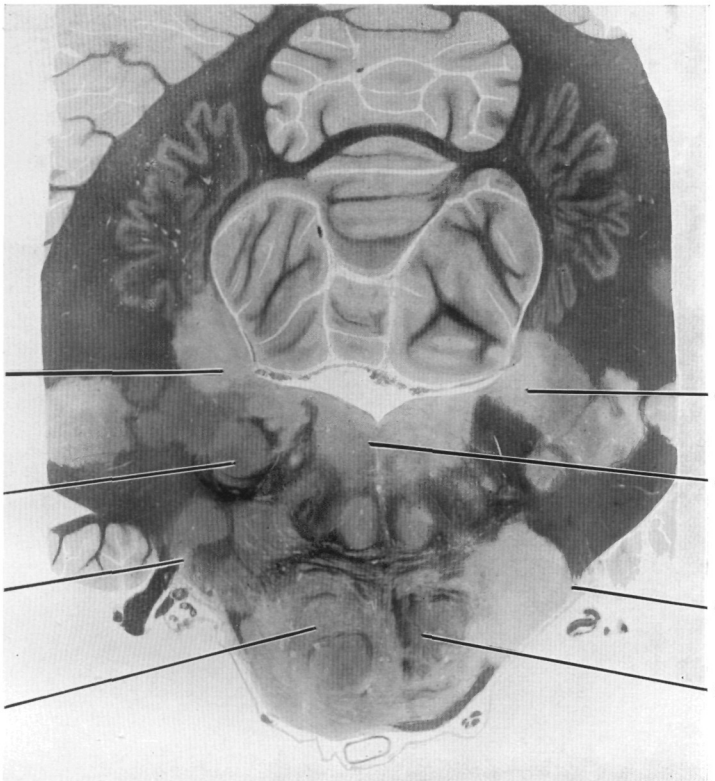

FIG. 156.

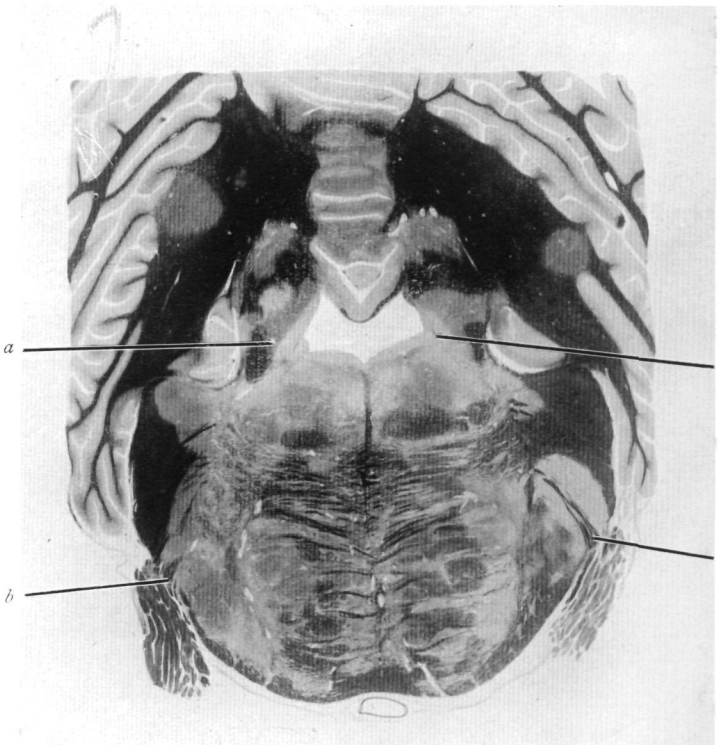

FIG. 157.

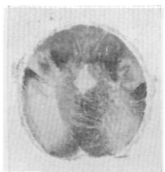

FIG. 158.

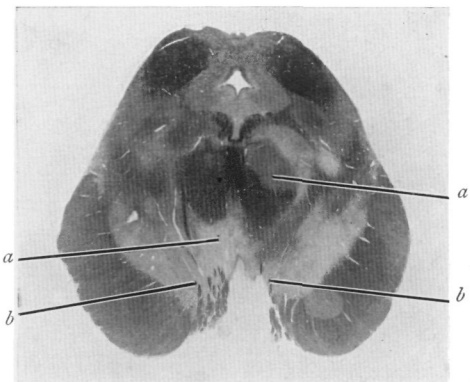

FIG. 161.

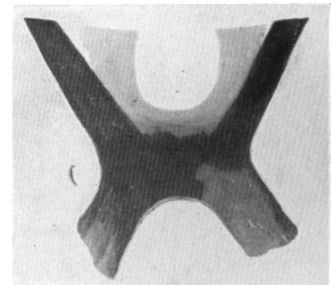

FIG. 163.

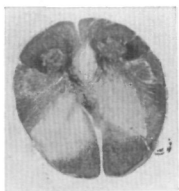

FIG. 159.

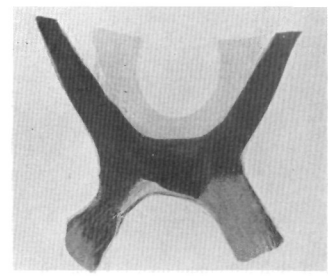

FIG. 164.

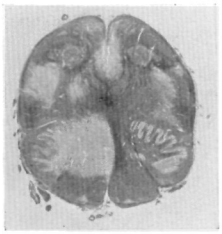

FIG. 160.

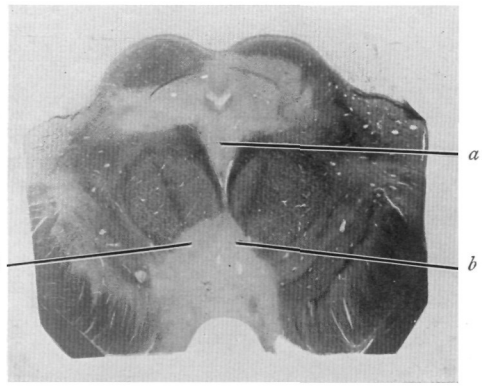

FIG. 162.

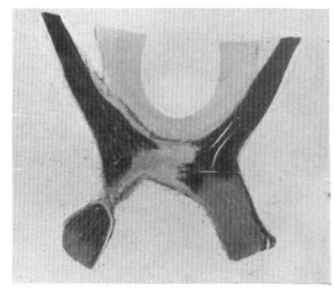

FIG 165.

DR DAWSON—HISTOLOGY OF DISSEMINATED SCLEROSIS.

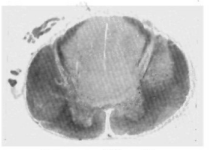

FIG. 166—C_4

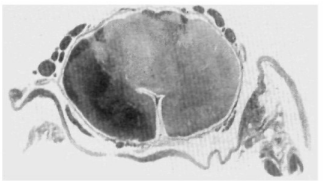

FIG. 167—C_5

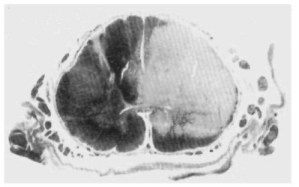

FIG. 168—C_7

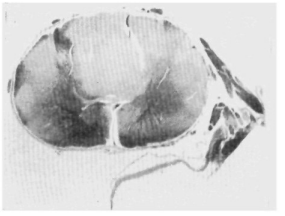

FIG. 169—C_8

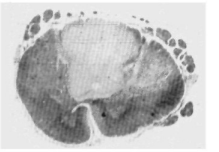

FIG. 170—D_2

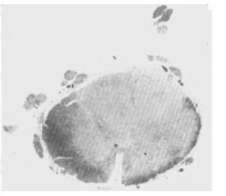

FIG. 171—D_4

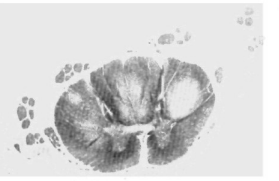

FIG. 172—D_5

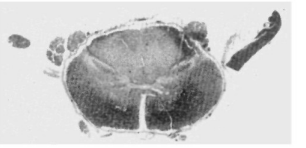

FIG. 173—D_{12}

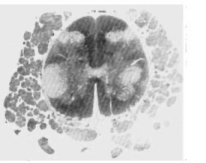

FIG. 174—L_4

FIG. 175—L_5

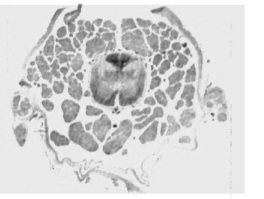

FIG. 176—S_3

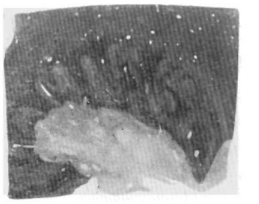

FIG. 177.

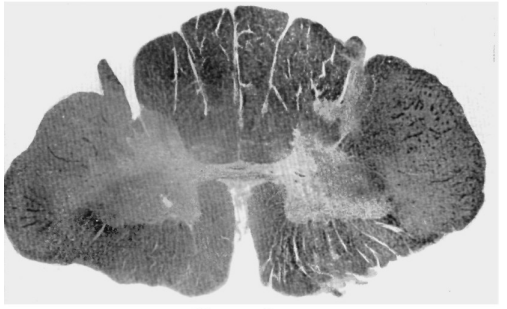

FIG. 178.

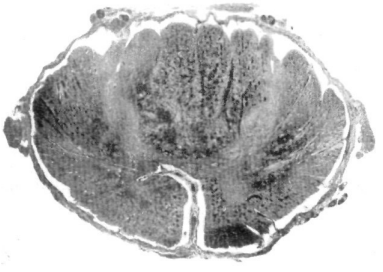

FIG. 179.

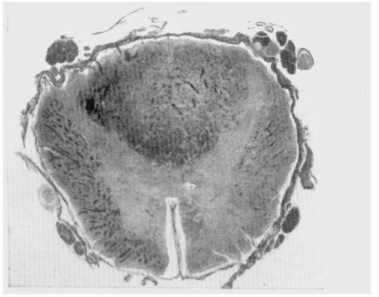

FIG. 180.

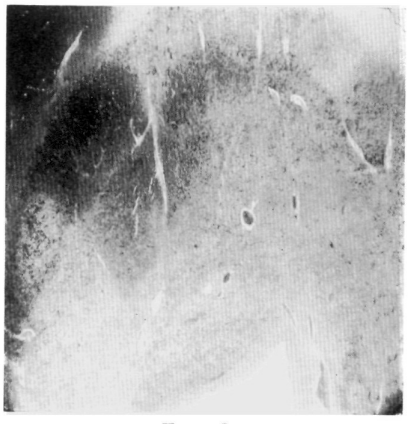

FIG. 181.

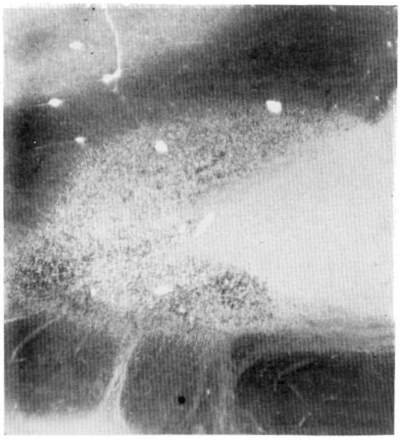

FIG. 182.

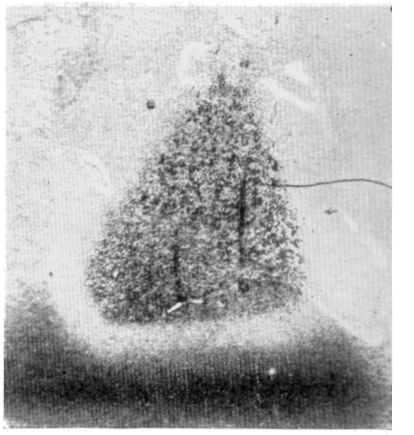

FIG. 183.

FIG. 184.

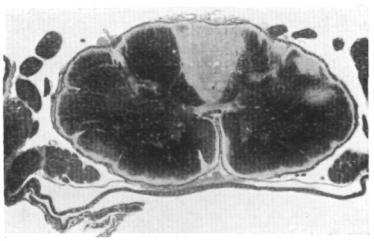

FIG. 185—C_6

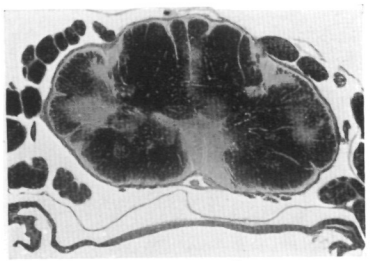

FIG. 186 - C_7

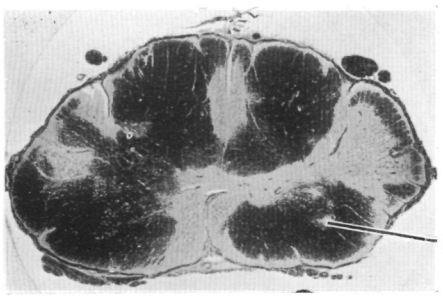

FIG. 187—C_7

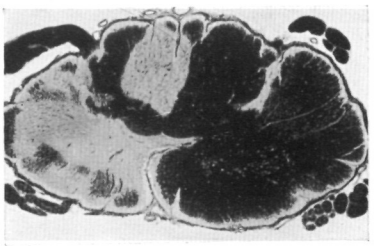

FIG. 188—C_8

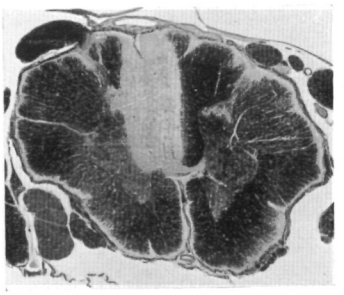

FIG. 189—D_1

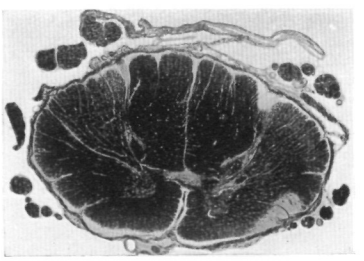

FIG. 190—Mid D

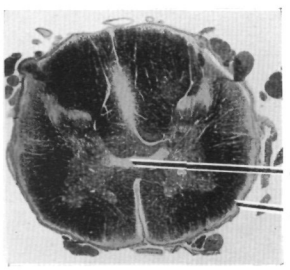

FIG. 194—L_2

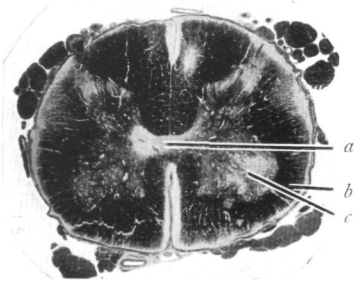

FIG. 195—L_2

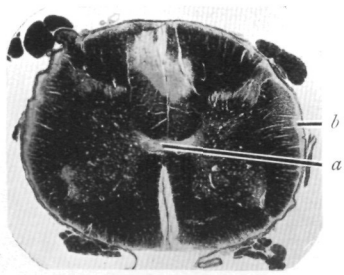

FIG. 196—L_3

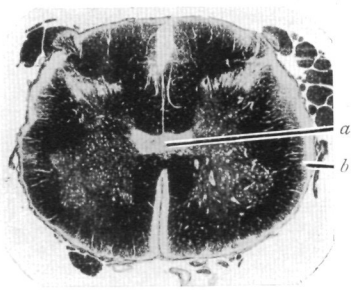

FIG. 197—L_3

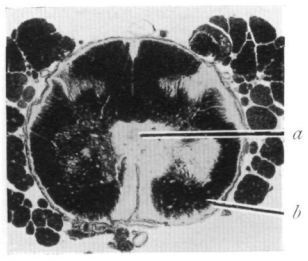

FIG. 198—L_4

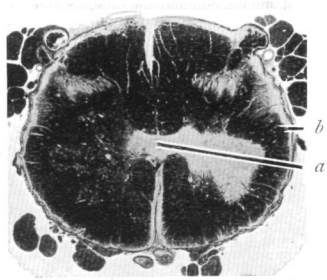

FIG. 199—L_5

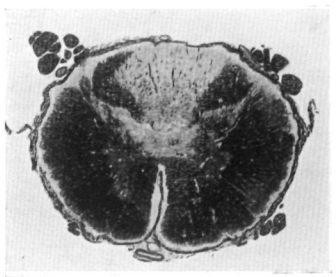

FIG. 191—D_{11}

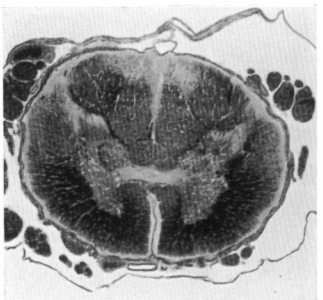

FIG. 192—D_{12}

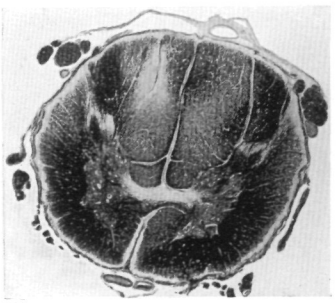

FIG. 193—D_{12}

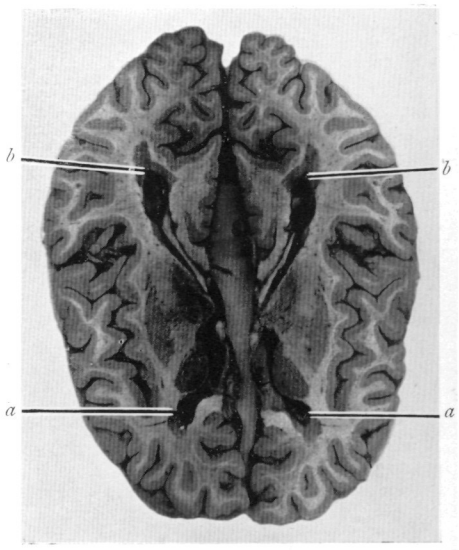

FIG. 200.

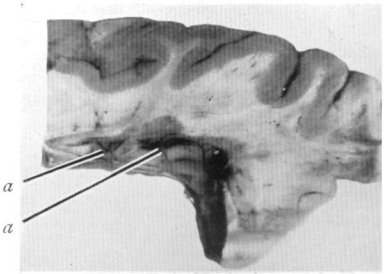

FIG. 201.

DR DAWSON—HISTOLOGY OF DISSEMINATED SCLEROSIS.

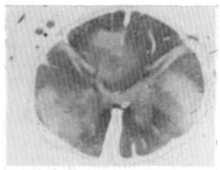

FIG. 202.

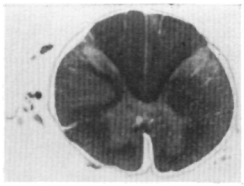

FIG. 203.

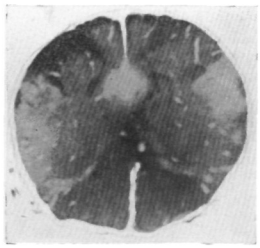

FIG. 204.

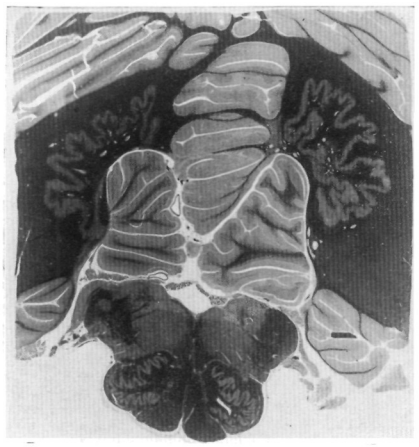

FIG. 205.

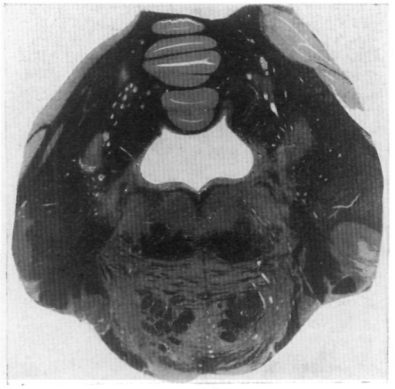

FIG. 206.

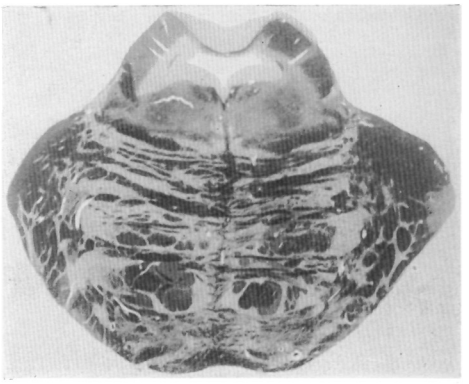

FIG. 207.

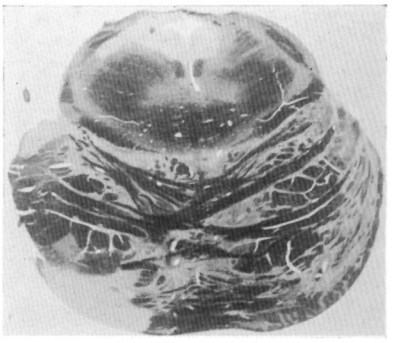

FIG. 208.

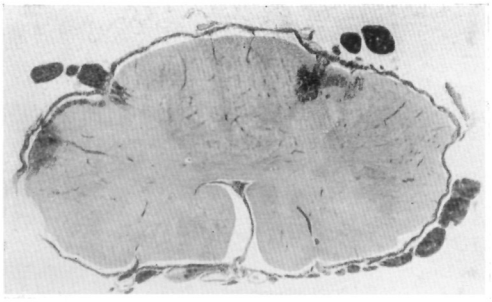

FIG. 209—C_6

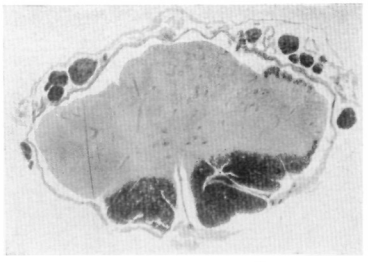

FIG. 212—Upper D.

