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SPINAL SYMPTOMS WITH LYMPHADENOMA

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INTRODUCTION

IN the course of lymphadenoma involvement of the central nervous system appears to be uncommon. Detailed observation shows however that the incidence of neurological complications is probably higher than is suggested by casual inspection. Ginsburg found clinical evidence of involvement of the brain or spinal cord in ten of 36 cases of Hodgkin's disease. On the other hand, Forrest found that during 20 years at the London Hospital only four cases had shown evidence of involvement of the spinal cord. In one of these cases autopsy revealed syringomyelic cavitation.

In a review of 37 cases of Hodgkin's disease with involvement of the central nervous system Johnsson found the brain involved in eight and the spinal cord in 29 cases. Weil, summarizing 46 cases of involvement of the spinal cord in Hodgkin's disease, found dorsal segments affected in 80 per cent., cervical segments in 16 per cent., and lumbosacral segments in 4 per cent.

PATHOGENESIS OF SPINAL SYMPTOMS

The spinal symptoms and the changes in the spinal cord are produced in various ways.

1. In a small number of cases the vertebræ are invaded by lymphadenomatous tissue. Destruction of the bone may be followed by dislocation of the spine and direct mechanical compression of the spinal cord. In Lemierre and Augier's case lymphadenomatous tissue had invaded the cervical vertebræ, the spine was dislocated and the spinal cord was compressed. In McCallum's case of typical Hodgkin's disease there was an area of softening in the ribs. The patient died suddenly. At autopsy the axis was found destroyed by erosion, the vertebral column was dislocated and the spinal cord was almost completely severed. A similar accident may have caused death in Paullin's case. The lower cervical and upper dorsal nerves on the right side were involved and the seventh cervical vertebra appeared to be destroyed. The patient developed what appeared to be an acute cerebral crisis and died.

Direct extension of lymphadenomatous tissue into the bodies of the vertebræ is probably more common than invasion of other bones because of the presence of large groups of lymph glands close to the vertebral column in the thorax and abdomen. In two of 13 cases analysed by Parkes Weber bodies of vertebræ were eroded and the spinal cord was compressed. In a case described by Forrest of a male, age 18 years, X-ray examination revealed extensive destruction of the upper dorsal and lower cervical vertebræ. In many cases, however, direct invasion of bodies of vertebræ does not occur even when large masses of diseased glands are adherent to the vertebral column in the thorax and abdomen. Parkes Weber and Bode, and East and Lightwood have described cases of this type.

Delius considered it possible that, after the vertebræ had been infiltrated, lymphadenomatous tissue might proliferate between the bone and the dura mater, press forward the dura and thus compress the spinal cord; but cases in which this sequence can be demonstrated or even assumed are rare. That of Carslaw and Young is the only one in the available literature in which it was demonstrated anatomically that infiltration of the vertebræ was associated with involvement of the membranes as a cause of symptoms of abnormality in the spinal cord.

2. The commonest finding is masses of abnormal tissue in the neighbourhood of the vertebral column, epidural deposits of lymphadenomatous tissue and no invasion of the bone itself. In Parkes Weber's original case a young man with Hodgkin's disease affecting the glands of the neck developed paraplegia late in the course of the disease. Autopsy revealed lymphadenomatous infiltration of the epidural fat. In a further case reported by Parkes Weber and Bode enlarged retroperitoneal glands, partly necrotic, were firmly adherent to the vertebral column. The bone was unaffected. There was 'diffuse lymphogranulomatous infiltration of the epidural fat on the dorsal aspect of the whole of the thoracic spinal cord, especially in the upper part.' Epidural deposits were present without direct invasion of the bone or dura mater in seven of Parkes Weber's 13 cases. Weil found invasion of the epidural space by lymphadenomatous tissue in 85 per cent. of 46 cases. In a

further 7 per cent. he found some disease of the retroperitoneal and intra-thoracic lymph glands, paraplegia and scar tissue in the epidural space. He interpreted this scar tissue as an indication that there had existed previously lymphadenomatous tissue capable of producing spinal cord symptoms.

