arsenic. That happens three or four times, and then the disease proves fatal.

REFERENCES.

- ¹ *Journal of Physiology*, vol. xxvi, p. 151. ² *Quarterly Journal of Medicine*, vol. i, p. 108, and *Guy's Hospital Reports*, vol. lxiii, p. 103. ³ *Guy's Hospital Reports*, vol. i, p. 349. ⁴ *Journal of Pathology and Bacteriology*, vol. xiv, No. 3, p. 411.

REMARKS ON A CASE OF SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD, SIMULATING DISSEMINATED SCLEROSIS, WITH THE RAPID DEVELOPMENT OF PERNICIOUS ANAEMIA SHORTLY BEFORE DEATH.

By BYROM BRAMWELL, M.D., F.R.C.P.E., F.R.S.E.
SENIOR ORDINARY PHYSICIAN TO THE EDINBURGH ROYAL INFIRMARY.

It is well known that the nervous symptoms due to subacute combined degeneration of the spinal cord may be developed a considerable time before the anaemia or cachexia which usually precedes or accompanies the symptoms due to the degenerative changes in the spinal cord. In cases of this kind the diagnosis is sometimes very difficult, more especially in the early stages of the case; disseminated sclerosis in particular may be very closely simulated. In the following case, in which the nervous symptoms were developed three years before the anaemia became sufficiently marked to attract attention, this difficulty in diagnosis was more striking than in any of the recorded cases of subacute combined degeneration with which I am acquainted. This was partly due to the early age (31) at which the cord symptoms developed, but chiefly to the facts: (1) That, in addition to ataxic-spastic paraplegia, nystagmus and derangements of the bladder and rectum, optic atrophy, exactly resembling that characteristic of disseminated sclerosis, was present; and (2) that remarkable periods of improvement and relapse, so characteristic of disseminated sclerosis, occurred. The case is also important and exceptional inasmuch as the profound anaemia which developed a fortnight before death was typical pernicious anaemia, megalocytes were present in the blood during life, and the free iron reaction was very marked in the liver and kidneys after death. The notes of the case are as follows:

A man, aged 33, married, a hairdresser by trade, was admitted to the Edinburgh Royal Infirmary on September 18th, 1906, complaining of difficulty in walking and a tight feeling across the stomach.

History.

The patient, who denied any venereal disease, stated that he enjoyed good health until October, 1904, when he had an attack of influenza. After this he noticed that his legs were weak, and that his sight was becoming impaired; he however continued to work without much complaint until January of the present year (1906); he then had another attack of influenza. After this his legs were for a time much weaker, and he complained of a feeling of numbness, tingling, and pins and needles in the legs, buttocks, and lower part of the back. Since this second attack of influenza his sight has become much worse. He continued to follow his occupation until three weeks ago, when his walking became very unsteady, and he noticed that in walking he dragged his legs. Two months ago he felt giddy when getting up in the morning or when he turned quickly. For the past five or six weeks he has felt a tight feeling across the upper part of the abdomen, and his water has at times dribbled away. Since January he has been obstinately constipated. He has had no pain in the back and no lightning pains. There has been no affection of speech. During the past year he has become much "shorter in the temper." His social condition was quite satisfactory, and he had been a very steady man.

Family History.

Father, aged 53, is alive and well; mother died a year ago, at the age of 52, cause unknown. There were twelve children in the family: all died in childhood (causes of deaths not known) except one brother, who is abroad, and, as far as the patient knows, healthy. The patient has had six children; two died, at the ages of 14 months and 2½ years respectively, from inflammation of the brain (? meningitis); the four surviving children are alive and well. There have been no miscarriages.

Condition on Admission.

The patient was a spare, thin man. The body was fairly well clothed with fat; muscularity was poor. His height was 5 ft. 3½ in., and his weight 7 st. 1½ lb.; when in perfect health he used to weigh 8 st. 8 lb. in his clothes. The temperature was 97.6°, the pulse 74, and the respirations 20 per minute.

The mucous membranes were slightly anaemic. (I have no record of any blood examination at this date.) The appetite was poor; the tongue was rather red and raw; the bowels were obstinately constipated.