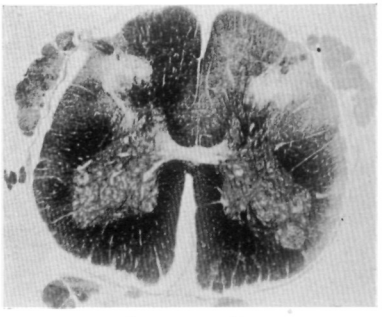

FIG. 215—L_3

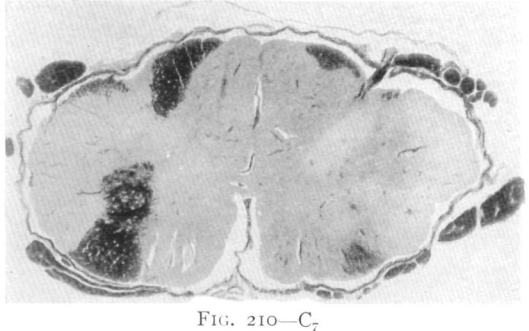

FIG. 210—C_7

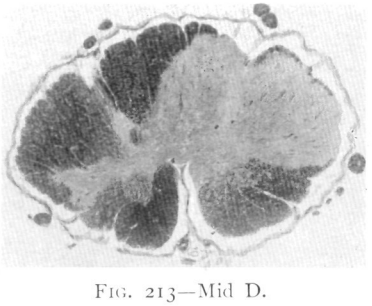

FIG. 213—Mid D.

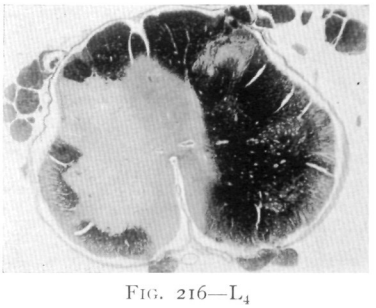

FIG. 216—L_4

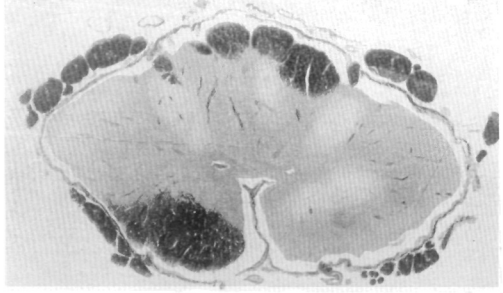

FIG. 211—D_1

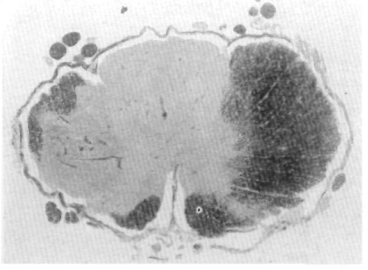

FIG. 214—Low D.

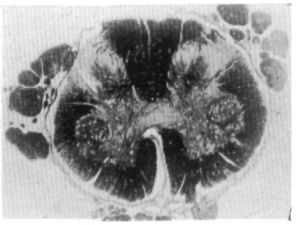

FIG. 217—S_2

DR DAWSON—HISTOLOGY OF DISSEMINATED SCLEROSIS.

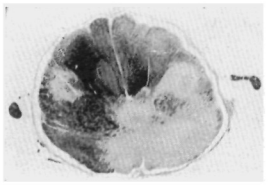

FIG. 218.

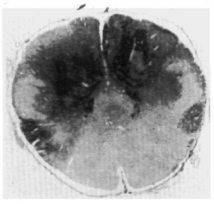

FIG. 219.

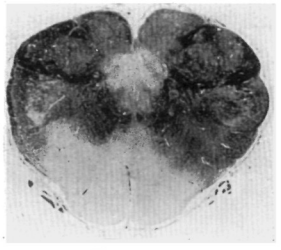

FIG. 220.

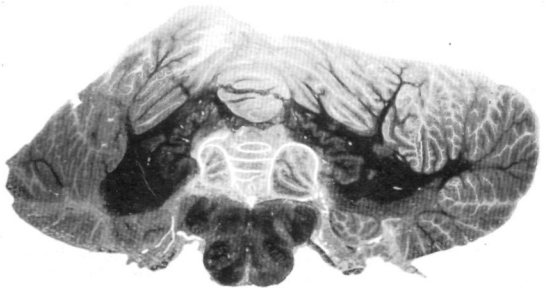

FIG. 221.

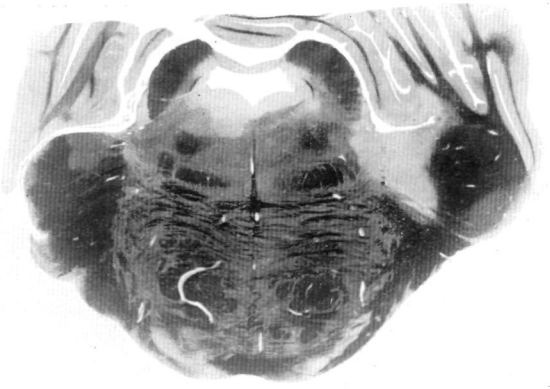

FIG. 222.

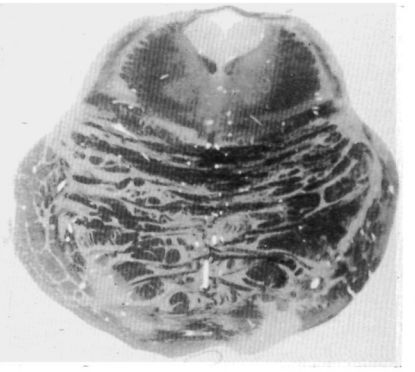

FIG. 223.

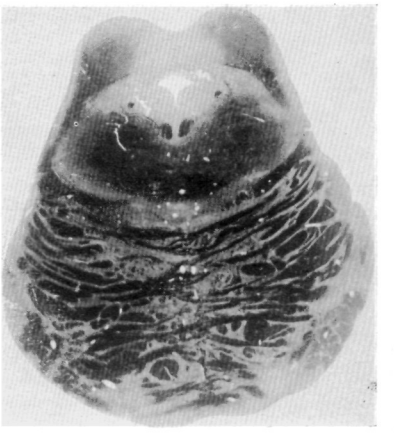

FIG. 224.

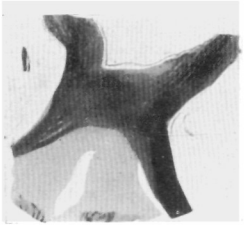

FIG. 225.

FIG. 226.

FIG. 227.

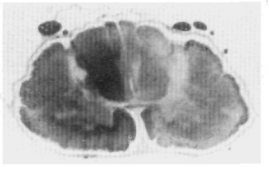

FIG. 228—C_5

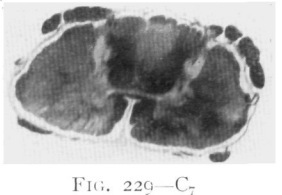

FIG. 229—C_7

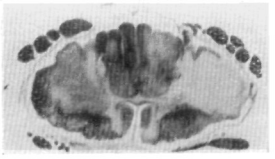

FIG. 230—D_1

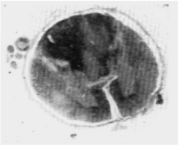

FIG. 231—D_2

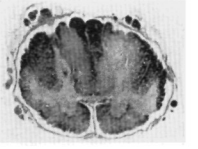

FIG. 232—D_2

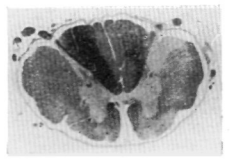

FIG. 233—L_1

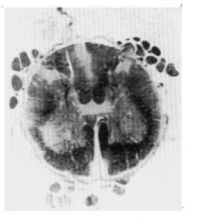

FIG. 234—L_3

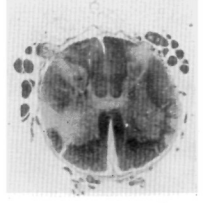

FIG. 235—L_4

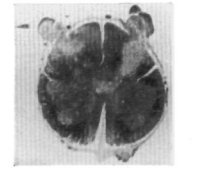

FIG. 236—L_5

FIG. 237—S_1

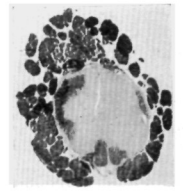

FIG. 238—S_3

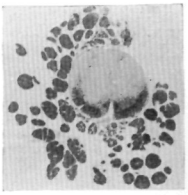

FIG. 239—S_4

DR DAWSON—HISTOLOGY OF DISSEMINATED SCLEROSIS

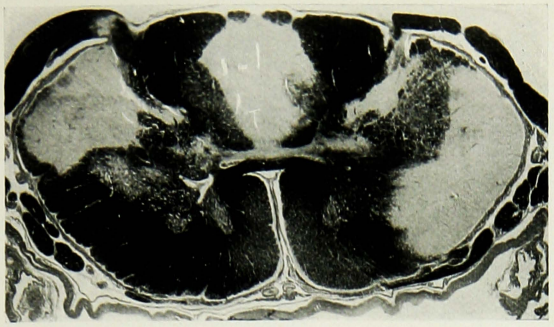

FIG. 240.

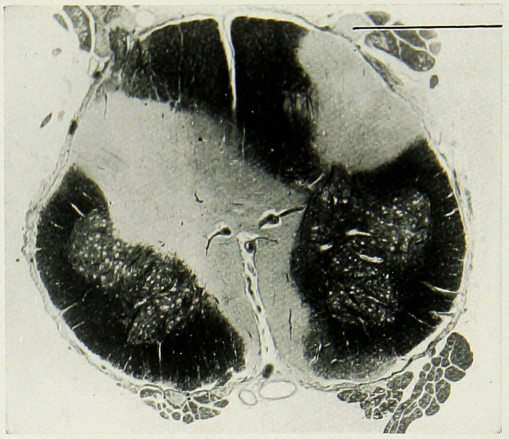

FIG. 242.

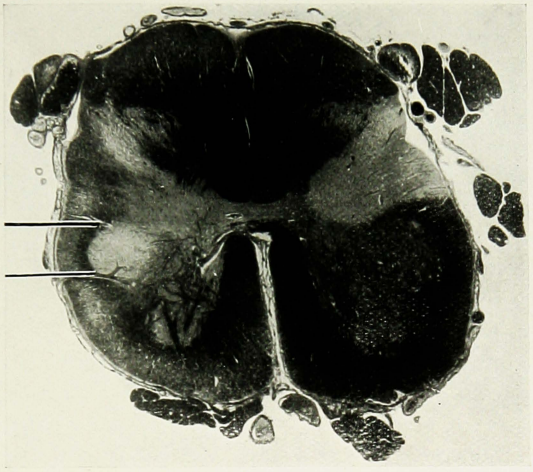

FIG. 241.

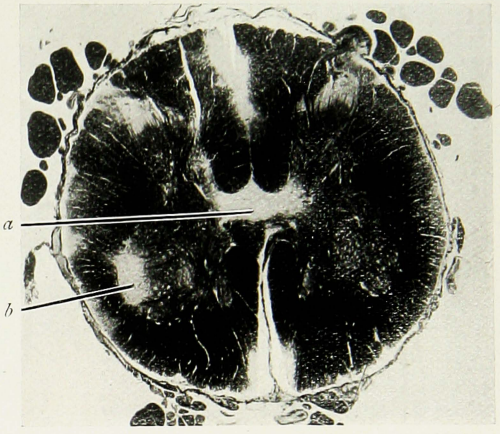

FIG. 243.

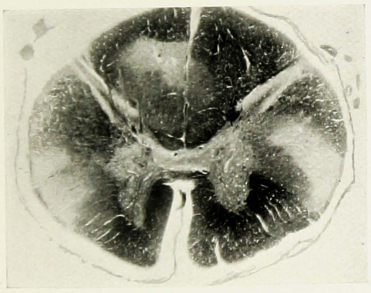

FIG. 244.

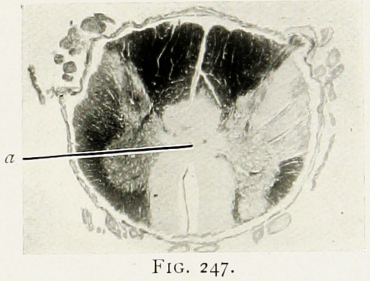

FIG. 247.

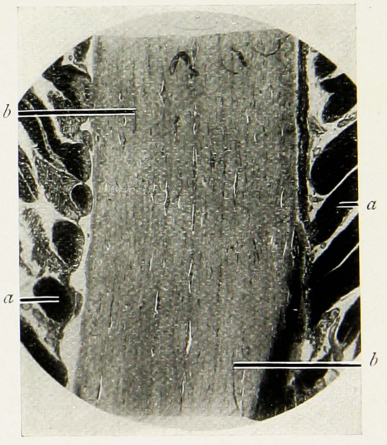

FIG. 250.

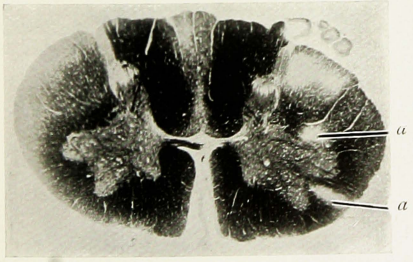

FIG. 245.

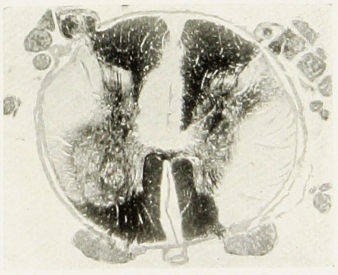

FIG. 248.

FIG. 251.

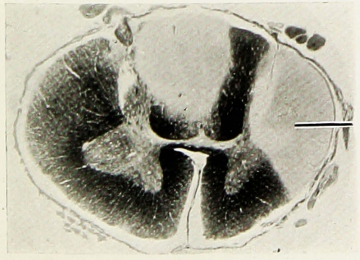

FIG. 246.

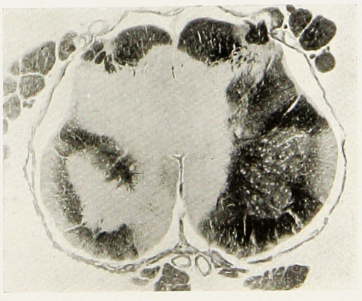

FIG. 249.

FIG. 252.

DR DAWSON—HISTOLOGY OF DISSEMINATED SCLEROSIS.

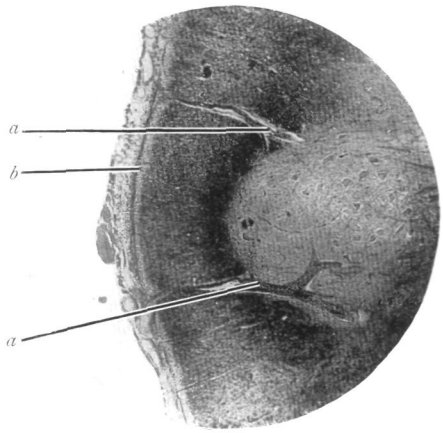

FIG. 253.

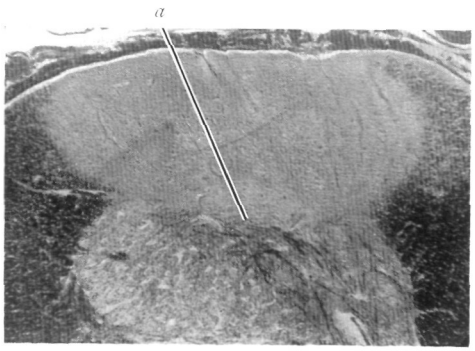

FIG. 255.

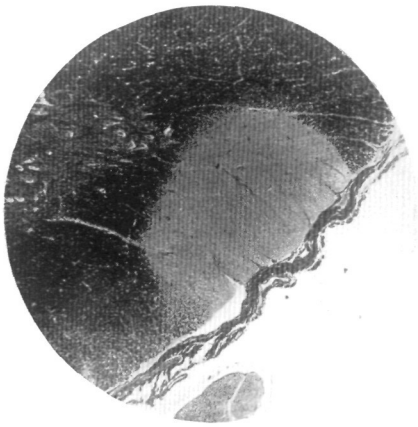

FIG. 257.

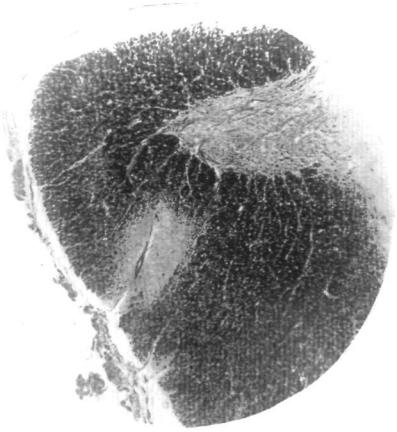

FIG. 254.

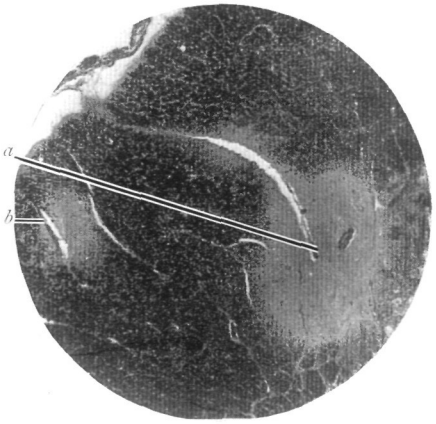

FIG. 256.

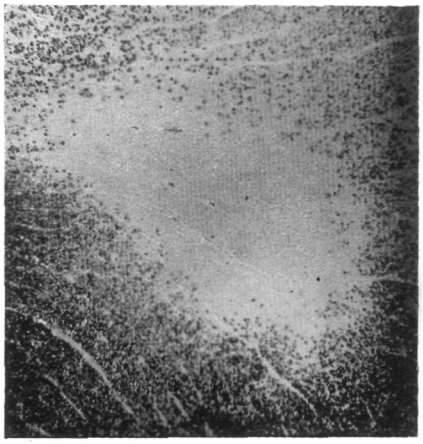

FIG. 258.

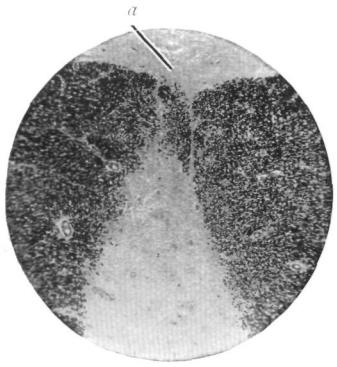

FIG. 259.

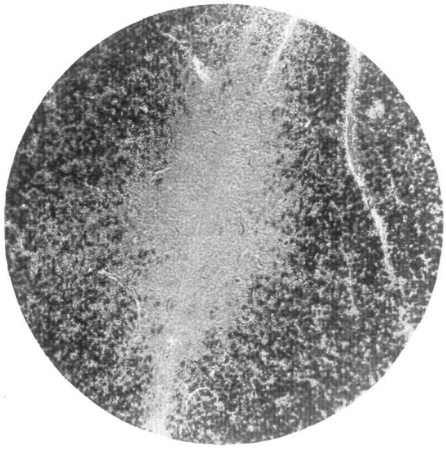

FIG. 261.

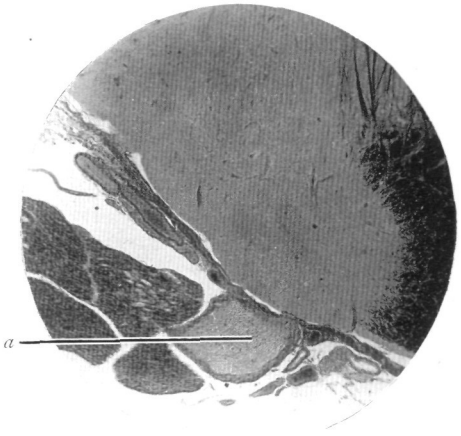

FIG. 263.

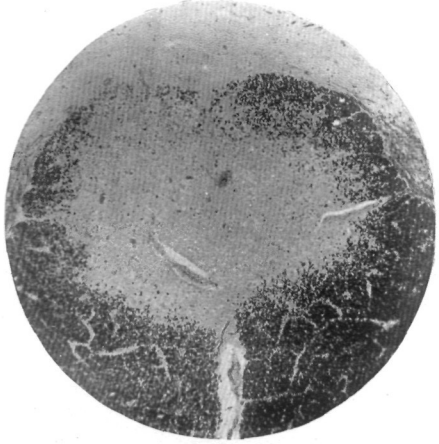

FIG. 260.

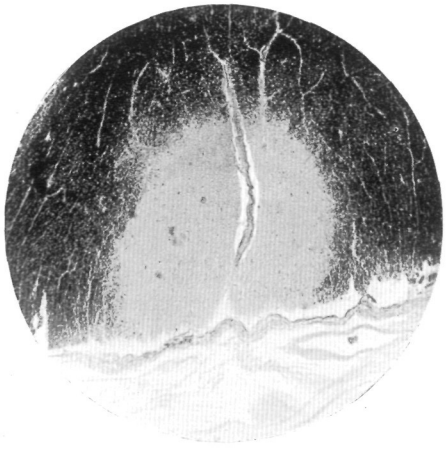

FIG. 262.

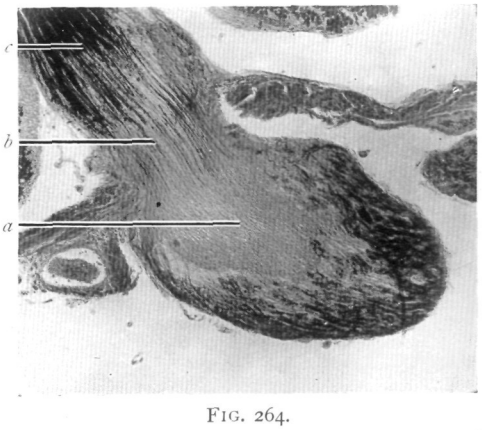

FIG. 264.

DR DAWSON—HISTOLOGY OF DISSEMINATED SCLEROSIS.

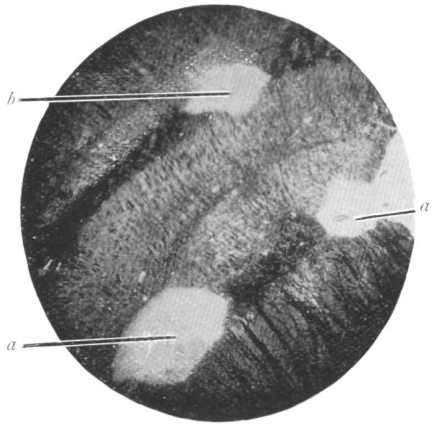

FIG. 265.

FIG. 266.

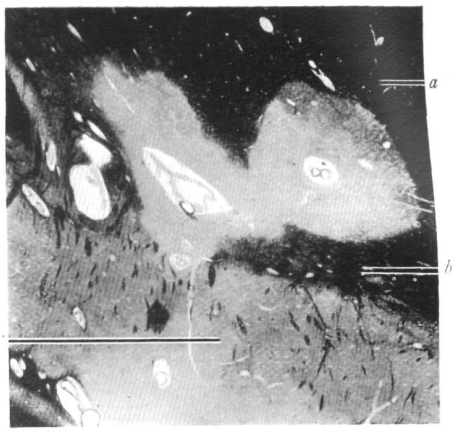

FIG. 267.

