where they acquire their highest degree of development. Whilst proceeding thus, from the circumference to the centre, we are led to recognize the existence of several concentric zones, which answer to the principal phases of the alteration.[1]

a. In the *peripheral zone* the following appearances are observed: The trabeculæ of the reticulum are markedly thickened; sometimes they have acquired a diameter twice as great as that possessed in the normal state. At the same time, the nuclei which occupy the nodes of the reticulum have become more voluminous; they are occasionally found to have multiplied, and you may count two, or three nuclei, rarely more, in each node;[2] the cellular form becomes more distinct, owing to the thickening of the trabeculæ; the nerve-tubes appear to be further apart each from each—in reality, they have chiefly diminished in volume, and this kind of atrophy goes on at the expense of the medullary sheath, for the axis-cylinder has preserved its normal diameter, or it may even be hypertrophied. The amorphous matter which surrounds the fibres of the reticulum, on all sides, appears to be more abundant than in the healthy state.[3]

b. The nerve-tubes in the *second zone*, which may also be called the *transition zone*, have become still more slender. Many of them seem to have disappeared; in reality, they have been merely deprived of their medullary sheaths, and are now only represented by their axis cylinders, which, indeed, sometimes acquire comparatively colossal dimensions.[4] As to the trabeculæ of the reticulum, these offer not less remarkable alterations. They have become more transparent, their outlines are less distinct; finally, in certain parts, and this is a really fundamental fact, they are replaced by bundles of long and slender *fibrils*, closely analogous to those which characterize common connective tissue (laminous tissue). These fibrils are disposed in a direction parallel to the greater axis of the nerve-tubes; hence but little of them is seen in transverse sections, except their extremities, which present the appearance of a multitude of very fine dots. They tend, we have said, to usurp the place of the fibres or trabeculæ of the reticulum; but they, also, invade the meshes which contain the nerve-tubes, according as these diminish in size by loss of medullary matter, so that the reticulated or alveolar appearance which the connective gangue or matrix shows so distinctly in the healthy state, tends to become more and more effaced.[5]

c. The *central region* of the sclerosed patch, you are aware is

[1] Charcot, 'Société de Biologie,' 1868.
[2] Occasionally some of these nuclei present towards their middle region an indentation which seems to indicate the beginning of scission.
[3] Frommann, 2 Theil, Pl. ii, fig. 1, and *passim*.
[4] Frommann, Charcot.
[5] Frommann 2 Theil, *loc. cit.*, P. iv, figs. 1, 2, 3.

that in which the most marked alterations are observed. Here all vestige of fibroid reticulum has disappeared; we no longer meet with distinct trabeculæ or cell-forms; the nuclei are less numerous and less voluminous than in the external zones; they are shrunken in every direction, appear shrivelled, and do not take so deep a tint as usual under the action of carmine.[1] They may be observed forming little groups here and there in the interspaces between the bundles of fibrillæ. The latter, however, have invaded every part. They now fill up the alveolar spaces, from which the medullary matter has completely disappeared. Nevertheless, a certain number of axis-cylinders, those last vestiges of the nerve-tubes, still persist in the midst of the fibrils; but they, in general, no longer retain that comparatively large volume they occasionally possessed in the early phases of the alteration; most of them, indeed, have even diminished to such a degree that they might be mistaken, so close is the resemblance, for the fibril filaments of new formation, from which, however, we shall soon learn how to discriminate them.

Such, gentlemen, is the final term of the morbid process, in that form of sclerosis which engages our attention. And this indefinite persistence, as we may call it, of a certain number of axis-cylinders in the midst of parts which have undergone the extreme of fibrillary metamorphosis, is, you will be careful to remark, a character which seems proper to disseminated sclerosis. It is certainly not observed, at least to the same extent, in the other varieties of gray induration, whether we have to deal with descending spinal sclerosis, consecutive on lesions of the brain, or with that which, primarily occupying the posterior columns, is justly considered to be the anatomical *substratum* of progressive locomotor ataxia.

