REMARKS

ON

THE CHANGES IN THE SPINAL CORD IN TWO CASES OF PERNICIOUS ANÆMIA.

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THE two following cases afford examples of the changes present in the spinal cord in pernicious anæmia, and also illustrate the fact that in one class of these cases careful examination failed to elicit clinical symptoms of the disease of the cord, a result possibly to be attributed in some instances to the severity of the general symptoms obscuring those due to the spinal cord affection.

E. W., aged 46, was admitted into the Bristol General Hospital on November 17th, 1896, complaining of great weakness, palpitation, and shortness of breath. Except that one sister had died of consumption the family history was good. The patient had been married twenty-six years and had one child; no miscarriages. She had rheumatic fever fourteen years ago, and jaundice one year ago, but had always been strong and healthy. She had suffered from piles but not from hæmorrhage from them. The catamenia ceased twelve months ago; previously to that she

normal; the pupils acted well to light and accommodation; the axillæ were pigmented. Blood: Red corpuscles 870,000 to 1 cm.; many poikilocytes, macrocytes, and microcytes, and a few nucleated red-blood corpuscles. White corpuscles, 10,000, consisted almost entirely of the finely granular oxyphil leucocyte; hæmoglobin, 30 per cent.; Blood decimal 0.6.

She was treated with arsenic, and oxygen inhalations every two hours. During the next few days she suffered from constant vomiting, pains in the abdomen, and from drowsiness, and she had retention of urine. On November 24th she began to suffer from nocturnal incontinence of urine, and the oedema increased in degree and extent. There was obstinate constipation. On November 26th the urine showed with the spectroscope a faint urobilin band, which it had not done before. Examination of the blood gave red corpuscles 830,000, white corpuscles 30,000 to 1 cm. of same characters as above. Hæmoglobin 25 per cent. The patient died on November 27th.

The post-mortem examination showed the body to be fairly well nourished. The lower lobes of both lungs were in the state of brown induration. There was a little serous fluid of a peculiarly bright colour in the left pleural cavity and pericardium. The heart was covered with a layer of bright yellow fat, and its muscle was in a most marked condition of fatty degeneration. The liver was rather small, smooth, and pale. A fairly well marked blue coloration to hydrochloric acid and potassium ferrocyanide was obtained in the periphery of the lobules. In the spleen, which was firm and dark in colour, this reaction was not obtained. The kidneys gave the reaction badly and only in parts of the cortex; the cortex appeared to have undergone a fatty change. On washing out the intestines and treating them with perchloride of mercury solution a faint rose pink was obtained in the duodenum, but not elsewhere in the small intestine; the large intestine was unfortunately not examined.¹

Fig. 1.—Cord at level of first and second cervical roots: Degeneration in posterior columns.

had always been regular, and had never suffered from menorrhagia. She dated her illness from a fall in June, 1896, after which she became pale, lost flesh, and suffered from increasing weakness in the legs, with a feeling of deadness in them. Nine weeks before admission she had an attack of "bronchitis and inflammation of the lungs," and was very ill for three weeks. This was followed by jaundice, with pains in the bowels, obstinate constipation, and vomiting after food. Her legs became swollen and weak, and either felt very cold or of a burning heat. She kept her bed during the whole nine weeks until admission. She had never suffered from melæna or hæmaturia.

On admission she was very pale and rather thin, the skin of a pale lemon colour. She was very weak and had to be fed. The mouth was dry, the gums pale, and the breath offensive; appetite bad; bowels constipated; pulse-rate 112, regular, compressible; temperature 38.4°. Examination of the chest showed the lungs to be normal, the breath sounds being rather jerky. The heart was normal in size, but a blowing systolic murmur was heard all over the præcordial area, and a venous hum was audible at the root of the neck. There was excessive tenderness in the left epigastrium but nothing could be felt there. The liver and spleen were not enlarged, and there was no ascites. The urine was acid, specific gravity 1.025, and contained a slight trace of albumin. The legs were swollen, pitting on pressure; there was great loss of muscular power in them. The knee-jerks and plantar reflexes were very active. Sensation to touch, pain, and temperature was everywhere normal. Vision was

Fig. 2.—Mid-cervical region of cord: Degeneration in posterior columns.