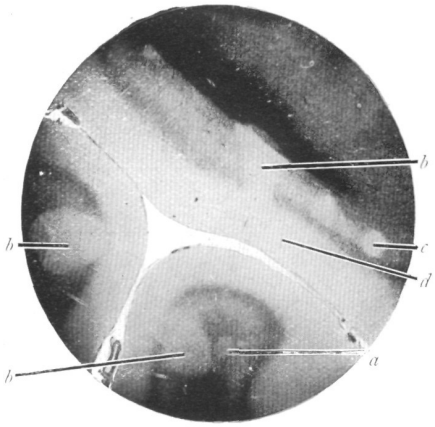

FIG. 268.

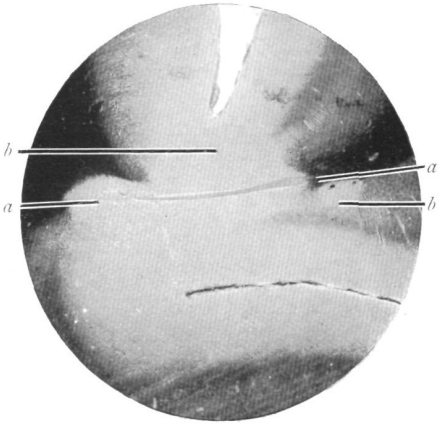

FIG. 269.

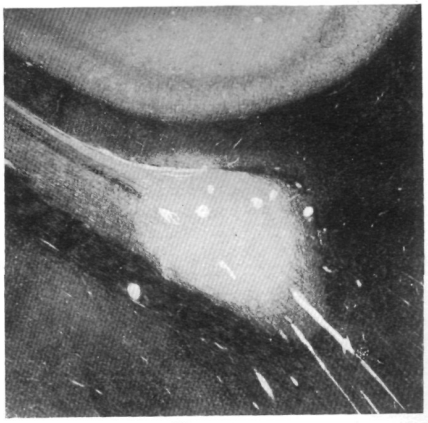

FIG. 270.

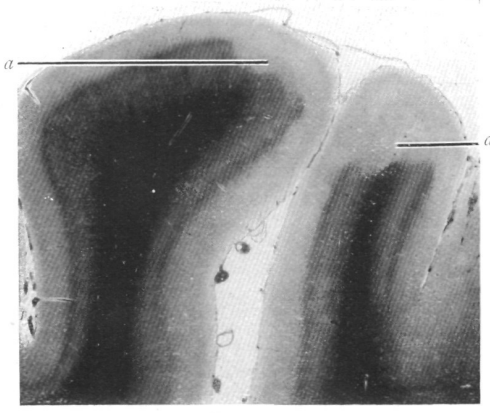

FIG. 271.

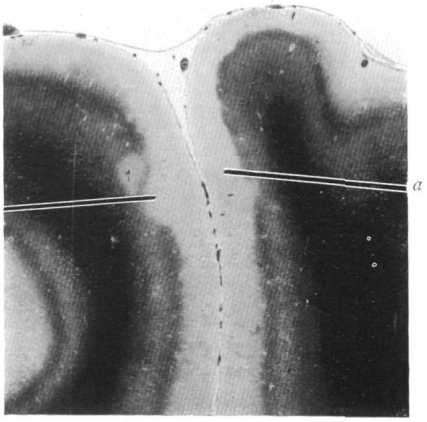

FIG. 272.

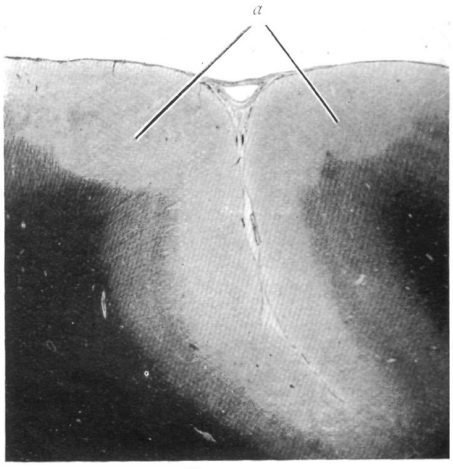

FIG. 273.

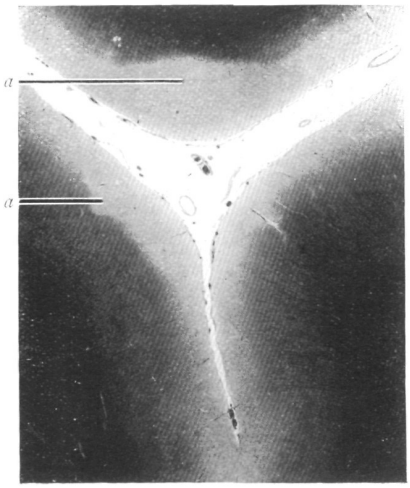

FIG. 274.

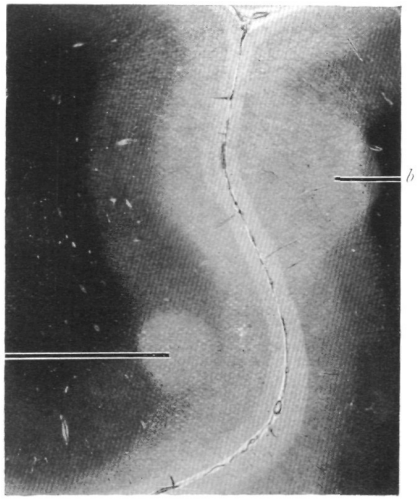

FIG. 275.

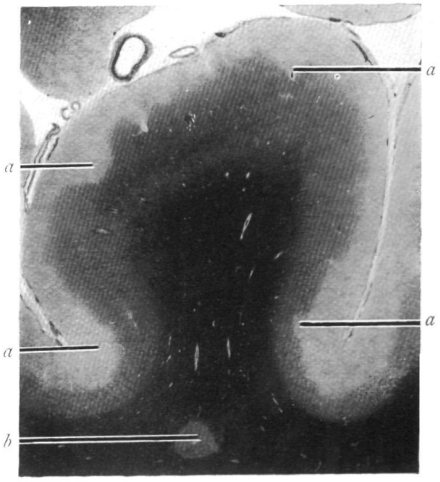

FIG. 276.

DR DAWSON.—HISTOLOGY OF DISSEMINATED SCLEROSIS.

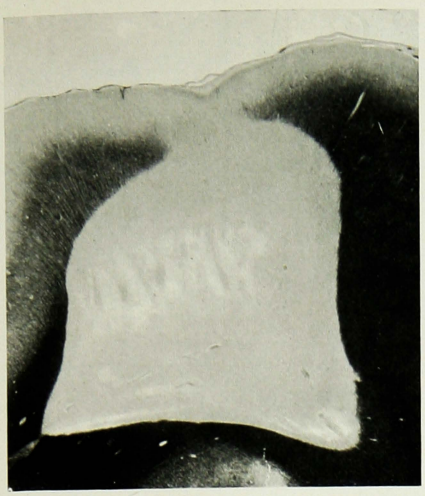

FIG. 277.

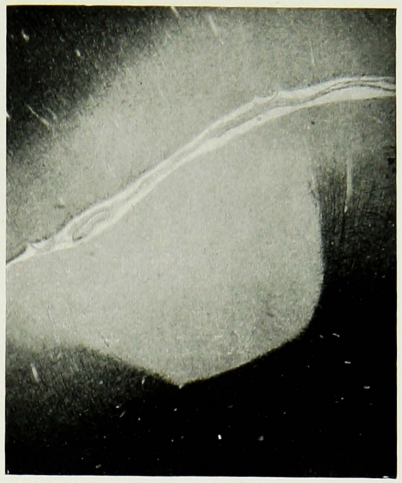

FIG. 278.

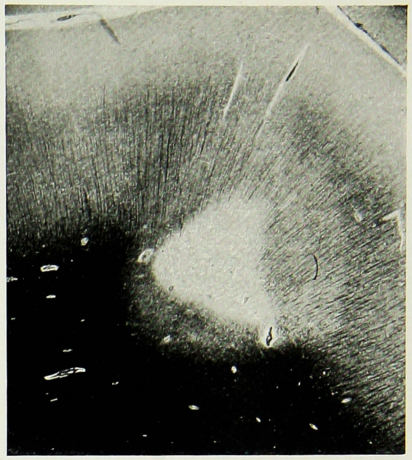

FIG. 279.

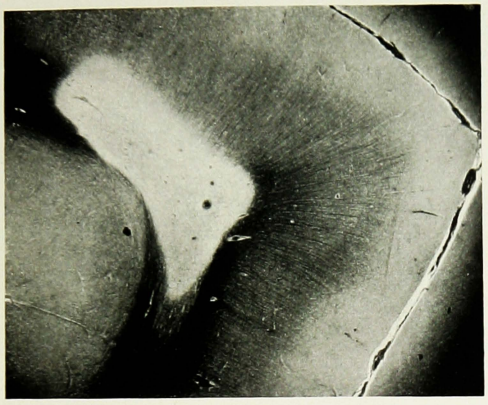

FIG. 280.

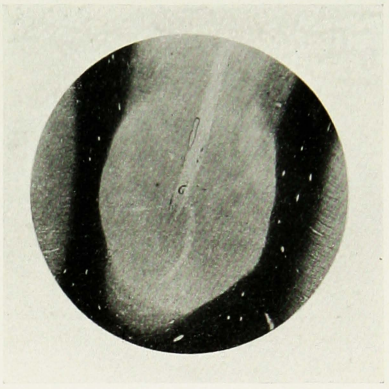

FIG. 281.

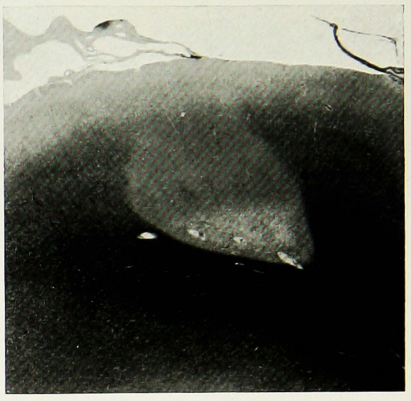

FIG. 282.

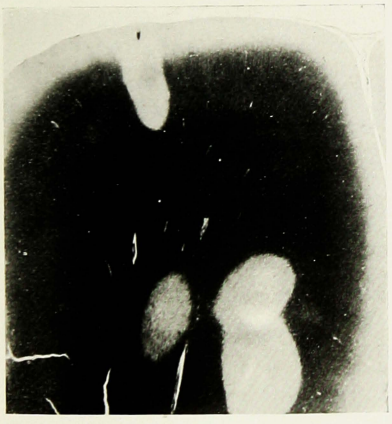

FIG. 283.

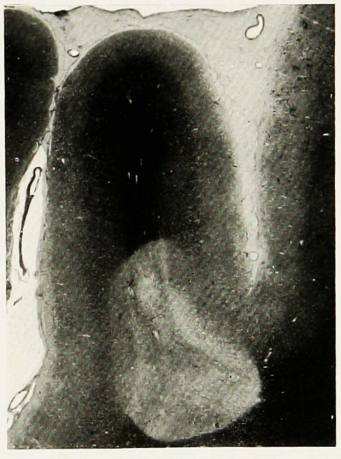

FIG. 284.

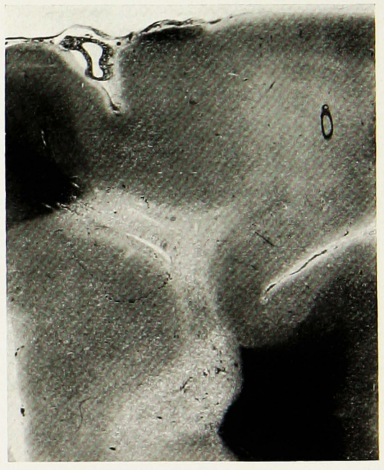

FIG. 285.

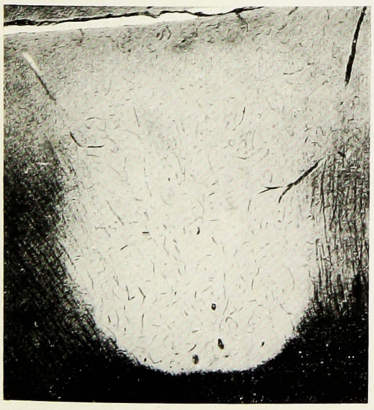

FIG. 286.

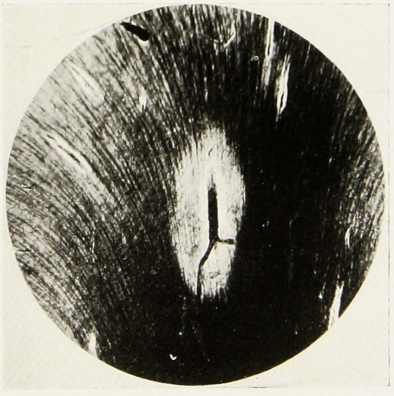

FIG. 287.

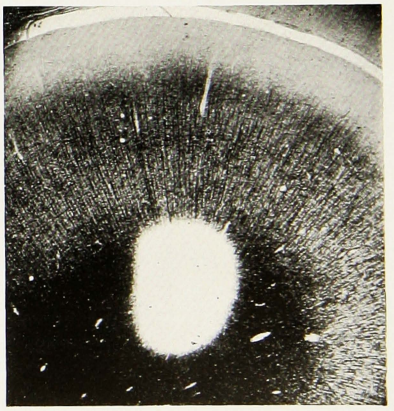

FIG. 288.

DR DAWSON—HISTOLOGY OF DISSEMINATED SCLEROSIS.

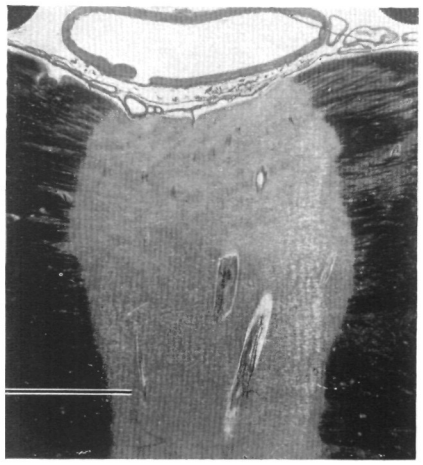

FIG. 289.

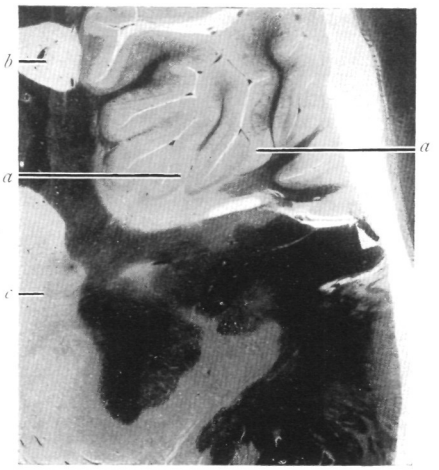

FIG. 290.

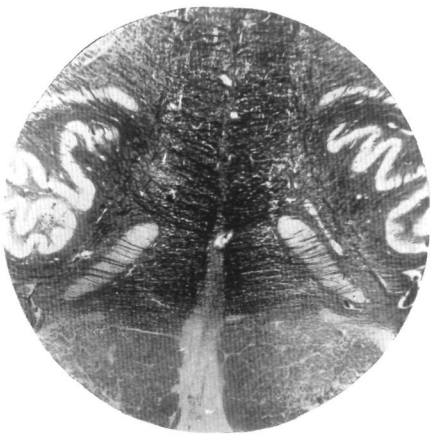

FIG. 291.

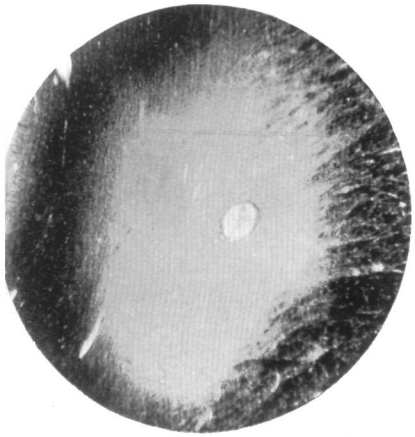

FIG. 292.

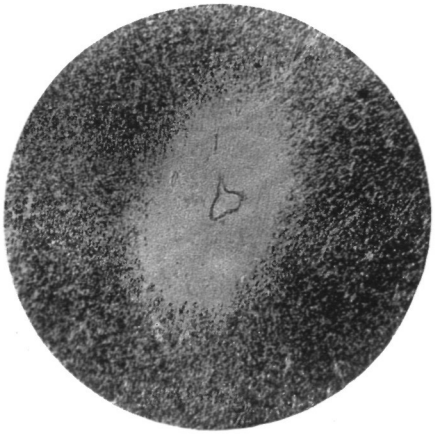

FIG. 293.

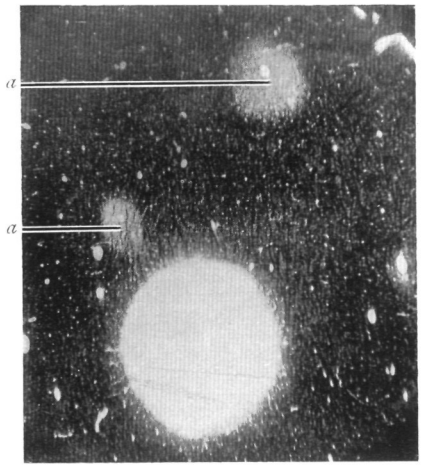

FIG. 294.

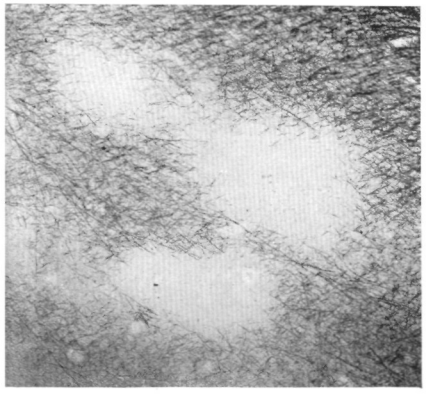

FIG. 295.

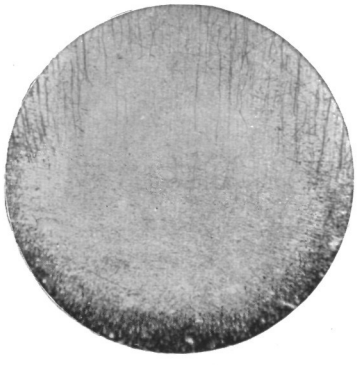

FIG. 296.

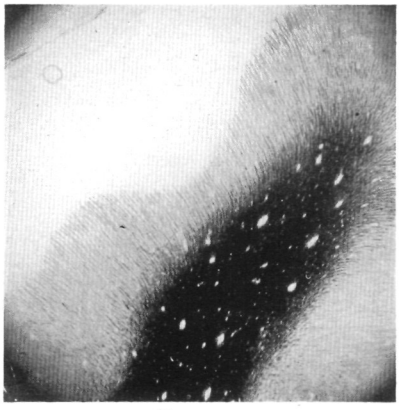

FIG. 297.

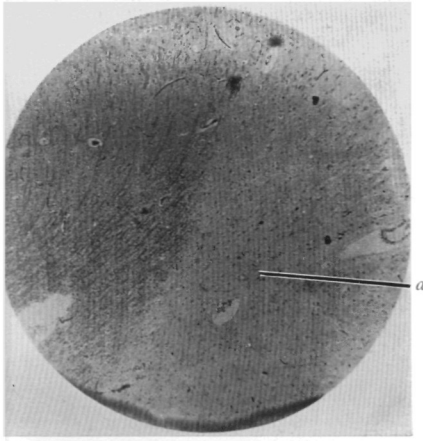

FIG. 298.

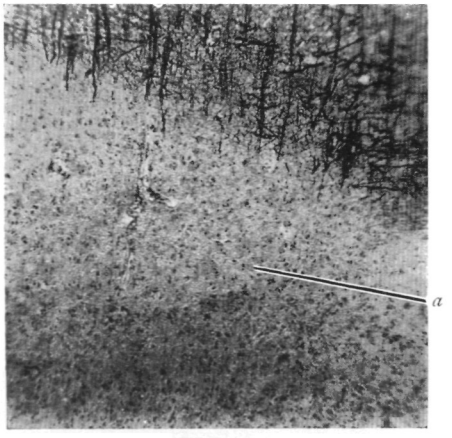

FIG. 299.

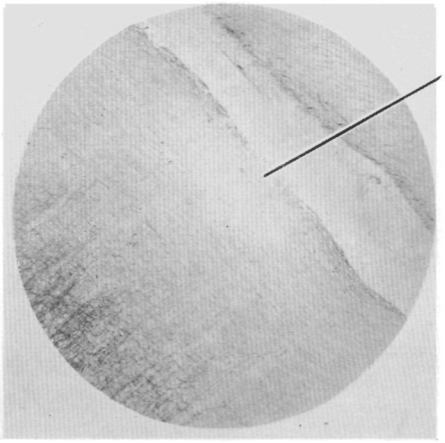

FIG. 300.

DR DAWSON—HISTOLOGY OF DISSEMINATED SCLEROSIS.

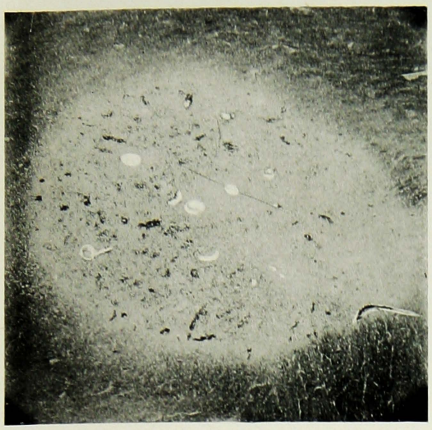

FIG. 301.

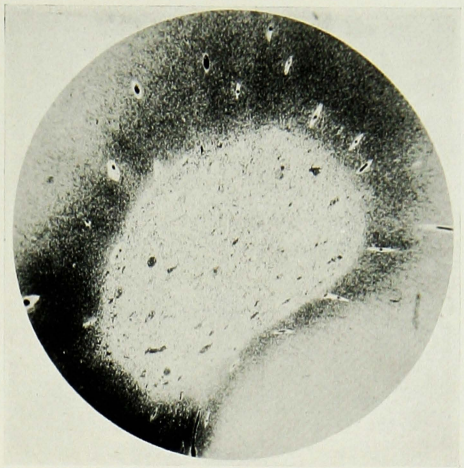

FIG. 302.