B. The results of the examination of longitudinal sections confirm, on the whole, the data which have been laid before you; I may, therefore, spare you any lengthy details, and confine myself to the following observations which will make you better acquainted with some aspects of the neoplastic fibril-formation. In sections of the kind mentioned, the characteristics of this tissue are well seen, and here you can best observe the longitudinal direction of the fibrils, their brilliant appearance which makes them resemble elastic fibres, and their arrangement in slightly undulating and ever parallel fascicles. On dilacerating these bundles, you will notice that the fibrils of which they are composed are extremely thin, that they are opaque and smooth, that they seldom divide and anastomose, whilst, on the contrary, they are frequently interwoven and entangled, so as to form a kind of felted tissue, and finally that they are scarcely tinted by the action of carmine (fig. 11). The latter characters sufficiently dis-

[1] Frommann, Charcot.

tinguish them from the axis-cylinders which, moreover, are generally larger, translucid, and never ramified. They may also be easily discriminated from the fibres of the reticulum, with which they are sometimes mingled, inasmuch as the latter are thicker, shorter, and their borders bristle with branching processes; finally, they differ from the elastic fibres which are so often found in common connective tissue by an important character; they swell up under the influence of acetic acid and form a hyaline transparent mass, which change does not occur in the case of elastic fibres.[1]

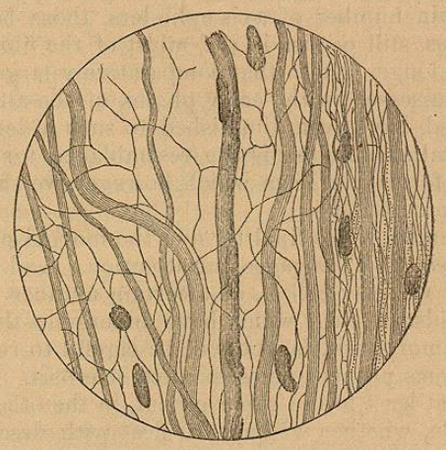

FIG. 11 represents a fresh preparation, taken from the centre of a patch of sclerosis, coloured with carmine, and dilacerated. In the centre is seen a capillary vessel, supporting several nuclei. To the right and left of this are axis-cylinders, some voluminous, others of very small diameter, and all deprived of their medullary sheaths. The capillary vessel and the axis-cylinders were vividly coloured by the carmine; the axis-cylinders present perfectly smooth borders, without ramification. Between them are seen slender fibrillæ of recent formation, which form on the left and in the centre a sort of network resulting from the entanglement or anastomosis of the fibrils. These are distinguished from the axis-cylinders, 1st, by their diameter, which is much smaller; 2d, by the ramifications which they present in their course; 3d, by taking no coloration from carmine. Nuclei are seen scattered about; some of them appear to be in connection with the connective fibrils; others have assumed an irregular form, owing to the action of the ammoniacal solution of carmine.

Can we proceed further in the study of the fibres, and endeavour to determine their mode of formation? Are they, for instance, as Frommann asserts, partially produced in the very substance of the fibres of the reticulum which they are destined soon to displace, and partially at the expense of the cells and the nuclei of the neuroglia? Do they arise, on the contrary, as others believe, either

[1] Valentiner, Zenker, *loc. cit.*; Vulpian 'Cours de la Faculté,' 1868.

from the pre-existing amorphous matter, or from a newly formed blastema? In other words, is there metamorphosis or substitution? The question, we think, must remain undecided yet awhile; all that we can say respecting it is that the fibrils have sometimes seemed to take root in the substance of the nuclei or cells, and that this fact, if it were confirmed, might be cited in support of Frommann's thesis.

I cannot pass over in silence the different alterations which those bloodvessels undergo that traverse the nodules of sclerosis. These changes may be well studied in the longitudinal sections of the cord, hardened by chromic acid. At the commencement, that is to say, in the peripheral zone, the parietes of these vessels, even of the finest capillaries, appear much thickened, and contain a larger number of nuclei than in the normal state. Nearer the centre of the nodule the nuclei are still more abundant, and, besides, the adventitious coat is replaced by several layers of fibrils quite similar to those which are simultaneously developed in the substance of the reticulum.[1] Lastly, at the final term of alteration, the walls of the vessels have become so thickened that their calibre suffers a notable diminution.[2]

I should notice, in passing, the habitual presence of a certain number of amyloid corpuscles in the midst of the fibrillary tissue. But I should at the same time mention the singular fact that these bodies are always less abundant in disseminated sclerosis than in the other varieties of gray induration.

