THE GOULSTONIAN LECTURES ON SECONDARY DEGENERATIONS OF THE SPINAL CORD.

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LECTURE I.

MR. PRESIDENT AND GENTLEMEN,—It was with feelings almost apologetic that I announced the subject of these lectures. I felt that it might be expected that a subject of wider clinical interest should be chosen. But, on referring to the terms of the bequest of the founder of this lectureship, I discovered that he had anticipated my difficulty. He was evidently aware that the younger Fellows would be more able to do useful work in the realm of pathology than in clinical medicine. He provides that the lecturer shall give what is more of a demonstration than a lecture on the dead body (if such be procurable).

Two hundred and fifty years and more have elapsed since his death, and yet the wisdom of the method implied in the wording of his bequest becomes not less, but more apparent. If our art is to be raised from the level of mere empiricism, it must be grounded on the sure basis of pathology. In ordinary pathological inquiries, it is usual to study the normal and to reason from it concerning the abnormal. This method is followed in my first lecture, on the Histology of Secondary Degeneration. But when we wish to study the course of the fibres in the cord we reverse the usual process, and make use of pathology to teach us anatomy. It is not too much to say that without this method our knowledge of the anatomy of the cord would be of the vaguest and most rudimentary description.

When we have learnt all the lessons that pathology can teach us concerning the paths in the cord which conduct the multitudinous motor, sensory, and visceral impressions, then, and not till then, shall we fully understand all the symptoms that present in many diseases, better known by name than by nature. Let it not, then, be supposed that the subject I have chosen is one of academic interest only. It is true that at present our knowledge of the anatomy of the cord and medulla is ahead of our diagnosis, and also that our diagnosis is far in advance of our treatment, but who dares to say how long this shall remain so? It is but a very few years since the workers at cerebral localisation, too well-known to need even mention by me, were looked upon as scientific dreamers, and now their dreams have become the most striking facts in the medicine and surgery of the day. Spinal localisation follows closely, and already begins to bear fruit. These facts, then, must be my justification (if, indeed, such be needed) for dwelling minutely on points that appear to be of little practical importance at the present moment.

Histology of Degeneration.—It is a common thing for observers to speak of degeneration of nerve-tubes in the spinal cord as being comparable to, and moreover of the same nature as, the corresponding lesions in nerves. As I wish to institute a close comparison between the two, it would be well to sum up the features of the so-called Wallerian degeneration first.

Wallerian Degeneration.—When a nerve is cut, its peripheral end degenerates, because it is cut off from the centre, which is believed to exert some nutritive or trophic influence over it. Certain changes make their appearance in the ultimate nerve-tubes. The first change that occurs is a loss of transparency of the nerve-fibres to the naked eye. This is coincident with, and probably caused by, a cleavage of the myeline, or white medullary substance of Schwann. This may be seen to occur in forty-eight hours, or later, up to four days. This change is more rapid in summer than in winter, and is associated with diminution of irritability of the nerve to stimuli. Under the microscope at this period, the white substance is seen to split across into masses or cylinders; these masses being separated from one another by distinct inter-

vals. Later on, about the seventh day, the medullary sheath undergoes further changes, likened by some authors to "fatty degeneration." At any rate, the altered myeline becomes more or less liquefied, and tends to run into droplets of all sizes, which lie about within the sheath of Schwann; at the same time the nuclei, or "nerve-corpuscles," of the nerve increase in size. So far, all accounts seem to agree. But there appears to be some difference of opinion concerning the state of the axis cylinder; some writers—Schiff, Vulpian, Weir Mitchell—contend that the axis cylinder remains while the medullary sheath goes. Schiff even maintains that it may persist for six months. But it is more probable that the earliest view of Waller, and later of Ranvier and others,¹ is the correct one; that the axis cylinder undergoes changes *pari passu* with those of the medullary sheath. *A priori* it would appear probable, inasmuch as the axis cylinder is the means of conduction of stimuli, and not the medullary substance, that it would be rather the first constituent of the nerve-tube to show signs of degeneration than the last. Another important feature in nerve-degeneration is the part played by the nerve-nuclei. These early swell and undergo proliferation; this process must be distinguished from the appearance of nuclei in the neighbourhood of the injury, which are inflammatory. Later on the myeline becomes more and more broken up, and, according to the latest accounts, becomes mixed with the degenerated remains of the axis cylinder, and finally tends to leave the primitive sheaths to become absorbed. The primitive sheaths then remain, and in them the nuclei. The result of separation of a nerve-fibre from its centre is, as Ranvier suggests, not exactly death of the fibre, but an active change, as evidenced by the proliferation of nerve-nuclei. This idea is further borne out by the tendency to regeneration which all peripheral nerves exhibit.

Regeneration of Nerves.—After the degenerated myeline material has disappeared, or even before that, in the second month or later, primitive fibrils make their appearance. These are said to appear in the primitive sheaths of the old nerves. They are at first without myeline; however, they soon acquire a medullary sheath, but are for a long time smaller than the natural nerve-fibre.

This slight sketch may serve for the purpose of comparison with the analogous condition in the spinal cord. I propose to show that though, as might be expected, the two processes resemble each other in the main, yet they differ in several rather important points of detail.

Distinction between Fibres of Cord and Peripheral Nerves.—It must be remembered that there are certain striking histological points of difference between the nerve-fibre of the peripheral nerves and that of the cord. The nerve-tube of the cord consists of an axis cylinder and a medullary sheath, which are indistinguishable from those of a nerve. A cord fibre has no definite primitive sheath; it is surrounded by the close network of the neuroglia, which takes the place of the tough, structureless sheath coating the nerve-fibre from end to end. We shall see that this may account for some of the histological phenomena of degeneration. The cord-fibre is apparently devoid of the nerve-nuclei or corpuscles which take such an important share in the nutrition of the nerve-fibre.

