

A CONTRIBUTION TO THE PATHOLOGY OF ACUTE INSANITY.¹

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To those who are daily brought in contact with the insane the subject of the acute forms of insanity must always be of interest, not only on account of the varied clinical pictures which cases of acute mental disorder afford, but also on account of the variety of ways in which such cases may terminate.

But the class of case which must be of the greatest interest to the alienist is that which unfortunately tends towards a fatal issue in spite of all that medical science can do; and it is only too often that those who have charge of our asylums have to record such cases as dying from "exhaustion."

Even in such a limited experience as the writer's, cases of this nature have occurred not infrequently, and one must be struck by the fact that to a naked-eye examination of the organs of such cases there is often nothing to account for a fatal termination.

It was therefore with the view of ascertaining the morbid changes found in the central nervous system of these cases that this study was undertaken, in the hope that a knowledge of the pathological anatomy might direct one's steps towards a further and future investigation into the factors which bring about these grave alterations of mental function. It was decided, therefore, to examine microscopically the nerve cells and conducting fibres of the central nervous system of six cases of acute insanity, always taking

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the precaution that these cases were of recent origin, and the writer has endeavoured to employ the most recent methods of research in order to eliminate as far as possible any appearance which might be construed as due to faulty technique.

It often happens that material from a case of interest from the pathologist's standpoint is rendered unsuitable for research on account of *post-mortem* changes.

In the present series one has had the good fortune to avoid this, so that before commencing a description of the morbid appearances found, one can definitely affirm that the changes detailed below are not complicated by the presence of putrefactive changes in the tissues previous to fixation and hardening.

Case 1.—S. D., aged 52, a widow.

HISTORY PREVIOUS TO ADMISSION INTO THE ASYLUM.

She has always been known in the neighbourhood in which she resided to be a hard-working woman of steady habits. A few weeks before the onset of her mental failure she complained of not being able to sleep, and it was noticed that she rambled somewhat in conversation and that she talked to herself a good deal.

Her symptoms progressed, until one week before admission she was so irrational in conduct and so noisy that her removal to the workhouse became necessary. While there it was noted:—She was violent, noisy, incoherent, restless and destructive, running round and round the room and tearing her bedding to pieces. She remained there four days, and was admitted to Prestwich Asylum on February 1, 1901.

STATE ON ADMISSION.

Physical Condition.—She is a tall, dark, thin woman; rather emaciated. Lungs apparently healthy. First sound of heart rather muffled and faint. Her reflexes could not be examined on account of her extreme restlessness and violence.

Mental State.—She is very excited and restless, wandering round her room continually, talking in a rambling and incoherent manner. Her attention cannot be arrested, and she does not answer questions put to her. She is destructive and dirty in habits. During the next few days she remained in much the

same mental state—excited, noisy, refused food, and was out of bed all night. On February 5 she was noticed to be becoming weaker on account of her extreme restlessness, and on February 6 her temperature was found to be 102° in the evening. This was ascertained with great difficulty, owing to her constant struggling.

On February 7 the restlessness and excitement were unabated, and she died suddenly at 10.30 a.m. on February 8. Only on one occasion could the temperature be taken.

AT THE AUTOPSY.

There was very little of a pathological nature visible to the naked eye.

Both lungs were cedematous, and in the right lung at the base there was a considerable degree of congestion. The heart muscle, to naked-eye examination, appeared to be normal. In the kidneys the capsule was found to be slightly adherent.

In the brain nothing was apparent to naked-eye examination beyond a distinctly patchy pink colouring of the grey matter seen on slicing into the brain. The following tissues were preserved for microscopic examination:—Tissue from the fronto-motor region of the left half of the brain; slices from the cervical and lumbar enlargements of the cord for nerve-cell examination, the remainder of the cord being preserved for the examination of the sheaths and axis cylinders; posterior root ganglia from cervical and dorsal regions.

The methods employed for the examination of the nerve-cells and fibres were identically the same in all the six cases to be described, so any details need only be given in the description of Case 1.

Cortex.

Fronto-motor-region.—In order to study the appearances in the nerve-cells, the tissue selected was treated by Heidenhain's corrosive sublimate method, and subsequently stained with toluidin blue and by Robertson's methyl violet method. The tissue to be stained with toluidin blue was embedded and cut in paraffin; for Robertson's method the tissue was embedded in dextrine and cut by Swift's ether-freezing microtome.

The following appearances are noted:—The giant cells and large pyramidal cells show the smallest degree of affection of the chromophile or Nissl bodies. At first sight one might think that many of those cells were normal, but the change, although slight, is revealed by high powers. One can see that the chromophile

elements throughout the cell show a distinct rounding of their outlines, and between the individual elements there is a deep, diffusely-stained substance which tends to obscure and render indistinct the outline of the Nissl bodies. The nucleus also stains diffusely, but the nucleolus stands out very sharply. This is the earliest morbid change noticeable.

While some cells may show this change, others present a distinct chromatolysis around the nucleus, the chromophile substance being here reduced to a fine powdery dust, while towards the external zones of the cell the normal blocks of chromophile substance are abundantly present. In a considerable number of cells the chromatolysis is found more advanced at the base than in the perinuclear region, and one finds it difficult to determine whether the disintegrative process is primarily basal or perinuclear.

But even where the disintegrative process does commence at the base of the cell, a rapid extension to the perinuclear region quickly follows. In the chromatolysed area minute granules of fragmented chromophile substance are found lying amidst a deeply-stained fundamental groundwork.

The protoplasmic processes are as a general rule rather paler than usual, and seem to be more deficient in chromophile substance the farther out one passes from the cell body. The nucleus almost constantly retains its central position, displacement towards the periphery of the cell being very infrequent.

In the medium-sized pyramidal cells one constantly finds chromatolysis, which, however, does not affect all the cells to the same degree.

In a few cells there is a slight fragmentary change which affects all the Nissl bodies generally throughout the cell, small pieces of chromophile substance being detached from the edges of those bodies and lying free in the fundamental amorphous substance. One region of the cell is not affected more than another.

The great majority of cells present a more advanced stage of disintegration, the type of chromatolysis being distinctly of the central or perinuclear variety. Here the space around the nucleus is quite denuded of chromophile material, and round the periphery of the cell only a band of chromophile substance is left, the elements of which are themselves affected by the fragmentary change, their outlines staining somewhat indistinctly and showing great irregularity. A more advanced stage of degeneration is met with, in which there is pallor of the nucleus, and the cell-body with its processes is reduced to a pale, diffusely-staining protoplasmic mass.

In studying the small pyramidal cells one is struck by the fact that their nuclei have a great affinity for the aniline stains, especially for the methyl violet. These nuclei colour very deeply and diffusely, so that the nuclear network is totally obscured, and in many cases the nucleolus is recognised with great difficulty.

The cell protoplasm stains very faintly, especially in the vicinity of the nucleus; and at the periphery of the cell, where the colour is deeper, slight traces of granularity are to be observed, and must be regarded as Nissl bodies in the last stage of dissolution.

Spinal Cord.

Cervical Enlargement.—Two thin slices were taken from this region and placed in a mixture containing equal parts of saturated corrosive sublimate and saturated solution of picric acid for twenty-four hours.

The pieces of tissue selected were hardened in spirit and embedded by the combined paraffin and celloidin method. The sections were stained with toluidin blue.

Among the large cells of the anterior horns a few show a slight degree of morbid change. The chromophile substance seems to be rather smaller in quantity than normal, and there is an increase in the interval between the individual elements. In addition, the shape of the elements is slightly changed, their edges being smoother and rounder, as if some of the chromophile material had been lost. It is evident that those cells show little departure from the normal appearance.

There are numerous cells in which a perinuclear chromatolysis is evident. This, as a rule, is limited strictly to the region immediately surrounding the nucleus, and here the chromophile material is greatly fragmented, appearing as a fine dust.

At the periphery of the cell and in the protoplasmic processes, the chromophile substance is normal in shape and quantity, while the nucleus retains its central position and stains well. Very occasionally in the large cells one finds a dissolution of the entire chromophile substance; very fine granules are alone left, and the cell body stains in an intensely blue manner throughout. Here the nucleus assumes an excentric position.

In the smallest cells of both anterior and posterior horns the chromatolysis is much more advanced; some show little or no chromophile substance, and they stain diffusely and weakly with the aniline dye. Here and there cells showing an increase of pigment in the cell-body are found.

Lumbar Enlargement.—The pieces of tissue taken from this



PHOTOGRAPH 1.

Note the slight degree of chromatolysis affecting one side of the larger cell.
Spinal cord.



PHOTOGRAPH 2.

Note how the process of chromatolysis has affected one side of the cell, and is spreading round the nucleus.
Spinal cord.



PHOTOGRAPH 3.

Three cells showing central chromatolysis, with excentric nucleus.
Spinal cord.



PHOTOGRAPH 4.

Note the peripheral situation of the nucleus. The chromophile elements are much fragmented and stain faintly.
Spinal cord.

region of the cord were fixed, embedded, and stained precisely in the same manner as those taken from the cervical region. The types of morbid change found in the nerve-cells are the same as those already described above, but in this situation some cells show a more profound degree of chromatolysis. The area around the nucleus, in which the chromophile elements are fragmented, is much larger than in any of the cells of the cervical enlargement, and the nucleus tends to assume an excentric or peripheral position (Photograph 3). Again, one notices, rarely, cells of a pale diffusely blue appearance in which there is complete dissolution of the chromophile elements and pallor of the nucleus, which is excentric. Sometimes in those cells the central portion of the cell-body stains more deeply than the peripheric portions.

Posterior Spinal Root Ganglia.

The fixation, hardening and embedding of these structures have been the same as in the case of the spinal cord, and the combined celloidin and paraffin embedding method has been of special value for the study of the delicate cells in those ganglia.

The cells of the posterior root ganglia are affected to a very considerable extent by chromolytic change; the form the degeneration assumes, however, is very different in appearance from that observed in the cervical and lumbar enlargements of the cord. The reason for this is evident when one considers that the cells here do not possess normally uniform characteristics, some of them having very delicate granuliform chromophile elements, while others have their chromophile material in the form of large definitely-shaped blocks as in the cells of the anterior cornua of the cord and in the cerebral cortex. The different types of cell normally met with in the posterior root ganglia have been fully described by Lugaro (16), and in a paper by the author written in collaboration with Dr. Rows (26), but it will be sufficient here to direct attention to two of the chief cell types, the recognition of which will help the reader to understand the morbid appearances to be described.

The first form of cell which interests us, on account of the frequency with which one finds it affected in the acute insanities, is the large type in which the chromophile elements are small and granuliform, both around the nucleus and in the central parts of the cell generally. Towards the edge the chromophile granules may either be found of a slightly larger size, or there may be a distinct single row of large, slender, elongated chromophile elements extending completely round the periphery of the cell.

Elsewhere the chromophile granules are exceedingly small and densely crowded together. One other point worthy of notice is that the nucleus is central, and around it there is a clear narrow ring, quite free from chromophile material, called the perinuclear space.

The second type of cell is that of medium size, in which the chromophile granules are much fewer in number but of larger size than in the above type. Here again the nucleus is central.

The degree of chromatolysis varies considerably in both the first and second cell types. In the cells containing small granuliform chromophile elements one finds these elements breaking up in the centre of the cell into still smaller fragments, losing their affinity for the stain and disappearing, until a condition of complete achromatosis results. The nucleus usually retains its central position, but may be excentric in some cases.

When a cell has become so degenerated as to lose its entire chromophile substance, it stains in a faint diffusely blue manner, but still retains its normal outline. But in many a further degenerative stage is shown by an increasing pallor and atrophy of the nucleus, which becomes reduced to a pale, diffuse, and shadowy structure in which no details are discernible. At this stage the cell—which may be safely assumed to be dead—is seen very often to be invaded by large oval or round nuclei.

In some of the large cells the amount of morbid change found in the chromophile elements is not great, being confined to a slight loss of their affinity for the stain and a slight reduction in their numbers. But here one frequently finds a definite degeneration of the nucleus, which stains deeply and diffusely blue in such a manner as to obscure the nuclear network entirely and the nucleolus partially. At the same time an atrophic process accompanies the alteration in staining reaction, so that a nucleus may be reduced by one-third of its original size, giving rise to a great increase of width of the perinuclear space. It would seem in those cases as if the nucleus had been less able to resist the tendency to degeneration than the chromophile elements in the cell-body.

In the cells possessing large chromophile elements normally, the chromatolysis can be shown to be a central one. The elements break down, in the central parts of the cell, into fine, minute, dust-like granules. The nucleus passes rapidly to the periphery of the cell, where the least degenerated elements persist, forming a ring round the cell margin, being especially dense in the neighbourhood of the nucleus itself.

In addition to the process of chromatolysis described above, vacuolar change may be present in the cells of the spinal root ganglia. In the large cells with minute chromophile granules a clear space may be present, occupying at times one-third of the entire cell-body, in which there may or may not be seen any detail of cell structure. When any structure is apparent in those spaces it is usually of a fibrillar nature. These vacuoles—if one is justified in calling them so—are entirely surrounded by chromophile elements, and more than one may be present in a cell whose chromophile elements show little or nothing of disintegrative change.