The patient walked with great difficulty and only with support. The gait was very ataxic and also spastic, the toes being dragged along the ground. There was marked Rombergism. The muscularity was poor, but there was no localized muscular wasting, and no definite paralysis of any muscle or group of muscles; the calves though small in size were firm. The knee-jerks and Achilles jerks were greatly exaggerated. There was no sustained ankle clonus, but a few clonic contractions were obtained in the right leg. The plantar reflex showed a double extensor response, more marked on the right side. The abdominal reflex was active on both sides. The deep reflexes in the upper extremities were normal. He complained of a feeling of numbness and tingling and coldness in the lower extremities, buttocks and lower part of the back, but no objective derangements of touch, pain, or heat and cold were detected. The sense of movement (muscular sense) in the lower extremities was distinctly impaired. The bowels were obstinately constipated; the functions of the bladder were distinctly affected (precipitant urination and some dribbling, but no loss of expulsive power). There was no lateral nystagmus, but distinct nystagmus on looking up, and especially on looking upwards and to the left. The pupils were equal, 4 mm. in diameter; they contracted actively to light and on convergence. The acuity of vision was much impaired— $\frac{1}{2}$ in each eye. There was distinct pallor of both optic discs, chiefly marked on the temporal sides, and greater in the right than in the left eye. There was no volitional tremor; no speech affection; and (at this stage) no pain in the back.

A soft systolic murmur was present in the aortic area, the aortic second sound was somewhat accentuated, but the heart, kidneys and other viscera appeared to be normal.

Diagnosis.

The condition was one of ataxic-spastic paraplegia. It was obvious that the patient was not suffering from tabes. The age at which the disease had developed, the absence of other cases in the family, the absence of foot deformity, and the presence of optic atrophy were against Friedreich's ataxia. The ataxic-spastic paraplegia, the nystagmus, the giddiness, the optic atrophy, the affection of the bladder and rectum, were indicative of disseminated sclerosis. The fact that the illness had commenced at the age of 31 in a perfectly healthy man who had not had syphilis, after an attack of influenza, seemed to support this diagnosis. The subsequent progress of the case—the marked improvement which resulted under treatment on two occasions (see *infra*)—was strongly in favour of this diagnosis. Granting, as was thought, that the patient was suffering from disseminated sclerosis, the peculiar character of the nystagmus (it was only present on looking up) was exceptional and interesting.

Treatment and Subsequent Course.

The patient was treated with rest in bed, massage and arsenic (5 minims of Fowler's solution three times daily). Rapid improvement took place; the patient's walking quickly improved; the bladder derangement disappeared. He was discharged from hospital on November 3rd, 1906, walking well and stating that he felt quite fit for work. The exaggeration of the deep reflexes, the double Babinski, the optic atrophy and the nystagmus were still present. For two months after his discharge from hospital the patient felt very well and was able to walk about and to do his work, which involved a lot of standing; weakness in the legs and difficulty in walking then again developed.

He was readmitted to the infirmary on February 20th, 1907. The ataxic-spastic paraplegia was very marked and he could only walk with support. The urinary difficulties had returned, and he now had to "force" in order to get the water away. He complained of an aching pain on the left side of the back, of numbness, pricking, and coldness in the legs, and of a sensation as if he were walking on rubber. The knee-jerks and Achilles jerks were markedly exaggerated; ankle clonus was now present in both legs; there was a marked double extensor response; the abdominal reflexes were still very active on both sides. The vertical nystagmus and the pallor of the optic discs were more marked. Dr. Sym kindly examined the eyes and reported as follows:

"The acuity of vision in right eye is $\frac{1}{2}$, and in left eye $\frac{1}{4}$. The optic discs are distinctly paler than normal, especially on their outer sides. The retinal vessels are slightly reduced in size."

The patient was again treated with arsenic and again improved. On May 8th he was discharged, able to walk well with the help of one stick and saying that he was fit for work.

For three months after his discharge he continued well and was able to follow his occupation. Then the weakness in the legs and difficulty in walking again occurred, and he began to suffer from pain in the back.

On October 15th, 1907, he was admitted to the infirmary for the third time, unable to walk without support; the gait was still very ataxic and spastic; Rombergism was marked. The patient complained of severe pain in the lower part of the back and in the legs, numbness and tingling in the feet, and a cold feeling in the knees and elbows.

The knee-jerks and Achilles jerks were still markedly exaggerated; ankle clonus and an extensor response were present on both sides. There was considerable difficulty in

making water; the bowels were still obstinately constipated. The vertical nystagmus and optic atrophy were still present. There was no volitional tremor and no speech affection.

He was treated by rest in bed, arsenic, and phenacetin (for the pain in the back and legs). For the first fortnight after readmission he distinctly improved, but on October 28th he complained of a discharge from the nose, and was sent to the throat department. Dr. Logan Turner, who kindly examined him, reported, "he has some obstruction and nasal discharge." He advised an alkaline nose wash.