Causes of Secondary Degeneration.—The causes of secondary degeneration come under three categories: 1, destruction of trophic centres in brain or medulla; 2, interruption in the continuity of fibres, or bundles of fibres, in their course—that is, either by complete section, crushing, slow pressure by new growths, or displacement of vertebrae, or, lastly, by invasion and consequent strangulation of fibres by new growths, or transverse myelitis; 3, section of, or other injury to, posterior roots, by which centripetal fibres are cut off from their trophic centres in the posterior root ganglion. Under the first we have principally to consider descending lesions from cortical injury. For our present purpose the first two may be considered together. The third requires special consideration.

"Traumatic Degeneration."—In the close neighbourhood of the initial lesion we have to consider the "traumatic degeneration." This was first described by Schiefferdecker² (1876), but more fully later by Homén.³ It is found both above and below the lesion for

¹ For the latest article on this subject, see Bowly's Hunterian Lectures, *Lancet*, 1887 p. 863.

² Schiefferdecker, "Ueber Regeneration und Architectur des Rückenmarkes," *Virchow's Arch.*, 1876, p. 642.

³ Homén, "Contribution Expérimentale à la Pathologie, et à l'Anatomie Pathologique de la Moelle Epinière," 1885.

about the distance of one centimètre. It is essentially inflammatory in character, and must be distinguished from secondary degeneration proper. It affects the whole diameter of the cord, but even here shows a tendency to affect certain tracts above and others below. There are many leucocytes crowding the tissues. The large cells of the grey matter are swollen and granular. There are many lacunae, some filled with "vitreous masses" (Homén), which do not take any stain easily. In some cases, even after many months, the inflamed tissue contains masses of material which stains faintly by Weigert's hæmatoxylin, and is presumably broken-down myeline. Homén describes oval masses lying in the long axis of the cord, believed by him to be altered axis cylinders. They stain deeply with anilines. There is a tendency often to the formation of small local collections of purulent matter, even as far as two roots from the lesion. Both Schiefferdecker's and Homén's accounts refer to cases of experimental lesions in which one would expect to find signs of inflammation as well as degeneration in the vicinity of the wound. In cases of crushing after fracture-dislocation, in which, of course, there could be no septic contamination, there is, in my experience, very little sign of active inflammation at all; and yet, in the immediate neighbourhood of the injury, both above and below, we find a more advanced stage of degeneration usually than in points remote from the injury; and in cases which have survived many months there is a considerable thickening of the neuroglia mesh-work. The endothelium of the perivascular lymphatics is also proliferated, even as late as six months, presenting an appearance analogous to catarrhal inflammation elsewhere; but inflammatory nuclei, in numbers comparable to what obtains in experimental lesions, are not present in my experience at any date after injury. In the neighbourhood of the lesion, however, the axis cylinders are remarkably enlarged in the first eleven days, as will be seen in Case 1 (*vide infra*), which enlargement may perhaps be of an inflammatory nature.

Secondary Degeneration Proper.—We now come to consider the secondary degeneration proper. The methods of examination followed are: Naked eye in the fresh state, or after hardening in bichromate of potash or ammonia. Microscopical: I have used the following methods in preparing material for these lectures: Weigert's hæmatoxylin and the modification by Pal for medullated nerve-fibres. In many cases Weigert's hæmatoxylin has been used for staining *in toto*; this is good for gross results, but at some loss of sharpness. Acid fuchsin, Weigert's method⁴ for medullated nerve-fibres, and also for the early change in the axis cylinders after Homén. Picrocarmine *in toto* for neuroglia and axis cylinders. Alum carmine, Upson's method⁵ for neuroglia and nuclei. Cochineal for nuclei only. Aniline blue-back. The sections were cut after imbedding in celloidin as a rule, but after staining *in toto*, the paraffin method was used.

Earliest Changes.—Although no doubt the fibres begin to degenerate the moment they are separated from their trophic centres, yet the changes are not appreciable till about the third day. (Homén) Schiefferdecker puts it much later, he says no change of any kind is visible till seven days have elapsed. In the fresh state, to the naked eye nothing can be seen very shortly after death, but according to Mr. Horsley,⁶ if the degenerated area be examined five days after section in the living animal under ether, "the dead white of the area as compared with the semi-translucency of the natural parts is very striking." In the course of twenty or thirty minutes after death, this translucency of the natural tissue disappears, and then the difference between the diseased and the healthy parts becomes invisible. This will explain the invisibility of even advanced lesions in the human subject after death. But after hardening by the bichromates the area of degeneration is very early visible—how early I am unable to say—but it is well marked in six days, and is probably visible before any microscopical changes have shown themselves, if not earlier. The area of degeneration appears as a yellow, or lighter brown patch on a brown ground. It indicates, no doubt, some preliminary chemical change. At this time (third day) the changes, according to Homén, are only visible in the tracts above the lesion. Under the microscope the axis cylinders of the affected area appear larger than natural. They also stain very deeply by the acid fuchsin method. In sections stained by other anilines and picrocarmine the fibre appears to be without an axis

cylinder, because the enlarged axis cylinder takes these stains so badly. Owing to this swelling, the whole diameter of the fibre is larger than natural. In five days the same changes have made their appearance below the lesion. In a semisection of the cord in the monkey between the eighth cervical and first dorsal, done for me by Mr. Horsley, the animal was killed on the sixth day. After hardening in ammonium bichromate the degenerated areas above and below in the cord can be seen perfectly by the naked eye. Microscopically in the neighbourhood of the section there was infiltration of leucocytes, showing traumatic inflammation. Close to the wound above the axis cylinders in the cerebellar tract and posterior column were many of them enlarged. They stained deeply with carmine and also by acid fuchsin. This enlargement of the axis cylinder was more apparent near the wound (probably traumatic; see Case 1 below); in the upper cervical region it was made out with difficulty, though the appearances to the naked eye were the same as lower down. Below the wound the appearances were much less marked, though several of the axis cylinders showed signs of enlargement. In the monkey, then, we may say that the changes in the nerve-tubes have begun at the sixth day, but that they are further advanced near the wound than remote from it, but that the naked-eye appearances after hardening exist equally well away from as near the wound.