Parkes Weber described the pathology in his original case as lymphadenomatous thickening of the periosteum of the vertebræ and quoted six cases (one doubtful) from other authors. In discussing the case reported with Bode however he drew a distinction between infiltration of the epidural space alone and the association with it in some cases of involvement of the periosteum in front of the epidural fat.

The manner and route of extension of lymphadenomatous tissue to the epidural space demand consideration. Infiltration of the bodies of the vertebræ and extension later to the epidural fat is obviously unusual. Equally improbable is extension by other than a direct route, for in a large number of cases abnormal tissue in the epidural space is associated with frank disease of glands in the neighbourhood of the vertebral column. Some observers have described lymphadenomatous tissue in the mediastinal and retroperitoneal glands, in the intervertebral foramina with the nerve-roots and in the epidural space, and have concluded that the abnormal tissue extends by a direct route from the affected glands through the intervertebral foramina to the epidural space. East and Lightwood, Delius, and Schaeffer and Horowitz demonstrated epidural deposits within the spinal canal and invasion of the intervertebral foramina. In East and Lightwood's case the lymph glands were involved generally and the back muscles were infiltrated with lymphadenomatous tissue which formed masses about the sixth and seventh and the first and second thoracic spines. At these levels the intervertebral foramina were full of deposit. A similar condition was present in Parkes Weber's Case 14. These workers also demonstrated invasion of the nerve-roots in the intervertebral foramina; and M. J. Cooper concluded from a study of his case and of the literature that the nerve-roots afforded a channel by which lymphadenomatous tissue might reach the subdural space, probably through the lymph spaces of the roots rather than by the substance of the nerve-fibres.

Thus symptoms of paraplegia may result from direct compression of the spinal cord by epidural deposits of lymphadenomatous tissue.

3. Extension of lymphadenomatous tissue from the epidural to the subdural space is less common, but has been demonstrated by Urechia and Goia, Johnston, During and Delius. M. J. Cooper regarded the spinal dura mater as relatively more resistant to extension than the septa of the nerve-roots, and from examination of his case concluded that penetration to the subdural space was probably by the latter route.

4. Invasion of nerve-roots in the intervertebral foramina has been demonstrated by East and Lightwood, Delius, and Schaeffer and Horowitz. Craver and Haagensen found seven cases of secondary herpes zoster in 329

cases of lymphosarcoma, Hodgkin's disease and leukæmia, and suggested that it was the result of invasion of nervous structures by the tumour masses. In four cases the herpes and the tissue mass were in the same general anatomical region.

5. M. J. Cooper concluded that spinal symptoms resulted not only from compression of the spinal cord by epidural collections of lymphadenomatous tissue, but also from compression or invasion of bloodvessels which accompany spinal roots. In Walthard's case the changes in the spinal cord were greater than would have been expected from direct pressure by an extradural tumour. They were thrombosis of bloodvessels, inflammatory and necrotic changes, and extensive softening in the spinal cord. It was suggested that the sequence of events was invasion of vessels in the tumour mass by lymphadenomatous tissue, congestion of vessels in the spinal cord and degeneration within the substance of the spinal cord.

6. It has been pointed out by E. L. Cooper that in the minority of cases there is no evidence of pressure on the spinal cord or spinal roots, or of obstruction of the circulation. In 8 per cent. of 46 cases analysed by Weil lymphadenomatous tissue had not invaded the spinal canal. In one case described by Forrest the spinal symptoms were due to syringomyelia. In the others there are found either long-tract degeneration, changes resembling those of acute myelitis or changes which are difficult to interpret or to relate directly to the lymphadenoma. Parkes Weber and Bode suggest however that if the epidural fat were examined as a routine, even when no nervous symptoms were recorded, lymphadenomatous infiltration of it would be found more often.