My clinical clerk, Mr. E. V. Foss, undertook the quantitative estimation of the iron in the liver after the method recommended by Dr. Stockman,² and found that 100 grammes of dried liver contained 0.1034 grammes iron. The bright yellow fluid from the pleural and abdominal cavities gave a very distinct spectrum of urobilin (single band just to the red side of F).

The brain and spinal cord were hardened in Müller's fluid. Sections of the cortex of the cerebrum and cerebellum were normal, and the basal ganglia and white matter of the cerebral hemispheres were also healthy. Sections of the pons, medulla, and cord, posterior roots and spinal ganglia were stained after the Pal-Weigert and Van Gieson's methods, and in carmine, methylene blue, and aniline blue black.

The spinal ganglia examined (lumbo-sacral and cervical regions) and the posterior roots in all parts of the cord were healthy. In the cord at the level of the first and second cervical roots there was complete degeneration of the posterior columns extending from the posterior surface half way towards the posterior commissure. The posterior root zone, Lissauer's column, and all other parts of the cord were healthy.

At the third cervical root complete degeneration of the columns of Goll and Burdach for their posterior two-thirds; immediately behind the posterior commissure the columns were healthy.

In the mid-cervical region, posterior columns, a narrow zone on the posterior surface, and a small area just behind posterior commissure, were healthy. Degeneration, however, affected a narrow zone of Goll's column next the posterior fissure right up to the commissure, $\frac{2}{3}$ of the rest of that column and $\frac{2}{3}$ of Burdach's column, sparing the internal posterior root zone and Lissauer's tract. At this level a few scattered fine nerve fibres only partly degenerated could be recognised in the otherwise fully degenerated areas. Other parts of the section were normal.

In the lower cervical region the changes were similar. From the complete removal of the affected fibres the cord had undergone a slight change in shape and was rather smaller in size than normal.

In the upper dorsal region the largest portion (central parts) of the posterior columns were completely degenerated, but a narrow zone of undegenerated fibres was left on the whole periphery of these columns next the grey matter, being broadest at the posterior part of Burdach's column internal to the posterior root-zone. A very few degenerated fibres were found in the posterior part of the left lateral column. In the mid-dorsal region the posterior columns were degenerated except for a narrow circumfer-

Fig. 3.—Cord at about ninth and tenth dorsal roots: Degeneration in posterior columns and in one lateral column.

ential zone next the grey matter, a narrow line of healthy fibres on the posterior surface, and in one section a few healthy fibres along the septa between the columns of Goll and Burdach. The nerve-cells in the anterior cornua and in Clarke's column contained much coarse pigment at this level.

In the lower dorsal region the degenerated area in the posterior columns was the same, but not so intense in Burdach's column. From the level of the eighth to the twelfth dorsal roots a distinct area of degeneration appeared in the left lateral column occupying the position of the crossed pyramidal tract and the part just anterior and internal to it. This was most marked in the dorso-lumbar region, and occupied there the lateral limiting zone of Flechsig and inner part of the crossed pyramidal tract not nearly reaching to the surface of the cord; it disappeared in the upper lumbar cord, ending abruptly above and below.

In the lowest dorsal region a narrow band of healthy fibres just appeared along each side of the posterior fissure, spreading out on posterior surface of the cord.

In the middle and lower lumbar regions the area of degeneration in the posterior columns was the same, leaving a circumferential zone of healthy tissue next the grey matter,

and a band extending along and on each side of the posterior fissure, and spreading out on the posterior surface of the cord (see later).