An opinion as to whether such a form of vacuolation can be taken as evidence of morbid change must be given with great reserve on account of the fact that it has been my experience to find exactly similar appearances in the posterior root ganglion cells of presumably normal dogs, rabbits, cats, and hedgehogs.

Vacuolation of quite a different type is met with in those cells already referred to as being in a condition of achromatosis with degenerated nucleus, and which one regards as dead. In the faintly blue stained protoplasm which is left, round or oval vacuoles are present, varying in number from one to five or six.

Medullated Fibres of the Spinal Cord.

In transverse sections of the spinal cord, stained by the *Wolters-Kulschitzky* modification of Weigert's method, the colouring of the crossed pyramidal and postero-internal columns appears lighter if the specimen is examined with the naked eye. Under the microscope many of the nerve-tubes stain feebly, and are thinner than normal.

To study the degenerations of the myelin sheath I have used a modification of Marchi's method published by me some time ago (25).

The mixture into which the tissues are placed differs from that of the original Marchi method practically only in the addition of one part of acetic acid, 1 per cent., to 4 parts of osmic acid, which is used in 2 per cent. solution.

Formerly bichromate of potash was omitted, but now I always add this to the osmic and acetic acids.

Pieces of tissue thus treated for ten days should be washed overnight in running water.

The addition of acetic acid favours penetration very considerably, and for two years my results have been invariably constant, and up to the present time the sections are permanent.

In transverse sections of the cord so treated one sees a small number of black dots—indicating degenerated fibres—scattered about all over the cord. These degenerated fibres are found in all the tracts, but in some tracts they are more numerous than in others. In the anterior and antero-lateral columns only a few are seen. In the crossed pyramidal and posterior columns they are more numerous. The degeneration in the crossed pyramidal tracts is equal on both sides; in the posterior columns slightly more degeneration is present in the postero-internal.

A considerable number of black degenerated myelin droplets are met occasionally in Lissauer's tract and in the posterior horns. In the above-noted columns the degeneration has not the character of that found in descending or ascending system lesions, for the affected fibres are separated from each other by considerable numbers of fibres which yield no reaction, so that the degeneration assumes a diffuse, scattered character.

In longitudinal sections the degree and nature of the myelin sheath and axis cylinder changes can be much better studied. By the Marchi method, looked at with a low power, one recognises the typical rows of black droplets indicating myelin degeneration. These rows do not exceed more than three or four in one field. Sometimes the rows are of considerable length; others, again, are much smaller. There are many black droplets scattered throughout the section.

A combination of the *Marchi method* and *safranin staining* has been found exceedingly useful. Sections from tissue prepared by Marchi's method are transferred without any further treatment into a dark red watery solution of safranin No. 0, and stained overnight. They are then washed in methylated spirit until the stain ceases to come out, transferred to absolute alcohol, cleared in xylol, and mounted in Canada balsam.

Adamkiewicz recommends washing in alcohol acidulated with nitric acid, and then differentiation in clove oil. This has been discarded, as the bleaching action is at times too great.

By this combination the finer myelin changes are brought out, and the contrast between the Marchi degeneration and the myelin atrophy and absorption, to be described, is very well demonstrated.

There are a few myelin sheaths in which there are no changes visible.

In those which are morbid, some parts of the myelin tube stain well with the safranin, assuming a rich pink colour, and inside the axis cylinder is visible. On both proximal and distal

sides of this well-coloured segment of sheath one finds other portions in which the staining reaction is much less, and instead of being pink is a light violet tint. Here there is dilatation and thinning, and at irregular intervals there are small clear vacuoles. In those thinned segments, which indicate an atrophic process, the axis cylinder also stains a light violet colour.

In the medullated fibres there are occasionally seen definite constrictions exactly like nodes of Ranvier, and on either one or other side of the constriction the myelin sheath may show the atrophic process very distinctly.

Many of the sheaths possess a beaded appearance, small collections of pink-stained myelin lying around the axis cylinder at intervals, while between the beads the myelin forms a very thin coating. The axis cylinder runs usually along one side of these dilatations, rarely through their centre, and in this situation may be very varicose.

At some points in the course of the nerve the myelin becomes broken up into lightly violet staining droplets or masses, and amongst these the axis cylinder lies faintly stained, and in many instances thinner than normal. The atrophy of the sheath may be complete at certain parts, leaving the axis cylinder completely denuded.

Very occasionally one sees rupture of this latter structure, the severed ends terminating in a swollen, curled-up bulb.

In this case, and also in the others, longitudinal sections were stained by Wolter's method, but the results were such as to lead one to discontinue its use, and rely solely upon the combined Marchi and safranin method.

Case 2.—A. C., aged 48, married.

HISTORY PREVIOUS TO ADMISSION INTO THE ASYLUM.

Twenty-one days before her admission to the asylum the patient was confined, giving birth to a living full-time child. Parturition was not accompanied by any accident or complication, and all went well until one week after the event, when one of her children died suddenly. The shock of this child's death seems to have affected the patient's mind, for according to her friends' account she immediately began to exhibit mental symptoms.

She imagined that the boy visited her in dreams at night, and conversed with her. She then failed to rally from the physical weakness in which the parturition had left her, and became very low-spirited.

This depression rapidly increased; she became restless, wandered about the house at night, could not be kept in bed, was rambling in her talk and noisy, finally could not be managed at home, so was sent to the workhouse. While there it is noted:—She is violent and restless; throws herself about, making grotesque grimaces, and staring wildly. After remaining there for four days she was admitted to Prestwich Asylum, on February 9, 1901.

STATE ON ADMISSION.

Physical Condition.—She is a small, thin, dark Jewess, very emaciated. Lungs apparently healthy. First sound of heart very faintly heard.

Her reflexes could not be examined, owing to her restlessness and resistiveness.

Mental State.—She is semi-stuporose, pays no attention to those around her, nor to questions put to her. Wanders aimlessly about her room, moaning, and shrinks when touched or spoken to, as if in fear of some impending evil.

February 10. Her mental state is exactly as above. She has not slept; has been crawling round her room moaning. Heart sounds are very feeble. Dirty in her habits.

February 12, 10 a.m. This morning she is much worse, restlessness continues, and she is very resistive; cannot stand without support. At 12.50 p.m. she suddenly collapsed, fell back and died of syncope.

AT THE AUTOPSY.

The thoracic and abdominal organs were found free from any morbid change visible to naked-eye examination, with the exception of a slight congestion of the liver. The normal process of involution seemed to have taken place without interruption in the uterus. On turning to the brain, a slight milkiness of the pia arachnoid was noted, most marked in the sulci. The surface of the hemispheres presented no abnormality, and on cutting into the brain the gray matter was found to be slightly darker in colour than normal.

On the posterior surface of the cord there was a thin, very recent hæmorrhagic effusion underneath the pia arachnoid, and extending from the lower part of the cervical enlargement downwards as far as the upper part of the lumbar region. This effusion was very slight in degree, thin, and varied from a thread to a quarter of an inch in breadth. At no place did the hæmorrhage seem sufficient to exert pressure upon the cord.



PHOTOGRAPH 5.

Of the two cells in the centre of the field, the one on the left-hand side of the photo shows advanced chromatolysis. The nucleus is very pale, and a faint fringe of chromophile substance remains around the periphery of the cell.

Spinal cord.



PHOTOGRAPH 6.

Note the vacuolation of the cell body and peripheral situation of the nucleus.
Spinal cord.



PHOTOGRAPH 7.

Note the vacuolation at the right hand side of the cell. The central chromophile bodies are broken up and the nucleus is peripheral. Observe the semi-lunar chromophile band attached to the nuclear envelope.

Spinal cord.



PHOTOGRAPH 8.

Observe the diffuse staining of the cells, indicating acute chromophile dissolution. The nucleus is markedly peripheral in position.

Spinal cord. Lumbar region.

As in Case 1, tissues from the brain, cord, and posterior root ganglia were preserved for microscopical study.

The same methods of fixation, hardening, embedding, cutting, and staining were employed as before.

Cortex.

Fronto-motor region.—Some of the large pyramidal cells do not show any definitely localised chromatolysis, but instead, a slight general fragmentary change at the edge of the individual Nissl bodies, the small detached pieces of chromophile material lying free in the fundamental amorphous substance. The great majority of the large and medium pyramidal cells, however, are readily seen to be affected by a central chromatolysis associated with pallor of the nucleus. The area around the nucleus denuded of chromophile substance is fairly extensive, and it is common to find that the peripheral chromophile elements are breaking down as well as the central ones, though to a much less degree. The nucleus maintains its central position in most instances, but when the chromolytic change has implicated the periphery of the cell to as great an extent as the central parts, the nucleus becomes excentric, and may even pass out to the edge. When this stage of degeneration is reached, the entire cell-body tends to stain somewhat diffusely, and is occupied by very minute granules of disintegrated chromophile substance. In the small pyramidal cells there is as great a degree of chromatolysis as in Case 1, but the nucleus does not show the same strong affinity for aniline dyes.

Cervical Enlargement.

Fixation in saturated sublimate and picric acid, embedded in celloidin and paraffin; stained with toluidin blue. The changes in this case are practically identical with those observed in Case 1.

There are many cells which deviate little from the normal appearance, the chromatolysis being very small in amount (Photograph 1).

In some of the large cells of the anterior cornua a well-marked perinuclear chromatolysis can be observed, and a few show a further stage of degeneration, where the entire chromophile substance is reduced to powder and stains faintly.

When this degree of chromatolysis is present the nucleus becomes peripheral in position (Photograph 4).

No cells showing the intense diffuse staining of the cell-body

mentioned in Case 1 have been met with in this case, and there is less pigmentary change present.

Posterior Root Ganglia.

Fixation in saturated sublimate and picric acid ; embedded in celloidin and paraffin ; stained with toluidin blue.

The pathological changes in the nerve-cells are found to be precisely the same as in Case 1.

In some of the cells, which belong to the large type, very little change can be detected in either the small granuliform chromophile elements or in the peripheral ring of large elements. As noted in the preceding case, however, the nucleus of some cells which present little appreciable change seems to have a strong affinity for the stain, and colours very deeply and diffusely blue ; occasionally it may undergo an atrophic transformation and be reduced to almost half its original dimensions, with the result that the perinuclear space becomes much wider than normal.

The earliest stage of degeneration in the above type of cell consists in the granuliform elements losing their affinity for the stain, and in an actual reduction in bulk of this granuliform mass.

As the chromolytic process extends this central granuliform mass gradually disappears, until the centre of the cell is left quite white, surrounded by the peripheral ring of chromophile elements, which now shows evident signs of breaking up. The nucleus is pale, and although sometimes excentric, remains in the majority of instances central in position (Photograph 10).

Occasionally one sees cells in which there has been apparently a more rapid chromatolysis. The whole cell-body is completely denuded of chromophile material, stains very pale blue, and the nucleus, to which is attached a small irregular chromophile mass, is markedly excentric (Photograph 9).

The large clear vacuoles surrounded by chromophile substance are seen in this case as in the preceding one ; and in the dead cells, which are invaded by the previously mentioned oval and round nuclei, one finds the vacuoles peculiar to this stage of degeneration present sometimes in large numbers.

Medullated Fibres of Spinal Cord.

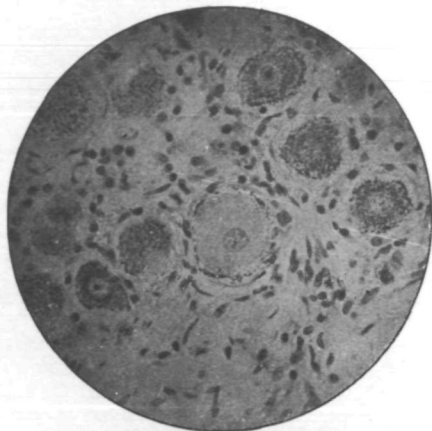
By *Wolter's method*, the crossed pyramidal tracts and the central part of the posterior columns are seen to stain a little more faintly than the other regions of the cord, on naked-eye examination of the sections. Microscopically many of the nerve-tubes in these more faintly stained parts have lost their affinity for the stain, and their walls are thinned.



PHOTOGRAPH 9.

Note cell in centre of field. There is here complete chromatolysis, with excentricity of the nucleus, surrounding which is a small amorphous chromophile mass.

Posterior spinal root ganglion.



PHOTOGRAPH 10.

Note cell in centre of the field. There is here almost complete chromatolysis, a few chromophile elements being left around the cell periphery. The nucleus is central and pale.

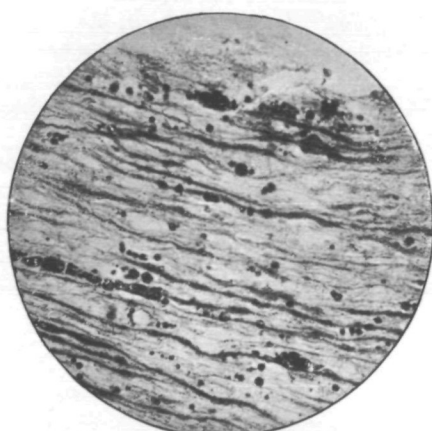
Posterior spinal root ganglion.



PHOTOGRAPH 11.

Observe the black droplets, indicating Marchi degeneration.

From longitudinal section of spinal cord.



PHOTOGRAPH 12.