In seven days the axis cylinder is more swollen, the whole tube is broader. Only a small layer of myeline is left round the swollen axis cylinder, but this myeline does not appear to be altered in character. This peripheral layer of the myeline in a normal cord fibre stains more deeply than the internal layer of the same. It is called by Weigert the "erythrophile substanz," from the strong affinity it shows for the acid fuchsin stain and also for the Weigert hæmatoxylin. It is therefore this erythrophile ring which remains. Homén suggests that this ring is a condensed form of neuroglia—this, to my mind, is more than doubtful. It

Fig. 1.—Fracture dislocation of the fifth cervical vertebra (Case 1). Trans. sect. close to compressed spot. Eleventh day. a: Greatly swollen axis cylinders. b, Axis cylinders less swollen than a. c. Normal axis cylinders. Picro-carmin in toto. Zeiss, obj. D. oc. 2.

is a question what becomes of the central part of the myeline sheath at this stage; if it be fused with the enlarged axis cylinder is has for the time lost its affinity for Weigert hæmatoxylin and osmic acid.

CASE 1. Degeneration in Human Cord at Eleventh Day; Fracture—dislocation of Fifth Cervical Vertebra; Compression of Cord between Sixth and Seventh Cervical Roots.—Patient, aged 58, fell out of a cart on to the back of his head on July 17th, 1887. Admitted to St. Bartholomew's Hospital, four days after, under Mr. Langton, who has very kindly allowed me to examine the cord; was then found to be paralysed in both arms, most in the left. Sensation fairly good. In the trunk, breathing abdominal only, sensation was much impaired, but not absolutely. Reflexes absent. Complete paralysis of bladder and rectum. There was the same loss of sensation in legs, with loss of knee-jerks. Temperature abnormally low all the time, varying only from 95° to 96°. Patient died on July 28th, eleven days after the injury.

The cord is specially interesting on account of the date. At the level of the crush there is no alteration of the shape externally; reduction must have followed rapidly. There was complete absence of inflammation of the meninges. This was at the level of the seventh cervical root. Here, on cutting across, the cord appears to be disorganised, soft, and the distinction between grey and white matter not to be made out. Under the microscope the posterior region seems to have fairly escaped damage, the lateral and anterior region being much more affected, but in all parts there seem to be many normal fibres. There are affected nerve-fibres of two kinds. Large rounded homogeneous masses (Fig. 1), staining deeply with carmine and acid fuchsin. They do not stain with Weigert hæmatoxylin, but round the periphery of the masses in section stained with hæmatoxylin we see a fine dark line, which is the remnant of the myeline. These masses, seen in

⁴ Weigert, *Centralbl. für die Med. Wissensch.*, 1882, p. 753.

⁵ Upson, *Neurol. Centralbl.*, 1888, p. 319.

⁶ Horsley, *Brain*, vol. ix, p. 52.

longitudinal sections, are obviously axis cylinders enormously enlarged. (Fig. 2.)

Fig. 2.—Fracture dislocation of fifth cervical vertebra (Case 1). Long. sect. eighth cervical. Eleventh day. *a.* Greatly swollen axis cylinders, one undergoing vacuolation. *b.* Axis cylinders less swollen than *a.* *c.* Normal axis cylinders. Picro-carmin in toto. Zeiss, obj. D. oc. 2.

These enlarged axis cylinders cannot be found except in the vicinity of the wound; they cease at the level of the fourth cervical above and the third dorsal below. They were found in monkey 9, just mentioned, and I have seen them in many other cases. Homén describes a similar condition near the wound in his experiments. It seems to me that this great enlargement of the axis cylinders must be distinguished from the enlargement of the same in true secondary degeneration at an early date. They differ in their affinity for stains from the true secondary enlargement. The former stain readily with carmine and anilines generally, but less readily with acid fuchsin, while the latter stain only with acid fuchsin. Again, the enlargement in true secondary degeneration is never so great as this near the wound. Lastly, I am not aware that the true secondary enlargement ever takes on the varicose appearance at all resembling Fig. 2. When the enlargement seems to have attained its greatest extent, vacuoles make their appearance. This, again, is peculiar. I think there can be little doubt that this change in the axis cylinders near the wound is traumatic in its nature.

Hayem⁷ describes and figures axis cylinders in a case of acute myelitis—that is, in undoubted inflammation of a very similar appearance to those in Fig. 2. At points above the fourth cervical and below the third dorsal the section is that of a perfectly normal cord, nor can anything be seen by the naked eye after hardening. It is not too much to say that, had the patient lived a week or two longer, there would have been well-marked degeneration of ascending and descending bundles of fibres.

The results of Homén's and Schieffendecker's experiments on animals and those in monkey 9 are misleading when applied to man. It is probable that in man degeneration is a slower process than in animals. When a fibre is cut off from its centre, every point in its length is believed to degenerate equally and at the same time.⁸ This was Bouchard's opinion. Westphal considers that the degeneration as it were creeps along the nerve as an inflammatory process. Singer found, after division of posterior lumbar roots in puppies, that naked-eye changes had appeared on the sixth day, but that microscopically no degeneration could be found above the twelfth dorsal. This accords with the results in monkey 9. It is probable, therefore, that Bouchard's view is correct as far as the early chemical changes are concerned, but that the actual histological changes pass along the nerve-fibre at varying rate.

Degeneration in Second Week.—During the second week there takes place a complete fusion of the remains of the axis cylinder with the myelone. Now we have a complete breaking up of the continuity of the degenerated tubule. In cross-section we fail to make out any differentiations between axis cylinder and medul-

lary sheath. The fused mass has become of a fine granular nature, which takes the ordinary stains, such as carmine, very faintly. In its extent it is larger than natural, and appears as a droplet of granular material in the meshes of the neuroglia. These granular masses stain deeply with Weigert hæmatoxylin, and the degenerated area now appears by this method studded with black masses, which have taken the place of the proper nerve-fibres. At this stage they occupy the exact position of the original fibres, as they do even at later dates (see Figs. 4 and 5), both in transverse and longitudinal sections.

Degeneration in Fourth Week.—As time goes on, during the fourth week no swollen axis cylinders are any longer to be seen anywhere in the section; the whole area is degenerated, and we cannot say that one fibre is in a more or less advanced stage than another. The black granular masses by Weigert hæmatoxylin are still very distinct.

