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PART 1.—ORIGINAL ARTICLES.

A Contribution to the Morbid Anatomy and Pathology of the Neuro-Muscular Changes in General Paralysis of the Insane.

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(Essay for Bronze Medal and Prize of Association, 1893.)

It is only within the last two or three years that alienists have learnt to recognize the importance of the existence in cases of progressive paralysis of the insane of certain extremely interesting neuro-muscular anatomical alterations. Too long was the teaching of Lockhart Clarke,[1] Tigges,[2] Westphal,[3] Magnan,[4] Voisin,[5] Mendel,[6] etc., that the cerebro-spinal changes represented the sole anatomical substratum of the clinical features in this disease, regarded as infallible, and it is pleasing to think that our erroneous conceptions have been removed by the energetic researches and discoveries of another generation, including among their number Déjerine,[7] Lubimoff,[8] Mierzejewski,[9] Bianchi,[10] Fürst-

[1] "On the Morbid Anatomy of the Nervous Centres in General Paralysis of the Insane." "Lancet," Sept., 1866.

[2] "Pathologische, anatomische und physiologische Untersuchungen über Dementia progressiva paralytica." "Allg. Zeitschr. f. Psychiatrie," Bd. xx.

[3] (a.) "Über Erkrankungen des Rückenmarkes bei der allgemeinen progressiven Paralyse der Irren." "Virchow's Archiv.," 1867.

(b.) "Ueber den gegenwärtigen Standpunkt der Kenntnisse von der Allgemeinen progressiven Paralyse der Irren." "Arch. für Psych. und Nervenkrank.,' Berlin, 1868.

[4] "De la lésion anatomique de la paralysie générale." Thése de Paris, 1866.

[5] "Traité de la Paralysie générale des Aliénés." Paris, 1879.

[6] "Die progressive Paralyse der Irren." 1880.

[7] "Archiv. de Physiologie," p. 317. 1876.

[8] "Virch. Archiv.," Bd. 57 ,p. 371.

[9] "Archiv. de Physiologie," 1875, p. 195.

[10] "La base anatomica della paralisi progressiva." "Ricerche istologische." 1887.

ner,[11] Bevan Lewis,[12] Colella,[13] and Ruxton and Goodall,[14] all of whom have directed attention to the structural changes in the peripheral nerves. Now all these later writers are more or less in unison in regard to their description of the alterations which occur in the mixed spinal nerves, but Colella, in an excellent Italian monograph, appears to be the only one who has at all fully described the condition found in the cranial nerves in connection with their nuclei of origin. The purely sensory and purely motor terminal branches of the mixed trunks have not received sufficient attention, nor have the changes in the muscles been accurately described.

I, having been provided with ample opportunities and exceptional advantages for the study of these conditions in an asylum in which this particular form of insanity is comparatively common,* am desirous of putting on record the results of an investigation which I have made into the condition of these parts in the case of twelve patients who succumbed to this disease.

Parts examined.—Cranial nerves.—Olfactory, optic (within the cranium and including the chiasma), oculo-motor, trochlear, trigeminal, facial, pneumogastric (both at origin and within chest), hypoglossal. (The oculo-motor, trigeminal, facial, and hypoglossal nerves were examined both at their origin and peripherally.)

Those nuclei of origin situated in the mesencephalon, pons Varolii, and medulla oblongata.

The spinal cord with nerve roots and some of the dorsal and lumbar posterior root ganglia.

Mixed spinal nerves.—Median, musculo-spiral, ulnar, radial, phrenic, some intercostals, sciatic, anterior crural, peroneal, anterior tibial.

Motor twigs to the biceps (brachii) muscle, supinator longus muscle, peroneus longus muscle, tibialis anticus muscle.

Sensory branches of the external cutaneous nerve (upper extremity), internal cutaneous nerve (upper extremity), middle cutaneous nerve (lower extremity), superficial plantar nerve (lower extremity).

[11] "Zur Path. und Path. Anatom. der prog. Paral. imbesondere über die Veränderungen des Rückenmarkes und der peripheren Nerven." "Arch. f. Psych.," Berlin, 1892, xxiv.

[12] "West Riding Asylum Reports," Vol. v., 1875.

[13] "Annali di Neurologia," 1891, pp. 115-200.

[14] "Brain," 1892, p. 241.

* The entire material, both clinical and pathological, for my observations has been afforded by the County Asylum, Rainhill.

Muscles.—Biceps brachii, supinator longus, biceps femoris, abductor longus, peroneus longus, anterior tibial, diaphragm and heart.

Methods of examination employed.—The small sensory and muscular nerve twigs were stained with osmic acid, some according to the method of Exner,[15] others by Marchi's[16] method, the mixed nerve trunks, the spinal ganglia and spinal cord also according to the method of Marchi, and afterwards with Weigert's hæmatoxylin method, and in some cases the modification of that method by Pal, of Vienna, to bring out the medullary nerve sheath. Also with ordinary hæmatoxylin to demonstrate nuclear structures, and with picrocarmine or China blue to reveal connective tissue and axis cylinders.

The pons, medulla, and mesencephalon, after primarily being hardened in Müller's fluid, and afterwards in alcohol of gradually increasing strength, were cut in celloidin and stained by Weigert's hæmatoxylin method, with ordinary hæmatoxylin and with picrocarmine or aniline blue black. The muscles were hardened and imbedded in the same material, and stained with picrocarmine, hæmatoxylin, and eosine, methyl blue and osmic acid.

Cases.

CASE I.—*Clinical history.*—Female, æt. 36, married. Admitted January 27th, 1890. The present attack is said to have commenced two years ago without traceable cause. She is of temperate habits. Has a phthisical family history.

On admission the pupils were equal, but did not react to light or accommodation. The reflexes were exaggerated; the tongue and lips tremulous, the labial tremors being most marked when speaking and immediately prior to speaking. Pulse 76. Her memory was good, but she was highly delusional.

The case ran a usual course. She became progressively demented, emotional, noisy, and dirty. Her speech and deglutition became affected; her reflexes more exaggerated; she lost weight, wasted, developed bedsores, and died on October 27th, 1892, from congestion of the lungs, having had several seizures prior to death.