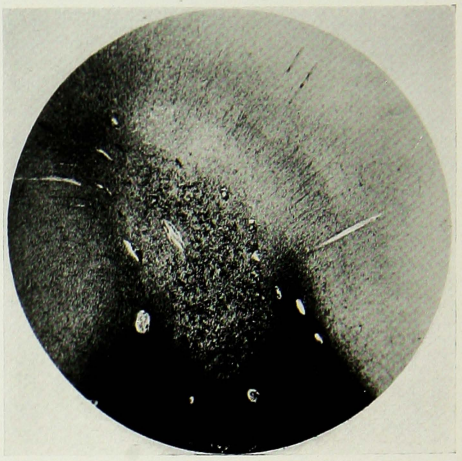

FIG. 303.

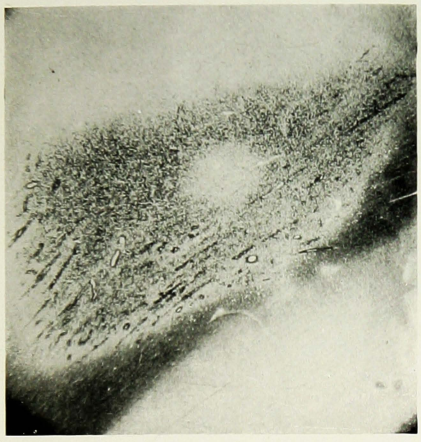

FIG. 304.

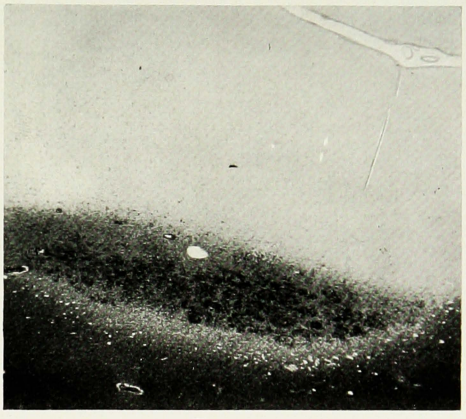

FIG. 305.

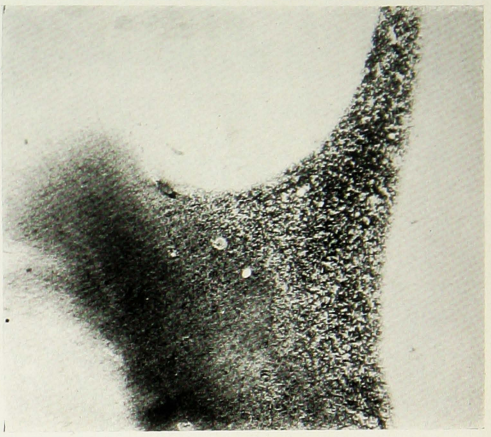

FIG 306.

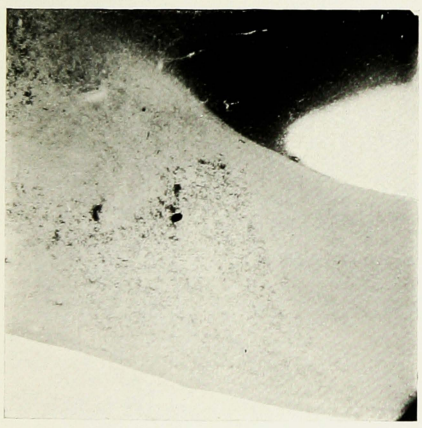

FIG. 307.

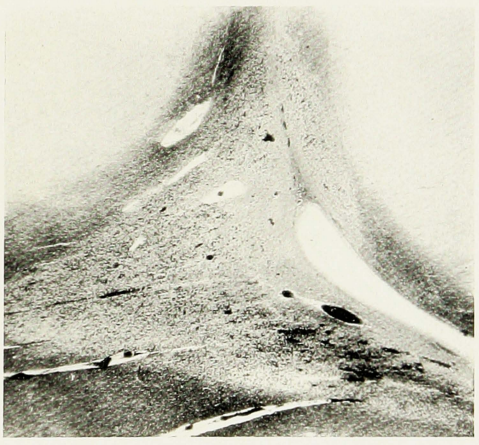

FIG. 308.

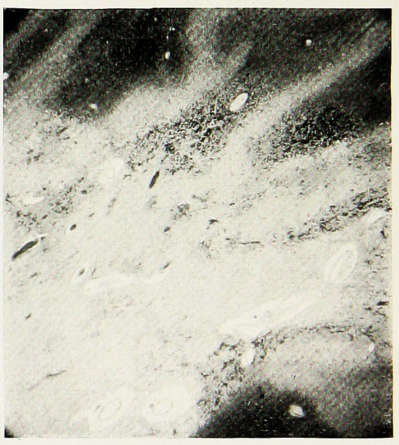

FIG. 309.

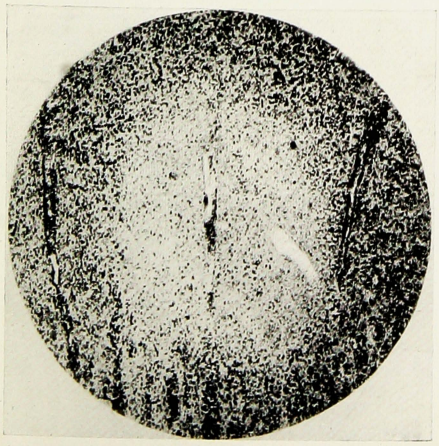

FIG. 310.

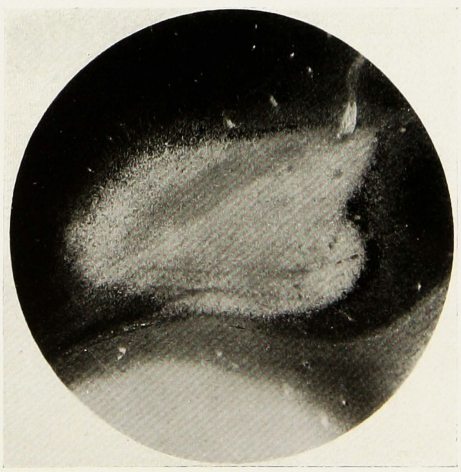

FIG. 311.

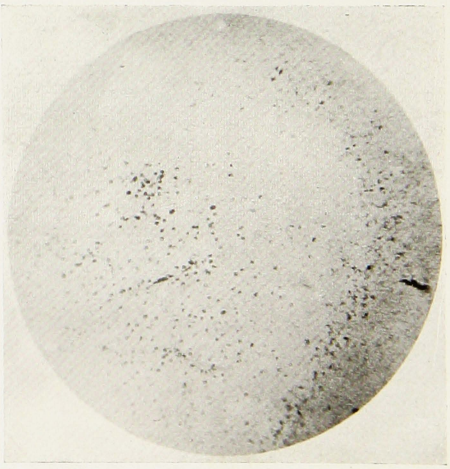

FIG. 312.

DR DAWSON—HISTOLOGY OF DISSEMINATED SCLEROSIS.

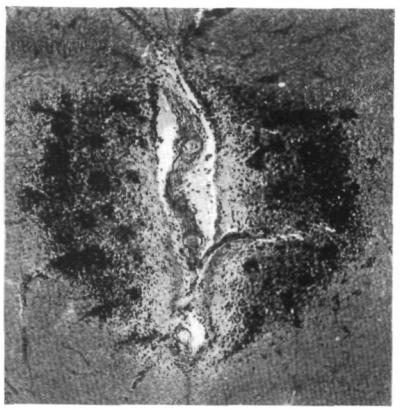

FIG. 313.

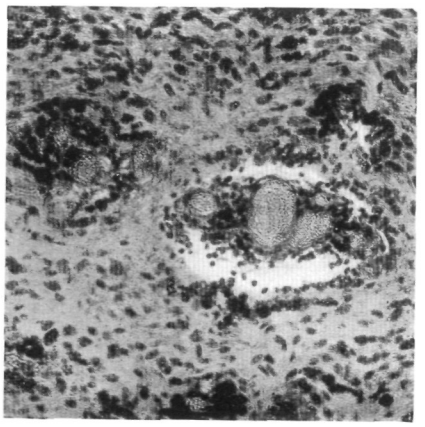

FIG. 314.

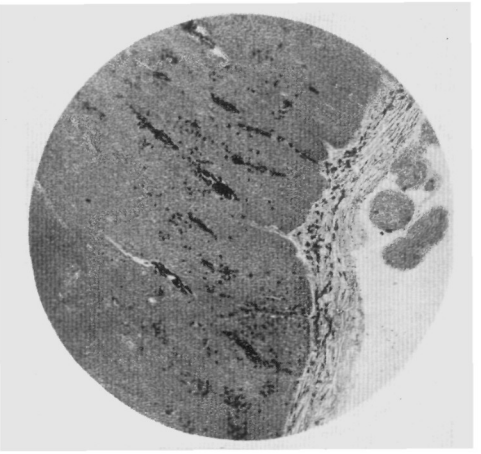

FIG. 315.

FIG. 316.

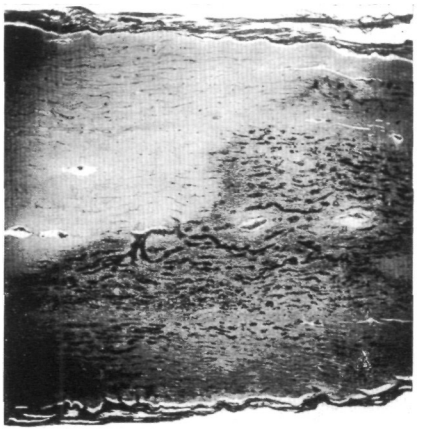

FIG. 317.

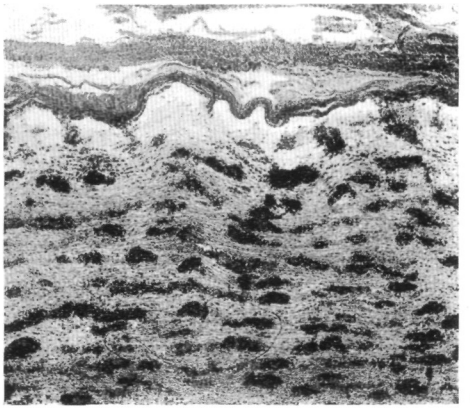

FIG. 318.

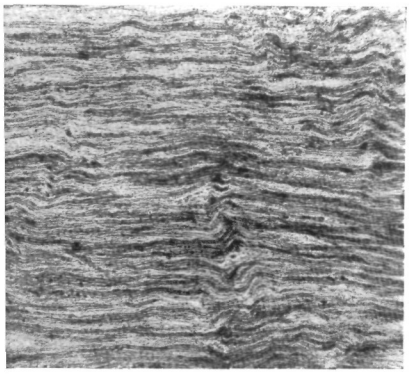

FIG. 319.

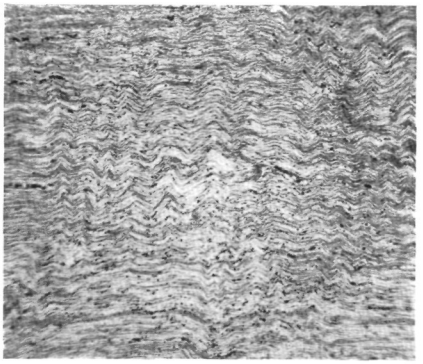

FIG. 320.

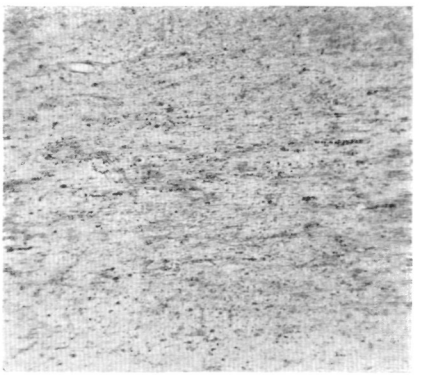

FIG. 321.

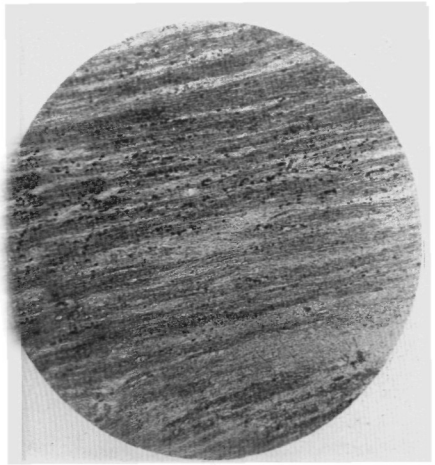

FIG. 322.

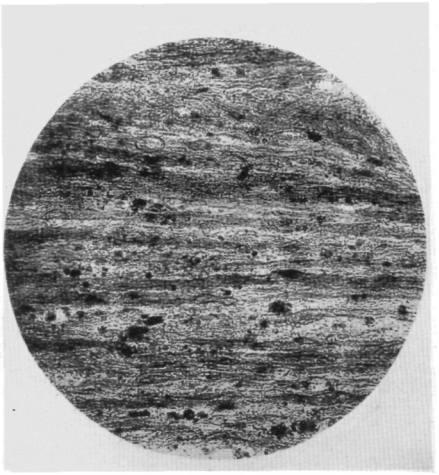

FIG. 323.

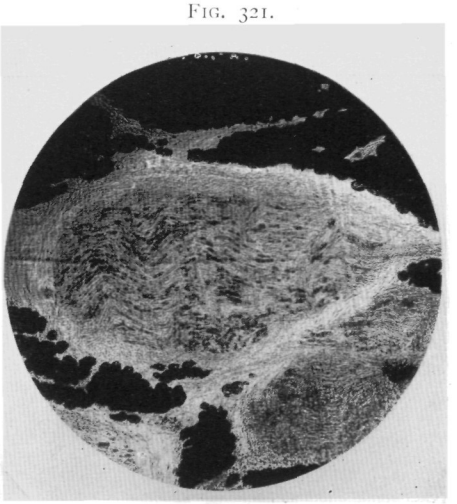

FIG. 324.

DR DAWSON—HISTOLOGY OF DISSEMINATED SCLEROSIS.

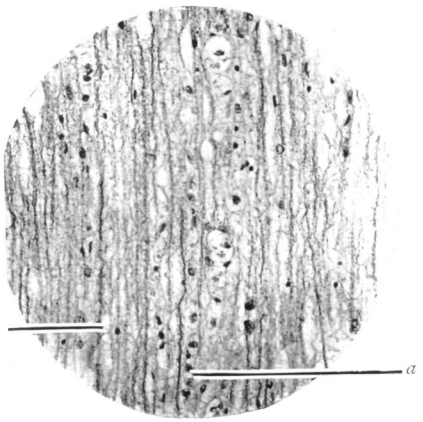

FIG. 325.

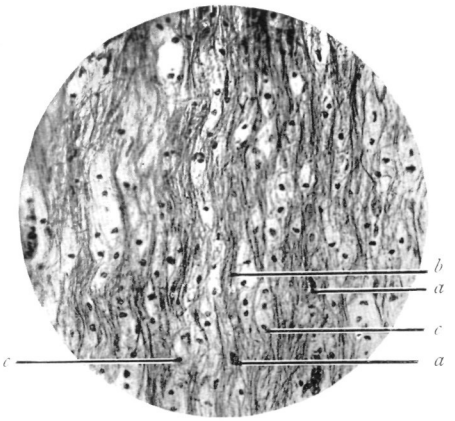

FIG. 326.

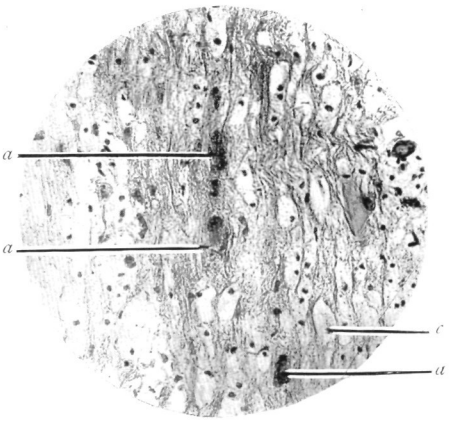

FIG. 327.

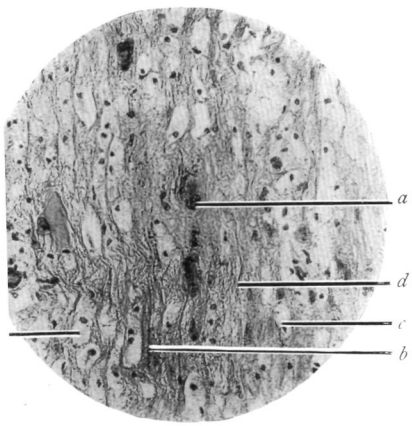

FIG. 328.

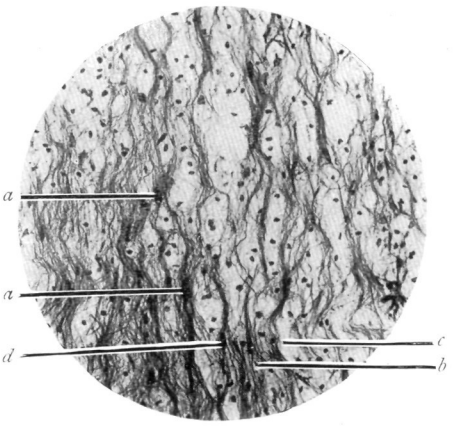

FIG. 329.

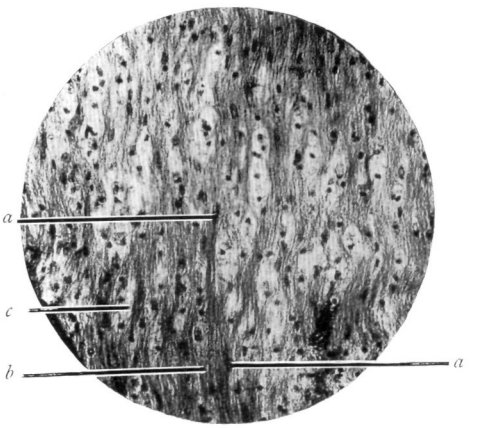

FIG. 330.

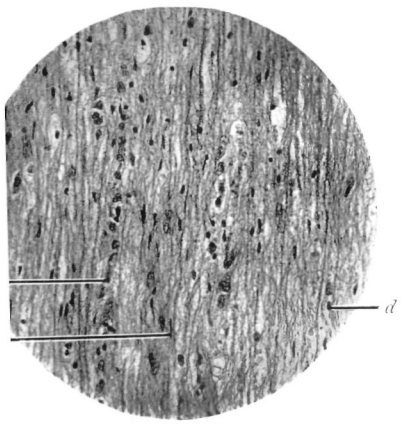

FIG. 331.

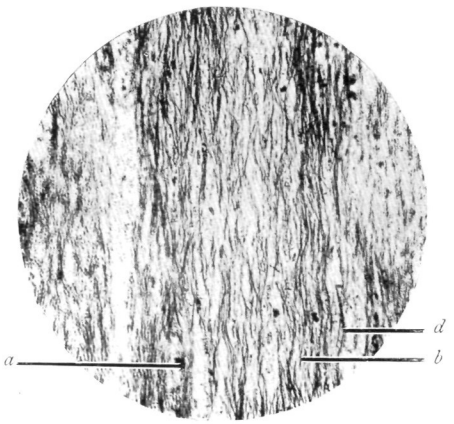

FIG. 332.

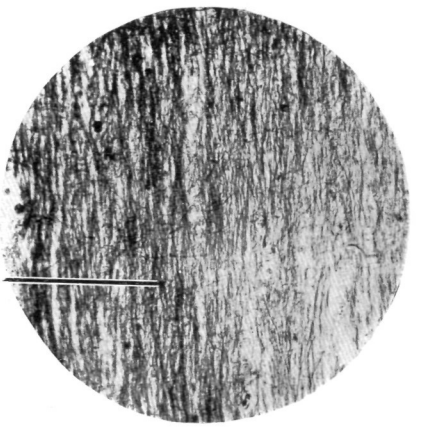

FIG. 333.

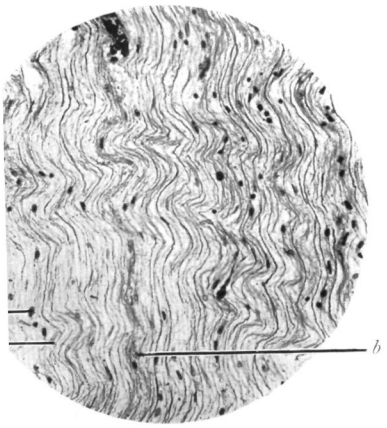

FIG. 334.

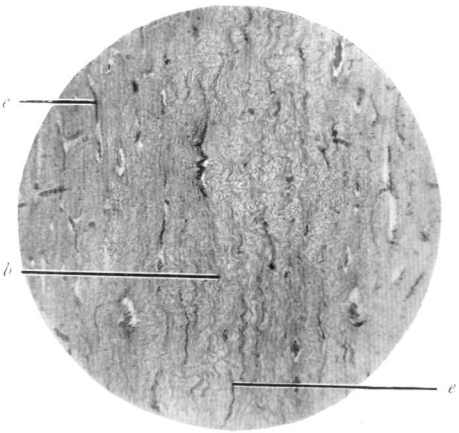

FIG. 335.

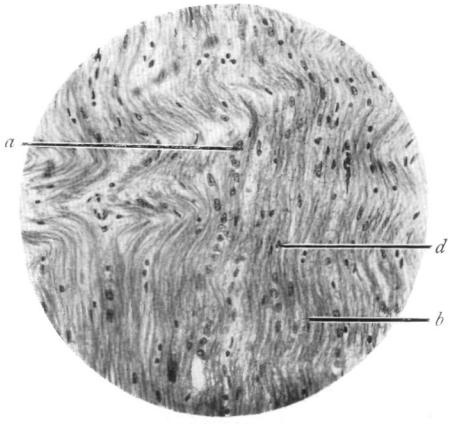

FIG. 336.

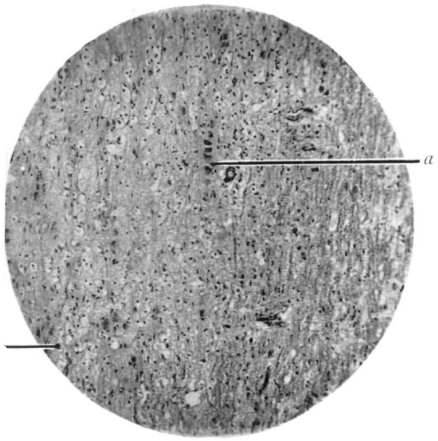

FIG. 337.