Photograph from section stained by the combined Marchi and safranin method. Observe at the left and lower edge of photograph a row of Marchi droplets; elsewhere one can see myelin tubes and axis cylinders stained by the safranin.

Longitudinal section of spinal cord

By the *Marchi method*, black droplets are found scattered over the entire cord, but, as in Case 1, the number of degenerated fibres is greater in the crossed pyramidal and posterior columns. In the grey matter there are a few black droplets scattered about, and, rarely, one sees a fibre passing from the anterior cornua to the anterior roots which yields the typical Marchi reaction.

Longitudinal sections treated by the Marchi method show here and there the row of black droplets indicating myelin degeneration. These rows are a little less frequently met with in this case than in Case 1.

Scattered throughout the field are a considerable number of black droplets, either isolated or arranged in groups of two or three.

With the *combined Marchi and safranin method* much change can be noted in the myelin sheaths.

Along the nerve the staining varies greatly, some portions colouring well, while others stain faintly or not at all.

Even in the segments where the affinity for the stain is good, one can see that the colour is not equal, small patches being more faintly stained and thinner than other adjacent ones. In certain segments the myelin is much atrophied, and only a few small faintly staining violet masses are seen surrounding the axis cylinder, which here is often flattened or ribbon-like, with it may be irregular edges, and stains exceedingly faintly. Often the marked difference in the appearance between one part of the sheath and another is well shown on either side of the nodes of Ranvier, which occasionally one notices in the course of the nerve.

On one side of the node the myelin is apparently healthy, but on the other side the myelin may stain quite faintly for a considerable length of its course, and in it the axis cylinder is flattened, irregular in outline, and of a faintly violet colour.

Sometimes, through a portion of well-stained myelin, one can see differences in thickness of the axis cylinder, and even fusiform swellings on it.

Scattered promiscuously throughout the section a few globules of degenerated pale violet staining myelin are seen.

Case 3.—M. A. H., female, aged 62, single.

HISTORY PREVIOUS TO ADMISSION.

From patient's friends no history is obtainable, unfortunately, so that one's information is necessarily scanty, and is obtained

from those who brought her to Prestwich. It would appear that the patient was one of two old maids who lived together on a very slender income, and so at times suffered considerable privation.

Her illness was of about six weeks' standing when admitted here, and seems to date from the time when she sustained a considerable shock, having been a witness of her brother's death in a carriage accident. Of the onset and early course of the mental symptoms we are unable to give any data, but when admitted to this asylum her condition was one of great depression. Previous to admission she attempted suicide by tying a garter round her neck.

General Condition.—She is rather tall and gaunt. Her face wears a very anxious expression. Hair grey.

Respiratory system apparently healthy. Sounds of heart loud. Radial arteries tortuous and dilated.

Mental Condition.—November 15, 1900.—She talks readily about herself and affairs. Says she was greatly distressed at her brother's death. Admits trying to destroy herself, as she thought she was in great trouble.

On the night of her admission she slept fairly well. She never showed any signs of mental improvement, and one week after admission it was noted that she objected to taking food and was developing hallucinations of hearing, saying that the people around called her names. Soon her condition was such as to necessitate her transfer to the infirmary ward; mentally there was no improvement; she was very miserable, facial expression very dejected; there was a slight tendency to diarrhœa.

December 14.—She is utterly hopeless, gloomy, silent, and miserable; appetite very poor; no diarrhœa. During the next fortnight her general condition became worse. She remained reserved and gloomy; took no notice of what went on around her; took very little food. She continued to go down in health, and was put to bed, when her condition became rapidly worse; she became prostrate, feeble, and almost pulseless; took very little nourishment and had to be hand-fed; remained in a state of great mental depression, and finally died on February 20, 1901.

AT THE AUTOPSY.

The heart muscle was found slightly softer than normal, and there was a moderate degree of atheroma of the ascending aorta. The left lung was apparently healthy, but in the right the base was somewhat congested.

Neither the stomach, intestines, nor liver showed any morbid change recognisable by naked-eye examination. The kidneys were small—left three ounces, right four. The capsules were rather adherent, and tore the renal surface on stripping. The cortices were narrowed, calices dilated, and general renal substance much paler than normal.

In the brain the pia arachnoid was slightly milky over the surface generally, but a little more marked in the sulci. The vessels at the base were slightly atheromatous.

On cutting into the brain the little pinkish patches seen in the other cases scattered along the cortex were present.

Tissues from the fronto-motor cortex, cervical and lumbar enlargements, and the posterior root ganglia were preserved for the microscopic examination of the nerve-cells. The cord was placed in bichromate of potash 2 per cent. for the study of the nerve fibres and sheaths.

Cortex.

Fronto-motor region.—Fixation, hardening, embedding, and staining, as in the two preceding cases.

The changes in the cells of this region are similar to those already described in Cases 1 and 2. There are many large pyramidal cells and giant cells which show a small degree of chromatolysis, consisting merely in slight fragmentation of the edges of the chromophile bodies generally throughout the cell-body, whereby those bodies lose their angular appearance and become more rounded in form. There are many of those large pyramidal cells, however, in which the chromophile elements around the nucleus are broken up, and in many cases the chromophile elements at the base, while at the periphery of the cell they remain as yet unaltered. As the area of chromatolysis increases in diameter, the central portion of the cell is seen to be occupied by a pale blue, almost homogeneous mass, which on high magnification is seen to be composed of very fine granules densely packed together. The peripheral chromophile elements now show distinct fragmentary change, as also do the elements in the protoplasmic processes; the nucleus tends to pass out towards the periphery of the cell.

The medium and small pyramidal cells show the advanced stage of degeneration noted in the two preceding cases. Very deep diffuse staining of the nucleus of the small pyramidal cells is quite exceptional.

Many examples of complete destruction of the nerve-cell are

met with, and small misshapen masses of cytoplasm alone remain, containing little or no chromophile substance. The nucleus is very pale in those.

Cervical Enlargement.

Fixed in saturated sublimate and picric acid; embedded in celloidin and paraffin; stained with toluidin blue.

In this region almost three-fourths of the large multipolar cells show a decided increase of yellow pigment. In some the pigment occupies almost the entire cell-body with the exception of a small band round the edge, where the chromophile elements are fairly well formed and preserved. Of true chromatolysis there are two forms, the most frequent consisting of a slight general fragmentary change involving the edges of the chromophile bodies, so that small particles are detached from them and lie free in the intervening spaces between the individual elements.

The other form of chromatolysis is much less frequent than the above, and is a true central chromatolysis. The perinuclear chromophile elements are reduced to powder, while around the cell periphery and in the protoplasmic processes the chromophile substance is plentiful and well formed; the nucleus remains central.

There are no diffusely-stained homogeneous-looking cells, such as are found in Case 1.

In the small cells, scattered throughout the grey matter of the anterior and posterior horns, the chromophile elements are broken throughout the entire cell body, and stain faintly.

Lumbar Enlargement.

The sections were prepared in exactly the same way as those from the cervical enlargement.

In the large multipolar nerve-cells, the fragmentation above noted is present.

In a few cells, the chromophile elements show the rounding of outline and the small detached portions of chromophile substance lying between the individual elements, as in the cervical enlargement.

The great majority of cells, however, show a fairly advanced central chromatolysis. The perinuclear chromophile elements are broken up into a fine dust, which stains very deeply; the elements at the periphery are well preserved. At this stage the nucleus is central.

As the change advances outwards, involving the peripheral zone of the cell, the central part stains more faintly and in a

somewhat diffuse manner, while the peripheral chromophile substance shows evident signs of disintegration. The nucleus now is excentric, and occasionally one sees a deeply-stained semilunar chromophile band attached to the outer side of the nuclear envelope on that side of the nucleus which looks towards the centre of the cell (see photograph 7). There are no homogeneous-looking cells as in Case 1. The small nerve-cells scattered throughout the grey matter stain more faintly than the larger ones, and while some show a distinct central chromatolysis, others are entirely denuded of chromophile substance.

Posterior Root Ganglia.

The ganglia were fixed, embedded, and stained in exactly the same manner as the slices from the cervical and lumbar enlargements.

A very considerable number of the large cells present an extremely slight degree of morbid change, which consists merely in a slight loss of affinity of the chromophile elements for the toluidin blue, whereby the minute granules in the centre of the cell appear less distinct than normal.

In those large cells, however, various degrees of chromatolysis are met with, from slight central chromatolysis to an advanced stage, where only a ring of chromophile elements is left around the margin of the cell. The nucleus remains for the most part central.

In the medium-sized cells, with large chromophile elements, central chromatolysis, with marked excentricity of the nucleus, is the rule.

As in Case 2, cells are found where there seems to have been a very rapid degenerative process. The cell is almost entirely denuded of chromophile substance, and stains very faintly blue, the nucleus is peripheral in position, and may have attached to the side of its nuclear membrane a mass of amorphous chromophile material, which represents all that is left of the Nissl granules. The outline of those cells is always quite regular (photograph 9).

Dead cells are fairly frequently met with, in which the cytoplasm is broken up and vacuolated, and contains oval or round nuclei which have wandered in from outside.

As in the spinal cord, the amount of pigmentation in the nerve-cells of the posterior root ganglia exceeds the normal physiological limits, and consists of two varieties, viz., a yellow-coloured pigment and a pigment of a greenish hue.

Homogeneous atrophy of the nucleus, a condition which will be described later, is fairly frequently met with in this case, and is found in cells which present a marked affinity for the stain and colour very intensely. The chromophile elements are almost entirely obscured, and seem fused together to form a deep-staining homogeneous mass. The nucleus can be made out small and stained deeply, showing no detail of structure. In the centre lies the nucleolus, which is coloured rather more strongly than the atrophied homogeneous nucleus.

Medullated Fibres of Cord.

By *Wolter's method*, sections on naked-eye examination show a slight pallor of the crossed pyramidal tract on both sides, just as in the two preceding cases.

In the posterior region the staining is fainter in both external and internal columns. In the external column the loss of affinity for the stain affects the anterior two-thirds, and the fibres nearest the posterior horn and those next the internal column stain more strongly than those in the centre. In the internal column the fibres around the postero-median septum stain more lightly than the more externally situated ones, and the pale area is more evident around the anterior half of the septum.

Microscopically the tubules in the paler areas are seen in many instances to be only partially stained, and many are atrophied.

By the *Marchi method*, one finds degeneration in the form of scattered black droplets, which are most numerous in the crossed pyramidal tracts and in the posterior columns, although they occur in considerable numbers in the anterior and antero-lateral columns as well.

There is a slight amount of degeneration in Lissauer's tract, and many small black dots are seen in the grey matter. The amount of degeneration in this case is a little more than in Case 2.

Rows of black degenerated myelin drops are seen in the longitudinal sections prepared by the Marchi method, and occasionally the altered myelin sheath at certain points is fused into a long slender black mass. Many black droplets of varying size are scattered over the field.

By the *combined Marchi and safranin method*, the earlier stages of myelin atrophy such as are described in Cases 1 and 2 are seen here also, but in many fibres there are long tracts of the nerve in which the myelin is unstained, and persists only as

shreds joined to each other or detached, leaving the axis cylinder practically bare. This latter structure stains very faintly, and varies in thickness in its course. At some points there are fusiform swellings, the edges of which stain a little more strongly than the centre, as if the fibre had been split longitudinally into two portions in this situation. Some fibres are less affected, and large parts of myelin stain well, but between two well-stained portions the intervening myelin is thinned, and stains a faint violet colour. In some violet staining parts there are distinct roundish vacuoles, but in other places the myelin may be almost completely atrophied, more along one side of the axis cylinder than on the other, for some distance.

A row consisting of several pale violet staining beads may represent all that remains of the myelin sheath, and the axis cylinder is left naked, pale, and ribbon-like. It is occasionally observed that a small segment of myelin yields the black Marchi reaction, and on either side of it the sheath stains red, and is apparently unchanged.

Case 4.—J. L., aged 34, single, a labourer.

HISTORY PREVIOUS TO ADMISSION INTO THE ASYLUM.

Previous to his admission into the Workhouse nothing is known regarding the patient.

In the workhouse, where he was detained for three days, it was noted :—He is confused, memory very defective, has no idea of time, nor does he know where he is.

STATE ON ADMISSION.—(*December 3, 1900.*)

He is a man of medium height, in fair physical condition. Lungs healthy. Heart regular. Patellar, plantar, and pupillary reflexes quite normal. Tongue tremulous.

Mentally he is very dull, stupid, and confused. Memory poor. Does not know where he came from, nor the day of the week. Has delusions of persecution, and cannot sleep for fear of men attacking him.

December 5.—Very impulsive; constantly jumps out of the chair; tries to run away, saying he is about to be murdered.

Sleeps fairly well; appetite good.

December 12.—Restless and delusional as before. Given chloral, grains 15, and potassium bromide, grains 20, twice daily. Appetite good.

December 19.—No better during daytime, sleeps better at night.

December 26.—Quieter and more tractable.

January 20, 1901.—Again excitable, restless and noisy.

February 20.—Restless and bad-tempered; surly in disposition; generally incoherent.

March 30.—Remains unchanged and continued excitable, restless, noisy and intractable until June 3, when he developed physical symptoms of a grave character, which ultimately led to a fatal issue.

June 3.—He is suffering from diarrhoea. Temperature 105° . Stools liquid and brown-coloured; no slime or blood in the discharge. Given chinisol, 2 grains per diem.