Autopsy.—In addition to bedsores there were several red purpuric spots due to capillary hæmorrhages on the skin of the ankles, legs, thighs, and iliac bones. The legs and arms were wasted, but the atrophy was not confined to any particular group of muscles.

[15] "Von Kahlden. Technik der histologischen Untersuchung pathologisch-anatomischer Präparate." Jena, 1892, p. 97.
[16] "Von Kahlden.," p. 90.

The subdural fluid was distinctly excessive in amount; there was a thin subdural hæmorrhagic membrane in the left superior parietal region. Arachnoid opacity very marked at the vertex. Cortical adhesions of pia with decortication in all parts of the brain, excepting the tip of the frontal and the occipital gyri. Well-marked general atrophy; weight of encephalon 1,187 grms. Cortex shallow, dark in colour, firm in consistence, indistinctly striated. Lateral ventricles dilated. Ependyma in descending horn of lateral ventricle, in the fifth ventricle, and in the fourth ventricle highly granular. In the spinal cord the only naked eye change detectable was a thickening of the inner meninges in the cervical region. The ribs were brittle, the lungs extensively tubercular. The liver and kidneys showed early fatty degeneration, and the small intestine tubercular ulcers.

Pathologico-anatomical diagnosis.—Dementia paralytica; leptomeningitis chronica; atrophia cerebri; hypertrophia ependymæ ventriculorum; tuberculosis pulmonum et intestini; degen. adiposa hepatis et renum (grad. levioris); decubitus et marasmus.

Microscopical examination.—Sections from the second frontal, ascending parietal, superior parietal, first temporal and hippocampal convolutions, examined by the fresh method (Bevan Lewis), showed a few corpora amylacea on the surface, marked thickening of the subpial glia forming a thick-felted network. Marked hyper-pigmentation, atrophy, distortion, and increase of pericellular nuclei round numerous cells. Many Deiter's cells, most abundant at the surface of the cortex and in the superficial part of the white matter and along the vessels.

Nerves and muscles.—*Vagi.*—Many fibres seen with a swollen medullated sheath and axis cylinder in a state of fatty degeneration; a disappearance of a great number of healthy fibres, their place being taken by fibrous, nucleated material. The degeneration is evenly distributed throughout the various bundles. The nervi nervorum are diseased, and some arterioles have markedly thickened intimæ. Collections of minute nerve tubules seen throughout.

Mediani very extensively diseased, about 65 per cent. of the healthy fibres having disappeared. Some vessels show a thickened middle coat.

Peroneus (right).—Some bundles contain almost no healthy fibres. One bundle seen which is almost untouched; extensive vascular alterations. In this nerve, as in all the other nerves, numerous minute nerve-tubules can be seen lying in the spaces from which the healthy nerve-fibres have disappeared. They are unstained by Weigert's hæmatoxylin.

Motor branches to the biceps brachii, flexor carpi longus, adductor magnus, and anterior tibial muscles, and *sensory branches* of the external cutaneous nerve of the upper extremity, and of the middle and internal cutaneous nerves of the lower extremity show

marked changes; many nerves are seen swollen and in a condition of acute parenchymatous degeneration, others in a more advanced stage. Some nerves are represented only by the nucleated outer sheath of Schwann, the contents having disappeared; and, again, many minute nerve fibres with delicate medullated sheath are seen (*vide* drawings IV. and VI.).

Muscles.—Biceps brachii (right).— Some fibres seen in a state of granular fatty degeneration and much swollen, others atrophied and showing a great increase of sarcolemma nuclei. The vessels of small calibre distinctly diseased.

Peroneus longus (left).—Similar changes.

Spinal cord.—A certain excess of connective tissue in the pyramidal tracts (direct and crossed), and in the posterior columns of Goll and Burdach. Disseminated degenerated fibres in all parts of the cord most marked in the above-mentioned regions.

The anterior and posterior roots distinctly diseased; this change most marked in the cervical and lower dorsal segments. The central canal obliterated throughout.

CASE II.—*Clinical report.*—Female, æt. 26; admitted July 14th, 1891. The present attack has lasted for a year, and she has had three previous attacks of acute mania. She has been intemperate.

On admission the pupils and reflexes were normal. The pulse 80. She was excitable, noisy, violent, emotional, deluded, dirty, and destructive. Three months later she was in the second stage of general paralysis; had unequal pupils and marked tremors, and was losing expression. A year later she was so paralyzed that she could hardly walk alone; she had to be fed, and was very demented. She died of erysipelas and lobular pneumonia on November 2nd, 1892.

Autopsy.—Legs below knees and forearms wasted, the wasting not being confined to any particular groups of muscles.

Calvarium thick, subdural and subarachnoid fluid much increased in amount; membranes (internal and external) thickened. Encephalon weighed 1,170 grammes. Marked wasting of convolutions, especially of the frontal lobes. Cortex dark, shallow, firm, and poorly striated. White matter firm. Ependyma of lateral ventricles in region of optic thalami thickened; that of the fourth ventricle very rough and thickened. The olfactory lobes enlarged and translucent. Lungs present scattered patches of lobular pneumonia. Pathologico-anatomical diagnosis:—Dementia paralytica, lepto-meningitis chronica, atrophia cerebri, pneumonia lobularis bilat., and cystitis et vaginitis chronica.

Microscopical examination.— Sections from various parts of the brain cut fresh and stained after the method of Bevan Lewis exhibit the usual characteristic changes.

Spinal cord.—Beyond a slight excess of connective tissue in the motor tracts and posterior columns, and an obliteration of the

central canal from ependymal overgrowth, nothing remarkable is to be observed.

The nerve roots are very slightly affected.

Mixed nerves.— Pneumogastric.—Very extensive parenchymatous degeneration, with resulting fibro-cellular transformation, leaving few healthy fibres. Sections prepared with a nuclear stain show an enormous increase in the number of the nuclei of the sheath of Schwann; while those stained with Weigert's hæmatoxylin bring out the paucity of healthy fibres in a most striking manner. Many peri- and endo-neural vessels have a thickened intima and media.

Median (*right*).—In a condition of early parenchymatous degeneration, only a few fibres have disappeared; some are much swollen and fatty, others devoid of axis cylinders. The vessels are not noticeably affected, and the nuclear proliferation is slight.

Ulnar (*right*).—Considerably more diseased than the median, but still not extensively affected.