In Forrest's case the columns of Goll in the cervical cord and the central part of the dorsal columns in the remainder of the spinal cord were slightly degenerated. The ventrolateral and left lateral pyramidal tracts in the upper cervical region, both lateral pyramidal tracts in the sacral region and the cells of the anterior horns throughout the spinal cord were similarly affected. Allan and Blacklock's case showed spastic paraplegia with sensory symptoms. Shortly before death the left arm and face became weak and hemiplegia developed. At autopsy there was found acute meningitis with purulent infiltration over the base of the brain and the upper cervical cord. On histological examination no lymphadenomatous tissue was found in any part of the central nervous system. Robinson treated a patient suffering from Hodgkin's disease for 12 years with X-rays and radium. X-ray examination showed increased density of the body of the eighth dorsal and fourth lumbar vertebræ. Symptoms of transverse myelitis developed rapidly and corresponded to the level of the ninth dorsal segment. Critchley and Greenfield drew attention to the appearance of the characteristic clinical picture of subacute combined degeneration of the spinal cord in association with Hodgkin's disease and quoted McAlpine's case.

Discussing the occurrence of spinal symptoms in the course of leukæmia

and chloroma Critchley and Greenfield found cell masses in relation to the dura mater in four personal cases, and considered that the supposition that paraplegia was produced by pressure was not altogether supported by microscopical examination. Infiltration of the spinal meninges was recorded in 12 cases of chloroma and five cases of leukæmia, and in some had involved the anterior and posterior spinal roots and later the neighbouring muscles outside the spinal column by way of the intervertebral foramina. The secondary changes in the spinal cord were due to anæmia, hyperæmia with the possibility of acute myelitis, or compression as a partial factor. It was possible that the partial anoxæmia inseparable from severe anæmia might in many cases contribute to the effect produced by compression or thrombosis of the spinal arteries, but it was improbable that any degree of anæmia compatible with life could, of itself, so lower the nutrition of the nervous tissues as to lead to its disintegration.

CASE REPORTS

The two cases described in this paper fall into the indefinite group of cases in which unequivocal evidence of Hodgkin's disease was associated with spinal cord symptoms without the extension of lymphadenomatous tissue inside the spinal canal.

Case I.—A male, age 34 years, was admitted on January 13, 1934. One week before he felt pain in the lower part of the back which he thought was due to jarring it at work. Since then he had felt tired and had suffered from vomiting, diarrhœa, loss of appetite and slight frontal headache. For three days vision had been dim. He had not felt perfectly well for 18 months. One year before, glands were noticed to be enlarged. They had varied in size since and were large for three weeks before admission.

He was pale and his skin was cold and moist. Temperature, pulse rate and respiration rate were normal. The heart was normal. There was fullness of the right lower chest, movement of this part with respiration was diminished, and breath sounds were faint at the base of the right lung. The abdominal wall was retracted. The edge of the liver was felt $1\frac{1}{2}$ inches below the right costal margin; and the spleen was felt 1 inch below the left costal margin. Examination of the central nervous system revealed no gross abnormality. The right submandibular, left and right axillary, and left and right inguinal glands were enlarged. The superficial cervical, upper and lower deep cervical and supraclavicular glands were slightly enlarged. The glands were firm, elastic, only slightly tender, discrete and mobile. Nothing abnormal was found in the spine.

X-ray examination of the lumbar spine showed no gross abnormality. The fæces contained occult blood. The urine was acid and contained a moderate amount of albumen. The deposit contained numerous hyaline casts, a few polymorph cells and numerous cylindroids. The blood Wassermann reaction was negative. The total non-protein nitrogen was 43 mgm. per 100 c.cm. of blood. The red blood count was 5,900,000; the hæmoglobin percentage 122; and the colour index 1. The white blood count was 18,000 and a differential count showed the following percentages: polymorphs, 9; lymphocytes, 11; mononuclears, 1; eosinophils, 78; and basophils, 1. The red blood cells were normal in the stained film.

During the first week in hospital he complained of weakness and numbness of the hands and legs. When examined on the ninth day the functions of the cranial nerves were normal. In the upper limbs, motor power was diminished, especially in the right arm and both hands; muscle tone was lowered; the biceps-jerks were absent and the supinator- and triceps-jerks were faint; and sensibility for pinprick was diminished over both hands to the wrists. In the lower limbs motor power was poor for all movements and muscle tone was below normal. The knee- and ankle-jerks were not elicited and both plantar reflexes were flexor. Sensation for pinprick was diminished over a short stocking area to above the ankles; and appreciation of changes in position of the left toes was impaired. The abdominal reflexes were not elicited.