C. It is not always without difficulty that we succeed in finding, in specimens which have not been prepared with chromic acid, all the details which I have just described. On the other hand, the fresh specimens offer this advantage, namely, they allow us to remark certain alterations which would have passed unnoticed if we confined ourselves to hardened preparations only. I allude here to the existence of globules and granulations of an apparently fatty or medullary nature, which we almost constantly[3] meet with in more or less considerable numbers in the substance of the sclerosed patches in the fresh state, and which soon disappear without leaving any trace when the preparation has been steeped some little time in chromic acid. Now, gentlemen, the presence of these fatty granulations is connected with an important phase of the morbid process, I mean with the destruction of the nerve-tube. However, before entering into a discussion of this subject, I think it useful to begin a little further back and to recall to your memory, by a

[1] Vulpian, 'Cours de la Faculté.'

[2] Frommann, *loc. cit.*

[3] This fact is, at least, mentioned by all the authors who have studied fresh specimens (Valentiner, Rindfleisch). It has not been absent from any one of the specimens which I have examined under similar conditions. See also Rokitansky in 'Bericht der Akademie der Wissensch. zu Wien,' t. xxiv, 1857.

succinct description, the modifications of structure which the peripheral nerves undergo when they are separated, by complete section, from the nervous centres.

At the outset I would remind you that, in the peripheral nerves the nerve-tubes are essentially constituted as in the spinal cord by a cylinder of medullary matter and by an axis cylinder, but that they also possess a sheath of connective tissue, the membrane of Schwann, which, according to the most recent researches,[1] does not appear to exist in the more slender tubes of the nerve centres, or at least only shows itself there in a rudimentary state.[2] You will perceive in a moment that this anatomical peculiarity, though apparently insignificant, is not devoid of interest from the point of view we occupy.

The following are the phenomena to which I wished particularly to call your attention. Eight or ten days after section of the nerve there supervenes a sort of coagulation of the medullary matter which breaks up into small masses, irregularly globular, with dark sinuous margins, showing a double outline, and having consequently preserved all the optical characters of myeline or medullary substance. Segmentation making new progress, in the following days, it will soon be perceived that Schwann's sheath no longer contains irregular masses of myeline, but globules presenting the appearance and the micro-chemical characters of fat. These globules, which are at first rather large, become gradually smaller and smaller as the process of division goes on, and finally they are replaced by very fine granulations, resembling dust, that fill the sheath of connective tissue. Mingled with these is found a certain proportion of paler granulations of a protein nature; and lastly, globules and granulations disappear, and Schwann's sheath, collapsing on itself, becomes so plaited and wrinkled that when you examine a certain number of such altered nerve-fibres, placed side by side in the field of the microscope, you would think you beheld a fascicle of filamentous connective tissue.

What becomes of the axis-cylinder during these changes? Composed as it is principally of proteine matter, it resists for a long time the action of the causes which have destroyed the medullary substance (or myeline), for it is occasionally still found in the sheath several weeks or even several months after section of the nerve.[3]

To sum up: under the new conditions of nutrition, in which the nerve-tubes are placed by section of the nerve, the medullary matter coagulates, then disintegrates and gives origin, on the one

[1] Frey 'Handbuch der Histologie,' etc., 2e edit., p. 354; Leipzig, Schulte, 'De Retinæ Structurâ,' 1867, p. 22; Kölliker, 'Geweblehre,' 5e édit., 1867, t. iv, p. 257.
[2] Vulpian, 'Leçons sur la Physiologie,' etc., p. 316.
[3] See Vulpian, 'Leçons de Physiologie,' pp. 237 and 298; Rindfleisch, 'Lehrbuch der Pathologisch Gewebelehre,' pp. 10 et 20, 1866.