Sciatic (*left*).—Affected to about the same extent as the ulnar; the nervi nervorum especially diseased, and some bundles more than others.

Posterior tibial (*left*); *peroneal* (*left*).—Both considerably more diseased than the sciatic.

Motor branches.—Twigs to the biceps brachii, flexor carpi ulnaris, gastrocnemius and peroneus muscles examined by tearing after immersion for 24 hours in a one per cent. solution of osmic acid exhibit marked parenchymatous changes; all the various stages of disintegration and fatty degeneration of the medullary sheath, swelling and breaking up of the axis cylinder, and swelling and proliferation of the nerve nuclei seen. Numerous empty sheaths seen and much fibro-cellular tissue representing the remains of destroyed fibres.

Sensory branches.—Cutaneous twigs from the external cutaneous nerves of the leg and arm of the superficial cervical and intercostal nerves, prepared in the same manner, show similar changes.

Muscles.—Heart (*left ventricle*).—Many atrophied fibres seen, and others which are hypergranular and over-pigmented. The nerves running in the epicardium and the small blood vessels throughout are extensively diseased.

Biceps brachii (*right*).—A striking excess of the nuclei of the sarcolemma; many fibres atrophied, others in a state of hyaline degeneration. Some arterioles have enormously thickened intimæ, leading almost to obliteration. The motor nerves contain few healthy fibres.

Flexor carpi ulnaris (*right*), *gastrocnemius* (*left*), and *peroneus* (*left*) show similar changes.

Case III.—*Clinical report.*—A sailor, aged 29; unmarried; admitted June 14th, 1892. Intemperate as regards both alcohol and sexual indulgence; his mother died of brain softening. Assigned cause of disease a head injury.

On admission he was in the second stage of general paralysis, markedly ataxic, and with exaggerated reflexes. On September 19th he had his first seizure, which was accompanied by twitchings of the left side of the face and left arm.

A series of seizures led to his death on November 3rd, 1892.

Autopsy.—No marked wasting of muscles was noticed. The brain presented all the macroscopic appearances characteristic of general paralysis; opaque swollen membranes, excess of subdural and subarachnoid fluid, cortical wasting, dilated ventricles, with granular ependyma, etc.

The lungs were much congested.

Microscopical examination.—Sections of the *cerebral cortex* cut and stained in the fresh state showed the characteristic changes and marked fatty degeneration of the nuclei of the vessel walls.

Spinal cord.—Examined fresh, and after hardening showed slight degeneration of the cells of the anterior cornua in the cervical region, scattered degenerated fibres in the anterior and crossed pyramidal tracts and the posterior root-zones. Degeneration of both anterior and posterior nerve roots. Obliteration of the central canal throughout.

Nerves.—Optic nerves unchanged.

Vagi extensively diseased.

Phenici.—Slight interstitial changes.

Median (left).—Not a great amount of degeneration; more in some bundles than in others.

Ulnar (left, at elbow).—More affected than the median.

Ulnar (left, at wrist).—Marked by more nervous and vascular degeneration than at the elbow.

Radial (right).—More extensively diseased.

Sciatic (right).—Not much affected.

Tibialis posterior (right and left).—Somewhat more diseased than the sciatic; that of the left side more affected than the right; vessel changes very marked.

Peroneal (right).—Very extensive disease. Some bundles much more involved than others.

The internal and external *cutaneous nerves* of the arms and legs and *muscular twigs* to the biceps, supinator longus, adductor magnus, and anterior tibial muscles all show marked parenchymatous degeneration, the sensory nerves being more diseased than the motor.

Intervertebral ganglia.—The 5th and 6th cervical and the 1st and 2nd lumbar show slight degeneration in the anterior roots, marked changes in that part of the posterior roots between the ganglia and the cord, with comparatively slight affection of the peripheral part, and hyper-pigmentation of the ganglion-cells.

Muscles.—The diaphragm, supinator longus, biceps cruris, gastrocnemius, and long peroneal muscles all show some degree of interstitial myositis, those situated most peripherally being most

affected. Some terminal nerve bundles show the condition described by Eichhorst, under the name "Neuritis Fascians."

CASE IV.—Male, æt. 39; admitted July 15th, 1891; died December 6th, 1892. Syphilis and drink are the assigned causes of the attack. Mentally he did not deviate from the ordinary type, and physically the only remarkable feature was that his gait was both spastic and ataxic.

Autopsy.—Extremities much wasted; the muscles of the inner side of the thigh, of the outer surface of the leg, and of the forearms and hands especially involved in the atrophy.

The microscopic encephalic changes were advanced and typical. The liver was syphilitic.

Microscopical examination.—Cortex cerebri.—Examined fresh. Showed the usual changes.

Spinal cord.—Many degenerated fibres in Goll's and Burdach's columns and Lissauer's root zones. An excess of connective tissue everywhere. Degeneration of the posterior roots more marked than of the anterior. Central canal obliterated throughout.

The following nerves, muscles, and intervertebral ganglia were examined:—

Nerves.—Vagi (right and left), phrenici (right and left), median (right), ulnar (right and left), radial (right), sciatic (right and left), anterior crural (right), posterior tibial (right and left), peroneal (right and left).

Muscles.—Biceps brachii (right and left), supinator longus (right and left), adductor magnus (right and left), flex. carpi uln. (right and left), peroneus longus (right and left), gastrocnemius (right and left), heart (left ventricle).

6th cervical
3rd and 4th cervical } Intervertebral ganglia.

Of the spinal nerves the phrenici were most affected, that of the right side only containing about half-a-dozen healthy fibres (*vide* drawings v*a* and v*b*). The remainder were all considerably diseased, those situated most peripherally, viz., the radial, posterior tibial, and peroneal showing most degeneration. The vagi were both extremely diseased (*vide* drawings i. and vii.), and the vascular changes most marked.

The intervertebral ganglia showed changes similar to those described in Case III.

All the muscles showed rather advanced interstitial myositis; the vessels were in many cases diseased, some hyaline. "Neuritis fascians" was frequently observed, and the terminal motor twigs contained few healthy fibres.

CASE V.—Male, æt. 35; cause of attack unknown; no history of alcoholic or venereal excess; death two years after admission in a condition of extreme dementia and feebleness with ataxia.