On November 11th a blood count showed: Red corpuscles, 4,200,000; haemoglobin, 70 per cent.; colour index, 0.8; whites, 8,000.

After this date the patient rapidly became profoundly anaemic, the blood picture being typically characteristic of pernicious anaemia. The legs became completely paralysed, the muscles soft and atrophied; the knee-jerks, Achilles jerks, and the ankle clonus disappeared; the Babinski sign remained; the legs and lower part of the trunk and abdomen became anaesthetic, and incontinence of the bladder and rectum developed; he became semi-comatose and finally comatose.

On November 19th the blood count was as follows: Red corpuscles, 1,500,000; haemoglobin, 28 per cent.; colour index, 0.9. On microscopic examination the red corpuscles were found to be markedly altered in size and shape; some normoblasts and megaloblasts were present. The feet and legs were oedematous, and the temperature, which had throughout the previous course of the case been normal or subnormal, began to rise, and showed marked fluctuations; the highest point reached was on November 23rd, when the morning temperature was 101.8°.

On November 25th the red corpuscles numbered 600,000 per cubic millimetre, and the haemoglobin was 28 per cent., the colour index = 2.3. On November 26th the patient became unconscious.

He died on November 27th.

The blood count at different dates was as follows:

Date.	Number of Red Corpuscles.	Percentage of Haemoglobin.	Colour Index.
November 11th, 1907...	4,200,000	70	0.8
November 15th, 1907...	1,500,000	28	0.9
November 21st, 1907...	1,190,000	25	1.0
November 23rd, 1907...	980,000	25	1.3
November 25th, 1907...	600,000	28	2.3

Post-mortem Examination.

This was made on November 28th, 1907. There was extreme pallor of the skin and mucous membranes; the muscularity was poor, the subcutaneous fat scanty; the feet and ankles were slightly oedematous.

The appearances were typical of progressive anaemia: Marked fatty degeneration of the myocardium, liver, and kidneys; very marked iron reaction in the liver and kidneys; typical red appearance of the bone marrow. There were no

punctiform haemorrhages. The spleen was firm and somewhat enlarged.

There was slight atheroma at the root of the aorta. The upper lobes of the lungs were somewhat emphysematous, the lower lobes oedematous and congested. There were no gross changes in the stomach, intestine, pancreas, suprarenals, or thymus.

The brain was markedly anaemic, but showed no gross lesions.

Spinal Cord.

After hardening, the spinal cord was cut and stained in various ways. The membranes and nerve roots, posterior and anterior, were healthy.

Degenerative changes, typical and characteristic of subacute combined degeneration, were found in the spinal cord (see Figs. 1, 2, 3, and 4).

These changes were most marked in the mid-dorsal region, and diminished as one proceeded upwards and downwards to the top and bottom of the cord.

In the mid-dorsal region there was extensive degeneration of

the posterior columns, the crossed pyramidal tracts, the direct cerebellar tracts, and the direct pyramidal tracts. In the lateral columns, more especially on the right side, the degeneration extended much further forward than the direct cerebellar

tract. In the anterior column, too, the degeneration invaded a much more extensive area than the direct pyramidal tracts. In the posterior columns in the mid-dorsal region a large area of normal fibres was present on the inner side of the grey matter and posterior horns. Lissauer's tracts were not involved.

In the cervical enlargement the lesion in the posterior columns was confined to the columns of Goll (postero-internal columns) and to a narrow tract of the postero-external columns (column of Burdach) on the surface of the cord. In the lateral columns the direct cerebellar tracts were completely sclerosed, and the crossed pyramidal tracts to some extent sclerosed; on the right side the sclerosis extended farther forward than the direct cerebellar tracts (as it did in the mid-dorsal region). In the anterior columns the sclerosis involved the direct pyramidal tracts more extensively

on the left than on the right side.

In the lumbar enlargement the posterior columns were sclerosed in a patchy manner, the involvement of this part of the cord being much less extensive than in the mid-dorsal region. The crossed pyramidal tracts at this level (greatest thickness of the lumbar enlargement) were also involved.

Many of the nerve cells in the anterior horn in the dorsal, lumbar, and cervical regions, and the cells in Clark's column, were degenerated, as shown by Nissl's method.