Decomposition compared with Degeneration.—The appearances here described may be simulated by decomposition. In decomposition the myelone and the axis cylinder appear to fuse and form a more or less liquid material. This process takes place in varying periods after death, according to the manner of death and the temperature of the air at the time. The result of this liquefying of the contents of the tubules is the varicosity of the fibres (see Fig. 3), which is very characteristic, and quite distinct from the

Fig. 3.—Longitudinal section from an undegenerated part of the cord in the dorsal region of Case v, to show an early stage of decomposition. Weigert staining in toto. Zeiss, obj. D. oc. 2. *a.* Globules of escaped myelone.

changes after degeneration. These varicose fibres take the Weigert stain well, as one might expect. Later, the myelone escapes and no normal fibre appearances are visible anywhere. This may be mistaken for degeneration; but the granularity of the degenerated fibre is absent. Then, again, the whole cord is affected equally.

Degeneration in Two Months.—In two months the myelone element of the degenerated fibre has begun to be absorbed. The masses above-mentioned now stain very lightly or not at all by Weigert hæmatoxylin. The result is that the whole degenerated area now for the first time becomes visible to the naked eye by this stain. I have sections, however, from a case reported by Dr. Harris,⁹ which I take to show typical degeneration at two months.¹⁰

CASE II.—A young man, aged 18, was admitted into Victoria Park Hospital with aortic disease and a pain in the side, supposed to be pleuritic. After lying in the hospital about two months, one morning, on trying to get out of bed, he discovered that his legs were quite paralysed and devoid of sensation. His urine was retained, and the reflexes were increased. In a few days girdle pains developed at the level of the ninth intercostal space, at the same time loss of all reflexes. Bed-sores rapidly formed, the patient lingered for two months, and then died. On *post-mortem* examination, a tumour of a sarcomatous nature was found growing from the laminae of the sixth, seventh, and eighth dorsal vertebrae. It blended with the dura mater, and pressed the cord to the side. The cord pressed upon was softened and disintegrated beyond recognition, and the softening extended to the whole cord below the lesion. But above the lesion we have very typical instances of ascending degeneration. In the posterior-median column, for instance, we find that the tract all the way up

⁹ Harris, JOURNAL, vol. ii, 1887, p. 1380.

¹⁰ I have already published a note of the cord of this case in *St. Bartholomew's Hospital Reports*, vol. xlii, p. 141, but the appearances are so typical, that I shall refer to it several times in these lectures.

⁷ Hayem, *Arch. de Physiol., Norm. et Path.*, 1874, p. 603.

⁸ Langley, "Critical Digest," *Brain*, 1886, p. 92.

is extremely plain to the naked eye by Weigert's hæmatoxylin method. But, on staining with carmine, we fail to make any gross difference between the degenerated area and the natural. The microscope, however, shows that in the degenerated area lower down there is scarcely a single natural fibre in this tract. The meshes of the neuroglia are filled with a granular mass of the nature already described, and staining more or less with Weigert hæmatoxylin. It is important to notice that even in two months we find but little increase of neuroglia tissue. There is also practically no increase of nuclei. I have said that the typical naked-eye appearances by Weigert hæmatoxylin staining are apparent at two months in the human cord. This, of course, means that there has been sufficient absorption of the altered myeline material to give the degenerated area a lighter colour than the surrounding natural tissue. I am inclined to put this absorption at two months at the earliest; I have a series of sections from a case of fracture dislocation of the sixth cervical vertebra with degeneration of five weeks, and another with degeneration of six weeks' standing. In both the naked-eye changes are distinct after hardening; but, after staining by any method, there is absolutely no distinction visible between degenerated and natural parts, because the degenerated parts are yet so full of altered myeline, which takes the stain well. Of course the microscope at once shows the degeneration. Fig. 4 was

Fig. 4.—Degenerated fibres of post. median column, after crushing of cord at level of seventh cervical pair. Longit. sect. Fifth week. Weigert hæmatoxylin. Zeiss, obj. D. oc. 2.

taken from the first of these two cases. As this date is an interesting one, I may here refer to the appearances in the degenerated areas in the monkey.

Degeneration in Monkey at Nine Weeks.—Mr. Spencer kindly did for me a semisection of the cord at a level between the seventh and eighth cervical roots. The semisection was not complete, that is, the anterior column and the posterior median column were not cut, but the whole of the lateral and most of the postero-external on the left side were divided. The monkey completely recovered from the operation, and was killed by ether nine weeks and four days after it. Very characteristic tract degenerations were found after hardening, to be described in my next lecture. The direct cerebellar tract offers special facilities for examination, because it contains in the cervical region almost only large nerve-fibres. Here we find by ordinary carmine staining the neuroglia meshwork exactly as on the opposite side with no appreciable increase of nuclei. But the greater part of the meshes contain no nerve-fibres at all, and by staining appear to be either empty or to contain a homogenous material which only stains faintly. On using the Weigert hæmatoxylin stain, however, the meshes are seen to be not empty, but each filled by a material which stains distinctly, but not so deeply as the normal fibres. This is the myeline material which is in process of absorption, and no doubt a few days more would have completed the process. (Fig. 5.)

Fig. 5.—Monkey 7. Degeneration of direct cerebellar tract, after semisection between seventh and eighth cervical. Ninth week. Granular remains of nerve fibres staining faintly by all stains. Pal hæmat. Alum carmine. Zeiss, obj. D. oc. 2.