hand, to proteine molecules, and, on the other, to corpuscles which at first preserve the appearance of myeline, but which, in consequence of ulterior modifications, soon present all the characters of fatty granulations.[1]

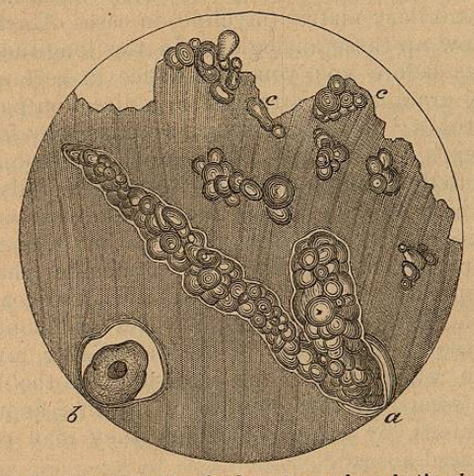

Fig. 12.—Patch of sclerosis in the fresh state: *a*, lymphatic sheath of a vessel distended by voluminous fatty globules; *b*, a vessel divided transversely. The adventitious coat is separated from the lymphatic sheath by a free space, the fatty globules which distended the sheath having disappeared; *cc*, fatty globules, gathered into small groups, dispersed here and there over the preparation.

Let us now return to the patches of sclerosis. Here we shall have to study phenomena closely analogous to those we have just been discussing.

In the substance of the sclerosed nodule, in fresh specimens, we almost constantly meet, as already mentioned, with globules or granules presenting the general appearance of fatty bodies. Their number is sometimes considerable. They show themselves under two principal aspects. Some constitute comparatively voluminous masses, whose dark and sinuous edges bound forms which sometimes represent irregular oval globules, sometimes are club-like, and occasionally kidney-shaped (Fig. 12). They present a double border like the myeline (or medullary matter), to which they also approximate in yet other respects. Other globules are true fatty droplets or granulations, sometimes free, sometimes aggregated so

[1] According to Robin, the myeline is a substance particularly rich in fatty principles, and it may, in this respect, be approximated to the contents of adipose cells ('Journal d'Anatomie,' 1868, No. 3, p. 309). Walter ('Virchow's Archiv,' 20, p. 426) has expressed the opinion that it is constituted by an amalgam or mixture of fatty and albuminoid bodies, which merely become dissociated in cases of degeneration of the nerve-tubes. See also Rindfleisch, *loc. cit.*, p. 20, § 52.

as to constitute confused heaps or coherent clusters, otherwise called *granular bodies*, devoid of nuclei and of enveloping membrane.[1] Proteine molecules are to be seen mingled here and there with these different granulations. All these products exactly resemble, you will observe, those which result from the disintegration of the medullary matter (myeline) in cases of nerve-section.

Let us follow up these analogies. In the longitudinal sections which I place before you, you will notice in certain parts long trails of fatty granulations arranged in a direction parallel to that of the nerve-tubes;[2] in the transverse sections they form here and there little heaps, like separate islets, which correspond with tolerable fidelity to the position of the alveolæ. Generally, indeed, the granulations have broken bounds, crossed the borders of the alveolæ, and become scattered over the adjacent tissues. But you cannot be surprised at this, when you remember that the nerve-tubes of the spinal cord are devoid of that cellular coat (Schwann's sheath) which, in divided nerves, incloses and contains all the products of the disintegration of the medulla or myeline. The meshes of the reticulum and the interstices of the fibrillæ offer easy ways of escape to the globules of myeline, as well as to the fatty granulations, by means of which they may permeate the tissue and spread abroad.[3]

Lastly, we would have you remark that the masses of (apparently) medullary matter and the fatty granulations are never met with in the centre of the sclerosed patch, that is, in the region where the work of fibrillary metamorphosis and of destruction of nerve-tubes has terminated; on the contrary they always occupy the external portions of the patch,[4] the peripheral and transition zones. Now, as you are aware, the morbid process is here in full activity; here it is that, compressed on all sides and strangulated by the thickening trabeculæ of the reticulum and afterwards by the fibrillary fascicles encroaching on the alveolæ, the medullary cylinder gradually diminishes in volume and then disappears altogether, leaving the nerve-tube at length only represented by the axis-cylinder. The accumulation of medullary or fatty globes and the destruction of the myeline-cylinder consequently take place simultaneously; we may even add that they proceed abreast, since