This case presents many points of great interest; the more important are the following:—

1. The fact that the optic atrophy and cord symptoms developed three years before the pernicious anaemia became sufficiently marked to attract attention. It is true that when the patient first came under observation the mucous membranes were slightly anaemic, but the anaemia was so slight that no blood examination was made; the anaemia only attracted attention and became a feature of the case a few weeks before death. The obvious lesson which this teaches is that a careful blood examination should be made in all cases of (supposed)

Fig. 1.—Section through the cervical enlargement of the spinal cord in the case of subacute combined degeneration described in the text. (Stained by Weigert-Pal.)

Fig. 2.—Section through the mid-dorsal region of the spinal cord in the case of subacute combined degeneration described in the text. (Stained by Weigert-Pal.)

Fig. 3.—Section through the lower dorsal region of the spinal cord in the case of subacute combined degeneration described in the text. (Stained by Weigert-Pal.)

Fig. 4.—Section through the lumbar enlargement of the spinal cord in the case of subacute combined degeneration described in the text. (Stained by Weigert-Pal.)

disseminated sclerosis and in all cases of ataxic and ataxic-spastic paraplegia. The facts of this case, in my opinion, strongly support the view that in cases of subacute degeneration the cord lesions are not directly due to the anaemia or to haemorrhages in the spinal cord the result of the anaemia (it has been stated that no punctiform haemorrhages were present in this case in any of the organs), but that the degenerative lesions in the spinal cord and the anaemia, which in this case was typically pernicious anaemia, are due to a common cause—a toxin, the exact nature of which we are still ignorant of. In the majority of cases of subacute combined degeneration which have been recorded, the anaemia was not pernicious anaemia. In speaking of their cases Risien Russell, Batten, and Collier state—"There was nothing in the blood of any of the cases in which it was examined to suggest pernicious anaemia."¹

2. *The very rapid way in which the pernicious anaemia developed and proved fatal.* The blood changes in the terminal stages of the case were characteristic of pernicious anaemia, and the post-mortem appearances (free iron reaction in the liver and kidneys and changes in the bone marrow) were typical of this disease. The Prussian blue (free iron) reaction in the liver and kidneys was intense; I have never seen it more marked in any of the cases of pernicious anaemia which I have examined. This is a very interesting point, for in his article on subacute combined degeneration in the forthcoming volume of Clifford Allbutt and Rolleston's *System of Medicine* (a proof of which he has kindly sent me), Dr. Collier states: "The reaction for free iron in the liver has not been obtained in any case."

3. *The difficulty in diagnosis in the early stages.* The symptoms were undoubtedly most suggestive of disseminated sclerosis—none of us who saw and studied the case doubted that we were dealing with a case of disseminated sclerosis.

4. *The age at which the cord symptoms developed* (31), as has been previously pointed out, was much more suggestive of disseminated sclerosis than of subacute combined degeneration. Subacute degeneration of the spinal cord very rarely develops before the age of 35; most cases occur between the ages of 50 and 60; while in the great majority of cases (85 per cent. of 110 cases which had come under my observation up to the year 1904) disseminated sclerosis develops before the age of 35. In my 110 cases of disseminated sclerosis no less than 47, or 42 per cent., commenced between the ages of 21 and 25 years (inclusive); 76, or 69 per cent., between the ages of 16 and 30 years (inclusive); and 85, or 77 per cent., between the ages of 16 and 35 years (inclusive).²

5. *The optic atrophy* was strongly in favour of disseminated sclerosis. Optic atrophy is not a feature of subacute combined degeneration of the spinal cord, but it occurs, in my experience, in about 40 per cent. of cases of disseminated sclerosis. In my 110 cases of disseminated sclerosis, definite optic atrophy was present in 40 cases, or 36.3 per cent., and in 7 other cases, or 6.3 per cent., doubtful optic atrophy was present.³ My additional experience since the year 1904 points in the same direction. The optic atrophy in this case exactly resembled that which is met with in disseminated sclerosis—partial in degree and chiefly confined to the temporal sides of the discs. The acuity of vision was in this case more markedly impaired than it is in most cases of disseminated sclerosis. Further, it is important to note that the dimness of vision was in this case one of the initial symptoms; it developed three years before the anaemia attracted attention. The dimness of vision and the pallor of the discs were without doubt due to optic atrophy and not merely to anaemia or debility.