June 5.—Diarrhoea rather better. He has some dyspepsia. Sleeps fairly well. Takes nourishment well.

June 6.—Signs of consolidation at base of left lung, extending up as far as the angle of the scapula. Little cough; no expectoration.

June 8.—Marked pneumonia, with all the symptoms. Much less diarrhoea. Pulse small and rapid. Respiration rapid.

June 9.—He is delirious. Heart is failing. Sleeps little.

June 10.—No abatement in the symptoms. Died at 4.40 p.m. His mental symptoms remained of an acute nature until the end.

AT THE AUTOPSY.

Heart weighs 15 ounces; both right and left sides are dilated, and the muscle softer than normal. One ounce of fluid in the pericardial sac.

Right lung weighs one pound eleven ounces. There is considerable congestion at the base, and œdema generally throughout.

Left lung.—The entire lower lobe and three-fourths of the upper lobe show pneumonic consolidation, which has reached the stage of grey hepatisation.

In the stomach and small intestines no lesions were found, but in the large intestine, at its lower end, just above the sigmoid flexure, there were two small round ulcers, with thickened and rather firm edges.

The liver weighed five pounds, and was greatly enlarged and congested. Spleen $4\frac{1}{2}$ ounces.

The capsules of the kidneys stripped easily, and there was no morbid change visible to the naked eye.

In the examination of the brain there was little to be seen on naked-eye examination. The pia arachnoid was slightly milky,

and on cutting into the brain the grey matter generally was rather pinkish and hyperæmic-looking.

The following tissues were preserved. Slices from the cortex—fronto-motor region—and from the cervical and lumbar enlargements. The entire cord was preserved for the examination of the medullated fibres and axis-cylinders. No posterior root ganglia were preserved from this case.

Fronto-motor Cortex.

Fixation in saturated sublimate; stained by Robertson's methyl violet method and by toluidin blue.

In the large and medium-sized pyramidal cells the type of chromatolysis differs very markedly from that observed in the three preceding cases, where it is perinuclear, or sometimes basal, at first, and seems to extend with comparative slowness outwards towards the periphery.

In this case, the degree of chromatolysis is much greater in the cell itself, and also in the number of cells affected.

All the cells stain in a diffuse manner, as if the chromophile elements had been dissolved, instead of showing the fragmentary appearance which is found in the three preceding cases. The cells stain more deeply than usual, and the colour is uniformly distributed throughout the cell. This uniform colouration might be explained by the fact that the amorphous fundamental substance of the cell-body is probably reinforced by the dissolved chromophile substance. The cell outline remains unchanged, and the protoplasmic processes, which are devoid of formed chromophile substance, stain diffusely blue, and can be followed for a considerable distance.

Although this description holds good for practically all the cells, one does encounter an occasional cell in which a few small granules of chromophile material are present. Those granules when present are always situated at the periphery of the cell, which seems to support the view that the degenerative change probably begins, and is at the first more intense, in the perinuclear and central regions of the cell-body.

The nucleus usually stains a little paler than normal, and retains its central position in the large majority of instances, although at times, where the cell is very degenerated, and has become pale and ghostlike, it is common to find the nucleus quite as pale as the cell-body, and closely applied to its periphery.

If one examines the above-described diffusely-stained cells with high-power apochromatic lenses, a fine network is visible.

This network is composed of faintly-stained meshes of equal size, and extends uniformly throughout the cell body. This has only been observed in sections stained with toluidin blue. In the nucleolus there is a very unusual appearance to be seen. The nucleolus, while retaining its rounded shape, seems to be vacuolated, as many as five or six small transparent vacuoles being observed, separated by well-stained partitions radiating out from the centre.

Many cells are observed so faintly stained as to earn the term "ghost cells." Their outline is very faint and irregular, and the nucleus is barely discernible. In addition to these cells, one can see small masses of pale, thin protoplasm, which are cell residues. The small pyramidal cells are much more faintly stained than the larger ones; their processes are completely destroyed in many instances, and they seem to have succumbed to the degenerative change much more quickly.

Lumbar Region.

Fixation in saturated sublimate and picric acid mixture; embedded in celloidin and paraffin; stained by toluidin blue.

In some of the cells of this region there is a small collection of yellow pigment, which in quantity rarely exceeds physiological limits. A small number of the large cells show very little of a morbid nature, the change being limited to a slight fragmentary change affecting the edge of the chromophile elements throughout the cell-body generally.

The typical change present in the majority of cells consists of a central chromatolysis.

The fragmentary change may occasionally be limited to the immediate neighbourhood of the nucleus, but much more often the entire central portions of the cell are affected, the chromophile material being broken up into a fine dust around a central nucleus.

In the protoplasmic processes, and at the margin of the cell, the Nissl bodies are well preserved. Some cells may show well-marked vacuolation in their interior. In these cells the chromatolysis is more advanced; the peripheral chromophile elements persist, it may be, as a single row, while the centre of the cell is occupied by a very fine chromophile dust. The vacuoles are clear, transparent, and round, with well-defined outline, and may vary in number from three to six in a single cell. The nucleus, though well stained, is always excentric, and on the side turned towards the centre of the cell, the nuclear membrane may be

indented, and in the cavity so formed one finds a small semilunar band of chromophile material (photographs 6 and 7).

Of the small nerve-cells scattered throughout the grey matter of both anterior and posterior horns, some show little change, others well-marked central chromatolysis, and others are completely denuded of chromophile substance, *i.e.*, in a condition of achromatosis.

Medullated Fibres of Spinal Cord.

In transverse sections stained by *Wolter's method*, the areas which take the stain with less intensity are identical with those in the last case. By the *Marchi method*, black droplets are seen scattered throughout the field, but in the crossed pyramidal tracts and in the posterior columns they are more numerous than in other situations.

In the anterior horns, especially in the lumbar region, one can see some of the fine medullated sheaths showing the black reaction. In longitudinal sections of cord, long and short rows of black globules indicate myelin degeneration, the number of degenerated fibres being about the same as in Case 3.

With the *combined Marchi and safranin method*, the previously-mentioned atrophy of the sheath is well shown, which in many fibres may leave the axis-cylinder denuded for a considerable part of its length.

Round globules of altered myelin are found, which stain a faintly violet tinge.

On some fibres there sometimes occur black dots scattered at irregular intervals, which clearly indicate foci of degeneration. Several of those dots may run together to form a small globule, and are present both in well-stained portions of sheath or in myelin which is atrophying. Such small foci yielding the Marchi reaction are fairly commonly encountered.

The changes in the axis-cylinders of this case are identical with those seen in the first three cases.

Case 5.—J. H., aged 39, married.

HISTORY PREVIOUS TO ADMISSION.

Patient has always been a hard-working man, but recently has been greatly worried concerning certain of his business affairs. No mental symptoms were noted by his friends until six days ago, when he became very restless, depressed, and latterly excited, and threatened to harm himself. He was taken to the workhouse, where he remained four days, and while there his mental state

was as follows :—" He says he is not fit to live ; he has deceived himself and everybody around him ; he has a dejected manner and furtive look at times."

His memory for past events was poor. Patient was admitted to Prestwich Asylum on May 23, 1901.

Physical State.—Fairly tall man. Lungs normal. Heart normal. Knee-jerks brisk. Pupils normal.

Mental State.—Very depressed, restless, and excited ; rarely speaks, says he wishes to die ; is very fearful, won't remain quiet, and rushes wildly about his room. Sleeps very badly.

May 24. Very restless, tries to break away or lies down on ground ; last night he butted his head against the door and bruised his scalp. Given milk, eggs, and whiskey.

May 26. Very depressed, and has to be fed with the tube ; rarely speaks ; very resistive ; restless, and out of bed most of the time ; has lucid intermissions.

May 28. Is taking his food a little better, otherwise unchanged.

May 30. Pulse not so strong, and there is œdema of the feet and legs. Given milk, eggs, and whiskey—8 ounces per diem.

June 3. Œdema has disappeared, and he is taking his food much better ; he is mentally as before ; his temperature is frequently 99.2° to 99.8°.

June 8. Condition remains practically the same. Temperature sometimes up to 101° in the evening and occasionally raised in the morning.

June 9. Up and down temperature persists. His bowels act rather frequently, but that is due to doses of calomel. No abdominal tenderness nor distension ; no increased dulness of spleen ; no lung symptoms. Mentally he is stuporose, with a tendency to catalepsy. He has to be fed ; swallows with difficulty. Passes urine in bed. Given milk, eggs, and whiskey.

June 10. Mentally much the same. Tongue dry and coated ; no diarrhœa. Sleeps fairly well.

June 11. Much worse this morning. Face cyanosed. Marked dyspnœa, crepitations over right lung. Pulse small, quick.

Died exhausted at 1.25 p.m.

AT THE AUTOPSY.

The lungs were healthy to naked-eye examination. The heart weighed 9½ ounces ; muscular walls firm and of good colour ; in the aorta there were several small patches of atheroma. The stomach and small intestines presented no pathological change appreciable to the naked eye, but on examining the large intestine a profound lesion of the mucous coat was found to be present.

At the upper end there were numerous small white scars scattered irregularly over the mucous surface. Half way down the gut and as far as the sigmoid flexure there was an intense ulceration. Some of the ulcerative patches were three inches in length and about half an inch in breadth; others were smaller, varying from a quarter of an inch to one inch in length. Those ulcers varied in shape, some being roundish, others oval, and all were of considerable depth.

The liver, beyond some congestion, showed no morbid change to naked-eye examination, nor did the spleen or kidneys show any appreciable alteration.

The pia arachnoid was very slightly milky, and the brain itself presented no morbid appearance beyond some pink patchy infection of the grey matter of the cortex.

The usual tissues were retained for microscopic study.

Cortex.

Fronto-motor Region.—Fixation in saturated sublimate. Stained by Robertson's methyl violet method, and by toluidin blue.

The description of the cortical cells in Case 4 applies precisely to the large majority of the cells in this case.

The deep blue diffuse staining of the cell-body, due to dissolution of the chromophile material, is present. Cells thus changed show either no formed chromophile material or faint traces only of such. In the diffusely-stained cell-body a network identical in form to that noted in Case 4 is seen, and in addition one can see in this case minute clear vacuoles in certain of the cells.

But this case differs from the preceding one in that a limited number of large pyramidal cells are comparatively little affected by the chromolytic change. Their chromophile elements are only slightly diminished in number, but the outlines of those bodies are irregular, shadowy, and look as if their edges had been dissolved away.

Further, the fundamental amorphous substance of the cell is more highly stained than normal. In the nucleolus one occasionally observes the vacuolated appearance referred to before, and in the nucleus the staining is good except where the cell itself is very pale.

The appearance of the pale, ghostlike cells found in this case, and of the small pyramidal cells, are identical with those noted in Case 4, so that any further description of them is unnecessary.

Cervical Enlargement.

Fixation in saturated sublimate and picric acid ; embedded in celloidin and paraffin ; stained by toluidin blue.

Many of the large cells in the anterior horns show little alteration. The chromophile bodies stain well and are very slightly fragmented at their edges. In some cells there is an accumulation of yellow pigment, which does not, however, exceed the normal physiological quantity except in a few isolated instances.

In a large number of the cells a central chromatolysis is present. Here one finds an area, around the nucleus, pale blue and diffusely stained, in which the minute fragments of broken chromophile material are with great difficulty seen.

As one passes out towards the cell periphery fine chromophile granules make their appearance, and finally, at the margin of the cell, the best preserved elements are found, showing either normal contour or commencing fragmentation. At the beginning of the chromatolysis a hyperchromic band may be seen surrounding the nucleus. This band can be seen with high powers to be composed of very fine fragments of chromophile material densely packed together. When the process of chromatolysis has reached an advanced stage, the zone surrounding the nucleus is often quite denuded of chromophile substance, and stains in the faintest manner possible.

In the early stages of the degenerative process the nucleus is pale, with a well-stained nucleolus, and retains its central position ; but later, when the process has involved the entire cell, with the exception of a narrow peripheral zone, one finds the nucleus pale, excentric, or it may be at the extreme margin of the cell.

Sometimes that part of the nuclear membrane which looks towards the centre of the cell is indented, and in the concavity so formed a small mass of deeply-stained chromophile substance lies.

In the advanced stage of chromatolysis the protoplasmic processes are devoid of chromophile material and very pale.

The small nerve-cells in both anterior and posterior horns are much paler than the large ones. Many stain diffusely blue, and show no trace of formed chromophile substance ; others show a few scattered granules. The nucleus is pale, but the nucleolus stains well.

Lumbar Region.

Fixation, embedding and staining as in the case of the cervical enlargement.

As in the cervical region, cells are seen showing little appreciable change ; the presence of pigment in some of the cells is to be noted also.

There are many cells, however, which are gravely altered. In those which show the least amount of degenerative change one finds the perinuclear region much more intensely coloured than the other parts of the cell. With high powers, this hyperchromic region can be seen to be composed of finely granular broken-down chromophile material, the granules being densely packed together and giving the intense colour referred to.

The peripheral elements, meanwhile, are practically regular in outline and of normal staining reaction.

A further stage is seen where the central chromophile elements become reduced to a fine dust and stain with much less intensity ; at the periphery only a fringe of chromophile substance is left, consisting of well-stained elements, one or two of which, however, may show fragmentary change.