In the sacral region the posterior columns were similarly degenerated, the healthy band of fibres along the posterior fissure on the posterior surface and the circumferential zone next the grey matter being a little broader. In the affected parts the degeneration was complete, or nearly so, and equal in degree at all levels of the cord, a very few scattered fine fibres being occasionally spared. Sections stained by Golgi's method showed very well the large size, richness, and abundance of the neuroglia cells in the degenerated columns, which in this respect also afforded a marked contrast with the healthy columns, in which the glia cells were unstained. These "spider cells" were so abundant in some parts of the degenerated areas as to form almost a network, although their processes were not in contact. The structure of the diseased part was that of a loose, open network of neuroglia rich in the above cellular elements.

In places where the disease appeared to be in an early stage, and some normal nerve fibres were still present, there was a marked increase or thickening of the neuroglial tissue, even down to its finer divisions, whilst the nerve-fibre sheaths were becoming swollen and granular, or were

Fig. 4.—Cord at mid-lumbar region: Degeneration in posterior columns. Area of septo-marginal and cornu-commissural tracts unaffected (air bubble unfortunately over posterior cornu on right hand of section).

disappearing. In the affected areas the walls of the vessels were noticeably thickened, and sometimes hyaline, and their peri-vascular sheaths were distended. This was also often the case in healthy parts of the cord.

The nerve cells in several parts of the cord appeared to be excessively pigmented, and in the anterior cornua in dorsal and cervical regions many contained a number of coarse granules staining deeply with logwood, and arranged concentrically around the nucleus in the cell protoplasm. Those of Clarke's column were normal, though there was perhaps a slight diminution in the number of fine fibres in this plexus in the lower dorsal region. The central canal of the cord was large, and its epithelium conspicuous. The anterior and posterior roots and all other parts of the cord were healthy. The meninges were healthy.

In the medulla at the level of the decussation, and just above this there were degenerated fibres, mostly large, in the

gracilis and cuneate columns, but the nerve cells in the nuclei of these columns were healthy and abundant, and the arcuate fibres leaving them seemed to be normal in number and appearance. The small oval band of medullated fibres that lies superficially in this floor of the fourth ventricle just internal to the lingula was very small on the left side, but otherwise no evidence of degeneration was traced in the other parts of the medulla or pons Varolii.

To sum up, the changes consisted in a fairly complete degeneration of the posterior columns extending the whole length of the cord, and in the lower dorsal and upper lumbar region a small area of degeneration in the posterior part of the left lateral column.

The preservation of the knee-jerk is explained by the escape of the internal posterior root-zone; it is also interesting to note the absence of any loss of sensation, although subjective feelings of heat and cold were complained of.

CASE II.—The patient was a labourer, aged 38. The family history was good. The illness began two years before admission to the hospital with great weakness and a severe attack of diarrhoea, which confined him to bed for six weeks. The weakness increased, and he suffered also from shortness of breath on exertion, from swelling of the feet, and from soreness of the mouth and tongue. He had also occasional attacks of diarrhoea, and once passed a small quantity of blood *per anum* when suffering

Fig. 5.—Sacral region of cord: Degeneration in posterior columns, which have become folded, and septo-marginal tract somewhat obscured thereby.

from piles, but with that exception he had never had any hæmorrhage from any source. He had had no previous severe illness, but had suffered from dyspepsia.

On admission May 9th, 1896, he was rather emaciated and extremely anæmic. He had diarrhoea, with the passage of pale loose motions. Pulse 96, regular, small, compressible. Blood—hæmoglobin 31 per cent., red corpuscles 810,000 per cm.; poikilocytes, microcytes, and many nucleated red corpuscles were observed; they did not form rouleaux. The white corpuscles were not in excess, and appeared normal in stained films. The heart was normal in size; a soft systolic murmur was audible over the whole precordial area. The lungs were healthy. There was a little ascitic fluid, but no enlargement of liver or spleen. The skin over the abdomen was somewhat pigmented. With the ophthalmoscope small retinal hæmorrhages were seen in both eyes. The urine was pale, gave a distinct, though faint, urobilin band, and contained no albumen or sugar. He was very weak, but walked with a normal gait. There was general loss of muscular power, but no localised paralysis; sensation was normal over the limbs and trunk; knee-jerk present; no muscular rigidity, nor ankle clonus; superficial reflexes present. Pupils dilated, but acted to light and accommodation. Special senses normal.