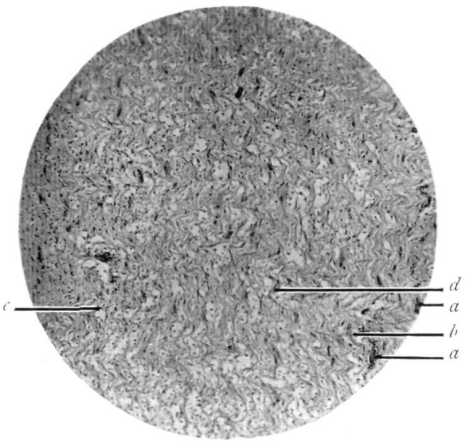

FIG. 338.

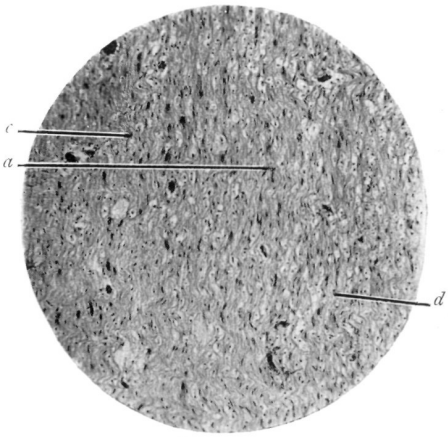

FIG. 339.

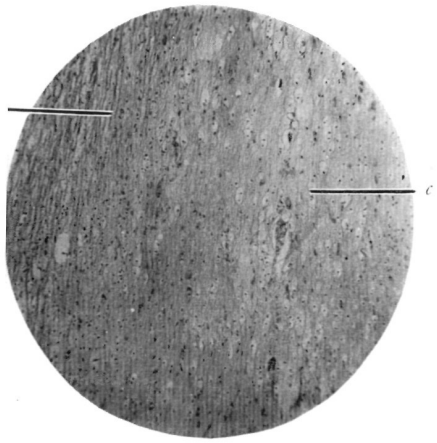

FIG. 340.

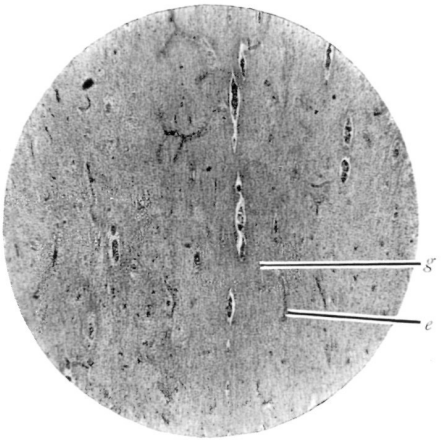

FIG. 341.

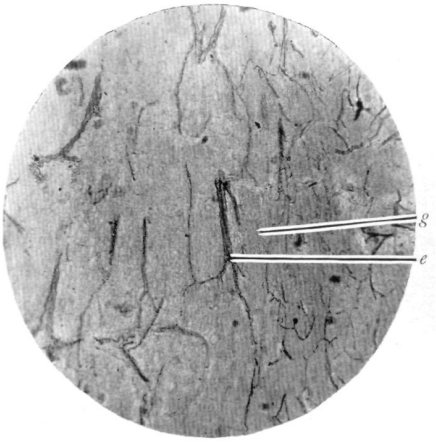

FIG. 342.

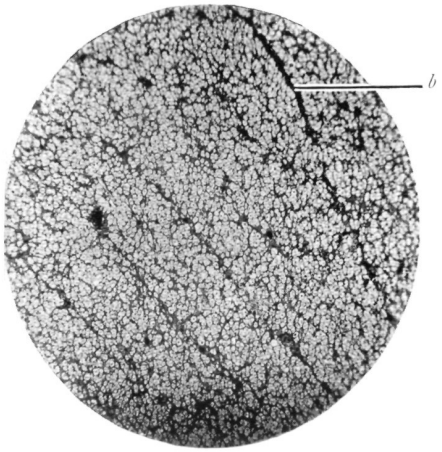

FIG. 343.

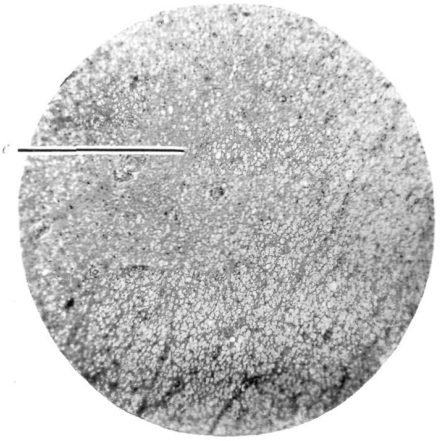

FIG. 344.

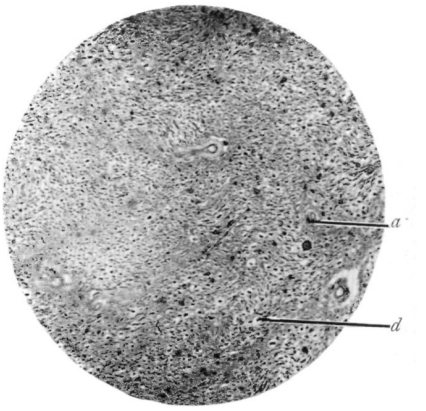

FIG. 345.

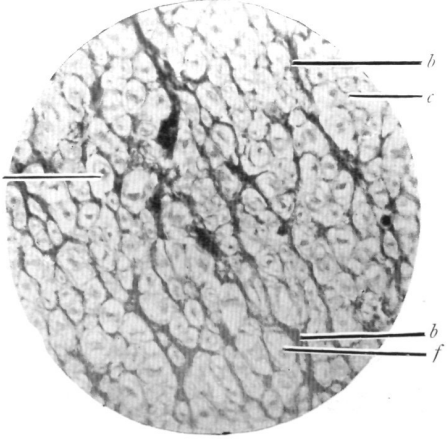

FIG. 346.

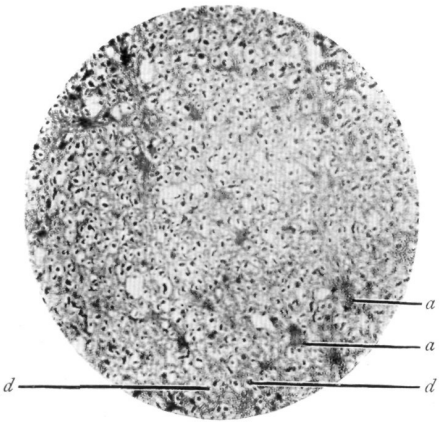

FIG. 347.

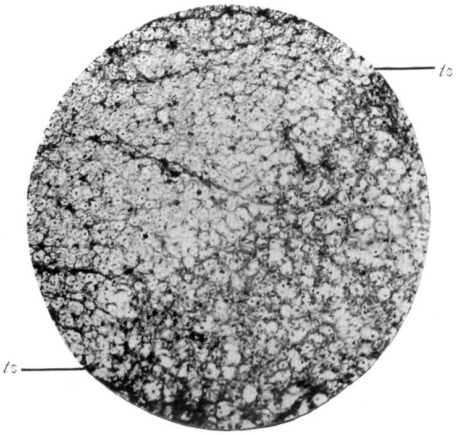

FIG. 348.

DR DAWSON—HISTOLOGY OF DISSEMINATED SCLEROSIS.

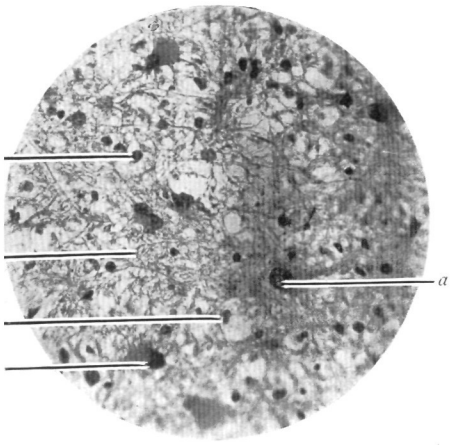

FIG. 349.

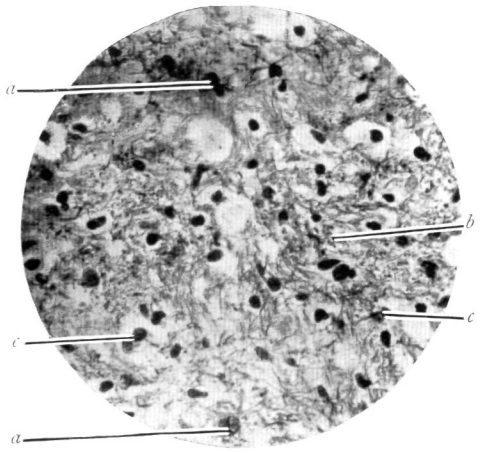

FIG. 350.

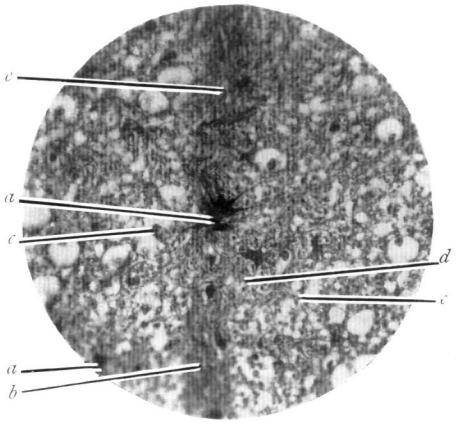

FIG. 351.

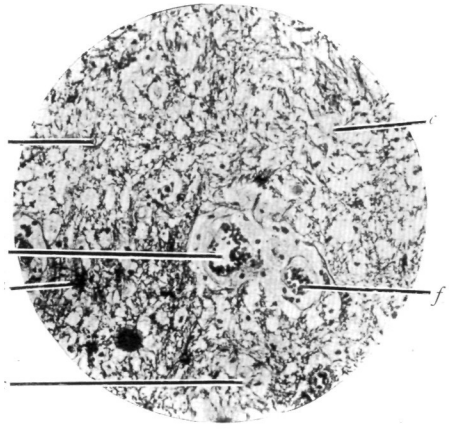

FIG. 352.

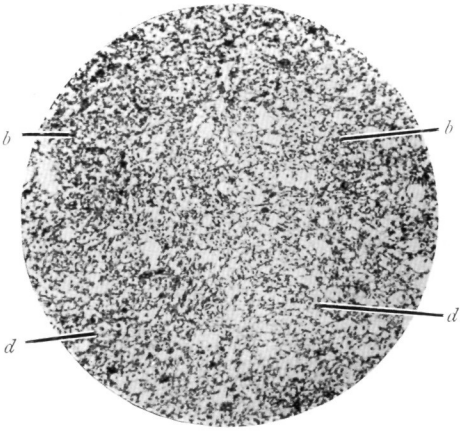

FIG. 353.

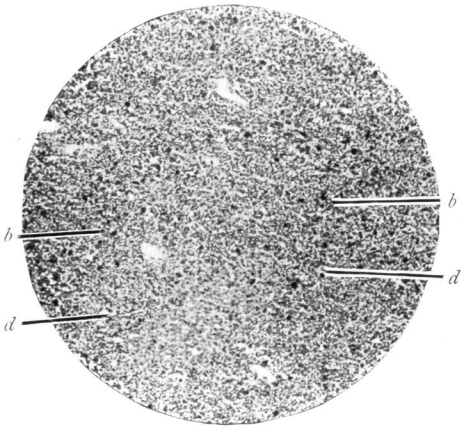

FIG. 354.

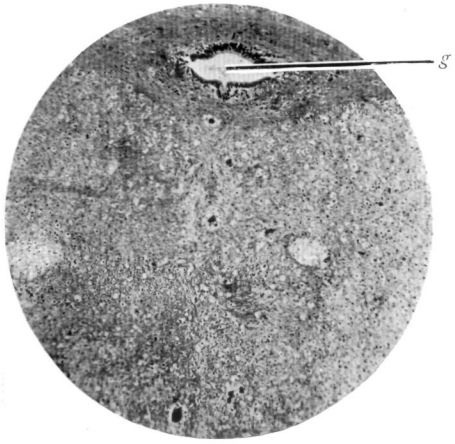

FIG. 355.

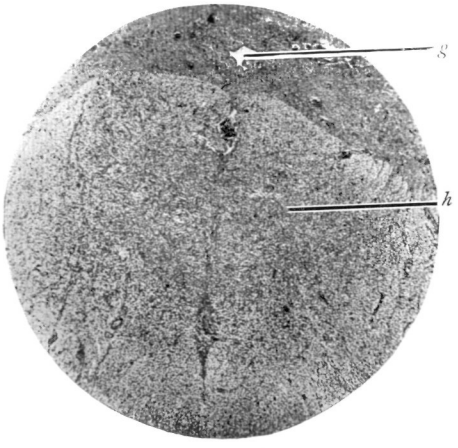

FIG. 356.

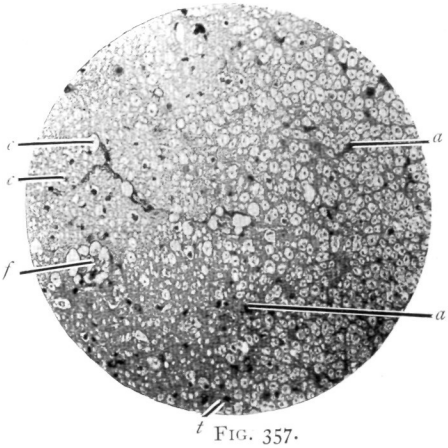

FIG. 357.

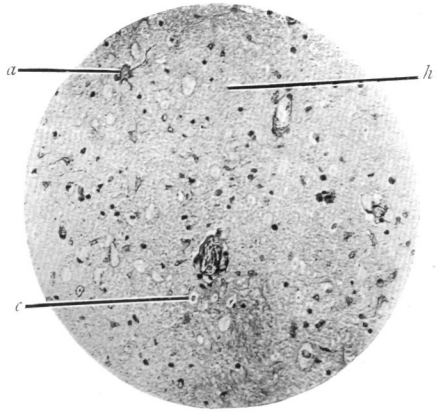

FIG. 358.

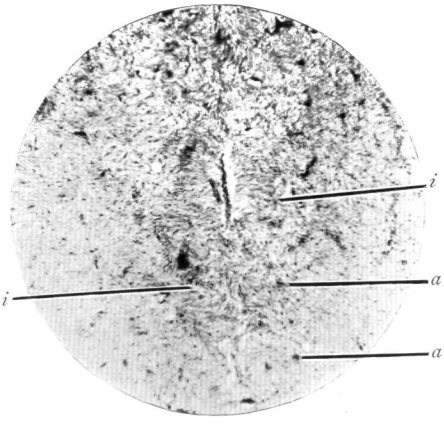

FIG. 359.

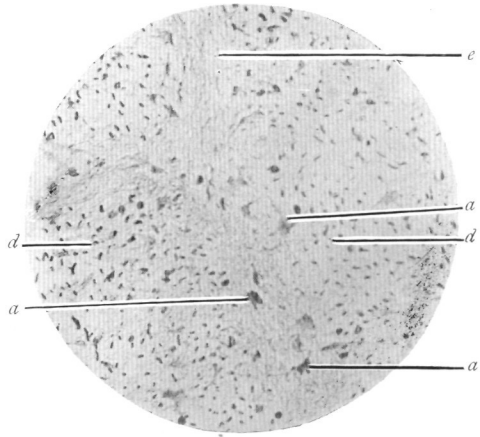

FIG. 360.

DR DAWSON—HISTOLOGY OF DISSEMINATED SCLEROSIS.

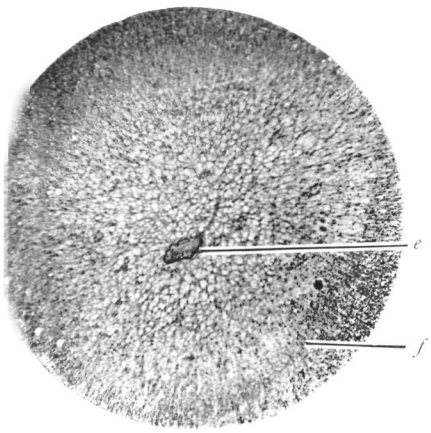

FIG. 361.

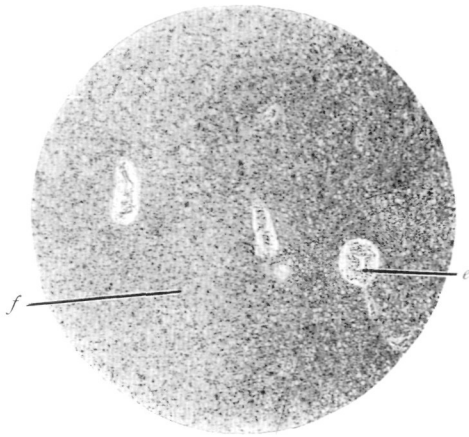

FIG. 362.

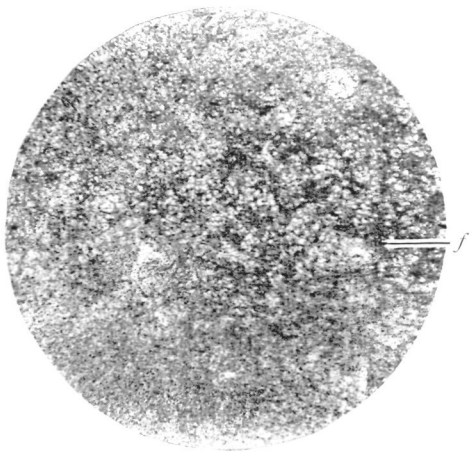

FIG. 363.

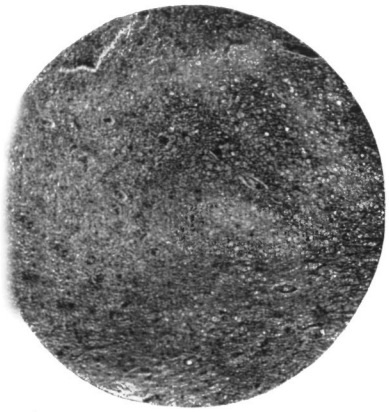

FIG. 364.

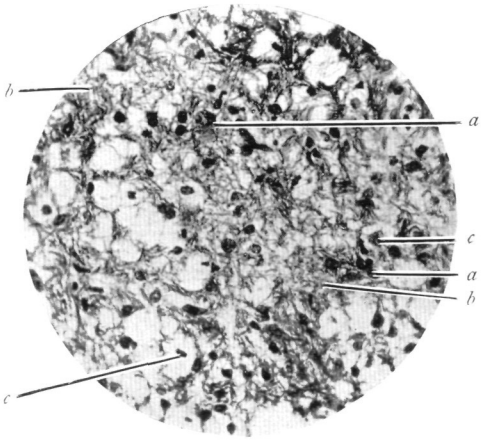

FIG. 365.

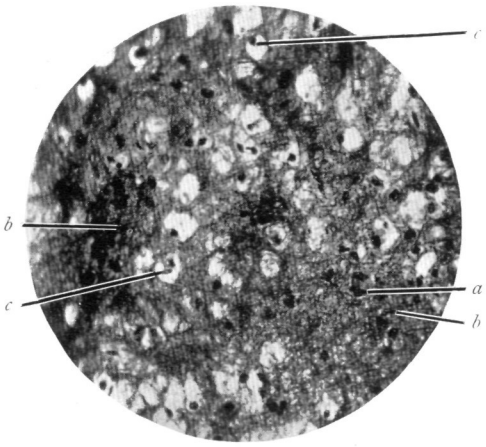

FIG. 366.

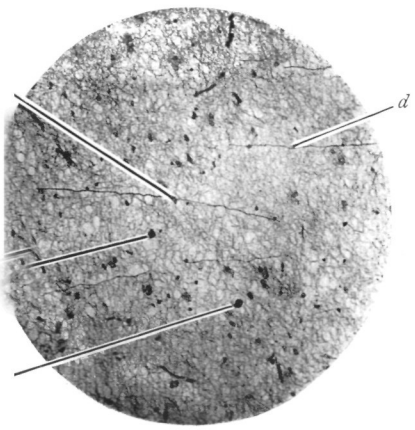

FIG. 367.

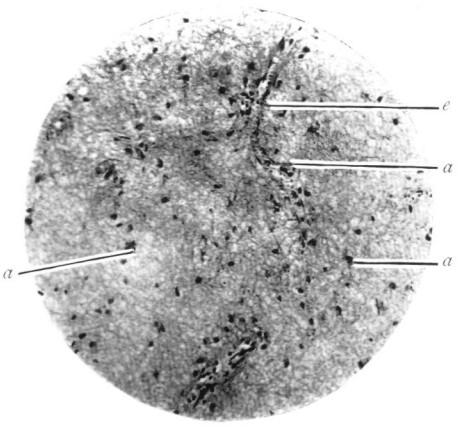

FIG. 368.

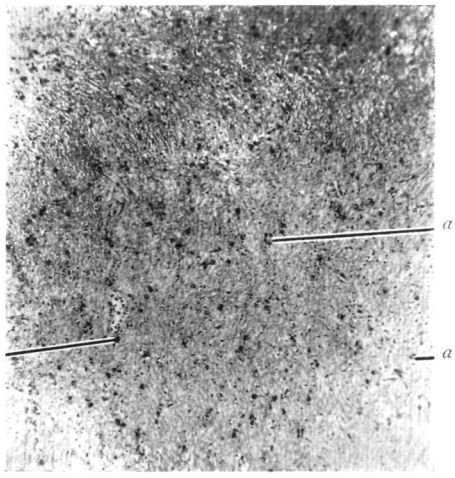

FIG. 369.

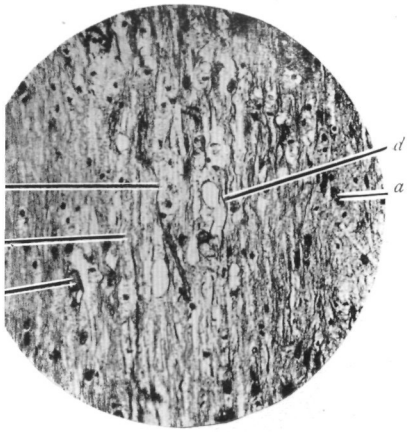

FIG. 370.

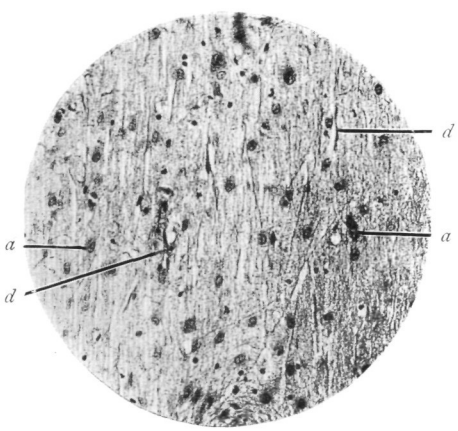

FIG. 371.