In the protoplasmic processes the chromophile elements are as yet normal.

The nucleus is pale, central, and the nucleolus shows no change.

As the cell becomes still more degenerated, both central and peripheral chromophile elements are reduced to a fine dust, a few formed granules alone remaining in the protoplasmic processes, and at the extreme margin of the cell. The nucleus now takes up a peripheral position, and is very pale.

Sometimes the chromatolysed perinuclear zone of affected cells stains diffusely and pale blue, as if the chromophile substance had been dissolved instead of being broken up. This change is a late one in the degeneration of the cell, as the peripherally situated elements and those in the protoplasmic processes are broken down into granules and stain more faintly than normal. The nucleus here is very pale and markedly peripheral, and in its interior no detail of structure is perceptible. The process of dissolution may in some cases spread to the periphery of the cell, leaving it pale, indistinct, and homogeneous-looking, with a mere shadow of a nucleus.

In the small nerve-cells scattered throughout the grey matter complete chromatolysis is the rule, but a few may show a marginal chromatolysis only, in which the cell periphery and processes are denuded of chromophile substance and stain homogeneously pale blue, while the central parts are occupied by fragmented granules weaker in staining reaction than normal.

It is seldom that one sees examples of peripheral chromatolysis like the above.

Posterior Spinal Root Ganglia.

Fixation, embedding, and staining as in cord.

The cells of the posterior root ganglia in this case present a very marked degree of degenerative change—much more so than has been observed in any of the preceding cases. In fact, there are extremely few cells which one can speak of as normal. In the cells which normally have granuliform chromophile elements throughout the cell, and in those which possess in addition a peripheral ring of large elements, one finds varying degrees of change. At first, the minute chromophile granules decrease markedly in number in the centre of the cell, giving to it a pallid appearance, and the nucleus stains more faintly with the toluidin blue. This degenerative change advances, and when the peripheral ring of large elements is present it is seen to undergo fragmentary change also, and ultimately to disappear as well as the central elements. The cell thus gradually assumes a very pale blue or bleached appearance, and the nucleus, which with few exceptions remains central, loses its affinity for the stain and its internal details of structure disappear. Occasionally it happens, however, that instead of finding a pallid nucleus in those cells, one observes it shrunken and stained diffusely and very deeply, showing the typical appearance of homogeneous atrophy.

Many of those pale achromatosed cells are liable to nuclear invasion, and it is common to find round or oval nuclei buried in the cell cytoplasm.

In the medium-sized cells, which normally contain large chromophile elements, one finds a typical central chromatolysis.

The centre of the cell is occupied by fine, deeply-stained chromophile dust, while the elements at the periphery are not affected to such a degree, although far from normal. The nucleus rapidly assumes a peripheral position.

Vacuolation of the cell is met with infrequently. The vacuoles are for the most part large, and may in some cases occupy two-thirds of the cell-body.

Medullated Fibres of the Spinal Cord.

In sections stained by *Wolter's method*, there is lighter staining of the fibres in the crossed pyramidal tracts and in the postero-internal columns. Microscopically, many myelin sheaths in these areas are seen to be thinner than normal.

With the *Marchi method*, many scattered black droplets are seen in all the tracts of the cord, and only in the posterior columns is there any appreciable increase in numbers.

In longitudinal sections Marchi degeneration is found, as in the previous cases.

By the *combined Marchi and safranin method*, atrophy of parts of the myelin sheath is observed, with intervening segments well stained and apparently uninjured.

Many sheaths are so atrophied and vacuolated as to be hardly distinguishable, and in the centre runs a pale and attenuated axis-cylinder. Some of those vacuolated segments may be of considerable length, as observed in Case 4. At some points in the nerve the medullated sheath yields the Marchi reaction. The parts affected vary considerably in length, and on either side of them no appreciable morbid change may be found.

Case 6.—E. A., aged 34, unmarried, cotton-weaver.

HISTORY PREVIOUS TO ADMISSION.

Patient was always healthy and fit for work until six years ago, when she suffered from a sharp attack of rheumatic fever, from which she recovered, but with impaired health. She became very anæmic and weak, and during the last four years she has been liable to faint on any unusual exertion, so that her previous occupation became impossible. Her mother states that frequently she had diminished power in her limbs for slight periods of time, and her sleep at night was very fitful and broken.

About the beginning of May, 1901, she became restless at night, slept very badly, and at times wandered about the house. On May 8 she had a convulsion, which, according to the mother's account, was of a general character. Her restlessness increased, and she gradually became excited and noisy, so that her removal to the workhouse was considered necessary. There her mental condition became worse; her conversation was rambling and incoherent, she could not answer questions put to her, and had exalted delusions, saying that she owned plenty of money. At the end of fourteen days she was admitted to Prestwich Asylum, on June 24, 1901.

General Condition.—A very thin woman, of medium height; fair hair, blue irides, right divergent squint. Lungs apparently healthy. Heart sounds pure, but action very rapid and feeble. Urine free from albumen.

The patellar reflexes were much exaggerated, and equally so

on both sides. Her lower limbs were very weak, so that she could barely walk without support.

Mentally, she suffers from considerable confusion, cannot understand questions put to her, answering at random, and repeating the same sentence over and over again. She has no idea where she is, or from whence she came. On account of her confusion, sensation cannot be tested.

For three days after admission she remained in much the same mental and physical state, but on June 28 the degree of mental confusion was more marked; her attention could not be engaged. She rambled constantly, muttering to herself.

June 29.—Heart's action very feeble. She seems to have difficulty in swallowing. Constant restlessness, twitching of arms and legs, nystagmus.

June 30.—In much the same physical condition. Restlessness continues, and difficulty in swallowing greater. Her patellar and elbow reflexes are as exaggerated as on admission. Her eyes were examined ophthalmoscopically, and in spite of the difficulty on account of nystagmus, the following appearances were noted:—The papilla is congested and swollen-looking; the margin very hazy and indistinct, and the veins much engorged.

On July 1 her physical condition was worse. Temperature 101.8° in the morning, 101.6° in the evening.

July 2.—Still weaker. Seems quite prostrate. Lies in bed with twitching arms and legs. Reflexes still exaggerated. Mentally she is comatose. Temperature 101° in the morning, 103.2° in the evening. She never rallied, and died at 4.30 a.m. on July 3.

From the date of admission to the patient's death, there was always present a general paresis of all the muscles, both of the trunk and limbs.

This did not affect one group of muscles more than another, but increased with the course of the ailment.

AT THE AUTOPSY.

The heart, lungs, intestines, liver and kidneys showed nothing of a pathological nature to naked-eye examination.

The pia arachnoid was very slightly milky over the vertex.

On cutting into the brain, the cortex was noted to be hyperæmic and pink-looking generally throughout the convolutions.

On examining the cord, marked hyperæmia was seen in the

lateral parts of the cord, especially in the situation of the crossed pyramidal tracts in the cervical region.

This appearance was much less distinct in the dorsal and lumbar regions.

The following tissues were reserved for microscopical examination.

Slices from the fronto-motor region from both sides of the brain.

A portion of the cervical and lumbar enlargements, the posterior spinal root ganglia.

All those tissues were examined for nerve-cell changes. The cord was placed in bichromate of potash 2 per cent., and examined for myelin-sheath and axis-cylinder degenerations.

Cortex.

Fronto-motor Region.—Fixation in saturated sublimate; stained by Robertson's methyl-violet method, and by toluidin blue. Better specimens were obtained by the latter method in this case.

The cortical nerve-cells are more profoundly affected than in any of the preceding cases.

Every cell without exception shows an entire absence of chromophile granules in the interior of the cell-body and in the processes.

The degenerative change has advanced to such a degree that the chromophile material seems to be entirely dissolved throughout the whole cell-body, causing it to assume a uniformly blue, homogeneous appearance.

The depth of staining is not equal in all the cells. In some cells the diffuse staining is very intense, and all detail in the cytoplasm is obscured, even to high powers of the microscope.

The nucleus is seen as a dense blue, oval body, in which the nucleolus is only faintly visible. The nuclear network is quite obscured, and the nucleolus is visible only on account of its intense affinity for the stain. Usually the nucleus occupies a peripheral position.

Other cells do not stain so deeply. They are diffusely pale blue, and in the cytoplasm, and for some distance along the protoplasmic processes, one can recognise a network, the spaces of which are for the most part of equal size, but here and there those spaces are wider than usual, and of irregular shape, as if rupture of the wall of adjacent spaces had taken place.

Clear, medium-sized vacuoles are present frequently. They may be round or oval, and lie for the most part towards the base of the cell; but one may meet with them in other situations.

As before mentioned, the nucleus is most commonly peripheral, and one occasionally sees a crescentic indentation of the nuclear membrane on that side of the nucleus which looks towards the centre of the cell.

The vacuolation of the nucleolus, referred to earlier, has been seen in this case also.

The paler the cell-body stains, the fainter does the nucleus become also, and many cells are so pale that their outline is only recognisable with very high magnification. The above-mentioned network can then be seen only with great difficulty; the nucleus is very pallid, no network nor nucleoli being recognisable. Small fragments of practically colourless protoplasm indicate complete destruction of cell life.

In both grey and white matter, the arterioles and capillaries are greatly engorged.

Cervical Enlargement.

Fixation in saturated sublimate and picric acid; embedding in celloidin and paraffin; stained by toluidin blue.

There is in this situation the same profound degree of change in the nerve-cells as observed in the cortex cerebri.

Even with a low power, one is struck by the absence of formed chromophile material of definite shape in the cell-body.

With a high magnification the following changes are recognisable:—There are a very few cells in which formed chromophile elements are present, small particles being scattered throughout the cell body, both centrally and peripherally, in such a manner that wide spaces are left between each.

Between the particles, the fundamental amorphous substance stains very lightly, and no detail of structure is visible.

The nucleus is pale, and occupies an excentric position, while the nucleolus is distinct, and stains well.

In ninety-five per cent. of the cells a much more grave degree of change is found.

There seems to have been here a rapid dissolution of the chromophile elements, causing the cell to assume a blue, homogeneous appearance, which varies in degree in different cells, some cells being entirely homogeneous, while in others a few minute particles of the chromophile elements are left (photograph 8). Those remains of chromophile elements are found, with the exception of a very few isolated instances, at the periphery of the cell. In those cells, around the nucleus which is peripheral, and in the central parts, the cytoplasm is homogeneously pale

blue in colour, but at the extreme periphery one finds a fringe of small broken-down chromophile particles. The nucleus, as before mentioned, assumes a peripheral position, is extremely pale, and its network is unstained. The nucleolus stains strongly.

The extreme tortuosity of the protoplasmic processes is worthy of note. We have in the above description of those cells strong evidence that the process of disintegration has commenced, and advanced further in the perinuclear and central parts of the cell, seeing that the peripherally-situated chromophile bodies are the last to remain.

Many cells are met with showing a still more advanced stage. The cell stains almost uniformly pale blue, and no trace of the chromophile bodies is to be seen, but at the cell edge the homogeneous blue colour is a little more intense than in the central parts, and no details are visible in the cell-body. The nucleus is very pale, situated at the periphery of the cell, and the nuclear network is unstained. Many cells are so lightly stained that their recognition is only possible with extremely high powers. The cell-body and nucleus are reduced to mere shadows.

While the majority of these homogeneous-looking cells show no detail of structure in the cell-body, there are a few in which a distinct reticulum is visible with high magnification.

The reticulum is present in the cell-body, and extends for a little distance along the base of the protoplasmic processes. The threads composing the network stain deeply, and the spaces enclosed by them are for the most part of equal size, but here and there throughout the cell the walls of adjoining spaces are ruptured, leaving clear structureless round or oval cavities in the cell-body. In these cells there are no traces of chromophile substance, although where the strands forming the reticulum are a little thicker and more distinct than usual, one may be justified in assuming that some dissolved chromophile substance is applied to the sides of the strand.

It is specially interesting to note that in the above-described cells showing a distinct cell network, the nucleus is in a condition of homogeneous atrophy. It stains very diffusely blue, is homogeneous, showing no nuclear network, but a deeply-stained nucleolus, while the nuclear membrane may be much crenated, and its actual size greatly reduced.

Lumbar Enlargement.

Fixation, embedding and staining precisely as in the cervical region. The appearances in this part of the cord are almost identical with those found in the cervical enlargement.

In a few cells one finds fine fragments of chromophile elements scattered irregularly in the central parts of the cell, while larger irregularly-shaped fragments are found towards the periphery.

The nucleus is pale, and the nuclear network unstained, while the nucleolus stains strongly with the aniline dye.

In the majority of the cells there is nearly complete dissolution of the entire chromophile material, the entire cell-body staining diffusely blue; but in the protoplasmic processes, and at the extreme edge of the cell, a few fragments of chromophile substance remain.

Cells showing a further stage of this process are seen where even the peripheral chromophile elements and those in the protoplasmic processes are completely lost. Such cells show a homogeneously blue centre and periphery, but the colour is somewhat deeper in the latter situation. No network is visible in the cell-body of those cells.

In this region, as in the cervical enlargement, there are a few cells in which a reticular structure is visible with high magnification. Rupture of the strands forming the meshwork can be seen, and often one finds in those the homogeneous atrophy of the nucleus previously described.