[1] Besides these granular bodies proper (*Fettkornchen Agglomerate*) may be found, in sclerosed patches, granular bodies having nuclei, that become coloured by the carmine test, and possess an enveloping membrane (*Fettkornchen Zellen*); these are simply cells of the neuroglia undergoing fatty degeneration. See, in reference to the distinction to be drawn between granular bodies, I. Poumeau, 'Thèse de Paris,' 1866; Rokitansky, 'Bericht der Akad. der Wiss. zu Wien,' t. xxiv, 1857; Wedl, 'Rudim. of Patholog. Histolog,' p. 292, London, 1855.

[2] It is not rare to meet, in the midst of the fibrillæ, with axis-cylinders partially denuded, to which globular masses adhere, at intervals, which have the appearance of medullary matter.

[3] Charcot, 'Société de Biologie,' 1868.

[4] *Ibidem.*

the former ceases when the latter is concluded. The coexistence of the two phenomena evidently cannot be fortuitous, and, taking note of what precedes, it seems to us legitimate to conclude that the medullary and fatty corpuscles in question are nothing other than the wreck and detritus resulting from the disintegration of the nerve-tubes.[1]

What becomes afterwards of these fatty granulations? They disappear in all probability by absorption; you know that no vestiges of them are discoverable in the central regions of the sclerosed patches. This is the place to submit to your notice a phenomenon which undoubtedly is connected with this act of absorption. In the preparations, which I am about to send round for inspection, you will observe that, in those parts where the products of nerve-disintegration are found, the lymphatic sheaths of the smaller vessels inclose within their cavities varying proportions of fatty granulations, or even, though more rarely, of corpuscles presenting the characters of myeline. In certain points, these different products are so abundant that the lymphatic sheaths are excessively distended; the vessels then appear to have swollen to twice and thrice their normal size, and they stand out, like little white tracks visible to the naked eye, on the gray ground of the sclerosed patch. Nevertheless, the coats of these vessels offer no other alterations than those indicated above, which certainly have no relationship with atheromatous degeneration. In short, we have here to deal with a fatty infiltration of the lymphatic sheaths, and not at all with a primary lesion of the vascular parietes. The same phenomenon is again met with in cerebral softening from arterial obliteration; in most of the forms of primary or secondary sclerosis; and, in short, in very different affections of the nervous centres, which, however, have this in common, that they all determine the fatty degeneration of the nerve-tubes. The true characters of this phenomenon appear to have been suspected by Gull,[2] and by Billroth,[3] but it has been principally cleared up by M. Bouchard, in his excellent studies on the secondary degenerations of the spinal cord.[4]

The description which has been given you of sclerosic alteration, disseminated in patches, relates chiefly to the white substance of the cord; but it may be equally applied, at least in a general way, to the gray matter. In both substances, in fact, the neuroglia is fashioned on the same model, and the alterations effected in it do not essentially differ; consequently, after the remarks already

[1] This opinion has been already very distinctly expressed by Rokitansky in 1858. 'Bericht,' etc., *loc. cit.*, 1857.

[2] "Cases of Paraplegia," 'Guy's Hospital Reports,' Third Series, 1858, t. iv.

[3] 'Archiv der Heilkunde,' 3 Jahr., p. 47.

[4] Bouchard, 'Archives Générales de Médecine,' Mars et Avril, 1866; Thèses de Paris, 1867, p. 44.

noted, I shall only make special mention of the modification which the nerve cells experience when, on the gray substance being invaded, they become comprised within the area of a sclerosed patch. These cells do not become the seat of nuclear proliferation, contrary to what under similar circumstances occurs in the cells of the connective tissue whose nuclei generally multiply; and this is, in fact, a characteristic which might, if needed, be a help to distinguish one from the other of these two orders of anatomical elements. The nerve-cells undergo a peculiar alteration which may be designated by the term *yellow degeneration*, on account of the ochreous tint which they assume, and which is occasionally somewhat intense; in this state they cease to be coloured by carmine as in the normal state; the nucleus and the nucleolus seem to be formed by a substance having a vitreous and brilliant appearance. It is the same as regards the body of the cell, which, besides, appears as if composed of concentric strata.