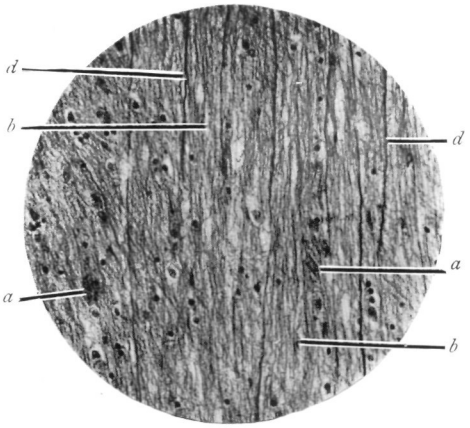

FIG. 372.

DR DAWSON—HISTOLOGY OF DISSEMINATED SCLEROSIS.

FIG. 373.

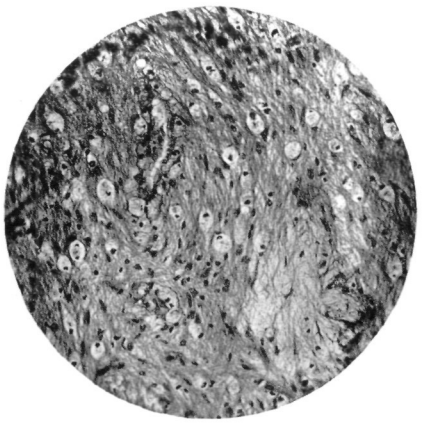

FIG. 374.

FIG. 375.

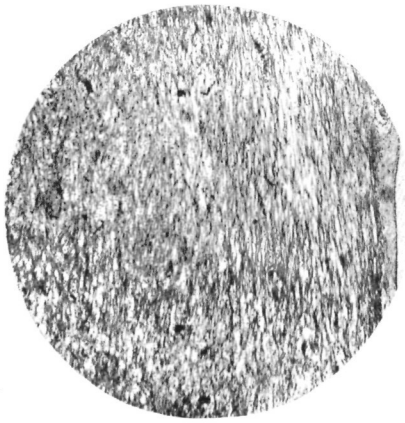

FIG. 376.

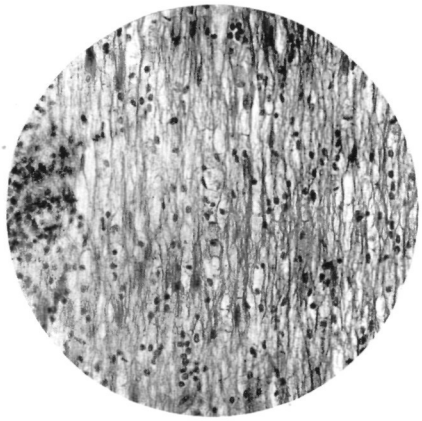

FIG. 377.

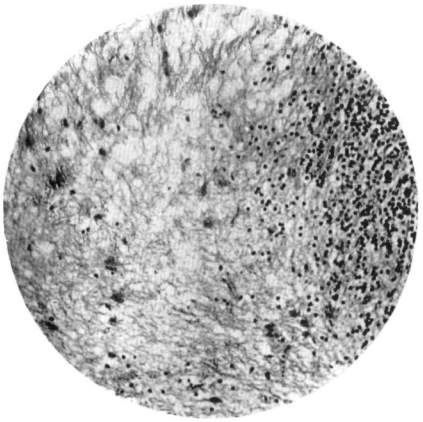

FIG. 378.

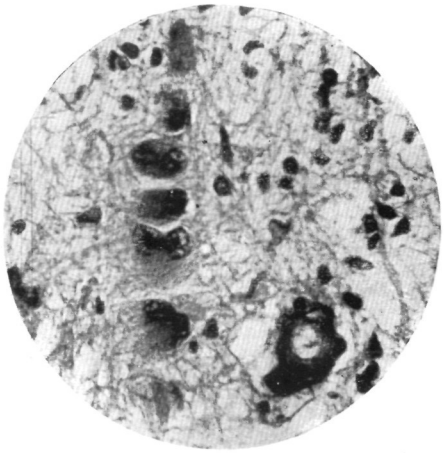

FIG. 379.

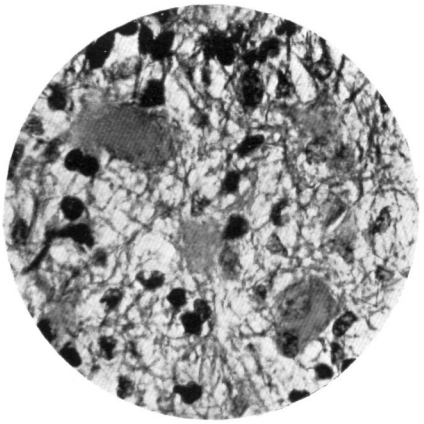

FIG. 380.

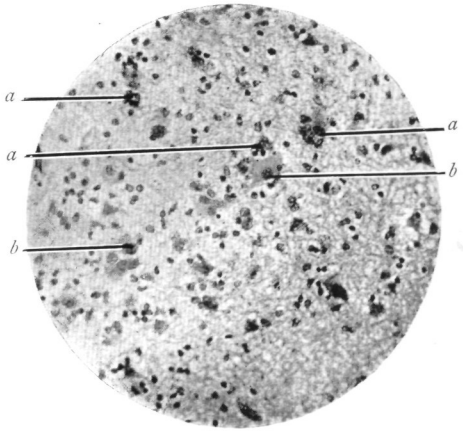

FIG. 381.

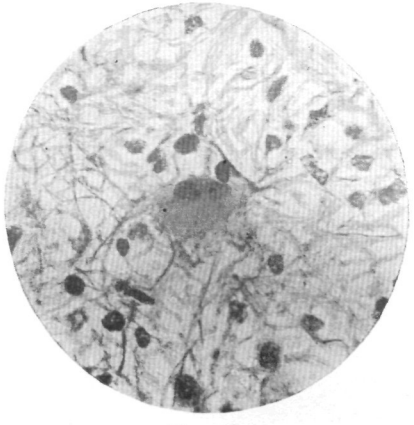

FIG. 382

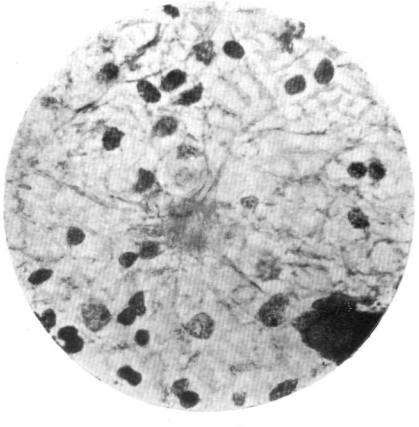

FIG. 383.

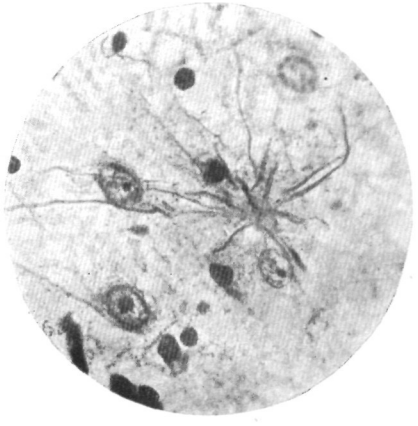

FIG. 384.

DR DAWSON—HISTOLOGY OF DISSEMINATED SCLEROSIS.

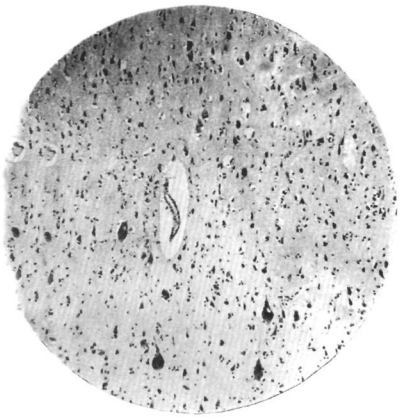

FIG. 385.

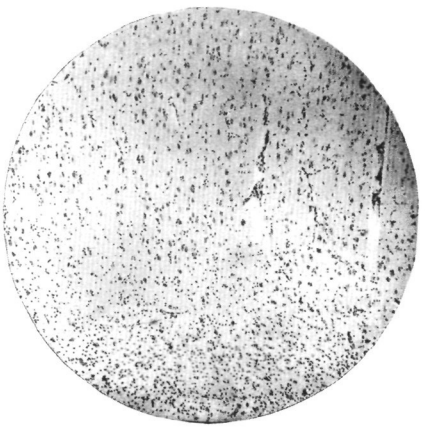

FIG. 386.

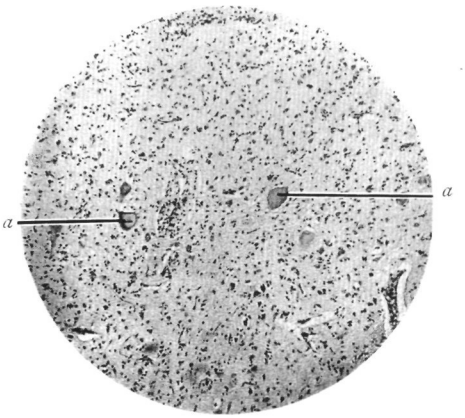

FIG. 387.

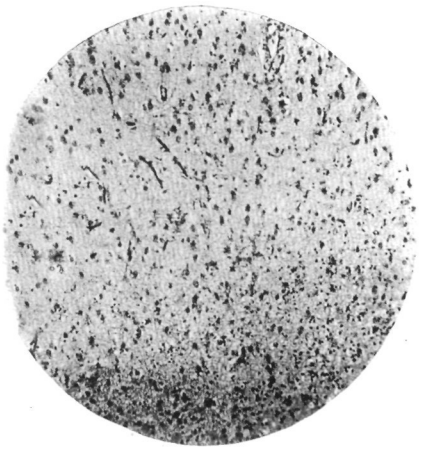

FIG. 388.

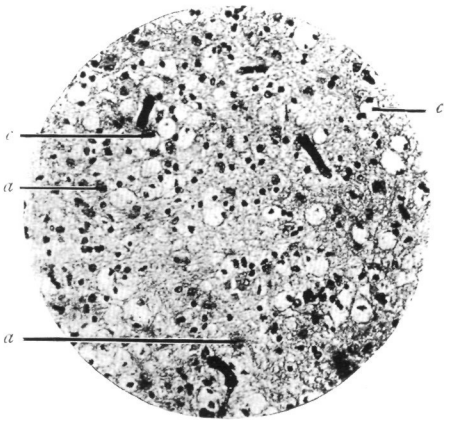

FIG. 389.

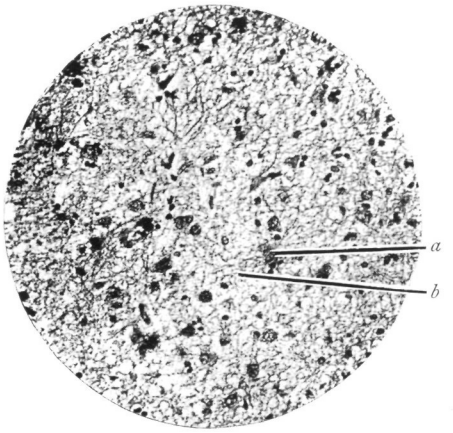

FIG. 390.

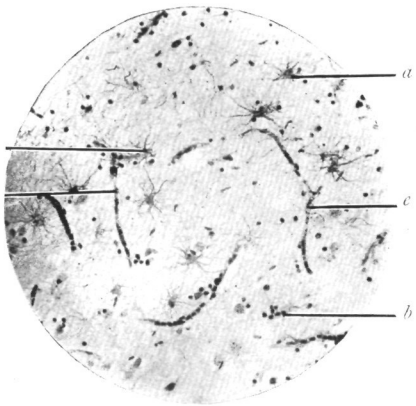

FIG. 391.

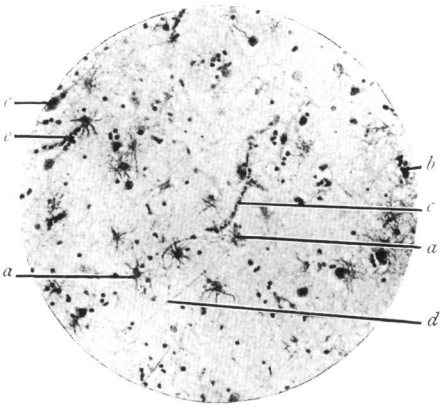

FIG. 392.

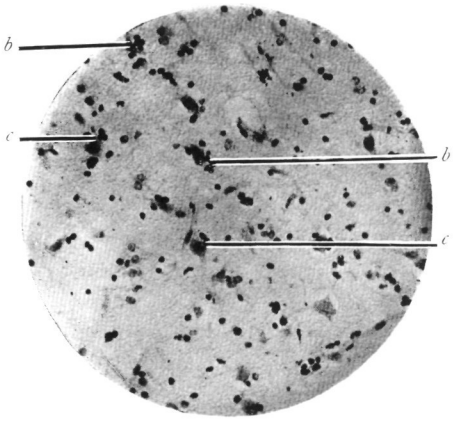

FIG. 393.

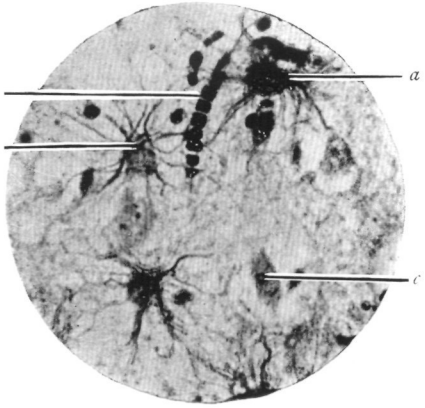

FIG. 394.

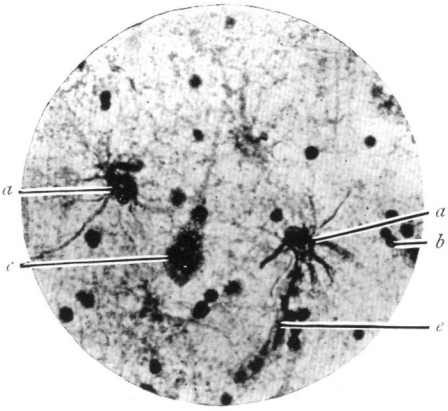

FIG. 395.

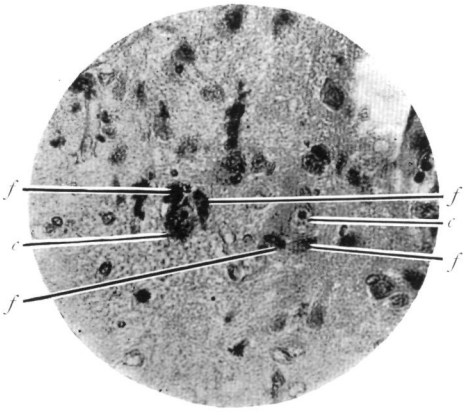

FIG. 396.

DR DAWSON—HISTOLOGY OF DISSEMINATED SCLEROSIS.

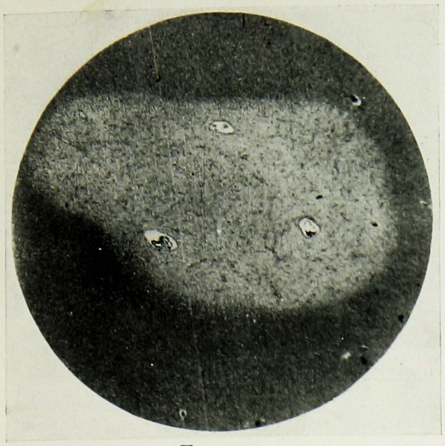

FIG. 397.

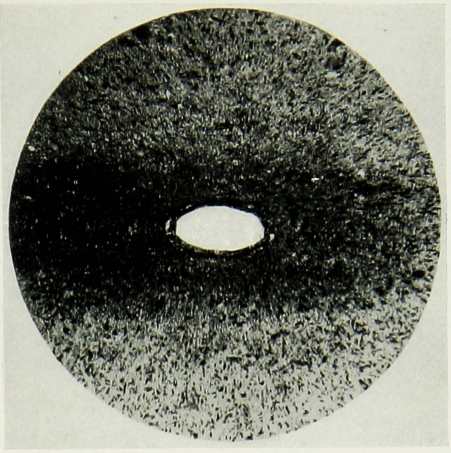

FIG. 398.

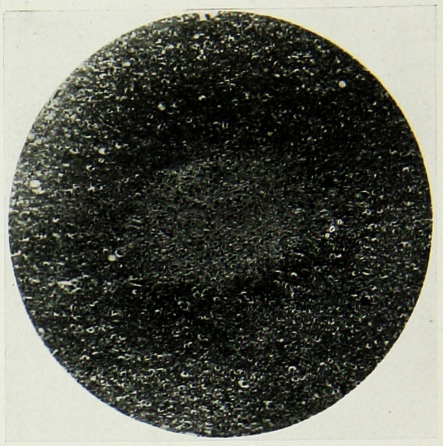

FIG. 399.

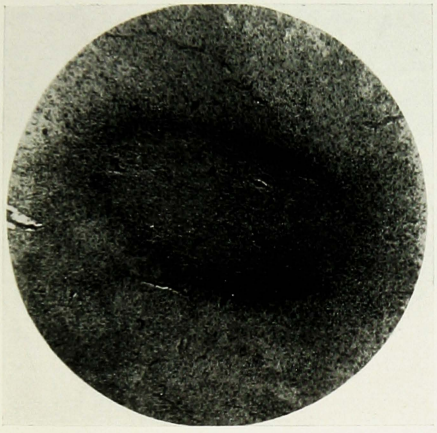

FIG. 400.

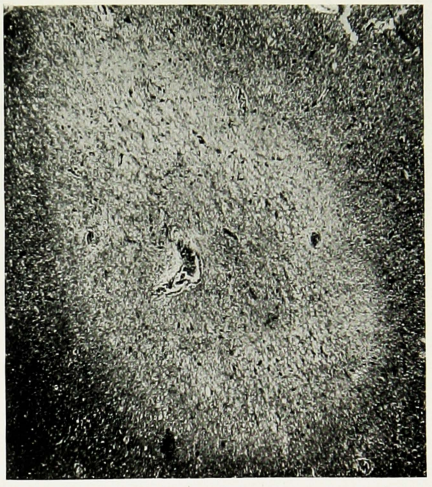

FIG. 401.

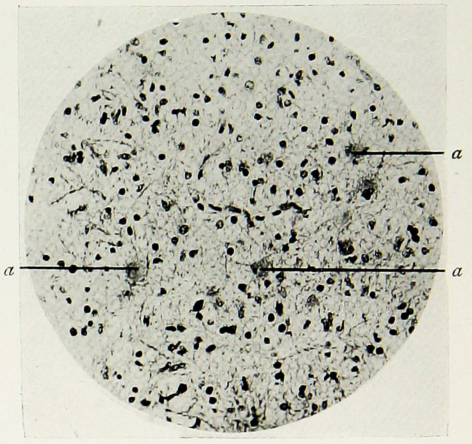

FIG. 402.

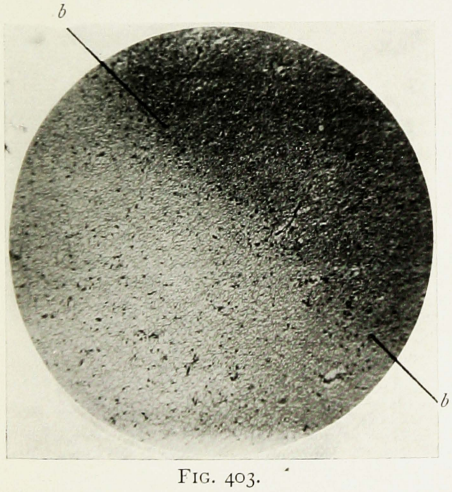

FIG. 403.

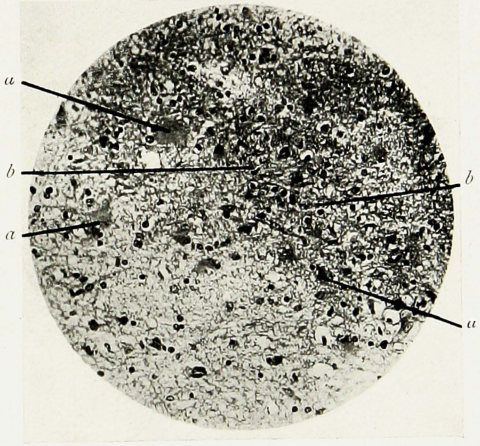

FIG. 404.

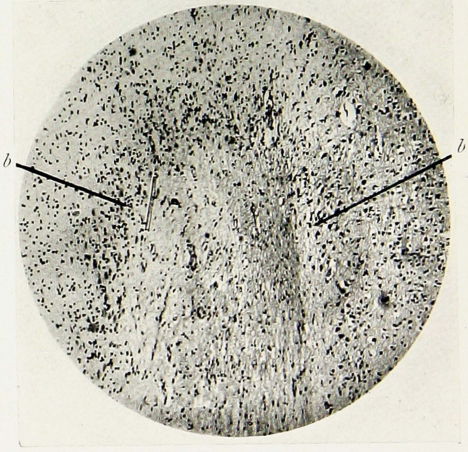

FIG. 405.

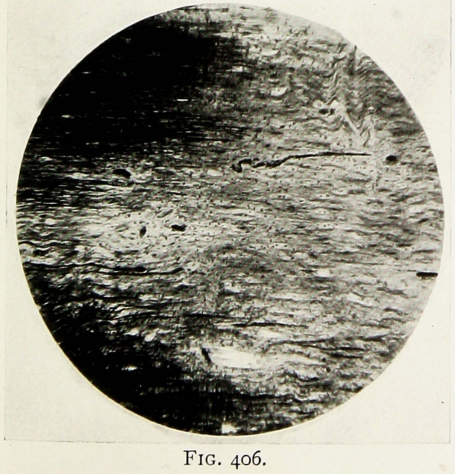

FIG. 406.

FIG. 407.

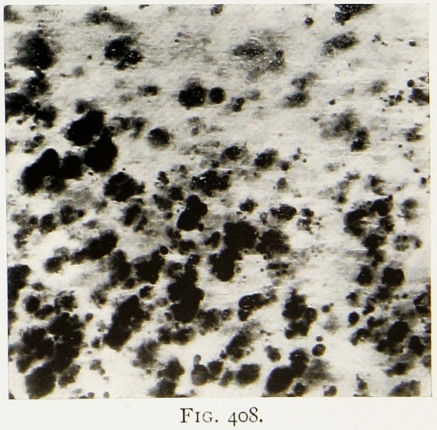

FIG. 408.