Degeneration at Four Months.—In four months the appearances differ surprisingly little from those of the second month. I re-

ported a case¹¹ in the *St. Bartholomew's Hospital Reports* of fracture-dislocation of the fifth and sixth dorsal vertebrae; the patient died four months after the accident, during which time he had complete paraplegia, with loss of sensation. The cord was found to be quite cut across, with well-marked lesions above and below. At this date there appears to be a decided thickening of the neuroglia, in other words, a tendency to sclerosis. This is well marked in the posterior median column high up in the cervical region, and, therefore, well away from traumatic influence. There is a general look of inflammatory process about it which has, in earlier cases, been absent. The effect of Weigert staining is more marked than in the preceding cases, that is, the mapping out of the degeneration is more distinct, and, under the microscope, the reason of this is obvious; there is much less of the myeline material in the granular masses lying in the neuroglia meshes. They are still there, and they are still granular, and under carmine stain appear exactly similar to the same in the cords above described, but they no longer take the Weigert hæmatoxylin stain. There is still, generally speaking, a marked absence of inflammatory nuclei. Here would be, perhaps, the best place to draw attention to the relative extent and intensity of the degeneration of the various tracts. Homén says that the ascending tracts are the first to degenerate, the descending not showing any signs of degeneration for two days after the former. This precedence of the ascending over the descending tracts may be said roughly to prevail all through. For instance, the posterior median column in any case of transverse section of the cord may be said to show the greatest intensity of degeneration. The crossed pyramidal tract comes next in degree, but after these the direct cerebellar, and then the direct pyramidal. The direct cerebellar is distinctly behind the posterior median, and also behind the crossed pyramidal tract in intensity of degeneration at a given time. Perhaps it would be more correct to say, instead of intensity of degeneration, amount of sclerosis or connective tissue increase. The direct cerebellar may be devoid of normal nerve-fibres equally with the posterior median column, but may present no sign of connective tissue increase, while the latter is thickly sclerosed.

Degeneration at Five Months.—In five months these appearances have altered somewhat. We have now a distinct thickening of the neuroglia. The material filling the neuroglia spaces that used to contain nerve-fibres is no longer granular, but homogeneous. Again, these spaces are distinctly smaller than they were in the last month, probably due to contraction of the tissue. There are nuclei scattered about over the area. We have now the beginning of a true sclerosis, but as yet there is no contraction of the same sufficient to cause any deformity in the shape of the section. In illustration of this stage I shall quote the following case.

Case III.—A woman aged 66, a patient of Dr. Hughlings Jackson at Queen Square Hospital, who has very kindly permitted me to use the case.¹² Her history was briefly this: Four months before admission into the hospital, she was suddenly seized with vomiting, which lasted half an hour, then lost her senses for about an hour, and when she recovered consciousness she was found to be paralysed on the left side; face and speech not affected. When admitted there was very slight affection of the mouth; none of the tongue. Paralysis and rigidity of both arms and legs with increase of reflexes. An extremely interesting point was that there was hemianæsthesia and hemianalgesia of trunk and limbs. *Post mortem* there was found a softening involving the middle and posterior third of the right internal capsule. I shall speak of the anatomical distribution of the lesions in my next lecture; suffice it to say now that the anterior median column or direct pyramidal tract and the crossed pyramidal tract were profoundly degenerated, the latter rather more advanced than the former. In double stained sections by carmine and Weigert hæmatoxylin, we find even so late as this a large number of black masses. The neuroglia connective tissue occupies considerable patches. It is of a granular structure. Here and there can be seen small holes in it filled with homogeneous material which takes the carmine stain fairly well. These are the remains of the original nerve-fibres, and it may be presumed that they are on the way to be closed up by contraction of the connective tissue. It can easily be seen that if only a few nerve-fibres were degenerated, say from a small cortical lesion, they would at this stage be probably quite unrecog-

¹¹ *St. Bartholomew's Hospital Reports*, vol. xxi, p. 137.

¹² This case was one of the subjects of a paper by Dr. Ferrier before the Medical Society (see *Transactions*, November 21st, 1887).

nisable. There is a distinct increase of nuclei, at any rate, in the crossed pyramidal tract. These nuclei are scattered broadcast over the area of degeneration, but they are found in the greatest number about the vessels. There are, of course, many natural fibres scattered over the degenerated area.

Degeneration after Six Months.—I have no instances of degeneration much later than the sixth month. The following case lived six months and twenty days; it was a case of Dr. Buzzard's at Queen Square Hospital, and I am indebted to him for his kindness in allowing me to use it.

CASE IV.—H. C., aged 16, one month before admission stumbled in getting out of bed. Legs weak all that day, most on the right side. Next day was obliged to take to his bed. Was found to have a rounded spinal curvature involving the fourth to tenth dorsal spines. Legs quite paralysed, with loss of tactile sensation, and also of sensation of pain in many parts. Knee-jerk much exaggerated on both sides, with ankle-clonus. Bed-sores developed, and the patient gradually sank.

Post-mortem Examination.—Advanced disease of the seventh and eighth dorsal vertebrae, extending to a less degree to two or three vertebrae above and below. The cord at the angle formed by the destruction of the seventh and eighth vertebrae was much narrowed, but not destroyed. I have had no opportunity of examining the compressed spot, but very decided ascending lesions were visible in the parts that I was able to examine. The cord is remarkably free from signs of decomposition, though it is not well hardened. The posterior median column is in a more advanced state of sclerosis than the direct cerebellar tract, though the latter is much more sclerosed than in the last case. The posterior median column consists principally of a dense connective tissue; few, if any, of the holes described in the last case as containing homogeneous lighter staining material; that is to say, the last trace of the old nerve-tubes has disappeared, and we now have little else but the connective tissue. Moreover, in longitu-

Fig. 6.—Compression from caries at about eighth dorsal vertebra. Trans. sect. Cervical III. Degen. at six months and twenty days. *a.* Coarsely granular neuroglia tissue without nuclei. *b.* Loculi filled with homogeneous material not staining by Weigert hæmatoxylin. Weigert hæmatox. and alum carmine staining. Zeiss, obj. D. oc. 2.

dinal section there is to be seen an occasional mass of myeline material faintly stained with Weigert hæmatoxylin, showing how long this material seems to be able to resist the process of absorption. At this date, again, one cannot say that there is any sign of contraction of the sclerotic tissue. At any rate, the cord retains its natural shape on section, while any considerable contraction would be certain to cause distortion of the shape of the cross section.