On the eleventh day the white blood count was 11,000. There were 28 per cent. of polymorphs, 7 per cent. of lymphocytes, and 64 per cent. of eosinophils. The red blood cells showed slight changes in size and colour. On the thirteenth day cerebrospinal fluid was withdrawn from the fourth lumbar interspace. Jugular compression increased the pressure of the fluid. The fluid was slightly yellow and a small web of clot appeared in it on standing. The Pandy test showed a marked increase of globulin. There were six small round cells per c.mm. The Wassermann reaction was negative.

The patient was examined personally 14 days after admission. Four days before he was described as very weak, and the left upper eyelid drooped. On the day of examination he complained of sensations of pins and needles in the hands. The patient was in distress and examination was limited. The functions of the cranial nerves were normal. In the upper limbs motor power was much limited. The patient could only lift both hands and let them fall. Muscle tone was poor. The supinator- and biceps-jerks were not elicited and the triceps-jerks were faint. The Mayer thumb-reflex was present on both sides. Sensation for cottonwool, pinprick, deep pressure, vibration and changes of position was normal. In the lower limbs motor power was limited to the following movements. He could dorsiflex the feet slowly, plantar-flex them slowly and lift the knees about 1 inch from the bed. Other movements were impossible. Muscle tone was poor to flaccidity. The knee- and ankle-jerks were not elicited; and stimulation of the soles of the feet was followed by a faint movement of flexion. Sensation for cottonwool and pinprick was normal. Deep pressure was not appreciated. Vibration was not felt over the right malleoli and only faintly over the left malleoli. Attempts to recognize changes in position of the toes resulted constantly in gross errors. The abdominal reflexes were not elicited. The abdominal wall was held rigid and there was no movement with respiration below the costal margins. The patient was breathing with difficulty. Inspiration was forced and with each inspiratory movement the accessory muscles became tense. With each inspiration there was general expansion of the chest above the level of the third or fourth ribs, while below that level there was no evidence of action of the intercostal muscles or of the diaphragm.

During the first week in hospital a gland was removed from the right inguinal region for examination. The gland architecture was entirely altered. The differentiation between follicles and sinuses was lost. The gland showed a uniform structure consisting of lymphoid cells and many large clear cells, some of which had giant multilobed nuclei. The gland was infiltrated throughout with eosinophils and there was a moderate amount of eosinophilic infiltration of the capsule.

The temperature rose to 101° F. the day before death; the pulse rate rose steadily from 70 to 130 during the time in hospital; and from the seventh day the respiration rate rose to 25. The patient died 18 days after admission to hospital.

The body was examined nine hours after death. There were masses of discrete glands on both sides of the neck, in the axillæ and in the groins; and similar masses of soft and fleshy glands in the mediastinum along the aorta, at the hilum of the lungs and at the root of the mesentery. The spleen was enlarged and weighed 2 lb. 6 oz.

The liver was enlarged and soft, and showed pale nodules on the surface. The internal organs showed some degree of decomposition, the lungs were congested and there was nothing abnormal in the heart. The spinal column was normal. The brain was congested.

There were no naked-eye changes present in the spinal cord or its coverings. No lymphadenomatous deposits could be found in the neighbourhood of the intervertebral foramina. The dura was of normal thickness and appearance. The cord itself presented no areas of softening and the normal outline in cross-section was preserved throughout its length. The microscopic appearances showed little departure from the normal. There was congestion of the small vessels, both in the cord substance and in the pia-arachnoid. This was associated with some oedema in all regions. In the midthoracic region there were isolated lymphocytes in both the white and grey matter; but neither perivascular cuffing nor definite inflammatory collections were present. There was no tract degeneration. In the thoracic segments the anterior horn cells were spherical in shape but no nuclear changes could be demonstrated.

Summary of Case I.—In the course of an illness of short duration, during which sections of a lymph gland showed changes characteristic of Hodgkin's disease, there appeared symptoms of interruption of the spinal cord. No collections of lymphadenomatous tissue were found in the intervertebral foramina or within the spinal canal. The changes in the spinal cord were very slight compared with the gross effects observed clinically.