DR DAWSON—HISTOLOGY OF DISSEMINATED SCLEROSIS.

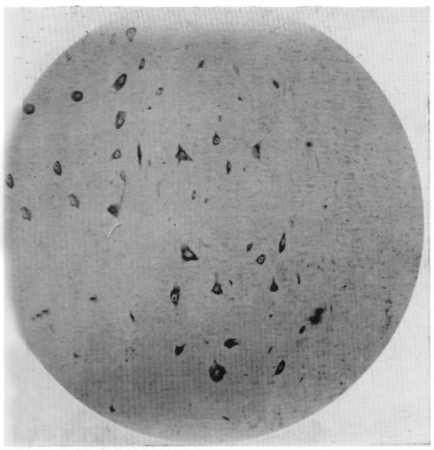

FIG. 409.

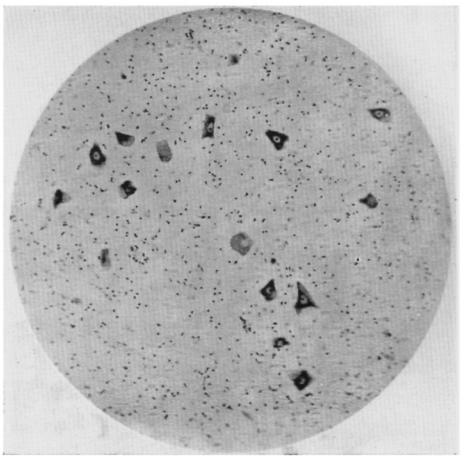

FIG. 410.

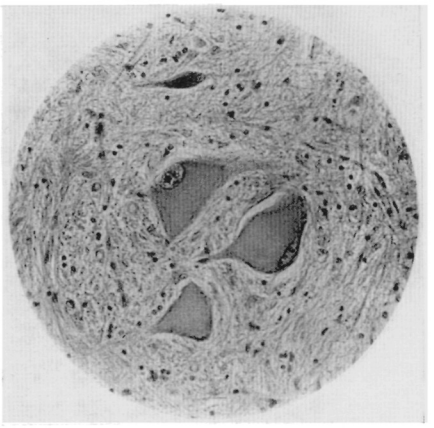

FIG. 411.

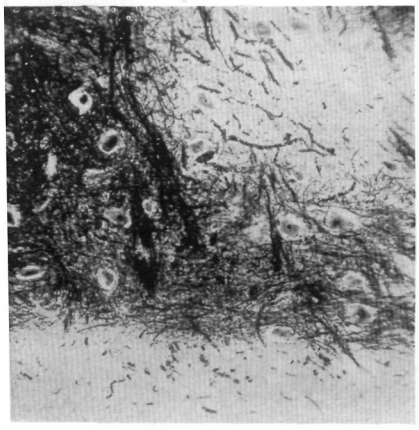

FIG. 412.

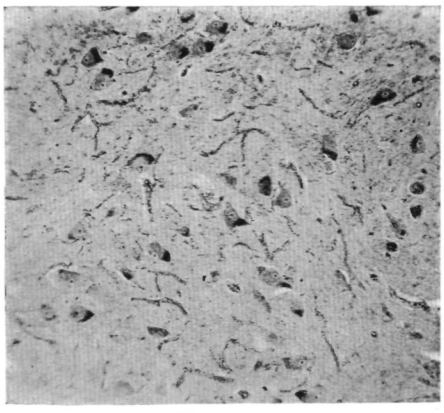

FIG. 413.

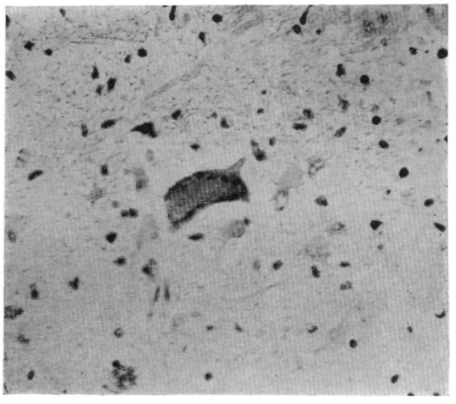

FIG. 414.

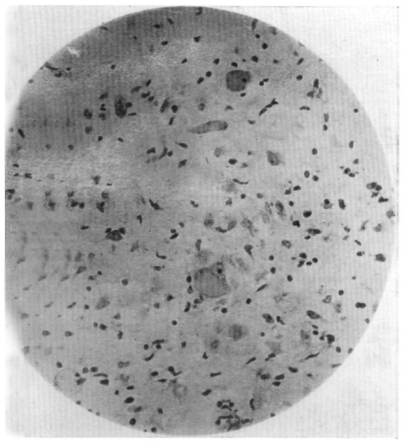

FIG. 415.

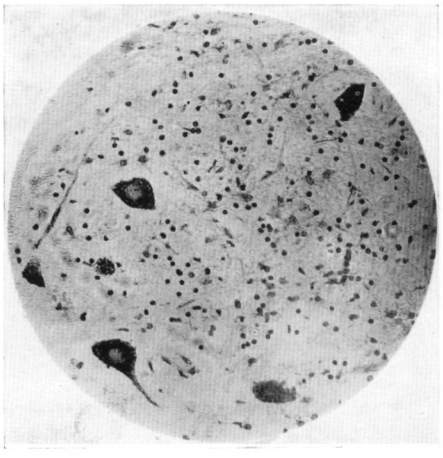

FIG. 416.

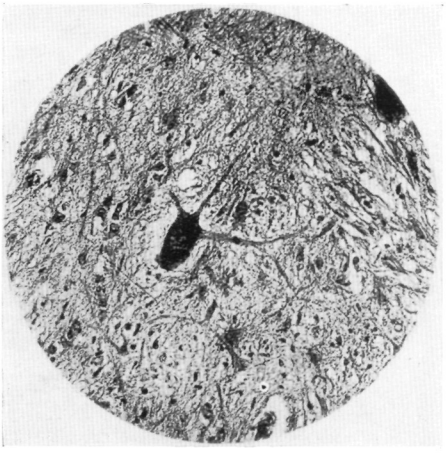

FIG. 417.

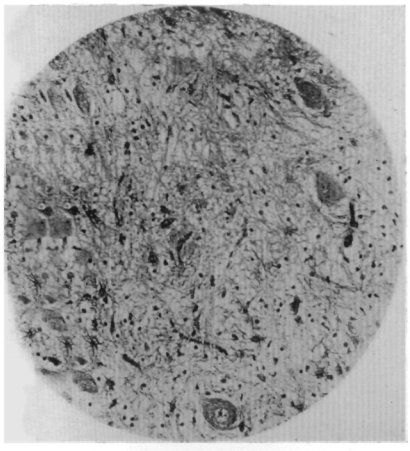

FIG. 418.

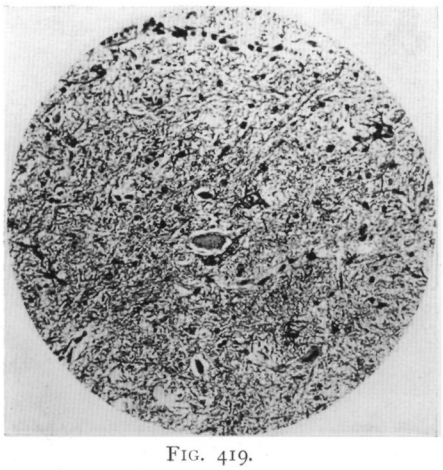

FIG. 419.

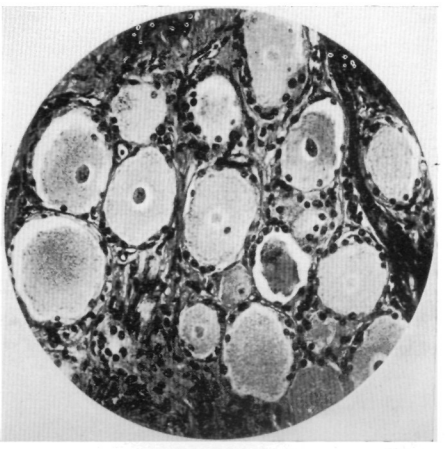

FIG. 420.

DR DAWSON—HISTOLOGY OF DISSEMINATED SCLEROSIS.

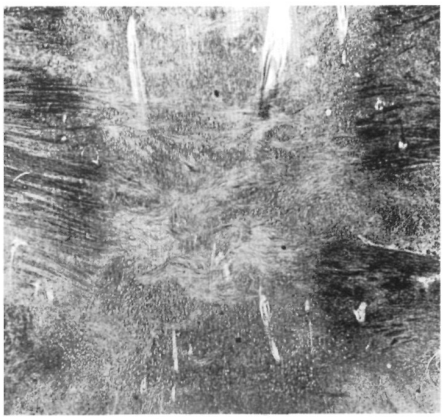

FIG. 421.

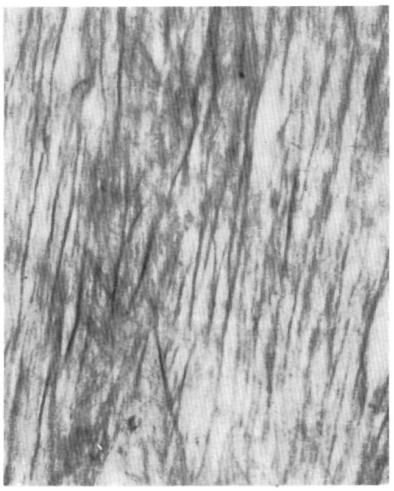

FIG. 422.

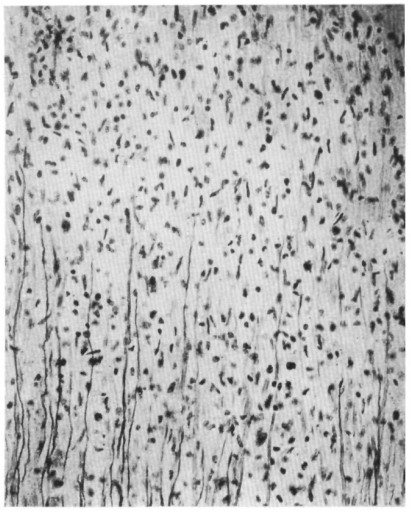

FIG. 423.

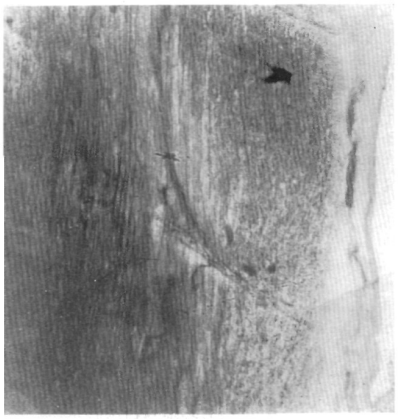

FIG. 424.

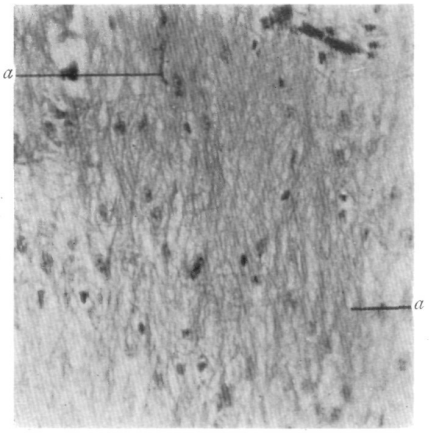

FIG. 425.

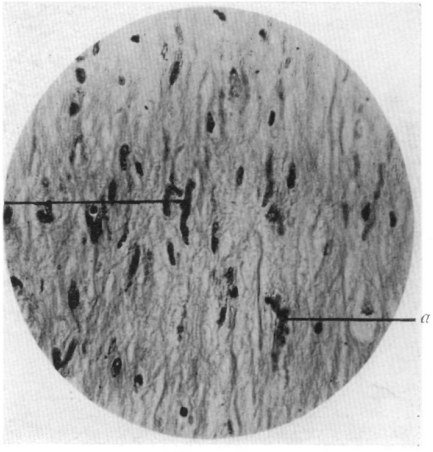

FIG. 426.

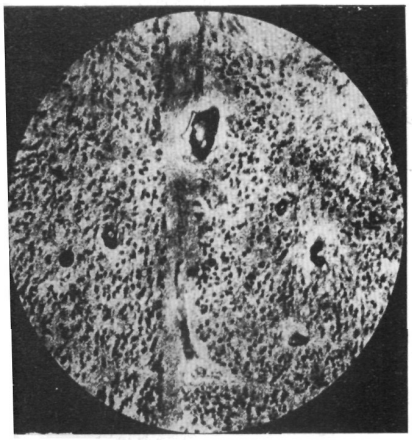

FIG. 427.

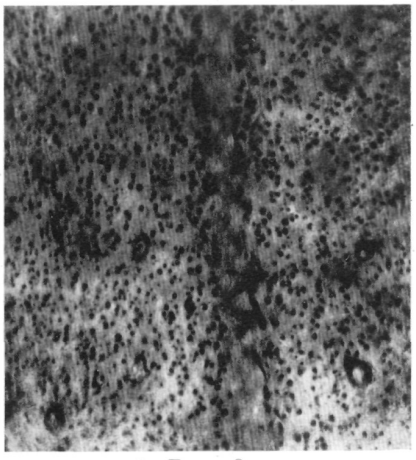

FIG. 428.

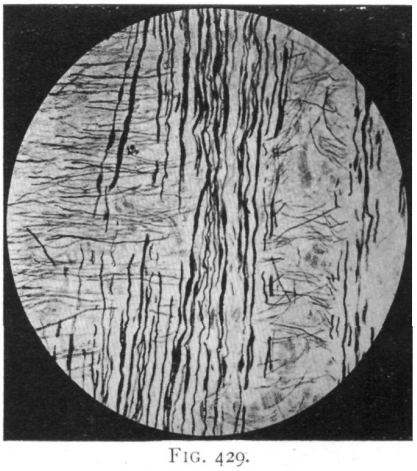

FIG. 429.

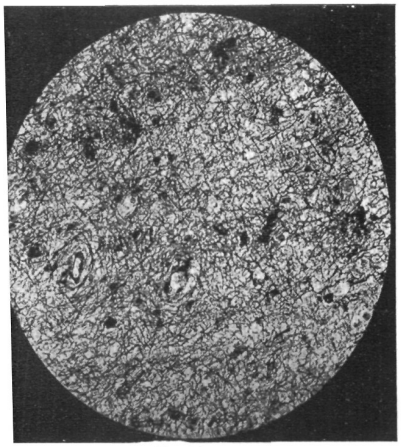

FIG. 430.

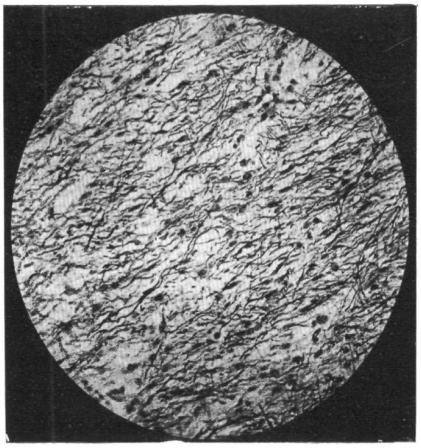

FIG. 431.

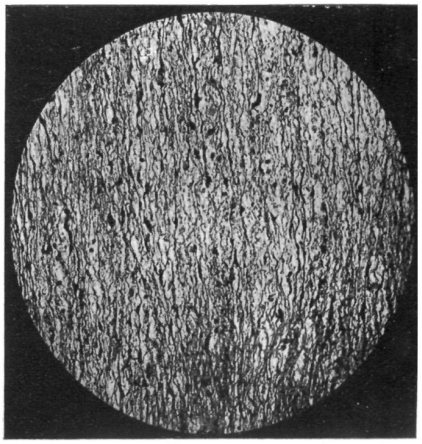

FIG. 432.

DR DAWSON—HISTOLOGY OF DISSEMINATED SCLEROSIS.

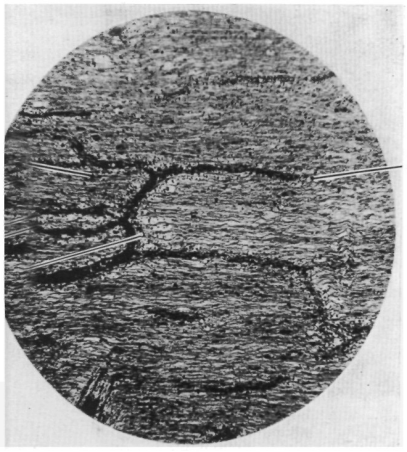

FIG. 433.

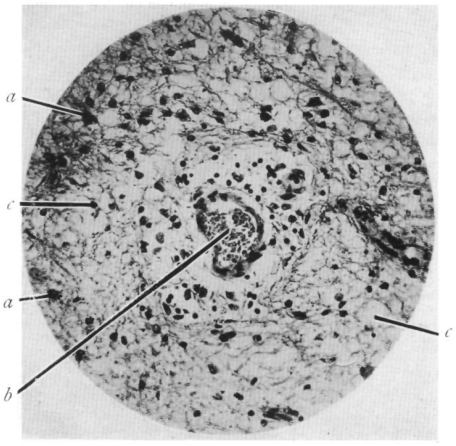

FIG. 434.

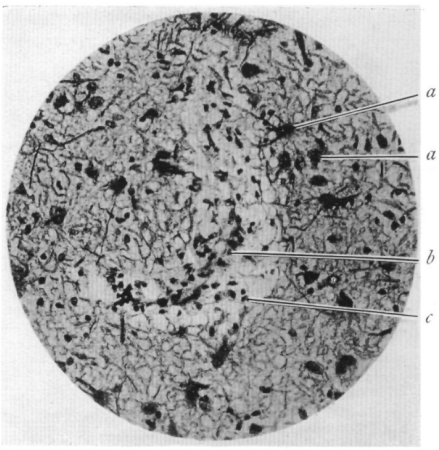

FIG. 435.

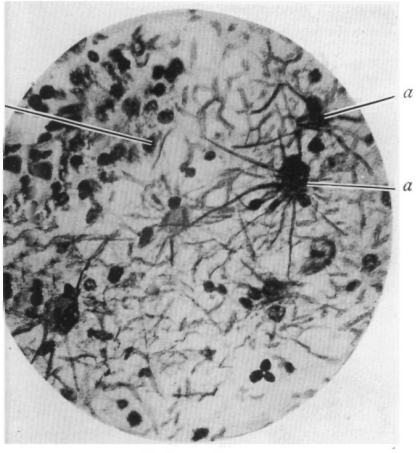

FIG. 436.

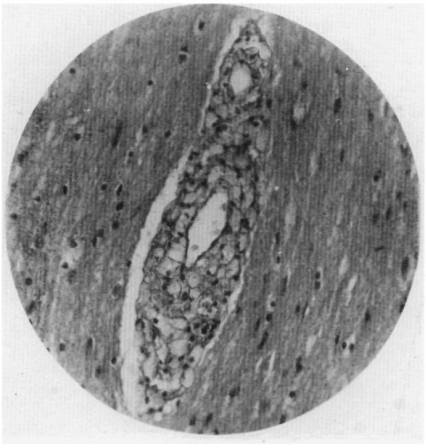

FIG. 437.

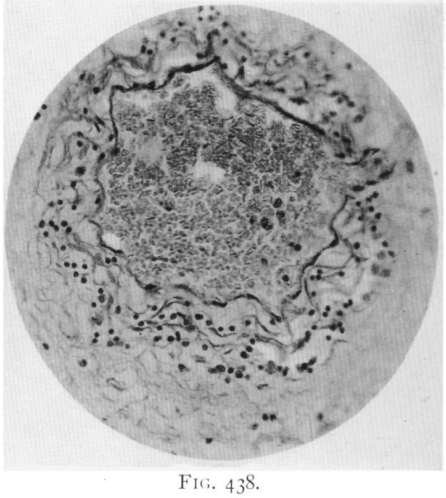

FIG. 438.

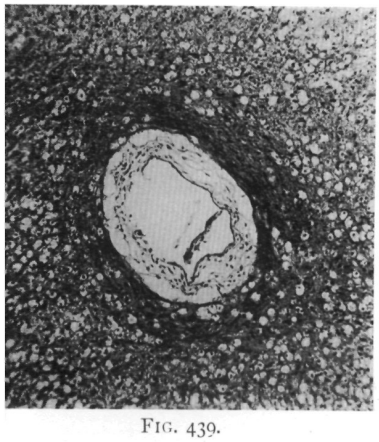

FIG. 439.

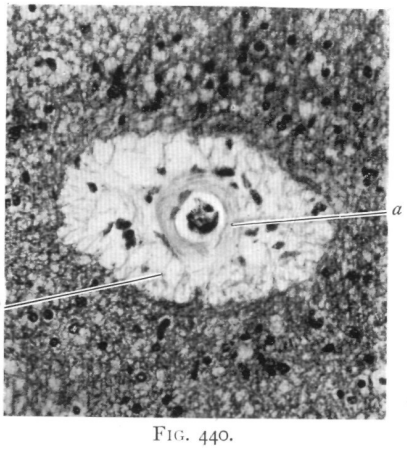

FIG. 440.

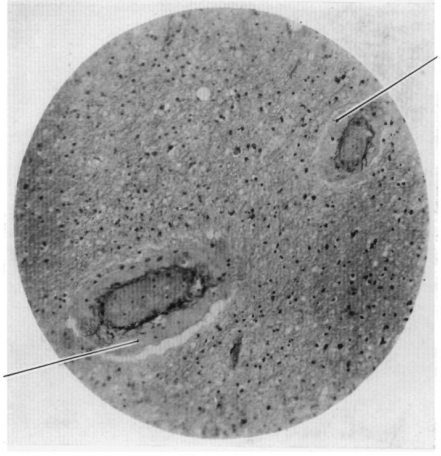

FIG. 441.

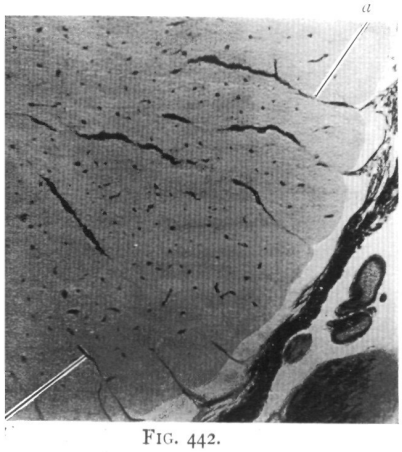

FIG. 442.