Tortuosity of the protoplasmic processes is again a noteworthy feature in the degenerative process, and the vascular engorgement is here present as in the other situations described.

Both small and large nerve-cells are affected to the same extent by the acute disintegrative process.

Posterior Root Ganglia.

Fixation in saturated sublimate and picric acid; embedding in celloidin and paraffin; stained with toluidin blue.

The degree of chromatolysis present is greater than in any of the ganglia examined in the other cases, and in the sections under medium powers the cells present a pale "washed-out" appearance. In order to study the chromophile elements of those cells, it is necessary to examine carefully with very high powers, as the degenerative process here has been of a much more acute type than we have previously studied. In none of the ganglia examined are there any cells unaffected by the chromolytic process. In the large cells, which normally contain granuliform elements, and in those which also possess a peripheral ring of elongated elements, a distinct change is found.

The fine granuliform chromophile elements in the centre of the cell become reduced to an exceedingly fine dust, which with

medium magnification is not visible, and the peripheric chromophile ring is no longer recognisable.

But in many cells the change has advanced farther, and now the fine central granules no longer persist, the cell centre staining very diffusely and faintly, while at the periphery there is a ring of more intense colour, in which a few minute granules can be made out, indicating the former site of the peripheral ring. It is remarkable how frequently one finds the perinuclear clear space quite obscured, as if the dissolved chromophile substance had passed into it along the cell canaliculi which normally empty into it. The nucleus is pale, with the nucleolus distinct, and frequently occupies an excentric or peripheral position. Occasionally early homogeneous atrophy of the nucleus is seen, the staining being deep and diffuse, obscuring the reticulum.

In the cells which normally possess large, well-shaped chromophile elements, one finds a definite and well-advanced central chromatolysis.

The centre of the cell is pallid, and colours diffusely blue, while at the periphery and around the nucleus, which has become excentric, a faintly-staining mass of finely-broken chromophile dust persists. In some of those cells the nucleus may be pale; in others early homogeneous atrophy is present, and occasionally the nuclear atrophy may be very advanced, even reaching the stage where the nucleus is intensely coloured and much reduced in size, with a markedly crenated margin.

Some cells, comparatively few in number, are observed to possess a very strong affinity for the dye, staining deeply and diffusely.

With the highest magnification, one observes that the chromophile material is reduced to a very fine dust, scattered generally throughout the cell, or it may even be wanting altogether. In the cell-body a distinct network is visible, whose spaces are of equal size throughout. The nucleus of those cells is always affected by homogeneous atrophy. It is greatly reduced in size, with a very irregular edge, stains so deeply as to totally obscure the nuclear network, and the nucleolus is only faintly discerned through the deep staining mass. Clear vacuoles are sometimes present in the degenerating cells. They are small and irregularly distributed for the most part, but occasionally one meets larger vacuoles, in the centre of which faintly-staining threads of tissue lie.

As in Case 5, dead cells can be seen invaded by nuclei. In cortex, cord and ganglia the vessels are more distended with blood corpuscles than in the other cases.

Medullated Fibres of Spinal Cord.

In transverse sections, stained by *Wolter's method*, there is a very noticeable light staining of the crossed pyramidal tracts, which merges slightly into the posterior part of the ascending antero-lateral column, and also into the lateral cerebellar tract of both sides. The posterior columns present the same appearance, but in the cervical region the diminution of affinity for the stain is confined to the fibres in the postero-internal tract; in the lumbar enlargement the entire posterior region stains with less intensity than normal. On microscopic examination the myelin change is very evident—much more so than in any previous case—and in the lightly-stained regions one sees that the well-stained fibres are greatly in the minority. The ring formed by affected sheaths is a very thin one, stains faintly, and may be incomplete.

On account of the atrophy of so many tubes, those which are normal stand out with great distinctness.

The *Marchi method* shows many more fibres to be affected than in the other cases. Black dots are found in all the tracts, but there is a marked increase in numbers in the crossed pyramidal tracts, posterior columns, and in the direct lateral cerebellar.

In the dorsal and lumbar regions, the number of degenerated fibres in the crossed pyramidal tracts is greater than higher up the cord, and the tract becomes more sharply marked off from the other columns.

In the lumbar region this is very well shown. There is some degeneration in the posterior roots just before they enter the cord, and also some in Lissauer's tract.

In longitudinal sections the number of degenerated fibres is found to greatly exceed that observed in the previous cases, the rows of black droplets being very numerous (see photograph 11).

Combined Marchi and safranin method.—In this case very many tubes are affected, and large portions of myelin are completely atrophied, leaving the axis-cylinder quite denuded. The degree of degeneration is not so marked in some sheaths. There may be a slight diminution of affinity for the stain seen at intervals along the course of the fibre, and where bulging of the sheath has taken place the axis-cylinder commonly shows distinct fusiform swellings with regular outlines, but may still stain red. In those myelin dilatations there may be great tortuosity of the axis-cylinder.

As the myelin atrophies it tends to assume a pale violet

colour, and the atrophy is patchy, picking out small spots or long segments, leaving well-stained, presumably healthy segments between.

In the vicinity of a node of Ranvier—which one rarely obtains a view of in sections, but which none the less can be seen to exist as a definite structure—this pale violet staining of the atrophied myelin is sometimes shown extremely well. The extremity of one node may stain quite normally, but on the other side of the constriction the myelin is thin, and vacuolated for some little distance, and is coloured a pale violet tint; the axis-cylinder is faintly violet also, and at some points unstained. Such pallor and atrophy may affect the nerve-sheath for a considerable distance, and many small vacuoles may be present. There may even be complete atrophy, leaving the axis-cylinder quite bare at some points, and here it stains very faintly violet, and shows fusiform swellings.

Pale violet-staining globules are seen arranged often in rows, representing the once healthy medullary tube, and at times one finds a row of red globules, the myelin between which has degenerated, and evidently been absorbed.

In the centre of these globules one frequently sees a spot which stains black with the osmic acid, the black patch showing up distinctly in contradistinction to the red-stained myelin which surrounds it.

Many droplets of this nature are met with in a more advanced stage of degeneration, where the patch of Marchi degeneration occupies almost the entire globule, a very faint rim of myelin surrounding the black more central portion.

In the fusiform swellings of the axis-cylinder above mentioned, the centre may be much paler than the peripheral portion, an appearance which has been referred to previously.

Résumé of the appearances met with in the nerve-cells :—

Case 1.—In the cerebral cortex, and in the cord, one finds some cells showing a very slight degree of fragmentary change affecting the edge of the chromophile bodies generally throughout the cell, and others showing a typical central chromatolysis. In the cortex the nucleus of the small pyramidal cells stains very deeply and diffusely. There are a few cells in the grey matter of the cord which colour intensely blue and appear homogeneous. In the

posterior root ganglia many cells show a central chromatolysis, and homogeneous atrophy of the nucleus is present in some instances. Vacuolation of the cells in this situation is not uncommon, when the chromatolysis is complete. Cells showing complete chromatolysis are present in the cord and cortex also.

Case 2.—In this case the nerve-cell degenerations are of the same types as given above, with two exceptions, viz., the nucleus of the small pyramidal cells of the cortex does not stain deeply and diffusely, and the deep blue homogeneous colour seen in a few cells of the cord in Case 1 has not been observed here.

Case 3.—The pigmentation of the nerve-cells in cortex, cord, and posterior root ganglia is in excess of the quantity found in Cases 1 and 2, but the hyperpigmentation does not exceed the physiological increase which one expects to find in a subject of 62 years of age.

The types of chromatolysis are the same as those given above. The nucleus of the small pyramidal cells stains deeply and diffusely, and in the posterior root ganglia also homogeneous atrophy of the nucleus is found, and is also present in cells which stain very deeply and have a homogeneous appearance throughout.

No deeply-stained homogeneous cells were observed in the cord of this case.

Case 4.—There is in this case a dissolution of the chromophile material in the cortical nerve-cells, and in the body of the cell a faintly-stained network can be perceived. The nucleolus is vacuolated.

In the spinal cord the types of chromatolysis are precisely of the same nature as in the first three cases, but of greater severity, as is indicated by the vacuolation found in the cell-body.

Case 5.—The cortical changes in this case are nearly the same as found in Case 4. In the cell-body one frequently finds vacuolation in addition to dissolution of the chromophile substance, and one meets with a very few large pyramidal cells in which there is no dissolution, but a slight fragmentation of the chromophile bodies.

In the spinal cord the changes are similar to those found in the preceding case, with the exception of vacuolation, but there are a few cells which show peripheral chromatolysis.

The changes in the posterior root ganglion cells are much more severe than in the first three cases.

Case 6.—Here one finds, in the cerebral cortex, dissolution of the chromophile bodies, a network in the cell, homogeneous atrophy of the nucleus in some cells, and vacuolation of both cell-body and nucleolus in others. In the cord there are a few cells with broken-up chromophile bodies, but the great majority show the same dissolution of chromophile material met with in the cortex cerebri. Some nerve-cell nuclei are in a state of homogeneous atrophy.

In the posterior root ganglia the greatest degree of change yet observed in those structures is found to exist. The chromophile substance is almost entirely dissolved away in the majority of the cells.

Some cells stain with great intensity, and homogeneous atrophy of the nucleus is always present in them.

Vacuolation of the cell-body is frequent.

Deeply-stained cells, with the nucleus in a condition of homogeneous atrophy, have been seen in the cortex also.

RÉSUMÉ OF CHANGES IN THE MEDULLATED FIBRES.

In all the cases the distribution of the degeneration and the form which it assumes are identically the same, and any difference in degree is very small, with the exception of Case 6.

In revising these morbid changes shortly, we find that:—(1) In transverse sections stained by Wolter's method, the crossed pyramidal tracts and the posterior columns possess less affinity for the stain than the tracts in the other regions of the cord. (2) Fibres yielding the Marchi reaction are found scattered in these columns, and to a less extent in other tracts also. The degeneration of the pyramidal tracts is much more intense in Case 6 than in the other cases, and is there most sharply defined in the lumbar region. (3) By the combined Marchi and safranin staining, two varieties of myelin alteration can be noted.

On some of the sheaths there are small round or oval points which stain black with the osmic acid, and around these points the myelin may be little altered. One or two of these black dots frequently coalesce to form a larger droplet. Sometimes, where the myelin has been broken up into round or oval globules, the centre of some of these may be stained black, while the peripheral part is stained partially by the safranin.

A form of degeneration differing in appearance from the above is met with, and consists in the atrophy and absorption of the myelin, leaving the axis-cylinder denuded partially or completely. Small and large segments of the sheath are affected, and portions on either side may show no apparent alteration. In this atrophic process there are to be noted the loss of staining reaction of the sheath, thinning and vacuolation often ending in complete atrophy along the parts affected, leaving the axis-cylinder bare.

Owing to an absorptive process having been superadded to the atrophic one in a complete atrophy of this nature, nothing is left to represent the once healthy myelin, so that this form of degeneration can be distinguished from that which ends in scattered globules or chains of droplets showing the Marchi reaction.

The axis-cylinder undergoes degeneration as well, and attention has already been drawn to such changes as impaired staining reaction, tortuosity, fusiform swellings, flattening, and in some instances thinning.

Actual rupture is an exceedingly rare occurrence, and has only been observed in one of the six cases.

From what has preceded, it will be seen that tissues from the central nervous system have alone been preserved and examined. The changes in the peripheral nerves, the liver, intestines and kidneys, have not been studied.

Since the commencement of this research, the importance of retaining portions of these organs for examination in order to form a more complete work has received due attention, and in all cases of acute insanity which have been met with since the above series was begun, this oversight has been rectified in view of future publications on the subject.

That an examination of all the organs of the body—and even of the blood itself—is of the utmost importance, is forced upon one's attention by a perusal of the recent literature upon acute mental troubles.

In two cases of insanity following influenza, Camia (2) found fatty degeneration of the liver and kidneys. In a more recent publication on the changes found in the nervous system in acute confusional insanity, the same author—in addition to the nerve-cell and fibre changes—describes the following definite alterations.

Kidneys.—Fat droplets in the cells of the convoluted tubules and of the glomeruli; the vessels between the tubules much dilated and congested. In the tubules dead cells are found, and in the loops of Henle the protoplasm of the epithelial cells is broken up and pale.

Liver.—Fatty degeneration of the hepatic cells and dilatation of the central vein of the lobule. Fatty degeneration of the muscular fibres of the heart has also been seen.

Zonder (39), in experimental subacute poisoning by aluminium, found definite changes in the nervous system, but in addition the kidneys and liver showed distinct lesions.

In the former he found cloudy swelling, and in many instances destruction and shedding of the epithelium of the convoluted tubules, which at times were full of these disintegrated structures, and in the mass so formed fat droplets could be seen.

In the loops of Henle there were large, deeply-staining particles, also destruction of epithelial cells. In the straight tubules, and in the glomeruli, the nuclei were swollen, and many showed karyokinetic figures.

The connective tissue nuclei were proliferated.

In the liver he found extravasation of leucocytes around the vessels, and many leucocytes scattered between the liver cells; near the small arterioles were small hæmorrhages.

According to Camia, the changes found in his cases are to be regarded as the result of an intoxication, but at the same time he contends that there is evidence to show that the stasis in the vessels of the liver and kidneys has played a part in the causation of the degeneration.

Turner¹ also explains in this way the fatty degeneration of the liver found by him in cases of acute delirium.