Date at which Degeneration is Complete.—The exact date at which the fibres of a bundle have disappeared is at present not determined. Loewenthal¹³ finds that the number of altered fibres increases with the date, that is, that there are fewer altered fibres at the third week than at the sixth, and that at three months all the fibres of a tract, say the pyramidal, are degenerated after transverse section of the cord. It is quite possible that different fibres of a tract degenerate at different dates, and therefore, of course, disappear at corresponding dates. I have very little material to reason from. In a semisection between fourth and fifth cervical, done for me by Mr. Horsley (monkey 5), the animal died on the thirteenth day, and at that date practically all the fibres of the crossed pyramidal tract below the lesion were degenerated.

In the later stages of degeneration we find that the definition of the diseased area becomes less and less distinct after hardening by the bichromates. Under the microscope the degeneration now appears as a simple area of connective tissue devoid of nerve-fibres or their remains. This area contracts, and may eventually occupy a much smaller space in the section than it originally

did. In other words, we have a scar and little more to mark the site of the lesion.

Degeneration after Section of Posterior Roots.—I designedly describe this form under a separate head because, in the first place, it differs somewhat in its histological appearance, and, again, because in cutting a posterior root we are cutting a nerve before it enters the cord, and therefore it is possible that its fibres in the cord may differ from those which run from point to point in the cord.

I propose to describe the gross results of the experiments in my next lecture, but I may say here that the experiments were performed on three monkeys by Mr. Horsley, whom I cannot sufficiently thank for his generous and eminently skilful help. The monkeys are known as 2, 3, 4.¹⁴ In each the surgical *modus operandi* was the same: strict antiseptic precautions, the use of pressure to stop bleeding, the removal of one or more laminae of the vertebrae, slitting up of the dura mater, section of the posterior roots close to the cord, turning back of their peripheral ends into the wound so as to preclude any possibility of junction. After this, irrigation of the parts with carbolic acid solution, stitching up of the skin wound with horsehair sutures, careful drying of the surface, and the application of a pad of antiseptic gauze soaked in collodion. The wounds always healed by first intention. In monkey 2 all the posterior roots of the right side of the cauda equina were divided. In monkey 3 the posterior roots of the sixth, seventh, and eighth cervical and first dorsal on the left side were divided; and in monkey 4 the posterior roots of the last dorsal and upper third lumbar. In each case there followed complete anaesthesia and analgesia of the parts supplied by these roots, and also probably loss of muscular sense—a point difficult to determine in animals. Monkey 2 lived thirty-eight days, monkey 3 lived twenty-eight days, monkey 4 lived fifty-two days after operation. The histological appearances in these cords were the same practically in each case. In monkey 2, unfortunately, twelve hours elapsed between the time of death and the *post-mortem* examination; but in the other two cases the animal was killed by ether, and the cord and brain removed immediately after death.

In all these experiments we have to consider degenerated nerve-fibres, 1, in the divided root; 2, in the white matter of the cord; 3, in the grey matter of the cord.

In the first situation of the degenerated fibres there is little to say. Both in transverse and longitudinal section of the root there is the picture of Wallerian degeneration near the point of section, however there is an enormous increase of nuclei. The ganglionic end of the divided root degenerates for a short distance, but this is probably traumatic. In the cord at the level of the division we find the fibres radiating through the postero-external columns showing marked signs of degeneration—that is, many interruptions in their continuity and varicosities in their calibre. On comparing the two sides at this level, we find a great diminution in their numbers on the side of the lesion, showing that many of the degenerated fibres have become absorbed. In the grey matter, which is the destination of a large number of these fibres, we notice the same degeneration, and can trace the affected fibres towards the posterior vesicular column of Clarke, or, still farther, towards the anterior horn. To return to the white matter, we find that at first the bulk of the degeneration is in the postero-lateral column, but very soon this column becomes free from altered fibres, which now are collected in the posterior median column. As to the degeneration itself, it shows one marked peculiarity from its earliest beginning to its highest distribution, and that is the large number of nuclei it presents. The monkey's cord has scattered over the section normally a considerable number of small round nuclei. These occur especially in the lines of the connective tissue trabeculae dipping in from the thin sheath which surrounds the cord. They are distinct from the branched neuroglia cells, but are probably of connective-tissue origin. This increase of nuclei appears to be peculiar to lesions following division of posterior roots. It does not occur to anything like the same extent in the transverse lesions of the cord in monkeys; and in man, as I have before remarked, it is conspicuous by its absence.

"Tertiary Degeneration."—I cannot omit to mention here the observation by Messrs. Langley and Sherrington¹⁵ concerning

¹⁴ As control experiments Mr. Horsley has since done two more similar operations, which, however, I have not had time to examine microscopically. I shall refer to them in my last lecture.

¹⁵ Langley and Sherrington, *Journal of Physiology*, vol. v, p. 42.

¹³ *D'générations Secondaires*, Dissertation, 1885.

what they call "tertiary degeneration." In Professor Goltz's dog, whose cord they carefully examined, several operations had been at different times performed on the cortex of the brain, the last being two months and a half before death. The secondary changes in the cord were all of comparatively advanced date then, but in the anterior and antero-lateral column they found a quite recent degeneration with swollen axis cylinders. They suggest that this may be consequent on degeneration of lower centres secondary to those in the cortex. I am not aware that any similar observation has been published.

Secondary Spinal and "Wallerian" Degeneration Contrasted.—Enough has been said now, I think, to show that it is scarcely correct to speak of degeneration in the cord as the same thing as Wallerian degeneration of nerves. Without doing more than mention the fact that the changes commence in the axis cylinders always, a condition of things which may, and probably does, obtain in the degeneration of nerves, the essential points of difference seem to come out in the later stages of the change. In the cord we apparently have no nerve nuclei comparable to those in peripheral nerve-fibres. When a cord-fibre is cut off from its trophic centre it dies, or undergoes a change analogous to necrosis, and yet it is not a true necrosis. If it were, the appearances of decomposing and degenerative nerve-fibres would surely be identical. This is not the case, as I have been at some pains to show. Neither has it the least semblance to an inflammation. Inflammatory nuclei are conspicuous by their absence. Moreover, the appearances in the immediate vicinity of the initial lesion, where, if anywhere, inflammation may be supposed to exist, are, as I have shown, very different from the appearances in true secondary degeneration. The nerve-fibres are rendered useless, and from that moment a change occurs, which does not cease till their last vestige has been removed by absorption; when that has happened, their place is taken by the thickened neuroglia. This thickening of the neuroglia is, however, of a languid nature, not inflammatory. Now, in the Wallerian degeneration of nerves, on the other hand, the changes are of a much more active nature. The breaking up of the axis cylinder and myeline are necrotic no doubt, but, at the same time, the nerve nuclei within the primitive sheath wake up, as it were, and show by their active enlargement and proliferation that the nerve is not dead. It is true that the old nerve-fibre dies and is absorbed; but, after a time, new fibres make their appearance; in other words, regeneration follows close on death.