He was treated at first with hydronaphthol and subnitrate of bismuth for the diarrhoea, and with oxygen inhalations; subsequently with arsenic, and on three occasions by transfusion of blood.³ It is sufficient to say here that he became steadily worse; towards the end a trace of

albumen appeared in the urine; he became drowsy, and died on July 26th, 1896. Throughout the case no paralysis appeared, except the loss of power due to extreme general weakness, and there were no pains in the limbs nor any disturbance of sensation.

At the *post-mortem* examination, made six hours after death, the following were the chief changes: Both pleural and abdominal cavities contained a little bright yellow serous fluid. Lungs: the lower lobes were slightly indurated and pigmented. The heart muscle showed slight fatty change. Liver small and pigmented; the periphery of the lobules gave a well-marked reaction for iron. The spleen also gave a faint iron reaction. The pancreas was large, firm, and very tough. The marrow in the shaft of the right tibia was red, soft, and diffuent. The brain appeared normal to the naked eye; it was not kept for examination. The spinal cord was hardened in Müller's fluid, and sections were stained by the Pal-Weigert and Van Gieson's method, and with borax carmine; no naked eye changes were seen in the cord. In the upper dorsal region there were symmetrical small patches of partial degeneration in the lateral column, just external to the grey matter; the areas were rounded and small, the neuroglia was much thickened in them, and the nerve fibres had in great part but not entirely disappeared; the vessels were much injected, and the small patches were contiguous to and appeared to be connected with the grey matter in its median part between the anterior and posterior cornua. These small areas of degeneration were very limited in longitudinal extent, corresponding to about one dorsal segment. With this exception the white matter of the cord was healthy throughout, no systemic degenerations being present; the anterior and posterior roots were also healthy. The posterior columns stained more deeply in Müller than the other parts, but no cause could be found for this microscopically.

In this case the stress seems to have fallen upon the grey matter, which in most parts showed marked changes. The vessels were intensely injected, and there were many hæmor-

Fig. 6. Section stained by Golgi's method to show neuroglia cells in degenerated posterior columns.

rhages, varying in size, but all microscopic, into the grey matter. These hæmorrhages were distributed chiefly about the central parts of the grey matter, posterior part of the anterior cornua, and neighbourhood of the commissure. Besides the hæmorrhages there were in places small areas in which the grey matter was granular, partly disintegrated, or sclerosed. The nuclei of the glia cells were either normal or slightly increased in number.

Certain of the nerve cells of the anterior cornua were swollen, opaque, and homogeneous, their nuclei obscured; others were highly granular and deeply pigmented, and a few appeared small and shrunken, but the large majority appeared normal. The walls of the small vessels were much thickened, and very many showed hyaline change. In places the anterior fissure was broadened by the distended arterial branches. The central canal was blocked. These changes in the grey matter were judged to be of fairly recent occurrence, and not of old standing, and were most marked in the upper dorsal region. No hæmorrhages were noticed in the other organs *post mortem*.

The two cases thus afforded a very decided contrast; in the first the spinal cord changes, affecting the white matter, and

being of a chronic degenerative kind, whilst in the latter they were on the other hand almost confined to the grey matter. In neither case were there any blue granules in the nerve cells after treatment with hydrochloric acid and ferrocyanide of potash. The duration of the anæmia appeared to have little to do with the difference in the disease of the cord, for in the first case it was only six months, and in the second two years.