Finally, all parts of the cell are seized by atrophy, which may lead to a comparatively considerable diminution of its bulk, whilst, at the same time, the cell processes dwindle away and disappear.[1]

In the encephalon, and also in the optic and olfactory nerves, the sclerosed patches present essentially the same characters as in the cord; hence we do not think it would be of any advantage to enter into details in relation to them.

Now that we have reached the conclusion of our study, we may try to array, in their natural order of sequence, the phenomena which go to make up the alteration in question, and thus endeavour to determine the pathological method by which this morbid change is produced.

Undoubtedly, the multiplication of nuclei and the concomitant hyperplasia of the reticulated fibres of the neuroglia constitute the initial, fundamental fact, and necessary antecedent; the degenerative atrophy of the nerve elements is consecutive and secondary; it had already begun when the neuroglia gave way to the fibrillary tissue, though the wasting afterwards proceeded with greater rapidity. The hyperplasia of the vascular parietes plays merely an accessory part.

In what consists the affection of the neuroglia which marks the beginning of this series of derangements? It is easy to discover there all the characteristics of formative irritation. But, after recognizing the fact that disseminated sclerosis is a primary and multilocular chronic interstitial myelitis or encephalitis, it remains for us to determine the histological characters which distinguish it from other forms of sclerosis of the nerve-centres, and also from several kinds of myelitis or encephalitis which, having their starting-

[1] Frommann, *loc. cit.*; Vulpian, 'Cours de la Faculté,' 1868; Charcot, 'Société de Biologie,' 1868.

point likewise in the neuroglia, nevertheless do not issue in fibrillary metamorphosis. We will endeavour, at an opportune moment, to fulfil this duty. At present, gentlemen, we hasten to leave the department of pathological anatomy for that of clinical observation in order to show you by what array of symptoms disseminated sclerosis of the nervous centres makes its existence known.[1]

LECTURE VII.

DISSEMINATED SCLEROSIS: ITS SYMPTOMATOLOGY.

SUMMARY.—Different aspects of disseminated sclerosis, considered from a clinical point of view. Causes of error in diagnosis.

Clinical examination of a case of disseminated sclerosis. Tremor: modifications caused thereby, in the handwriting; characters which distinguish it from the tremor of paralysis agitans, chorea, general paralysis, and the motor incoördination of ataxia.

Cephalic symptoms. Disorders of vision: diplopia, amblyopia, nystagmus. Impeded utterance. Vertigo.

State of the inferior extremities. Paresis. Remissions. Absence of disorders of sensibility. Commixture of rare symptoms; tabetic phenomena; muscular atrophy. Permanent contracture. Spinal epilepsy.

IN the preceding lecture we minutely described the anatomical lesions of multilocular sclerosis of the nervous centres. Leaving aside, therefore, this portion of its history we shall proceed, to-day, to point out the series of symptoms by which it makes its existence clinically known.

I.

A. It is singular that a morbid state which possesses so distinct and so striking an anatomical substratum, and which, in short, is

[1] In a note published in the 'Archives de Physiologie' (1873, p. 753), one of Professor Charcot's students, Dr. Debove, has shown cause for the modification of the generally received opinion in reference to the histology of disseminated sclerosis. According to his researches, the sclerosed parts are formed of fibrillæ and of flat cells, quite similar to the cells of common connective tissue. He has succeeded in demonstrating this, through having employed the method of interstitial injections.

These facts are very different from what was believed with respect to the structure of the neuroglia (see note, p. 138), before M. Ranvier demonstrated that the connective tissue of the nerve-centres does not essentially differ from that of other organs; the only striking peculiarity being, according to M. Ranvier, the small diameter of the fibrillary fascicles.—(*Note to the Second French Edition.*)