Autopsy.—Pathologico-anatomical diagnosis, dementia para-

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lytica (leptomeningitis chronica, atrophia cerebri, etc.), pleuritis (bilateralis), myocarditis, cirrhosis renum.

Microscopical examination.—Cortex cerebri.—Examined fresh showed the unmistakable changes of general paralysis.

The following nerves and muscles were examined :—

Nerves.—Vagi, phrenici, median (right), ulnar of both sides at the wrist and elbow, anterior crural (right), anterior tibial (left), and sensory and motor nerves from both extremities.

Muscles.—Heart (left ventricle), biceps brachii (right), supinator longus (of both sides), peroneus longus (right), and tibialis anticus (left).

The vagi nerves again extremely diseased, the phrenic nerves only slightly affected, and the remaining mixed nerves, with the exception of the anterior tibial, similarly to those of Cases I., II., III., and IV.

The anterior tibial nerve was most extensively degenerated, but few healthy fibres remaining. The perineurium was to a large extent infiltrated with fat, and the vessels greatly altered. The tibialis anticus muscle supplied by this nerve showed pronounced fatty infiltration of many of its fibres, the remaining muscles slight myositis. The sensory nerve twigs examined were more diseased than the motor.

The heart muscle was extraordinarily affected; few healthy fibres remained, and they were widely separated by numbers of round or oval nucleated bodies in which adventitial blood channels ran (*vide* drawing ii.).

CASE VI.—This case is of particular interest in furnishing an example of the neuro-muscular changes in those cases of *juvenile general paralysis* as described by Shuttleworth, Clouston, and Wiglesworth.*

Clinical report.—Male, æt. 15; admitted November 2nd, 1892; family history good; active and intelligent at school, but disinclined for lessons; neglect at the hands of his parents and privation were the assigned causes of his mental aberration, and his attack, on admission, had lasted over a year.

On admission he was undersized, giving one the appearance of being only about eight years old; height, 4ft. 3in.; weight, 5st. 4lb. Both legs were flexed and spastic; the knee reflexes much exaggerated; he had nystagmus and irregular pupils; pulse 80, small and irregular; heart sounds weak. Evidence of phthisis pulmonalis.

Mentally he appeared happy, but cried when touched; his legs could be straightened apparently without occasioning severe pain. He took no notice of questions, and was regardless of his surroundings. He spoke little, and was dirty in his habits.

* A brief account of this case was given by Dr. Wiglesworth in this Journal in his paper on "General Paralysis about the Period of Puberty," July, 1893.

The further course of the disease was a progressively downward one. He developed tubercular enteritis, and died on the 20th March, 1893 (less than five months after admission, and less than two years after the commencement of the disease).

Autopsy.—Body extremely emaciated; legs drawn up and acutely flexed at the knee and hip joints; a slight bedsore over the right ilium; circumference of the head 21in.; calvarium thick and dense in parietal and occipital regions; sutures very close; sagittal suture measuring 5in. in length; vessels of the brain tough; dura mater rough and bulged. The subdural space, containing 13oz. of opalescent fluid, thin, firm, pale, and organized bilateral subdural hæmorrhages; pia-arachnoid opacity and thickening extreme; subarachnoid fluid if anything diminished, and adhesions of pia to cortex with decortication on stripping almost universal. Cerebral atrophy also extreme. Weight of encephalon, 912 grms.; right hemisphere, 367½ grms.; stripped of its membranes, 320 grms. Left hemisphere, 346 grms.; stripped, 285 grms. The convolutions of a simple type; sulci shallow; cortex shallow, dark, soft, congested and unstriated; white matter soft, boggy and atrophied; puncta cruenta numerous; basal nuclei small, with dilated perivascular spaces; ventricles dilated, ependyma thick. The cerebellum weighed 103 grms.; the pons and medulla together, 20 grms. Ependyma of ventric. iv. markedly granular.

On the spinal dura without that membrane, and particularly noticeable in the dorsal region, was a soft, easily detached membrane resembling a fibrinous subdural hæmorrhage of the brain.

The left optic nerve was much smaller than the right, and there was a left-sided iritis.

Lungs extremely tubercular; heart exceedingly small, weighing only 2½ ounces; muscle dark and firm; remaining organs all small; the kidneys cirrhotic; some tubercular ulcers in the intestines.

Microscopical examination.—Sections from various parts of the cerebral cortex cut fresh reveal the typical changes of advanced general paralysis.

Spinal cord (examined at the level of the third and sixth cervical, third and ninth dorsal, and fifth lumbar pairs of nerves). Shows an increase of connective tissue elements in various tracts, most prominent in the crossed pyramidal tracts along the whole length of which it is continuous. In the sixth cervical region the inner portion of the posterior columns is sclerosed, and in the lumbar region Lissauer's root zone is in a similar condition. Some of the nerve cells of the anterior cornua give indications of degeneration. Clarke's columns are healthy. The anterior and posterior nerve roots are slightly and equally diseased in the upper cervical and dorsal regions; in the lower cervical and lumbar segments the change predominates in the posterior roots. Thickening of vessels is almost universal, and the central canal is almost obliterated throughout.

Nerves and muscles.—The following were examined:—

Vagi (right and left), phrenici (right and left), median (left), ulnar (left), sciatic (right), peroneal (right and left), oculo-motor (right and left), biceps brachii (right and left), peroneus longus (right and left), gastrocnemius (right and left), heart (left ventricle).

The vagi nerves were most extensively diseased, a great number of healthy fibres had disappeared, there was a marked increase of connective tissue; numerous nuclei and minute nerve fibres not staining with hæmatoxylin were seen. The vessels were markedly diseased.

The left vagus was more affected than the right. The remaining nerves were all diseased, but not to so great an extent. The vessel changes in all formed a prominent feature.

Sections of the heart and of all the limb muscles showed most striking changes; the muscle fibres were almost all small, while many others were degenerated in addition. There was a most pronounced increase of nuclei, numerous instances of Eichhorst's "neuritis fascians" were seen, and the small vessels and terminal motor nerves were greatly diseased (*vide* drawing iii.).

CASES VII., VIII., IX., and X.—These were all cases examined to ascertain the changes in connection with the cranial nerves and their nuclei. They were all marked cases of general paralysis clinically, and the necropsy in each case fully confirmed the clinical diagnosis.