The frequency with which changes in the cord have now been found in cases of pernicious anæmia and the similarity of the changes in all cases leave no room for thinking that the association of disease of the cord and anæmia is an accidental one. As Dr. James Taylor concludes in his valuable paper on the subject,⁴ we may best regard the anæmia and cord changes as both resulting from a common cause, and look for this cause in a toxic condition of the blood, together with, as a further cause for disease of the cord, the tendency to the occurrence of hæmorrhages, which is so marked a feature of pernicious anæmia. Since Dr. Taylor's paper many additional instances of the affection of the spinal cord in pernicious anæmia have been published.

The lesions found separately in my two cases were combined in a case reported by Teichmüller.⁵ The patient died of pernicious anæmia after eleven months' illness. The knee-jerks were exaggerated, but there was no ankle clonus. *Post mortem* in the cord the anterior fissure was widened by a hæmorrhage that had occurred into it. In the grey substance there were numerous hæmorrhages, with increase of neuroglia and thickening of the vessel walls. The posterior columns were degenerated, especially in their middle third. In the lateral columns were scattered small hæmorrhages, and one also in the anterior columns, which were otherwise normal. Teichmüller insists on the importance of the changes in the grey matter, and thinks that both the small patches of degeneration in the white matter (small foci of sclerosis) and the degeneration of special tracts or columns owe their origin to small hæmorrhages. According to Rothmann, indeed, the combined sclerosis are of endogenous origin, conditioned through a primary disease of the grey substance.

With regard to the occurrence of hæmorrhages in the cord in pernicious anæmia K. Pétiou⁶ reports 5 cases in which small hæmorrhages or small sclerotic foci, the result of hæmorrhages, were distributed through the cord, and as regards changes in the grey substance, Burr⁷ has found important alterations in this. Pétiou considers that small hæmorrhages in the cord lead on to sclerosis, and that the varying pathological changes in different cases are in great measure explained by the process being in different stages, the degeneration following a regular type.

On the other hand, Nonne puts most stress on an affection of the intramedullary white substance. He has examined 21 cases of fatal anæmia, and in 13 of them found morbid changes in the cord. In his paper he reports two fresh cases which he considers to represent the early stage of the disease.⁸ In these cases there were a few very small foci in the lateral columns of the cord in which a number of nerve fibres were in a state of acute myelitis. The grey substance was normal. Briefly, he thinks that these cases represent the early stage of the disease, and show that it begins in the form of very small and irregularly situated patches of acute myelitis, and that the grey substance is not notably affected.

Böedeker and Juliusberger, in describing two cases in which the clinical symptoms were well marked and the pathological changes those of the form of the "combined sclerosis," think that the affection must be considered to be a disseminated myelitis with especial predilection for certain columns of the cord, and that the more or less clearly marked symmetry points to the dependence of the disease on the vascular distribution.

Bastianelli¹⁰ makes a useful division of the cases into two categories:

I. Cases in which the general symptoms of anæmia predominate, in which those due to affection of the nervous system are slight and do not correspond with the anatomical changes in the cord, which latter consist of irregular foci of degeneration, chiefly in the posterior, and a few in the lateral columns. The course is a short one, extending to months only.

Under this category would come the cases of Lichtheim, Minnich, and some of Nonne's.

II. Cases of longer course—two to four years—in which the nervous symptoms predominate, and those due to anæmia appear later in the disease. The nervous symptoms and anatomical changes in the cord fully correspond (group of combined system-scleroses). Bastianelli does not agree with the theory which refers the degeneration in the white columns to primary changes in the vessels. He is inclined to attribute both spinal cord changes and anæmia to one cause, probably the action of a toxin. I would suggest that the first group be provisionally divided from a pathological standpoint into two sub-groups: (a) The cases above given under I, and (b) cases in which clinically, like those in (a), symptoms of cord lesion are masked by the symptoms due to profound anæmia, but in which the chief anatomical change consists of hæmorrhages into the grey matter.