The six cases under consideration can be divided into three groups, according to the character of the nerve-cell change met with, and also according to the severity of the alterations produced.

In the first three cases the changes, with slight exceptions, are very similar in appearance, the most predominant feature common to all being the central chromatolysis found in the cells of the cortex, anterior cornua of the cord, and in the posterior spinal root ganglia.

This central chromatolysis is found to be associated with excentricity of the nucleus when the nerve-cell reaction has reached a fairly advanced stage.

In Cases 4 and 5 the chromatolysis found in the cortex is of a more acute type, and if one excepts the limited number of large pyramidal cells in the fifth case, in which there is not a dissolution but a slight fragmentation of the Nissl bodies, then the appearances will be seen to be precisely similar and the degree of the lesion almost equal in each.

In this group the type of chromophile disintegration in the nerve-cells of the cord is identical with that found in the first group, but the greater amount of damage inflicted on the nerve-cells is shown by the presence of vacuolation in them in the cord of Case 4, and by the more acute chromatolysis in the cells of the posterior root ganglia of Case 5.

Case 6 stands out markedly from all the other cases on account of the grave nerve-cell degeneration which is found throughout the entire central nervous system. Here, too, the fibre reaction is greatly in excess of that found in the previous cases.

Unlike Cases 4 and 5, where the cortical changes are more severe than in the centres lower down, we find that with the exception of a few cells in the cord, in which fragmentary changes are present, the type of cell change met with is the same in all regions.

¹ J. Turner. "Acute Delirious Mania." *B. M. J.*, No. 2073, 1900.

Let us now look at the various forms of nerve-cell reaction, and see in how much they agree with the changes found by others in cases of a similar nature, and in recent experimental work.

The slight fragmentary change which affects the edges only of the chromophile elements generally throughout the cell has been observed in Cases 1, 2, and 3, in some of the large pyramidal cells of the cortex, and in the large multipolar cells of the anterior cornua.

In Cases 4 and 5 this change is found only in the latter situation. Such a slight degree of alteration in the nerve-cell occurs with much less frequency than the others to be described, but is none the less of considerable importance as pointing to the greater stability of the large cells, rich in well-formed chromophile material.

Camia (4) has found such changes in acute mental confusion and in insanity following influenza, in both cortical giant cells and in anterior cornual cells.

This same author has found a similar degree of alteration, in the same situations, in certain experimental poisonings (3), and notes the fact that the smaller varieties of nerve-cells show in many instances a more profound degree of alteration than the larger ones.

But the type of nerve-cell change which one finds most frequently in all the cases cited above is a central chromatolysis, which is seen in various stages of its development, and which varies from a slight degree, limited almost entirely to the area in the immediate vicinity of the nucleus, to a more profound alteration, in which normal chromophile bodies are only found at the periphery and in the protoplasmic processes. At this stage there is displacement of the nucleus outwards.

Central chromatolysis has been found in the cortex, cord, and posterior root ganglion cells in the first three cases, in the cord of Case 4, and in the cord and posterior root ganglia of Case 5.

Only in certain cells of the posterior root ganglia is the change really identical in appearance with that met in the cortex and cord. I refer to the medium-sized cells, in which the chromophile elements are large.

Various writers within recent times have met with and described this form of nerve-cell alteration in different forms of mental derangement.

Ballet and Faure (1), in cases of mental confusion, found the cortical giant cells swollen, and affected by a central chromatolysis with excentricity of the nucleus. In one case, which also presented marked symptoms of polineuritis, a similar type of alteration was present in the cord.

Camia, in confusional insanity, found the same change in the cortex, cord, and to a less extent in the posterior root ganglion cells.

Meyer (22) figures a giant cell showing the same condition.

Trömner (35) describes a similar appearance in the spinal ganglion cells of a case of delirium tremens, as also does Turner (37) in the cortex of cases of dementia, melancholia, and of delirium.

But although found present in the above mental states, there are other conditions in which such an alteration as the above has been found. For example, Marinesco (17) found the same change to occur in the cerebral cortex secondary to lesions of the internal capsule; and in a case of pellagrous insanity, described by Righetti (28), in which the spinal roots were affected, the cells in the anterior horns of the cord, and to a less extent the cells of the posterior root ganglia, showed well-marked central chromatolysis with peripheral displacement of the nucleus.

Again, Schüpfer (32), in a case of tetanus with left facial paralysis, found central chromatolysis in the cells of the cortex, and also in the left facial nucleus.

In poisonings, experimental and otherwise, the same type of reaction has been seen, *e.g.*, by Nichols (24) in typhoid fever, and after infection of rabbits with the typhoid bacillus; by Rossi (30) in poisoning with phosphorus; and by Tschernischeff (36), as a result of grave gastro-intestinal symptoms following fish-poisoning. In the last-mentioned author's cases, however, peripheral and diffuse chromatolysis was also noted, and also the presence of vacuoles in the cells.

It will be remembered that in the cortex of Cases 4 and

5 and in the entire central nervous system of Case 6 there was a much greater degree of cell alteration than was seen in the first group, and the appearances suggest that instead of a fragmentary change, as is found in the central chromatolysis above described, one has here to deal with a process of dissolution of the chromophile material.

The remarkable way in which the cell stains in a diffuse manner throughout the body and processes, and the almost total absence of chromophile material, indicate the profound degree to which these cells are affected. There are indications in some cells, however, which would lead one to the belief that the process of dissolution has commenced in the central parts of the cell, for when any chromophile bodies persist they are found around the periphery and in the processes.

Associated with this process of dissolution one sometimes finds vacuolation of the cell-body and also of the nucleolus, conditions which are commonly met with in certain toxæmias.

Daddi (11), in examining the nervous system of animals infected with hydrophobia, found that the cells stained in a diffuse homogeneous manner, and that vacuolation of the cell-protoplasm was present.

De Buck and De Moor (12), in experimental tetanus, described a rapid dissolution of the chromophile substance, causing intense colouration of the cells.

In some cells they found a faint protoplasmic reticulum.

Tschernischeff (36) has found a similar change in some of the cells in the cases of fish-poisoning already referred to.

In other disturbances of the nervous system vacuolation is frequently found:—By Ciaglinski (8) in the cells of the anterior cornua in death from acute tuberculosis, and in the posterior root ganglion cells of a fatal case of diabetes; by De Buck and De Moor (13) as a result of induced acute anæmia (in some of the cells vacuolation of the nucleolus was present); and by Nartowski (23) in rabbits infected with the diphtheria toxine. Similar conditions have been described by Soukhanoff (33) and Zonder (39) in experimental poisonings with arsenic and aluminium.

From the above results it is evident that vacuolation in the cell-body is liable to occur secondary to the entrance of toxins or poisons into the system, and also as a result of interference with the blood supply, and the vacuoles are usually found associated with grave alterations in the chromophile material, such as advanced chromatolysis, or, as we have seen, with chromophile dissolution.

Vacuolation of the nucleolus is much more rarely found, and in the present series was only observed in the last three cases.

If one refers to the description of the posterior root ganglion cells of Case 3, and the cortical and spinal root ganglion cells of Case 6, a rare type of degeneration will be found, which is clearly quite different from either a true chromatolysis or a chromophile dissolution. The cells which come under this type are recognised by the deep, homogeneous manner in which the cytoplasm stains, and also by the presence of homogeneous degeneration of the nucleus associated with the cytoplasmic change. This intense homogeneous colouration of the cell has been found by Marinesco (19) in acute encephalitis, and was first called by him "partial or superficial coagulation with corpuscular formation," on account of the fact that some parts of the periphery of the degenerated cell were detached, and lay closely applied to its edge. In a later publication (20), he alludes to the same coagulation process, or, as he sometimes terms it, coagulation necrosis, and admits that the centre of the cell may be affected, and in addition he has found the nucleus in a condition of homogeneous degeneration.

Homogeneous degeneration, or atrophy of the nucleus was first described by Sarbó (29), and its development can be divided into two stages. In the first stage the nucleus is stained very deeply and diffusely, the nuclear network is obscured, but the nucleolus remains visible.

The second stage is characterised by the intense colour already noted, and in addition the nucleus is now greatly reduced in size and its contour is very irregular.

Trömner (35), in some spinal cells in delirium tremens, has found similar very deeply-staining cells, in which he

has seen a thick felted network and homogeneous atrophy of the nucleus.

Schukowsky (3), in acute delirium, has found cells which present exactly the same appearance, and Guizzetti (14) has described them also in a fatal case of chorea in which there was vegetative endocarditis with septicæmia, and staphylococci were present in the vessels of the brain.

But even in cells in which the above cytoplasmic change is not found one may see both early and late phases of this homogeneous atrophy of the nucleus.

In the small pyramidal cells and in the spinal root ganglion cells of Case 1, in the posterior root ganglion cells of Case 2, and in the small pyramidal cells of Case 3, this nuclear alteration has already been noted, and it is remarkable how often it has been found present in cells whose chromophile material shows little alteration.

It is very difficult to account for this early nuclear atrophic change in cells otherwise practically normal in appearance, for it is one's experience to find that with interference of the nerve-cell function the chromophile material shows changes before any are noticeable in the nucleus, and alterations in the latter structure are shown by a progressive pallor. But in homogeneous atrophy the opposite is the case, and the nucleus is the first part of the cell to suffer.

De Buck and De Moor (13) have found after occlusion of the abdominal aorta that homogeneous atrophy of the nucleus occurs early in the nerve-cell degeneration brought about by the acute anæmia, and Righetti (27) has noted a similar change from the same cause.

Amongst others who have drawn attention to this nuclear homogeneity with atrophy in toxic conditions are Nartowsky (23) and Shüpfert (32); while Rossi (30) and Soukhanoff (33), in metallic poisonings, have found the nucleus more highly coloured than usual, an appearance which may be interpreted as an early stage of homogeneity.

Although our knowledge of the conditions which bring about such an early and profound nuclear alteration is very deficient, yet, whatever may be the cause of it, there can be

little doubt that the cell in which such an early nuclear alteration occurs can never recover, for it is generally admitted that the integrity of the nucleus is necessary for the life or regeneration of the chromophile material. Once a nucleus becomes affected by this homogeneous atrophic process, not even the removal of the exciting cause of the degeneration can lead to restoration of the nuclear function.

The same, naturally, can be said of the cells which are in a state of coagulation necrosis, and as homogeneous atrophy of the nucleus has always been found present here, perhaps one is not wrong in assuming that the said atrophic nuclear change is the precursor of the coagulative necrosis in the nerve-cell.

In some of the nerve-cells of Cases 4, 5 and 6 a network can be seen. This is rather faint in Cases 4 and 5, but in the last it is quite distinct. The network is composed of meshes of equal size, pervades the whole cell-body, and extends for a little distance into the processes. From the characteristics described, this seems to be identical with the fine network of Donaggio (29).

The alterations of the myelin-sheath and axis-cylinders in the cord have been seen to be as constant a feature in all the cases as the changes in the nerve-cells, and are found to vary very little in intensity in the first five, but in the sixth the degeneration of myelin is of a much more severe character. The distribution of the degenerated fibres has been studied in transverse sections, but in order to examine into the nature of the myelin and axis-cylinder change it has been necessary to study them in longitudinal section, and to use a stain which would allow of both being examined at the same time. Safranin has answered the purpose admirably, especially after tissues had passed through the Marchi process.

Alterations of a similar nature to those described under each case have been observed in certain mental affections and in certain toxic poisonings.

Camia (4), in acute confusional insanity, has described in detail the changes found in the white matter of the cord, but here one can only give briefly his results and views.

By the Marchi method he found a slight degree of degeneration in the pyramidal tracts, which was more marked in the dorsal region. In sections stained by the Weigert method these tracts were more lightly stained and the volume of the individual fibres diminished. The fibres nearest the grey matter were more affected. In the dorsal cord he found small areas in which, with high magnification, the myelin was seen to be quite destroyed, leaving the axis-cylinders bare.

Destruction of myelin-sheaths has been seen by Schukowsky (31) and by Carrier (5) in acute delirium, and in the same condition Cristiani (9) found in the central nervous system and in the cranial and peripheral nerves a degeneration of the myelin, which according to him was of a primary nature. Primary degeneration of the sheath has also been described by Mager (21) in acute myelitis. Nichols, in his experiments already referred to, in addition to the nerve-cell changes, has drawn attention to a parenchymatous degeneration of the peripheral nerves; and Homen and Laitinen (15), after injecting cultures of streptococci into the sciatic nerve of an animal, were able to trace diffuse alterations, ending in granular fragmentation of the medullary tube.

The term "primary atrophy" of the myelin-sheath has been given by Vassale (38) to a special form of degeneration in which the appearances are quite different from those found in degeneration of the fibre as a consequence of its destruction, or breach of its continuity with its trophic centre.

Briefly, the features which characterise the primary degeneration of Vassale are loss of staining reaction, thinning and slow disappearance of the myelin, occurring in a scattered manner along the sheath, and until complete demyelination of the axis-cylinder results. According to this author, the degeneration is toxic in origin, and may be caused by either exogenous or endogenous poisons, and he accentuates, as an important differential sign between primary and secondary degeneration, the fact that in the former the axis-cylinder persists for a great length of time, although showing slight alterations; whereas, as is well

known, there is grave destruction of both the myelin-sheath and axis-cylinder in the secondary degenerations.