The parts examined were—(1) The pons and medulla at the nucleus of origin of each individual nerve (some being examined and stained fresh, others after hardening). (2) All the cranial nerves (with the exception of the spinal accessory) at their point of origin. (3) The third, fourth, fifth, sixth, seventh, and hypoglossal nerves also at a point in their peripheral distribution.

Shortly summarizing the more important points in connection with this investigation. (1) The nuclei of origin did not show marked degenerative changes, the pneumogastric nuclei were most affected, but still not extensively. The changes noted were isolated instances of nerve cell atrophy, hyper-pigmentation of nerve cells, and an increase of nuclei in the neuroglia. (2) The nerves at their origin, that is to say intracranially, did not show highly pronounced alterations either, though in few cases could it be said that they were quite free from disease. The preponderating change was an interstitial one, and in no case had such an extensive disappearance of fibres occurred as in the peripheral nerves. The nerves most diseased were the optic and

olfactory, the oculo-motor, trigeminal, and hypoglossal. The ascending root of the fifth nerve within the medulla oblongata was in three instances discovered to be the seat of very extensive interstitial changes, with disappearance of many healthy nerve fibres, and in one case the ascending root of the glosso-pharyngeal nerves presented like changes. (3) The more peripheral segments of the nerves examined by teasing after staining in osmic acid and carmine showed changes more marked than those observed in the nerves next their origin.

Cases XI. and XII.—These cases were examined with the chief end in view of testing the constancy of the changes in the vagi in this disease. In both instances the disease ran a rapid course, and marked cardiac irregularity, arhythmia and feebleness were observed clinically. At the a utopsy in one case the heart was fatty, in the other dark and firm. Microscopical examination of the brain and spinal cord revealed characteristic changes. The vagi were in both instances extensively diseased. The phrenici nerves and nerves from the upper and lower extremities showed less marked changes.

Synopsis with Remarks.

Changes in the vagi nerves.—It will be observed that in all my cases the pneumogastric nerves were extensively and strikingly diseased, more so almost than any of the peripheral nerves, and decidedly more than any cranial nerve. My observations in this connection entirely agree with those recently made by Colella (*loc. cit.*), and in my opinion it is impossible to attach too much importance to the remarkable singling out of the vagi for such extreme degeneration in this disease.

It is of interest, as Déjerine[17] and Sharkey[18] have pointed out, and as I[19] have further drawn attention to, that a similar affection obtains in alcoholic polyneuritis, a disease distinctly produced by a toxic infection. A similar affection also occurs in other diseases (diphtheria, etc.), and in all it is unquestionably accountable for serious clinical changes; in general paralysis it explains the cardiac troubles so often met with, I

[17] "Contribution à l'étude de la névrite alcoolique." "Arch. de phys. norm. et path.," 1887.

[18] "Alcoholic Paralysis of the Phrenic, Pneumogastric, and other Nerves." "Transactions of the Path. Soc. London," 1888.

[19] "Ein Beitrag zur path. Anatomie der sog. Polyneuritis alcoholica." "Zeitschrift für Heilkunde," Prag., 1892.

refer to the tachycardia, arhythmia, and feebleness of pulse (*vide* Mickle's[20] observations); and, as Hebold[21] remarks, it probably also accounts for the sudden death of many general paralytics. (In addition to the clinical evidence of cardiac affection, I have been able to demonstrate, anatomically, the existence of most pronounced changes in the muscular elements of the heart in cases in which the vagi nerves were diseased.)

Further, disease of the vagi in other diseases has been held accountable for the indirect production of pulmonary tuberculosis, and Bianchi[22] and Vulpian[23] lay great stress on the ætiological importance of this affection as a factor in the production of phthisis pulmonalis in general paralysis; their assumption bears greater weight when we consider the great frequency with which phthisis occurs in this disease (Mickle[24] and Browne[25]).

The phrenic nerves, which are akin to the vagi in the importance of their function, though always diseased to a certain extent, are not as a rule so much involved as the vagi, yet it is not impossible that in some cases they may be very extensively diseased, and give rise to such a diaphragmatic palsy as occurs in other varieties of neuritis, and which Gerhardt[26] has recently associated with locomotor ataxia.

Changes in the mixed spinal nerves and their peripheral terminations.—Concerning the changes in these nerves it is seen that the alteration appears to be a combination of a parenchymatous degeneration* and an interstitial or adventitial inflammation. I cannot agree with Colella that the change is a purely parenchymatous one, as numbers of my specimens amply demonstrate the existence of marked peri and endoneural fibro-cellular proliferation, while in some, in addition to the interstitial change, a superimposed secondary

[20] (*a*) "Journal of Mental Science," Apr., 1872, p. 31. (*b*) "On General Paralysis of the Insane," 2nd Ed., p. 186.

[21] "Ein Fall von Vaguserkrankung bei progressiver Paralyse." "Allg. Zeitschrift für Psychiatrie, Berlin," 1888, xliv, p. 495.

[22] "La pulmonite dei paralytici e la degenerazione dei nervi vaghi." "La Psichiatria," 1889.

[23] "Les Nerfs vasomoteurs," v., ii.

[24] *Loc. cit.* (*b*), p. 296. This writer found tubercle in an average of 25 per cent.

[25] "The Pulmonary Pathology of General Paralysis." "Brain," 1883-84, vi., pp. 317-341.

[26] "Tabes mit Zwerchfellslähmung." "Berliner klinische Wochenschrift," No. xvi., 1893.

* So called by Vanlair, Déjerine, Gombault, etc.; described as "degenerative atrophy," or simple degeneration of the nerve fibres, by others.

fatty infiltration has supervened, similar to that seen in the neuritis of phosphorus poisoning; nevertheless, it would be a mere premature conjecture to state that this interstitial change is a primary essential one, as, judging from one's experience of other neurites, much similar interstitial alteration can arise secondarily to parenchymatous degeneration, and the acuter the degeneration the greater is the production of connective tissue elements.

The existence in that portion of the nerve trunk, from which healthy nerve fibres have disappeared, of a number of exceedingly small nerve tubes with extremely thin medullated sheaths, unstained by Weigert's hæmatoxylin, or the modifications of Weigert's method, is very remarkable. Now it is highly doubtful whether these minute fibres could ever develop into large, functionally healthy ones again. The change, therefore, appears rather to be a textural reversion to an embryonic or lower type, comparable with the pial adhesions, the subpial feltwork, and the enormous nuclear proliferation occurring in the cortex cerebri (*Cf.* Mickle, 2nd Edition, p. 340).