Regeneration of Cord-Fibres.—This brings me to a point of cardinal importance. Is there in the cord any tendency to regeneration at all comparable to that in nerves?

There has been considerable controversy round this subject, and I propose to give a short summary of the most important observations.

In 1849, Brown-Séquard¹⁶ made experiments on guinea-pigs, rabbits, and pigeons, of transverse sections of the spinal cord. In some cases slight movement returned in the paralysed limbs, but they read more like reflex than voluntary movements.

In 1850¹⁷ he made a complete section of the cord in the pigeon; three months after, the ends were quite reunited; very slight return of voluntary movement, and none of sensation, resulted. In some of his cases he says he found nerve-fibres in the scar-tissue.

In 1851¹⁸ he was apparently more successful. After complete section high up in the pigeon there followed, of course, complete paralysis and anaesthesia. At the end of three months attempts at voluntary movements were seen as well as reflex. In six months the bird could stand, but not walk. In seventeen months it could walk with the help of its wings, and in eighteen months could walk fairly well. His results with guinea-pigs were very inconclusive.

In 1864, Müller,¹⁹ in studying the regeneration of the vertebral column in lizards and triton, says also that the cord was regenerated at the same time. There was also slight return of movement. These are the only experiments recorded on reptiles, so far as I know.

In 1869, Masius and Van Lair²⁰ excised pieces 1 to 2 millimètres long from the cord of the frog. There was complete loss of sensation and motion. Both returned after a time, they do not say how long; movement first, sensation later. In the scar-tissue between the two ends they claim to have found ganglion-cells and nerve-fibres.

It is not necessary to do more than refer to Dentan's dissertation, and to say that what he mistook for return of voluntary movement was obviously reflex (*cf.* Schiefferdecker's trenchant criticism).²¹

Eichorst,²² in 1874, records some careful experiments on dogs and rabbits, very young—three or four days old. The advantages of using young animals are: the rapid tendency to regeneration of all tissues; cartilaginous vertebræ; less tendency to bladder and rectal trouble than in adults; and nourishment by the mother.

The lesion was either section or crushing; fifty-five operations were performed, thirteen of which were casualties. The usual traumatic degenerations followed. In two weeks regeneration had commenced, and in four weeks new nerve-elements had appeared. These new nerves had, however, nuclei in them or on them, which are not seen in normal cord-fibres. It is suggested that these nuclei are the means by which regeneration takes place. Eichorst found no regeneration of ganglion cells. He found in no case degeneration of the cord away from the lesion. Regeneration took place only in the scar-tissue.

Conclusions as to Regeneration.—Our conclusions from these researches, then, as to regeneration in the cord are that the tendency to regeneration appears to be stronger as we descend the animal scale. It is claimed to have been established in birds and amphibia; it is very doubtful in reptilia, and equally so in adult mammals. But it must be remembered that the cord itself possesses more of automatism in lower animals than in higher. As a centre for reflex actions, also, its activity becomes more and more marked as we descend, till in the frog we find it at its highest development, perhaps. Everybody knows how difficult it is to distinguish purposive from reflex acts in that animal. It is also an extremely difficult thing to determine in any animal whether or not sensation is altered or even absent. I am inclined to doubt every one of the results that I have yet read of as pointing to a real regeneration of degenerated nerve-fibres. The clinical evidence is questionable, and the histological still more so.

My own observations lead me to the same conclusion. I have never seen anything, after the most careful research, which can be construed into even an attempt at regeneration of cord-fibres. It is true that I have not had for examination cords with lesions of later than seven months' standing, but the absorption of degenerated fibres is complete at that date, or nearly so, and their place is taken by dense neuroglia tissue.

It is, however, extremely encouraging to read the excellent results obtained in the case reported by Dr. Gowers and Mr. Horsley in the *Medico-Chirurgical Transactions*.²³ Here a tumour had, by pressure on the cord, caused not only paralysis of the lower limbs and bladder, but also greatly increased reflexes. The tumour, moreover, indented deeply one side of the cord, and it is almost impossible to suppose that there was not actual destruction of nerve-fibres at that spot, and yet the removal of the tumour was followed by complete recovery. The results here encourage further operations in cases of compression from whatever cause.

The subject of regeneration is one of immense importance. It involves the question of surgical interference in injuries and tumours of the cord; it enters into the question of prognosis in a large number of nervous affections.

One of the saddest of all the accidents to which the body is liable is fracture-dislocation of the spinal column. The actual lesion of the column is of the smallest account; it is nearly always reduced, that is, the pressure is taken off the cord, but the damage done is practically irreparable. If we could hold out any hope of regeneration, modern surgery would no doubt be able to step in. As I have elsewhere described the spinal lesion,

¹⁶ Brown-Séquard, *Expériences sur les Plaies de la Moelle Epinière*, *Gaz. Méd.*, 1849, p. 232.

¹⁷ Brown-Séquard, *Régénération des Tissus de la Moelle Epinière*, *Gaz. Méd.*, 1850, p. 250.

¹⁸ *Id.*, *Sur plusieurs Cas de Cicatrisation des Plaies faites à la Moelle Epinière avec Retour des Fonctions perdues*, *ibid.*, 1851, p. 477.

¹⁹ Müller, W., *Ueber Regen. d. Wirbelsäule und d. Rückenm. bei Tritonen und Eidechsen*, *Canstatt's Jahrb.*, 1864, I, p. 53.