Case II.—A male, age 53 years, was admitted on February 10, 1933. He complained of pins and needles in the lower limbs and weakness of the legs of three weeks' duration. Previous illnesses were erysipelas and an operation for hydrocele. On examination, glands below the left angle of the jaw were enlarged; there was a systolic murmur in the aortic region and the lower pole of the right testicle was swollen. The remainder of the clinical examination revealed no abnormality.

Before the patient came under personal observation the following special examinations were made. The urine was normal. The blood Wassermann reaction was negative. The red blood count was 5,070,000; the percentage of hæmoglobin 100 and the colour index 1. The white blood count was 7,400 and a differential white count showed the following percentages: polymorphs, 62; lymphocytes, 24; eosinophils, 3; and basophils, 1. The red blood cells were normal. The pressure of the cerebrospinal fluid was increased by jugular compression. The fluid was clear and contained 17 small round cells per cubic millimetre. The Pandy test showed a marked increase of globulin. The Wassermann reaction was negative. Histological examination of a gland from the right groin showed the following. The gland was swollen and its structure was abnormal. Isolated germ follicles were absent, and diffuse endothelial hyperplasia was apparent throughout the tissue. A few large mononuclear cells closely resembling Dorothy Reed cells were seen.

On February 23, the glands of the axillæ and groins were enlarged. The lower limbs were becoming weak. On examination, the functions of the cranial nerves were normal. Sensation for pinprick was impaired over the hands and forearms. Motor power was diminished in the lower limbs. The right knee-jerk was more active than the left; and both plantar reflexes were extensor. Sensation for pinprick was diminished over the feet.

The patient was examined personally on March 3. Cooperation was good but failed steadily during the examination. The voice was weak and there was some weakness of the facial muscles for voluntary movements. Otherwise the functions of the cranial nerves were normal. In the upper limbs motor power was moderate and

muscle tone was diminished. The supinator- and biceps-jerks were not elicited, and the triceps-jerks were present. Sensation for cottonwool, pinprick, deep pressure, vibration and changes of position was normal. The abdominal reflexes were not elicited. In the lower limbs only slight and limited movements were possible at the knees, ankles and toe joints. Muscle tone was diminished to flaccidity. The knee- and ankle-jerks were present and equal; both plantar reflexes were extensor. Sensation for cottonwool and pinprick was normal; that for deep pressure, vibration and changes in position was absent. The submaxillary, upper cervical, epitrochlear and inguinal lymph glands were slightly enlarged. The abdomen was distended; no enlargement of the spleen was found. The heart and chest were normal. The bladder functions were undisturbed.

On March 14, the patient's general condition was unchanged. The voluntary movements of the lower limbs were less than before. There was no difficulty with the bladder. Two days before, spontaneous sensations of numbness and pins and needles had disappeared from the upper and lower limbs. A loose cough had appeared. On examination, the functions of the cranial nerves were unchanged. In the upper limbs motor power and muscle tone were decreased. Movements of the fingers, hands and forearms were weak and clumsy. The supinator- and biceps-jerks were not elicited; the triceps-jerks were present; and the Mayer thumb reflexes were absent. Changes in position of the fingers were not recognized. Other types of sensation were normal. In the lower limbs only faint movements were possible at the knee and ankle joints. The tone of the extensor muscles at the ankles was increased; elsewhere the muscles were flaccid. The knee-jerks were present; the ankle-jerks were not elicited; both plantar reflexes were extensor. Sensation for deep pressure, vibration and changes in position of the toes was absent. The skin was glossy and firm and pitted on pressure. In the chest, at the left base expansion was diminished, the percussion note was dull, and breath sounds were faint. The white blood count was 8,600 and the percentage of eosinophils had risen to 13.

On March 22, the patient stated that he often had sensations of feeling solid objects in the right and left hands. He felt that a solid object was present in his hand and on looking was surprised to find that there was nothing there.

On April 17, it was noted that for two weeks wasting of the upper limbs was becoming evident. It affected chiefly the small muscles of both hands and to a lesser extent the muscles of the forearms and upper arms. It was more obvious distally and in the right upper limb than in the left. The supinator-, biceps- and triceps-jerks were active. The bladder functions were normal. The lower limbs were unchanged.