In accordance with Goodall and Ruxton's observations in general paralysis, and Lorenz's[27] and my own in other forms of neuritis, I have noted in all my cases a marked affection of the small blood-vessels accompanying the nerves. This condition is by no means peculiar to general paralysis, and its pathology is still enigmatical.

The result of my investigations coincides with those of others in regard to the remarkable fact that the more peripheral the site examined in the mixed trunk, the more extensive will the degeneration be found to be; and when one reaches the motor and sensory branches the degeneration is still more advanced and pronounced. The affection is on the whole symmetrical, but the nerves of the lower limbs are more diseased than those of the upper extremities, and in some cases the purely motor twigs are more affected than the purely sensory ones, and *vice versâ*.

I have not been able definitely to determine whether it is in those cases of dementia paralytica with tabetic symptoms that the sensory branches are most diseased, but that hypothesis does not appear unlikely.

Spinal nerve roots.—The anterior roots and that portion of the posterior roots lying between the cord and the ganglion

[27] "Beitrag zur Kenntniss der multiplen degenerativen Neuritis." "Zeitsch. für Klin. Med.," 1891.

offered fairly constant change. The degree of degeneration was always considerable, but never extensive. It is difficult to decide in which segments of the cord the roots were most affected, but those of the cervical, lower dorsal, and upper lumbar seem to have suffered most. In the posterior root ganglia no obvious degeneration of nerve cells beyond some hyper-pigmentation was noticed, and the posterior roots beyond the ganglia were but little diseased.

Changes in the muscles.—When we consider the extreme degree of muscular atrophy which occurs in this disease, it is not remarkable that extensive microscopical alterations should reveal themselves, but as regards the main features of these alterations they do not differ to any noteworthy extent from those changes described in connection with other neurites, and do not appear to possess much primary character, being, in all probability, chiefly secondary effects of the nerve degeneration. In brief, the changes I have noted are fatty degeneration, atrophy, and complete or partial disappearance of a number of muscle fibres, with proliferation and increase of the nuclei of the sarcolemma and connective tissue; the number of normal motor end plates is decidedly lower than in health, while some are seen in process of degeneration; in some muscles the condition described by Eichhorst[28] under the name of "neuritis fascians" can be seen.

Since Eichhorst holds that the vagi nerves are the trophic nerves of the heart, and that death after vagotomy is due to the resulting fatty degeneration of the muscle, it is again not astonishing when we remember the extreme degree of affection of the vagi nerves, that severe changes should be found in the muscle fibres of this organ. In my cases I have almost invariably found changes of a degenerative myocarditic nature, resulting in the disappearance of a number of healthy fibres, increase of the nuclei of the sarcolemma, and thickening of small vessel walls.

Cranial nerves and their nuclei of origin.—My examination of the series of cranial nerves (with the exception of the vagi) has not led to any discovery much further than those which have been reported by previous writers on this subject (Wiglesworth,[29] Mickle, *loc. cit.*, Colella, *loc. cit.*). I am

[28] "Neuritis fascians. Ein Beitrag zur Lehre von der Alcoholneuritis." "Virchow Archiv.," 112 B., 1888.

[29] Note on optic nerve atrophy preceding the mental symptoms of General Paralysis of the Insane. "Journal Ment. Sci.," 1889, pp. 389-391.

enabled to confirm the existence of more or less constant interstitial degenerative changes in many of these nerves, and to add that in these nerves, as in the case of the peripheral nerves, the changes seem most marked at the periphery. (This was at any rate the case in the oculo-motor, trigeminal, facial, and hypoglossal nerves, portions of which were examined, both peripherally and at their origin.) The ascending root of the fifth nerve in the medulla oblongata was also found in many cases to be markedly sclerosed. This point is of more than passing interest, as the same thing occurs, as Oppenheim first pointed out, in tabes dorsalis. A similar degeneration is incidentally mentioned in a case cited by Bevan Lewis.[30]

In regard to the nuclei of origin, the changes noted were not at all proportionate to those found in the nerves, still, in many of them there were evident traces of degeneration, in the shape of cell atrophy, hyper-pigmentation and connective tissue hyperplasia, and this change, as one would expect, was most marked in the vagi nuclei (Colella states that these nuclei will not be found to be diseased).

Pathology and Conclusion.

Indubitable evidence has now been adduced of the widespread distribution of the disease in the great controlling nervous apparatus. Undeniable clinical signs point to the fact that that system is the one which is primarily affected, but what factor it is that generates that nerve destruction is, and must for some time remain, a pure matter of conjecture, and since we know practically nothing of the precise character of the pathogenic influence or factor which determines the malady in question, it is extremely difficult to frame a distinct pathology for the attendant neuro-muscular changes; still, taking the neuro-muscular changes in this disease separately into consideration, and comparing them with the changes in other varieties of multiple neuritis, we find that there exists a close resemblance, from an anatomical standpoint, between the neuro-muscular changes in general paralysis and each of the five groups of multiple neuritis, and there is, further, one group with which the changes of general paralysis can be pathogenetically compared, viz., the *primary intrinsic toxæmic;* the secondary toxæmic, the purely toxic, the endemic, the rheumatic, and the cachectic, or senile, being out of the question.

[30] "Text-Book of Mental Diseases," London, 1889, p. 283.

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(This naturally refers only to purely idiopathic cases of general paralysis, and not to those cases in which syphilis or alcohol has played a pathogenetic *rôle*, and necessarily induced their well-known secondary toxæmic effects upon the peripheric nerve system. Grave nerve changes I claim to have found in such uncomplicated cases, and in spite of the statements that juvenile general paralysis usually occurs in those children with syphilitic taint, I claim the juvenile case I have cited as an excellent example of the point in question, since no trace whatever of hereditary or primary syphilitic infection was discoverable in that case.)