²⁰ Masius und Van Lair, *Anatomische und Functionelle Wiederherstellung des Rückenm. beim Frosch*, *Centralblatt. f. die. Med. Wissensch.*, 1869, p. 609.

²¹ Schiefferdecker, *op. cit.*

²² Eichorst, *Ueber Nerven-Degeneration und Nerven-Regeneration* *Virchow's Archiv*, 1874, p. 1.

²³ Gowers and Horsley, "Tumour of Spinal Cord: Removal: Recovery," *Medico-Chirurgical Transactions*, vol. lxxi, p. 377.

the cord is cut across without injury to the membranes, in the same manner as the middle coat of an artery is cut by the ligature. The parts are in perfect apposition. Is it the crushed or scar tissue intervening that prevents possibility of regeneration? It is not so in the peripheral nerves; regeneration begins even though the severed ends be never brought into apposition. The surgeon does no more than place the new nerves into continuity with each other, and even then it is inconceivable that no scar tissue intervene. The new nerves have apparently the power to pierce a thin layer of scar tissue.

Could we hold out hope of regeneration of cord-fibres, with what renewed energy should we strive to find out the *fons et origo* of such lesions as obtain in the terrible diseases known as tabes dorsalis, lateral and disseminated sclerosis, to say nothing of the numbers of old hemiplegias that haunt the out-patient rooms of our hospitals!

I propose in my next lecture to trace the course of the degeneration in the cord, both above and below the lesion.

ERASMUS WILSON LECTURES

ON THE PATHOLOGY OF

GLAUCOMA.

Delivered at the Royal College of Surgeons of England, March, 1889.

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LECTURE I.

MR. PRESIDENT AND GENTLEMEN,—The healthy human eye presents to the educated touch of the surgeon a certain elastic resistance; its flexible walls are kept in a state of moderate tension by the fluids which traverse the chambers. Any eye which presents a decided variation from this characteristic condition, whether in the direction of hardness or of softness, is, as we know by experience, an unhealthy eye. I propose to speak in these lectures of the disorders which are associated with an increased tension of the eyeball, disorders to which we apply the name glaucoma.

With the advance of knowledge the word glaucoma has changed its meaning. In the early days of our art, it was applied without discrimination to the various diseases in which a grey or greenish blue appearance replaces the normal blackness of the pupil. In later times, when a clear distinction had been made between the opacities which lie in the crystalline lens and those which lie behind it, the name was reserved for some of the deeper seated and more destructive disorders, the nature of which remained unknown. Hardness of the eyeball, as a part of such disorders, received at that time only casual notice. In the year 1830, Mackenzie pointed out the frequent overfulness of the chambers in glaucoma, and made the first attempt to relieve that condition by puncturing the tunics. Twenty-five years later, von Graefe, studying the subject with the aid of the ophthalmoscope, convinced himself that this overfulness was no mere complication of the disease, but was the essential cause of the leading symptoms, and was led by this conviction to his beneficent discovery of the curative action of iridectomy. Since that time the name glaucoma, losing its original meaning, has been used to indicate a disease characterised by increased tension of the globe. Certain other characteristics (cupping of the disc, contraction of the visual field) are recognised as consequences of the pressure.

Some writers, however, still deny that what we call glaucoma is necessarily connected with increased pressure. They point to certain exceptional cases in which the contracted field and the excavated disc are found in company with normal tension, and on the strength of these exceptions they maintain that glaucoma is the expression of some unknown agent which usually raises the pressure and excavates the disc at the same time, but which occasionally excavates the disc without raising the pressure. This assumption is, I think, unnecessary. The excess of pressure is sometimes slight; it is often intermittent; it may even be absent for long periods of time; it is very probable, therefore, that these cases of glaucoma with normal tension are cases which have been

examined only during the intermissions of increased tension. Permit me to mention a case in illustration.

Sir William Bowman was consulted by a lady in 1865. He noted (and he has kindly placed the notes at my disposal) increased tension and commencing excavation, diagnosed glaucoma, and spoke of iridectomy. No operation was performed. Twenty years later this lady came under my own care with deeply excavated discs, contracted fields, and impaired vision. I saw her many times; sometimes the tension was quite normal, sometimes it was increased. Vision was still useful, but failing rather rapidly. After consultation with Sir William Bowman, iridectomy was performed on both eyes with good result.¹ Now this lady must have had for years an unmistakable glaucoma, but at times, and probably very frequently, a normal tension. Yet pressure was there at the beginning and it was there at the end. One cannot doubt that it was an essential factor in the process.

Glaucoma, then, may be broadly defined as an *excess of pressure within the eye plus the causes and the consequences of that excess*. To understand the morbid process in its entirety, we must study first the normal intra-ocular pressure and the processes by which it is maintained; secondly, the causes which lead to an excess of pressure; and, thirdly, the consequences of such excess.

Estimation of the Intra-ocular Pressure.—It will be well, in the first place, to consider the means by which the intra-ocular pressure has been measured or estimated.

Fig. 1.

Manometer.—In certain of the lower animals the pressure has been accurately determined by means of the manometer, an instrument which brings the intra-ocular fluid into direct communication with a column of mercury or other fluid. The average normal pressure, the variations due to pulse and respiration, and those produced by ligature of arteries and veins, by section and irritation of nerves, and by the action of certain drugs, have all been ascertained. The manometer has also been applied in a few cases to the living human eye, namely, to eyes doomed to excision, the measurement being made immediately before the operation.

Finger Test.—Under ordinary circumstances it is impossible to measure the pressure in the living human eye, and we have to content ourselves with measuring, as an index to it, the resistance of the tunics. We apply the tips of the two forefingers with light alternate pressure to the upper eyelid while the eye is directed downwards, and we record our observations by means of Bowman's symbols (TN, T+1, T+2, etc.). For daily use no better method than the finger-test has been, or is likely to be, found, and it must be employed constantly by everyone who would deal successfully with diseases of the eye, but it is ob-

¹ *Ophth. Rev.*, 1885, p. 261.