Righetti (28), in the spinal roots of a case of pellagrous insanity, has described and figured appearances which he terms primary atrophy of the fibres as shown by swelling, diminished staining, and thinning of the myelin covering, accompanied by swelling and pallor of the axis-cylinder.

In the six cases under discussion, slight and more advanced modifications of staining reaction are common appearances in the axis-cylinder, and both thinning and fusiform swellings have been noted.

But actual rupture has been very infrequently observed, and no appearances resembling the fibrillation or disintegrative changes such as Thomas (34) has figured as occurring in multiple sclerosis have been met with.

Taking into consideration, then, the patchy atrophic character of the myelin changes, and the comparatively slight affection of the axis-cylinder, it is evident we have here a typical primary degeneration.

But while one can definitely affirm that the myelin atrophies seen by safranin staining are primary in origin, one finds it difficult to account for the Marchi degeneration which we have seen in the crossed pyramidal and posterior columns. Turner (37) and Camia have noticed the Marchi degeneration in the pyramidal columns in acute mental affections, while Marinesco¹ has found a similar affection of the same regions; and Camia also notes that many experimenters have described degeneration in the pyramidal columns brought about by the action of toxic substances which attack the fibres in these regions primarily.

But in all the six cases we have found that the posterior columns show fibres yielding the Marchi reaction as well as the pyramidal, and this association of posterior and lateral column degeneration has already been noted by Donaggio² ("nelle psiconevrosi acute"), and is, according to him, to be ascribed to a toxic origin.

¹ Marinesco: "Lésions des Centres Nerveux dans la Pellagra" (*Comptes Rendus de la Soc. de Biol.*, No. 35, 1899).

² Donaggio: *Rivista Sperimentale de Freniatria*, Fasc. IV., 1897.

It is a curious coincidence that the pyramidal and posterior tracts should show a preponderance of fibres showing the Marchi reaction, and the question before us now is whether this Marchi degeneration is of a primary or secondary nature, and if primary, why should not other regions of the cord show an equal amount of it.

Of course it must not be forgotten that, by the combined Marchi and safranin stain, definite primary atrophies and typical rows of Marchi degeneration have been seen side by side in the same section, taken from a longitudinal slice along the middle of the cord.

But, as Camia points out, there is now sufficient evidence to show us that the pyramidal and posterior columns possess less resistive power to the action of toxic substances, and he is of opinion that the degeneration in these regions is primary, and due to the same cause as the alterations found in the nerve-cells of his case.

To account for the presence of Marchi degeneration, however, he is inclined to lay great stress upon the proliferation of neuroglia found in the cord of his case of confusional insanity, and suggests that this proliferation may strangle the axis-cylinder in its course and impair its continuity, thus accounting for the positive results obtained by Marchi's method.

Such a breach of continuity of the axis-cylinder would cause a definite Marchi reaction to arise in the myelin-sheath, and Vassale admits that even in primary degeneration it might be possible to obtain this reaction provided that the toxic substance at work was powerful enough to bring about this rupture.

It is highly improbable that these Marchi degenerations are secondary to nerve-cell change, for we have seen that there is not enough to cause this, and as I have not observed any neuroglia proliferation in any of the cases, I am inclined to the opinion that all the medullated sheath and axis-cylinder changes are primary. Even in Case 6, where the lesions in the pyramidal tracts are so intense, one does not feel justified in stating that such lesions are secondary to nerve-cell change, as the cells are only destroyed in a few in-

stances, while the large majority of them are in a state of acute chromatolysis, a condition from which they can recover granted that the causative agent is withdrawn.

Further, although Vassale holds that Marchi droplets are not found in typical primary degeneration on account of the slow atrophic nature of the process, yet there are certain appearances, especially in Case 6, which can be advanced against this view, for we have seen small patches of Marchi reaction, situated in segments of the sheath, which still stained with safranin, and in other parts of the same sheath the typical atrophic primary degeneration was present.

It is thus possible that some parts of the myelin succumb to the local action of the toxine more quickly than other portions, and so give rise to changes which differ considerably in appearance, but which are nevertheless caused by the same factor.

It is certainly difficult to believe that in Cases 1 and 2, which it will be remembered ran a course of short duration, there was time for the neuroglia to proliferate to such an extent as to cut off the axis-cylinders from their trophic supply and so give rise to secondary degeneration, and it is certain that the nerve-cell change was quite insufficient to exert a similar influence.

It may be, however, that, given a cell in a condition of partial chromatolysis, its trophic influence may be so reduced as to render the fibre less capable of resistance to toxic influences; and there is now evidence to show that the most peripheral parts of the conducting fibre are affected more easily by the toxine.

On this supposition one may be able to explain why, in Case 6, the degeneration found in the pyramidal columns is greater in the lumbar region than in the cervical.

If we take into consideration the facts that morbid changes are found in the nerve-cells of the cortex, cord, and posterior spinal root ganglia, in the myelin-sheaths and to a less extent the axis-cylinders of the cord, and that the liver, kidneys and heart show definite alterations as well, we must come to the conclusion that all such alterations in the acute insanities are the result of an acute general

intoxication. There is no doubt that the changes in the myelin-sheaths and axis-cylinders are primary, and the same can be said of the nerve-cell alterations, although some might not be inclined to accept the view that the central chromatolysis with peripheral displacement of the nucleus is so.

This latter change is similar in appearance to the alterations found in the nerve-cell as a result of the division of its axis-cylinder, and has been described in the work of Marinesco, Lugaro, Van Gehuchten, and many others (29); but although similar in appearance, we are not justified in concluding that the presence of central chromatolysis in our acute cases of insanity is to be accounted for by injury of the conducting fibre.

In a general intoxication it is inconceivable that such a highly differentiated and delicate structure as the nerve-cell could possibly be later in reacting to the toxine than the other nervous tissue, for we must bear in mind the fact that each nerve-cell has been shown to be provided with canaliculi which permeate it and distribute the nutrient fluids from the blood throughout the cytoplasm, so that the cell must react readily to all modifications in the constitution of the circulating media. The fact that the chromatolysis commences in the central parts of the cell can be explained satisfactorily on developmental grounds. Marinesco (18), in his studies on the involution and evolution of the nerve-cell, has shown that the chromophile elements in the centre are the last to be developed, and one is inclined to agree with him when he says that their stability is less than that of those at the periphery of the cell, which are the first to be developed.

It is obvious, then, that in a general intoxication such as we are at present discussing, these central elements must present less resistance to the toxic agent, and succumb more quickly, thus giving an appearance like that of the *reaction à distance*.

Moreover, in all the six cases described, only slight changes have been seen in the axis-cylinders, so that on anatomical and developmental grounds, together with the

absence of sufficient alteration in the fibre to cause secondary reaction in the cell, we must consider that even the central chromatolysis is due to the direct effect of a toxine acting on the cell itself. This at present is the view which most authors adopt who have worked at the subject.

Although the pathological changes found in the acute insanities point clearly to an acute general intoxication, in which the toxic substances attack the nervous system and all the other tissues of the body, yet we are still far from having a clear idea of the source of this intoxication.

The rôle of toxines in the production of nervous disorders now rightly receives a considerable share of attention, for sufficient evidence has been put forward of late years to show that there is a close connection between toxic conditions of the blood and affections of the nervous system.

A concise classification of the various sources of toxic infection which one has to consider in studying nervous diseases, is given in "Robertson's Textbook of Pathology in relation to Mental Diseases."

These are as follows:—(1) Exogenous poisons, *e.g.*, alcohol, cocaine, morphia, &c. (2) Poisons formed within the body in the course of various infective and non-infective diseases, *e.g.*, influenza, syphilis, rheumatism. (3) Poisons generated within the body owing to disorders of metabolism—auto-intoxication, *e.g.*, Bright's disease, myxœdema, diabetes, &c. In this group are placed the toxines which are developed as a result of bad hygienic conditions, mental shock, or overstrain. (4) Poisons generated in the intestinal canal as a result of derangement of the digestive organs. When these toxines pass into the system, we have to deal with an auto-intoxication of gastro-intestinal origin. (5) Poisons developed by the action of organisms which have passed from the alimentary tract into the blood. This condition of infective toxæmia has been worked at by Bianchi and Piccinino, and more recently by Ceni, whose results are of the greatest interest, and will be referred to later.

D'Abundo and Agostini, in the *Rivista Sperimentale di Freniatria*, fasciculus iv., 1900, have entered fully into the

question of the rôle of intoxications and infections in the pathogenesis of nervous disorders, and the accumulation of facts given in their conjoint paper is quite sufficient to show the importance of these factors as causative agents.

In discussing the source of the intoxication, these authors draw attention to certain facts in order to demonstrate to what an extent the individual is constantly exposed to the risk of infection through the mucosæ, especially through that of the intestinal tract.

The cavities of the body are normally full of organisms, and the mucosa itself is one of the natural barriers which offer a constant resistance to the entrance of either the toxins or the organisms themselves.

Now, according to D'Abundo and Agostini, there are certain mental conditions which are known to so modify phagocytic action, and therefore resistive power, that the line of defence—as they call it—is weakened. Such conditions are mental shock, fright or worry, and any other condition which brings about a lowering of tone of the nervous system, which naturally reacts upon the tissues of the body generally, for the integrity of the former is, as we know, necessary for the proper carrying on of the function of the latter.

If we look back to the third group of poisons, we see that mental shock, overstrain, and bad hygienic conditions can induce a condition of auto-intoxication. The toxins so produced ought to be neutralised by the secretions of the protecting organs of the body, *e.g.*, the liver, pancreas, kidneys, and lymphatic glands; but if through defective function of these organs the process of neutralisation is not sufficiently carried out, then an accumulation of toxins takes place in the organism, which will immediately react on the nervous system, to its further detriment.

Now, according to D'Abundo and Agostini, this induced primary intoxication paves the way for the production of secondary intoxications, which may either be caused by chemical modifications in the viscera due to disturbance of nervous influence, or by the circulation of the primary toxin itself in the blood.

But the presence of a primary intoxication may so lower the resistive power that micro-organisms may gain access to the blood-stream, and so induce an infective condition which complicates greatly the nervous symptoms.

The work of Ceni (6) in this connection is of so much importance that it seems of advantage to note some of his results and his conclusions.

In studying cases of delirium he has examined the blood in order to ascertain at what period of the disease micro-organisms were present.

Prior to his researches Bianchi and Piccinino found and described a special bacillus in the blood and meninges of cases of acute delirious mania, and they held the view that, given heredity and poverty of the system, micro-organisms could attack the individual and induce delirium.

But Ceni differs from these authors, and holds that their theory may be right only for cases in which their special bacillus is found, because he himself has frequently observed the common micro-organisms to be present in the blood of epileptics not suffering from delirium.

Ceni, in his bacteriological examinations, has found that in the early phases of delirium no organisms are present in the blood; but as soon as the excitement is accompanied by fever, then organisms make their appearance. With the elevation of temperature the symptoms are more grave, and death rapidly follows.

The organisms which he found in one case were the *staphylococcus pyogenes aureus*, and a short, slightly mobile bacillus which had all the characteristics of the bacterium *coli*; in a second case the blood contained the *streptococcus pyogenes* and the *micrococcus tetragonus*.

The bacterium *coli* was only found in the blood immediately before death.

According to Ceni, this late infection is not the cause of the mental symptoms, but it nevertheless constitutes a very grave complication. He thinks that the nerve-cell changes reduce the alkalinity of the blood, alter the bactericide and phagocytic functions of the blood and tissues, so that there is an invasion later by the common germs which normally occupy the the cavities of the body.

In a later publication Ceni (7) gives the result of his examination of forty-six cases of various psychopathic forms, including acute delirium, severe mania, uræmic convulsions, maniacal attacks in general paralysis, prolonged status epilepticus, &c.

In fourteen cases, during the acute stage, he found in the blood streptococci, staphylococci, pneumococci, micrococcus tetragonus, bacillus coli, and bacillus pyocyaneus.

He has concluded that these organisms never appear in the blood at the beginning of an attack, but shortly after an exacerbation, and their appearance is accompanied by febrile change.

Generally, the infection is determined by a single form of organism, but when death is approaching, then mixed forms are found in the blood.

These investigations of Ceni are worthy of the highest commendation, for they definitely prove that the entrance of organisms into the general circulation influences the course of mental disorders markedly for the worse, especially if the infection is bacillary.

At the same time, his postulate that there must be some functional or organic disorder of the nervous system first present must never be forgotten, for the complicated processes involved in this primary disorder form the crux of the whole question of the causation of insanity.

The hereditary taint is universally admitted to be the greatest of predisposing factors, and there can be no doubt that causes such as mental shock, worry, overstrain and privation of all kinds, acting on one the subject of hereditary weakness, will induce a condition of auto-intoxication, and so precipitate an attack of insanity.

Yet, unfortunately, we are still far from having any definite knowledge of the obscure chemical processes which lead to a general intoxication. That a general intoxication exists cannot be denied if one considers the fact that primary lesions of both nerve-cells and medullated fibres are found throughout the central nervous system, accompanied by lesions in other organs of the body.

It is only, however, by a complete study of all cases of

acute insanity which one may meet, from a neuropathological, physiochemical, and pathochemical standpoint, that our knowledge of this subject will advance.

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