Continuing in support of this comparison, I would say that the changes occurring in general paralysis are certainly compatible with those seen in those toxæmic neurites in which the virus, so far as is known, is primarily and intrinsically produced within the body independently of any definite or known disease, and, further, such a morbid blood state provides us with a far more reaching and sufficient explanation of the general widespread disposition of the disease, the affection of columns in the spinal cord not in physiological connection with the cranial centres or the peripheral nerves, the symmetrical distribution of the disease in the peripheral nerves, and the universal implication of the small vascular channels; further, the proliferation of cells in the lining membrane of the ventricles of the brain and spinal cord, which is so essential a feature of general paralysis, and so often observed in other pure toxic neurites (*e.g.*, alcoholic neuritis), obviously supports this theory by pointing to the presence of a toxic material in the cerebro-spinal fluid, which, as we know, is intimately connected with the blood.

In advancing this hypothesis, it is seen that it is impossible for me to reconcile myself to the view that the peripheral neuro-muscular alterations are of an entirely secondary character, that is to say, dependent upon general malnutrition induced by primary brain changes. That they may be partially so I have no desire to deny, since it is clearly established that imperfect tissue changes may generate a toxic agent capable of acting injuriously upon the nerves (*cf.* diabetes and anæmia). Still, in fatal cases of general paralysis, in which the cerebral and mental disease has not been at an advanced stage, I have found most pronounced changes in the peripheric nerves, and abundant clinical evidence exists proving the early appearance of these changes;

further, the general anatomical appearances are not at all compatible with such a view; and in Case VI., which I have cited, where the muscle changes were far in advance of the nerve changes, it is impossible to imagine that these changes are entirely secondary to the brain affection. This case, indeed, is comparable with Siemerling's[31] case of alcoholic neuritis, which led him to formulate the theory that the extreme changes in the muscles in that disease are a result of the direct action of the toxæmic poison upon the muscular tissue.

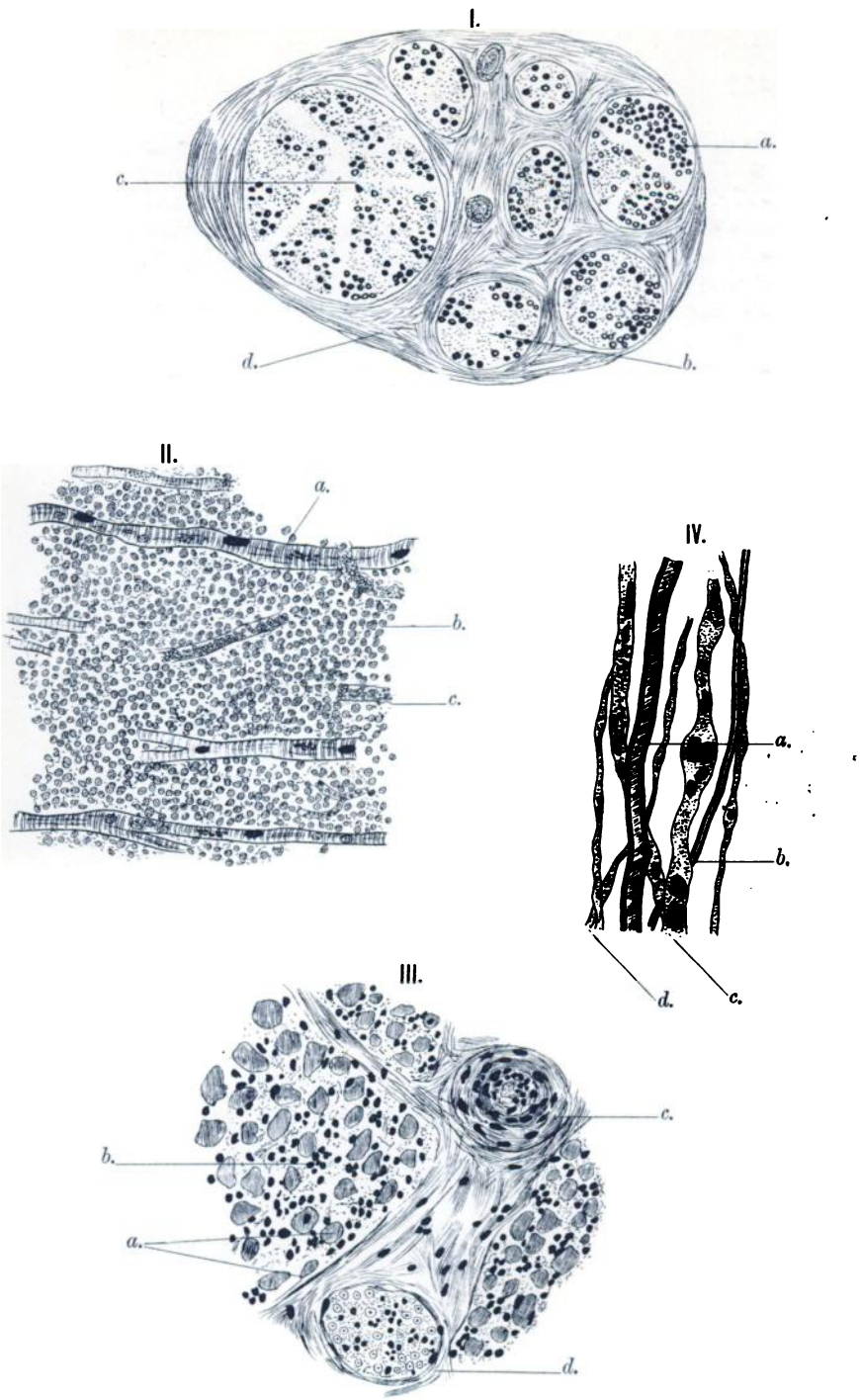
With regard to the many other theories concerning the pathology of general paralysis, the vaso-motor so strongly credited by Klippel,[32] the inflammatory, the congestive, and so on, in support of each of which strong arguments have been put forward, even if it were in my province to discuss them, space would not allow it. Suffice it to say that I do not consider that any of them afford sufficient explanation of the changes which I have described.

The fact that the more peripherally situated portions of nerves are most diseased is explained in this condition as in some other neurites by their situation; there they are furthest removed from their trophic supply and being the most highly-organized and functionally susceptible parts of the nerve, they are placed at a disadvantage. A toxic agent would, in this situation, operate with greatest effect. We assume this applies to motor and sensory nerves alike.