6. *The remarkable periods of improvement with subsequent relapses* which occurred in this case were highly suggestive of disseminated sclerosis; such alleviations in the severity of the symptoms are not a feature of subacute combined degeneration, but are most characteristic of disseminated sclerosis. On this point, Risien Russell, Batten, and Collier state: "A remarkable feature of the cases was the absence of any improvement of the nervous symptoms under treatment. From the first appearance of the disease to the fatal event, the tendency was for the symptoms to increase, sometimes halting, sometimes progressing rapidly, but never showing any remission. Under

treatment the general health and the anaemia improved markedly in some cases, but the nervous symptoms never."⁴

Dr. James Collier, whom I have consulted with regard to the occurrence of optic atrophy and relapses, remissions and periods of improvement in cases of subacute combined degeneration, kindly writes me as follows:

I have just written the article on subacute combined degeneration for *Allbutt's System*, and I have been carefully into all the cases we have had at Queen Square, and also into all the cases that I have found in the literature. I make the following statement upon optic atrophy: "Optic atrophy has been reported in a good many cases, but it is possible that the pallor of the disc, which is striking in some of the anaemic cases, has been confused with optic atrophy, for I have never myself seen undoubted atrophy of the disc. Dimness of vision is common when anaemia and debility are severe." In several of our cases at Queen Square the note that optic atrophy was present had been made by the house-physician, but in no case was this opinion upheld by Mr. Marcus Gunn and Mr. Paton, who subsequently saw these patients. We have not as yet found any lesions higher than the mesencephalon, and, from the anatomical point of view, one would not expect optic atrophy in this disease. Your second question is of great interest, and is one that I should have answered in the negative two years ago. But since then I have followed to autopsy (1) cases in which the onset was an apparently functional paraplegia which improved for a time, (2) cases in which there was marked temporary improvement, and (3) one case in which the onset was so rapid as to suggest acute myelitis, and in which temporary attacks of paraplegia lasting a week or two had occurred eight months and four months before the onset respectively and had been completely recovered from. This last case was an unusually rapid one, but the pathological condition found by Dr. Holmes was typical. I have always pointed out that the diagnosis of this disease in the early stages from the ataxic paraplegic form of disseminated sclerosis was an important one, but we have not had a case in which this differential diagnosis has been difficult. From our knowledge of the disease and its anatomy it seems to me easy to conceive cases of slow onset in which the clinical picture might be exactly that of typical disseminated sclerosis, for many cases present no anaemia till late.

7. *The vertical character of the nystagmus* was peculiar and interesting.

With regard to the differential diagnosis of subacute combined degeneration of the spinal cord and disseminated sclerosis, Risien Russell, Batten, and Collier make the following statements:

The early clinical picture of combined degeneration, that of slight ataxy and spasticity, resembles closely that of the common paraplegic form of disseminated sclerosis in an early stage. . . . In attempting to distinguish these two diseases careful attention should be paid to the history. The age at which combined degeneration occurs is not the most common for the appearance of symptoms of disseminated sclerosis. The preponderance of subjective sensations in the legs, the absence of the functional manifestations, of exacerbations and remissions of the symptoms, of nystagmus, and of sphincter trouble, which are so usual in disseminated sclerosis, and the presence of irregular pyrexia are probably of great importance in the early diagnosis of combined degenerations.

The presence of anaemia in an early case of spastic paraplegia should give rise to a suspicion, but the possibility of chlorosis associated with disseminated sclerosis in young women must be borne in mind. A symmetrical affection of all limbs with slight ataxy and spasticity, preponderating in the legs, is a most important distinguishing symptom of combined degeneration.⁵

In the case I am recording all the differential points mentioned by Risien Russell, Batten, and Collier in favour of disseminated sclerosis were present, and, in addition, there was optic atrophy. According to these authorities, the preponderance of subjective sensations in the legs was in favour of subacute degeneration; but, on the other hand, the absence of any objective disturbance of skin sensation until the final stages of the case was, in my opinion, in favour of disseminated sclerosis.

8. The cord lesions were striking, and corresponded exactly with those which have been described by Risien Russell, James Taylor, and other observers as characteristic of subacute combined degeneration of the spinal cord associated with anaemia.

REFERENCES.

- ¹ *Brain*, 1900, vol. xxiii, p. 56. ² *Clinical Studies*, 1904, vol. ii, p. 201.
³ *Ibid.*, 1905, vol. iii, p. 23. ⁴ *Ibid.*, p. 54. ⁵ *Brain*, 1900, vol. xxiii, p. 58.

THE eighty-second congress of German scientists and medical men will be held at Königsberg from September 18th to the 24th. Full particulars can be obtained from Dr. Rosenstock, Königstrasse 80, Königsberg.