Both my cases would fall under Group I. The exact proportion and relations between the two groups remain to be determined, and also the relation of Group II to the cases which Sir William Gowers has described under the name of ataxic paraplegia.¹¹

Out of 9 cases collected by Pétiou,¹² in two the clinical symptoms clearly indicated a spinal cord affection, and degeneration of the posterior columns, and in one case of a part of the lateral columns. In the other cases without such symptoms in two there was degeneration of the posterior columns, and in 5 small hæmorrhages or small sclerotic foci (sequels of hæmorrhage) were found scattered through the cord.

Hun, in a paper on 7 cases,¹³ makes the observation that the posterior columns are most often affected, and may be the only parts involved, but that the lateral columns are never affected alone. He also remarks on the frequency with which a peripheral zone of healthy fibres separates the diseased parts from the grey matter. This is well exemplified in my first case, and was most marked in the lumbosacral regions. Respecting the degenerations in this case, another point of interest may be more especially alluded to, and that is the clear preservation of the tracts of fibres described by Dr. Alexander Bruce as endogenous or intrinsic fibres in the lumbosacral cord, under the name of the "septo-marginal tract." Possibly the unaffected zone next the grey matter in the posterior columns also represents the cornu-commissural tract," also mentioned by him.¹⁴

Most observers appear to have remarked changes in the vessel walls. The evidence above given shows clearly that extensive changes may be present in the cord in cases of pernicious anæmia without any marked clinical symptoms, and that the lesions are of somewhat diverse character. Whether the degenerations of systemic tracts depend on hæmorrhagic or myelitic foci in all cases, there seems hardly yet sufficient evidence to show; the predominant affection of the posterior columns in the majority of cases, and their degeneration throughout the whole length of the cord on both sides, rather points to an independent affection of these tracts.

I am much indebted to Mr. James Taylor for his kindness in preparing photographs of the sections.

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- 2 BRITISH MEDICAL JOURNAL, May 2nd, 1896. ³ For details of treatment see *Bristol Medico-Chirurgical Journal*, September, 1896. ⁴ On Nervous Symptoms and Morbid Changes in the Spinal Cord in certain Cases of Profound Anæmia, *Med.-Chir. Trans.*, 1895. ⁵ *Abstr. Neurol. Centralt.*, 1896, p. 746. from *Deut. Zeit. f. Nervenheilk.*, 1896, viii, 5 6 H. ⁶ *Nord. med. Ark.*, 1896, N.F. vi, quoted in *Neurol. Centralt.*, 1896, p. 747. ⁷ *Univ. Med. Mag.*, April, 1895. ⁸ Aerztlicher Verein in Hamburg, January, 1896. *Neurol. Centralt.*, 1896, p. 137. ⁹ *Ibid.*, p. 327. ¹⁰ Le Sclerosi combinati del Medollo spinale nelle Anæmie Perniciose, *Bull. I. R. Accad. med. di Rome*, 1895-96, xxii; *Neurol. Centralt.*, 1897, p. 97-98. ¹¹ See Dr. James Taylor, *loc. cit.* ¹² *Loc. cit.* ¹³ *Univ. Med. Mag.*, April, 1895. ¹⁴ BRITISH MEDICAL JOURNAL, June 12th, 1897, p. 1481.

THE late Mr. James Billinge has by his will bequeathed £500 to the Surgical Aid Society, Salisbury Square; £1,000 to the Metropolitan Free Hospital, Kingsland Road; £500 to the Hospital for Diseases of the Skin, Stamford Street, Blackfriars; £500 to the London Fever Hospital; £1,000 to the Royal Hospital for Incurables, Queen Victoria Street; £500 to the West End Hospital for Diseases of the Nervous System, Welbeck Street; and £500 to the Hospital for Diseases of the Throat, Golden Square.