Now that we are clearly decided as to the existence of these degenerative changes in the peripheral nerves, it is much easier for us to explain many of the motor and sensory changes which crop up clinically in the course of the disease; much of the paralysis and paresis is undoubtedly due to the peripheric nerve affection. The muscular atrophy and wasting, and numerous cutaneous, sensory, and trophic changes, etc., are in the same category. Articulatory failure and troubles of deglutition can be based on a similar pathology, and cardiac and pulmonary troubles I have already referred to.

[31] "Ein Fall von Alcoholneuritis mit hervorragender Betheiligung des Muskelapparates." "Charitè Annalen," 1889.

[32] "Lésions des poumons du cœur, du foie et des reins dans la paralysie générale." "Archives de méd. expérimentale," July 1, 1892.



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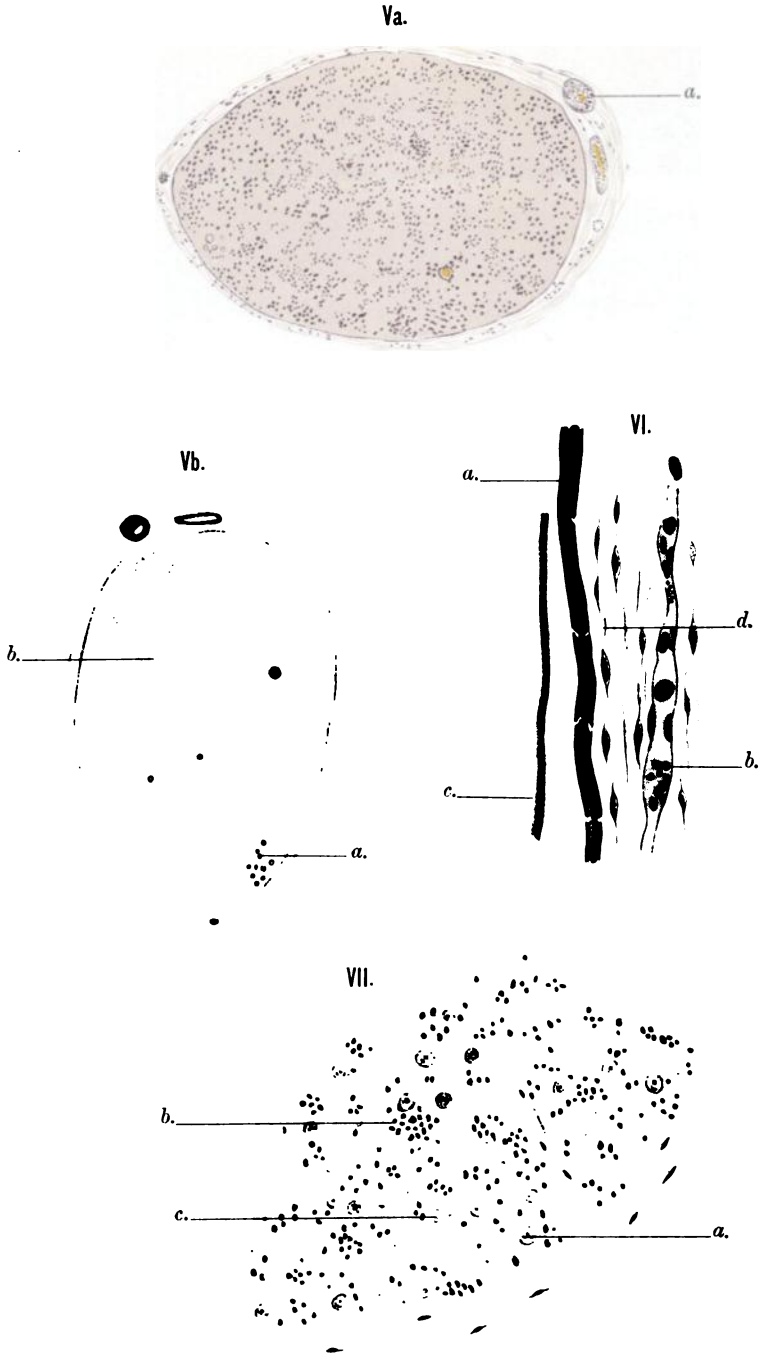

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KEY TO ILLUSTRATIONS.

I.—Transverse Section: Pneumogastric nerve. Case IV. Method of Weigert. × 70.

A. Healthy nerve fibres.
B. Unstained fibro-cellular tissue (remains of diseased nerve fibres.)
C. Extremely diseased large bundle containing few healthy fibres.
D. Thickened perineurium.

II.—Heart: Left ventricle. Case V. Hæmatoxylin and Eosine. × 250.

A. Comparatively healthy muscle fibre.
B. Round celled growth replacing muscle fibres.
C. Adventitial blood channel.

III.—Transverse Sections: Biceps brachii. Case VI. Hæmatoxylin and Eosine. × 250.

A. Muscle fibres of small size.
B. Proliferation of nuclei of sarcolemma.
C. Artery showing thickening of all coats leading to partial obliteration of lumen.
D. Intra-muscular nerve twig, showing signs of disease.

IV.—Intra-muscular Nerve, bundle-teased. Case I. Osmic acid.

A. Healthy nerve fibre.
B. Small nerve fibre.
C. Nerve fibre undergoing acute parenchymatous degeneration.
D. Advanced stage of degeneration.

V.—(a). Transverse Section: Phrenic Nerve. Case IV. Hæmatoxylin and Eosine. × 70.

The nerve is extremely diseased. Nerve fibres almost entirely replaced by fibro-nuclear hyperplasia.

A. Thickened blood vessel.

(b). Same nerve stained by method of Weigert.

A. The only remaining healthy nerve fibres, tinted violet.
B. Fibro-cellular tissue, undifferentiated.

VI.—External Cutaneous Nerve (arm), teased. Case I. Osmic Acid and Picrocarmine. × 300.

A. Comparatively healthy nerve fibre.
B. Nerve fibre in condition of acute parenchymatous degeneration.
C. Minute nerve tubule with well-marked axis cylinder, but thin medullated sheath.
D. Altered neurilemma, the sole remains of diseased nerve fibres.

VII.—Portion of Transverse Section of Vagus Nerve. Case IV. China Blue and Hæmatoxylin. × 400.

A. Healthy nerve fibre.
B. Nuclear hyperplasia.
C. Collection of minute nerve tubules.

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