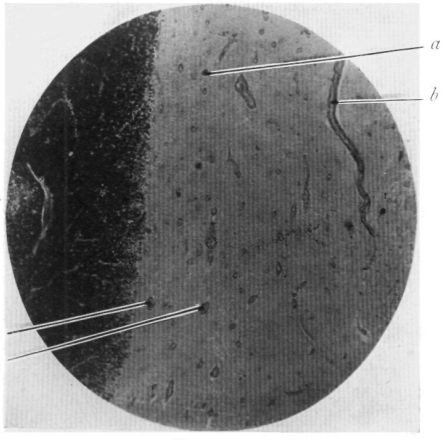

FIG. 443.

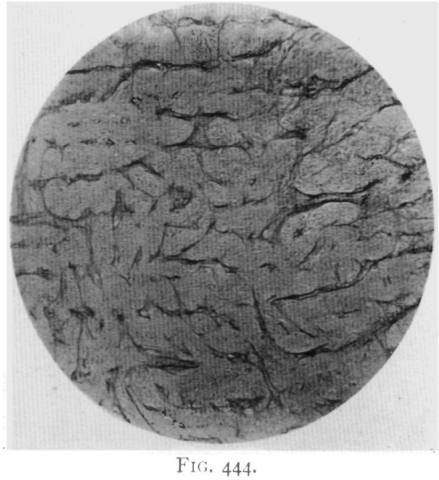

FIG. 444.

DR DAWSON—HISTOLOGY OF DISSEMINATED SCLEROSIS.

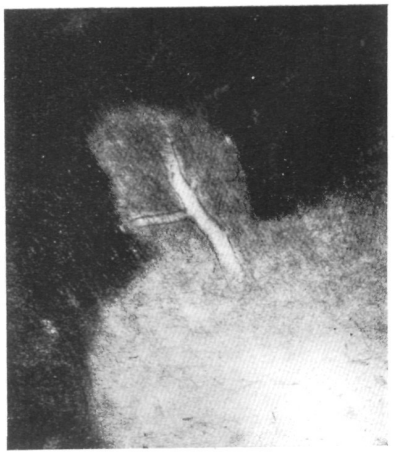

FIG. 445.

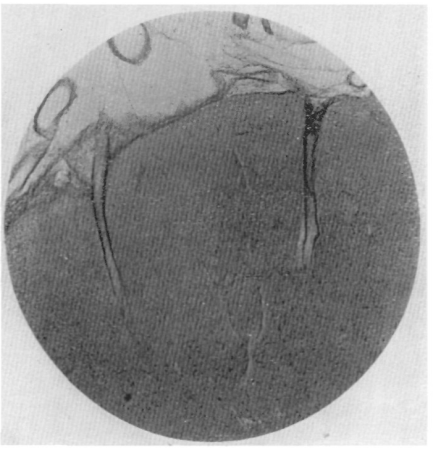

FIG. 446.

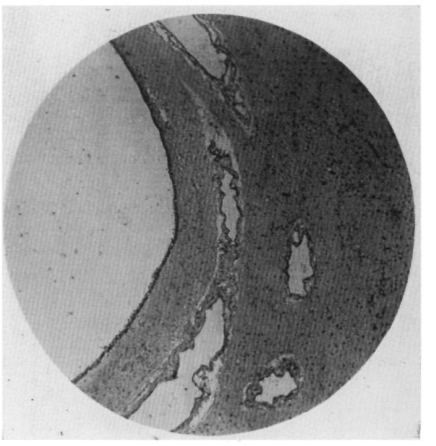

FIG. 447.

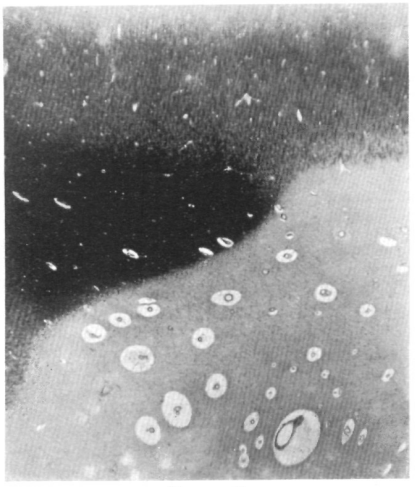

FIG. 448.

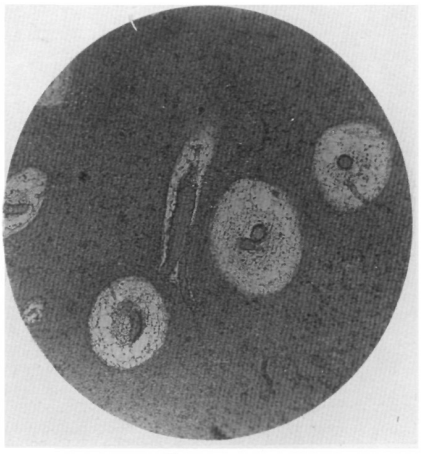

FIG. 449.

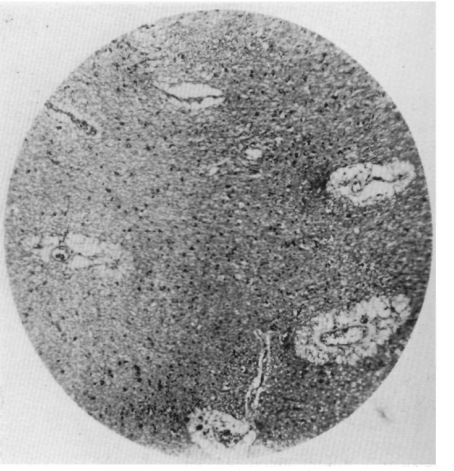

FIG. 450.

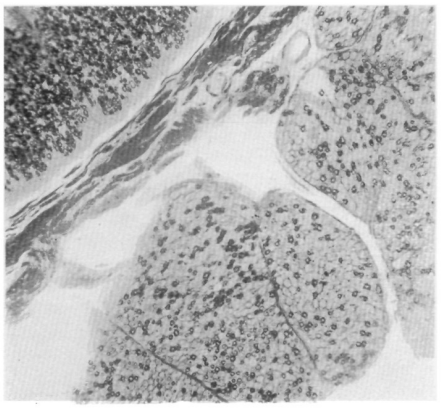

FIG. 451.

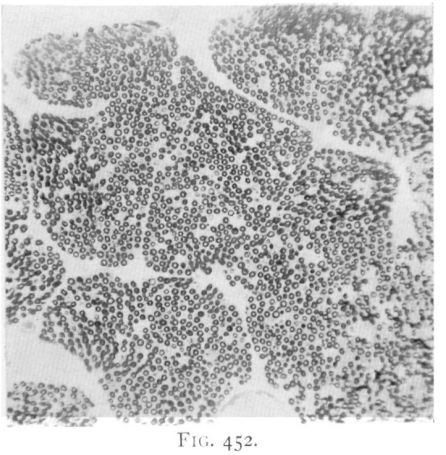

FIG. 452.

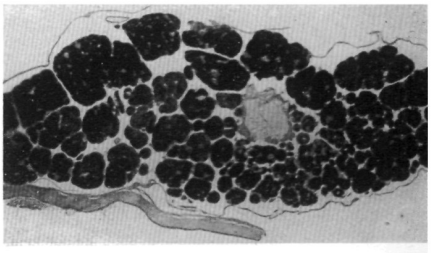

FIG. 453.

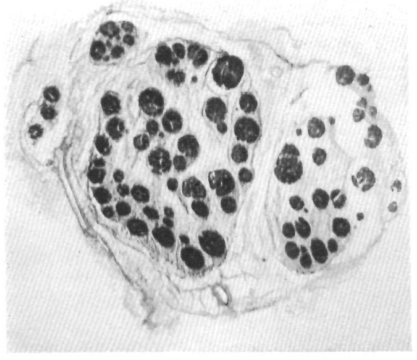

FIG. 454

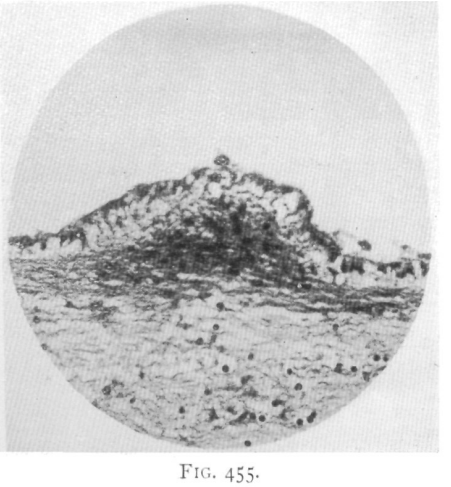

FIG. 455.

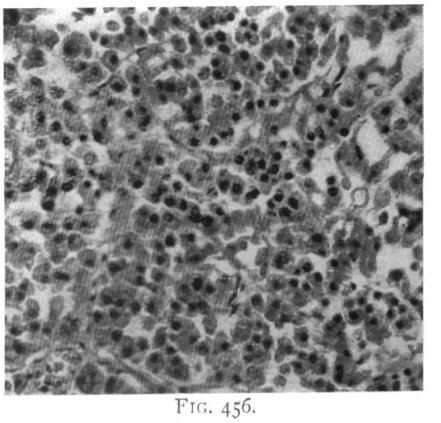

FIG. 456.

DR DAWSON—HISTOLOGY OF DISSEMINATED SCLEROSIS

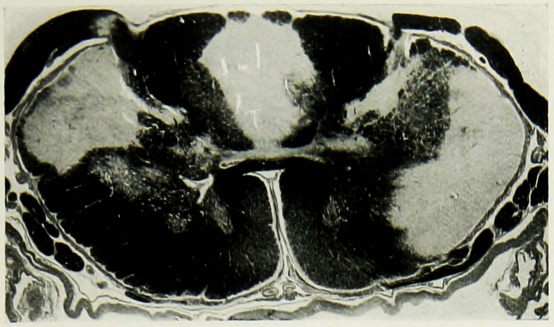

FIG. 240.

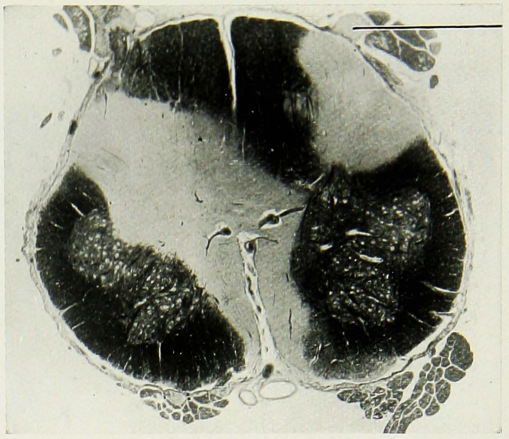

FIG. 242.

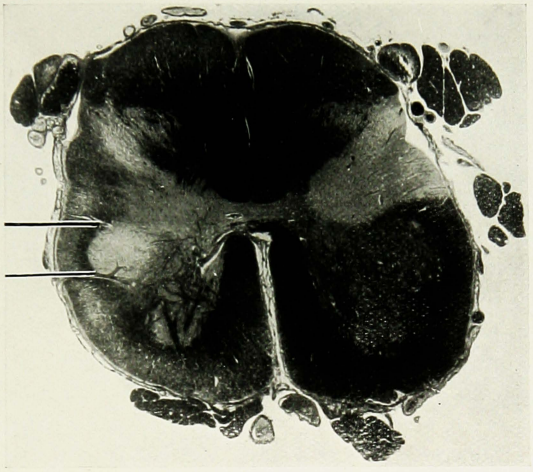

FIG. 241.

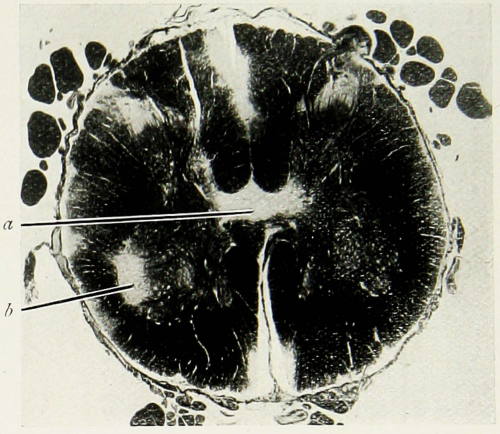

FIG. 243.

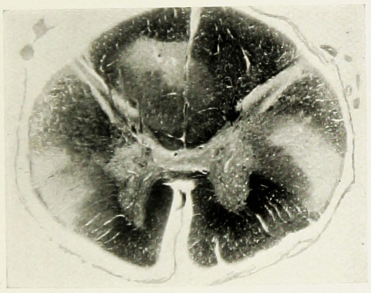

FIG. 244.

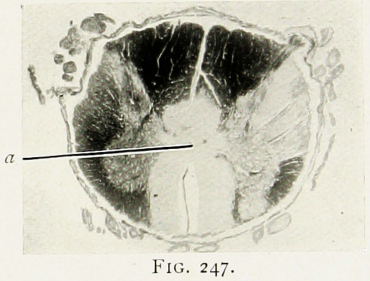

FIG. 247.

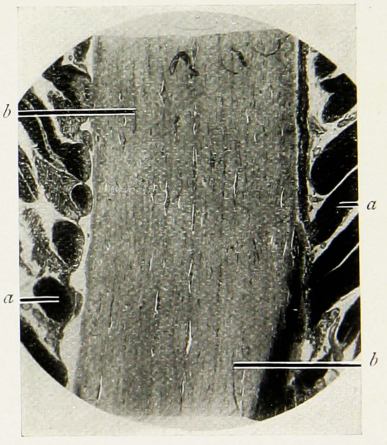

FIG. 250.

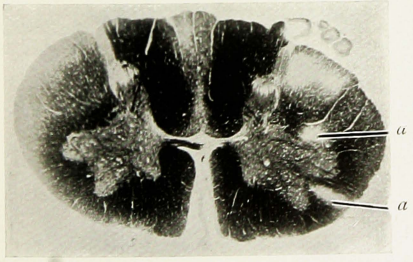

FIG. 245.

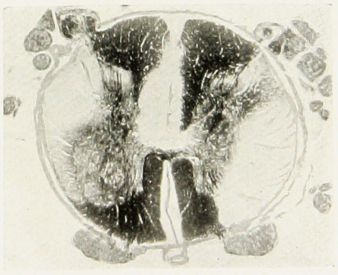

FIG. 248.

FIG. 251.

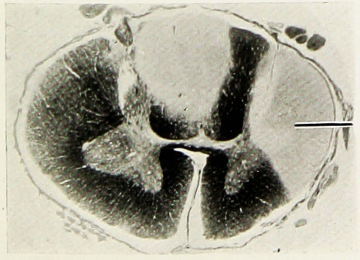

FIG. 246.

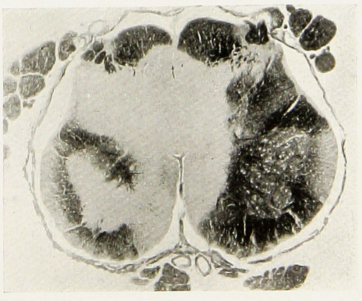

FIG. 249.

FIG. 252.

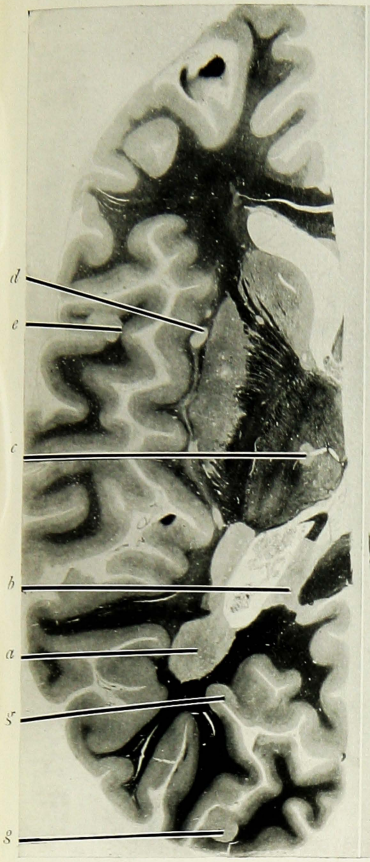

FIG. 23.

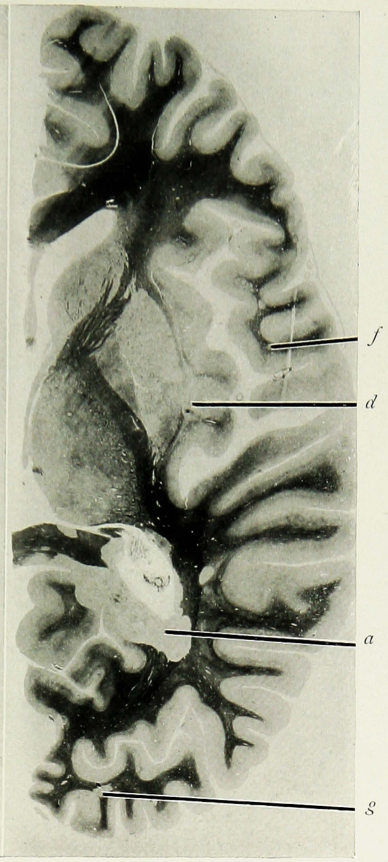

FIG. 24.

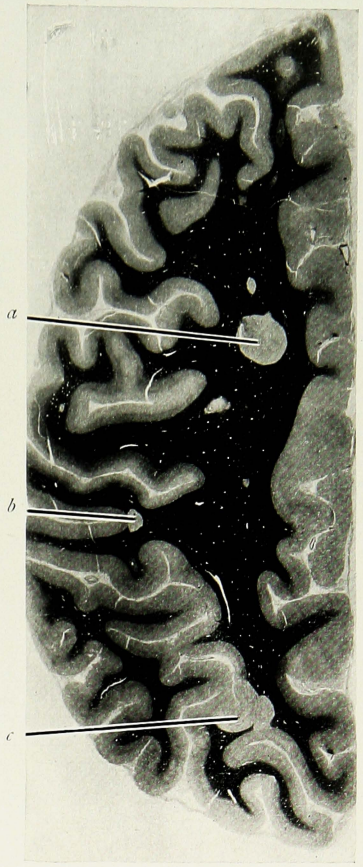

FIG. 25.

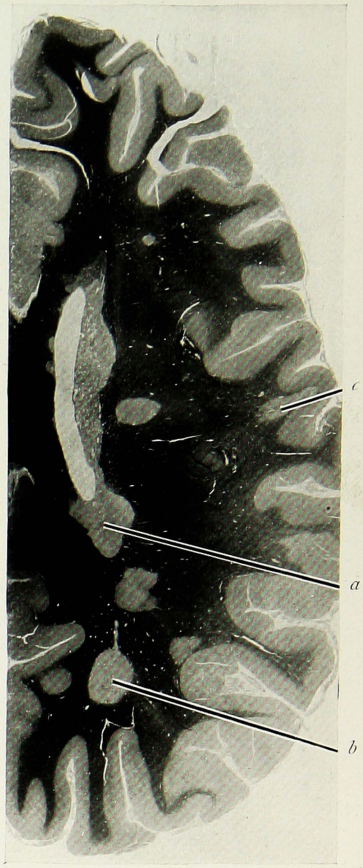

FIG. 26.

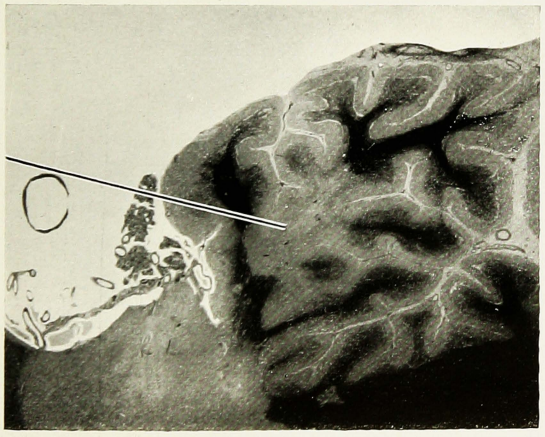

FIG. 27.

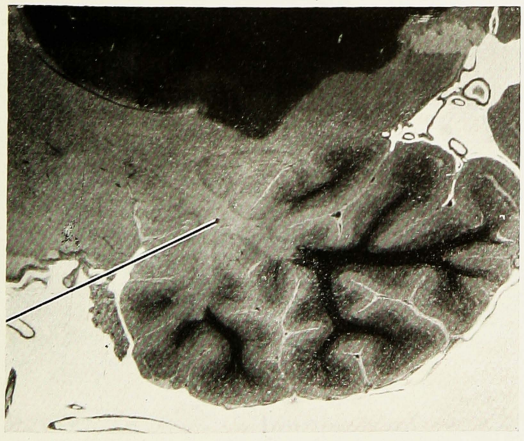

FIG. 28.

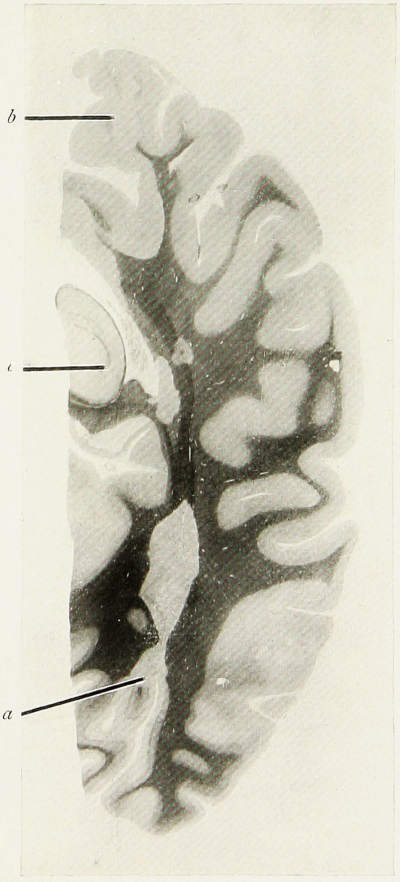

FIG. 29.

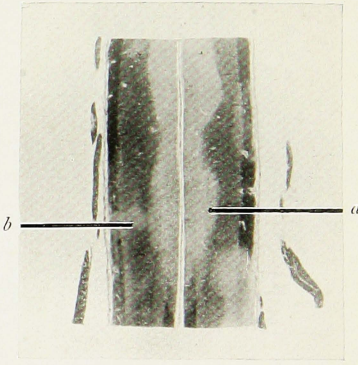

FIG. 30.

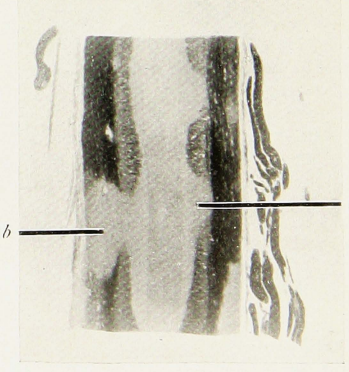

FIG. 31.