In the meantime examination of the blood and cerebrospinal fluid was repeated. The red blood cell count was 5,160,000, the percentage of hæmoglobin 100 and the colour index 1. The white blood count was 8,000, and a differential white count showed the following percentages: polymorphs, 51; lymphocytes, 23; eosinophils, 6; transitional cells, 5; and basophils, 4. The red blood cells were normal. The cerebrospinal fluid contained 23 small round cells per c.mm., and the Pandy test showed a moderate increase of globulin.

The condition of the patient then continued unchanged for 10 months with the following exceptions. In June, 1933, there was precipitancy of micturition for one week followed by a week during which there was delay in beginning micturition. In August, 1933, the bowels sometimes moved involuntarily. The bladder was unaffected. In November, 1933, there occurred a respiratory infection. Histological examination of an inguinal lymph gland showed changes similar to those at the previous examination. Masses of large clear cells like hyperplastic endothelial cells extended throughout the gland, as did also masses of eosinophils. The amount of fibrous tissue was insignificant. The large clear cells seen before were now numerous.

An attack of erysipelas of the face occurred in December, 1933. In February, 1934,

the patient complained of aching in the suprapubic region. There had been precipitancy of micturition. Blood was passed by the rectum. The upper limbs were recovering and the patient could use his hands. Only slight movements were possible in the lower limbs. In March, 1934, the knee- and ankle-jerks were elicited and both plantar reflexes were flexor.

In August, 1934, motor power was fairly good in the upper limbs and control over their movements was satisfactory. Motor power was improving in the legs and muscle tone was increased in the extensor muscles. The knee-jerks were very active and both plantar reflexes were extensor. Sensation for pinprick over both lower limbs was delayed. The red blood count was 4,300,000, the percentage of hæmoglobin 80 and the colour index 1. The white blood count was 12,000; the percentage of polymorphs was 58, of lymphocytes 26, and of basophils 16. The red blood cells varied in size and shape. The cerebrospinal fluid contained five small round cells per c.mm., and the Pandy test showed no increase of globulin.

The patient died on May 4, 1935. Post-mortem examination 18 hours after death showed the following. The lymph glands all over the body were enlarged to the size of a walnut, softened and matted together. When they were cut, they were very soft and the cut surface was of a peculiar grey colour. In the groin the enlarged glands were necrotic. The spleen was enlarged to three times the normal size and weighed 2 lb. The cut surface was red, the pulp was soft and there was no fibrosis. The liver was normal in size and showed only toxic changes. The left kidney was enlarged. Its cortex was swollen and contained numerous pinpoint abscesses. There was much pus in the left renal pelvis and ureter. The lungs were œdematous, and toxic changes were apparent in the heart muscle. There were no changes in the brain.

Nothing abnormal was discovered in the gross appearances of the spinal cord, meninges or vertebral column. Microscopic examination showed no tract degeneration. There was no excess of leucocytes in any part of the cord and no marked vascular changes could be demonstrated. There was some œdema of the cord in all parts. No histological changes could be demonstrated in the anterior horn cells.

Summary of Case II.—Within three weeks of the onset of an illness with enlargement of lymph glands there appeared symptoms of gross damage to the spinal cord. Section of a gland showed changes characteristic of Hodgkin's disease. Though some improvement of the neurological condition occurred, paraplegia persisted until death 28 months later. No collections of lymphadenomatous tissue were found in the intervertebral foramina or within the spinal canal. Neither naked-eye nor gross microscopical changes could be demonstrated in the spinal cord.

PATHOLOGICAL COMMENTARY

In the cases described the pathological findings were both negative and positive. In neither case were there involvement of bones of the vertebral column, collections of abnormal tissue in the epidural space or compression of the spinal cord. Bloodvessels were not obstructed. Within the spinal canal there were no abnormalities other than those of the pia-arachnoid and spinal cord. The positive pathological features differed somewhat in the two cases. In Case I the structure of the abnormal lymph gland was characterized by lack of definition, infiltration of the gland and capsule with eosinophil cells and the presence of many large clear cells with giant multi-

lobed nuclei. Other organs showed changes usually associated with an acute toxic process in the body. Changes in the spinal cord were diffuse and widespread. They consisted in extensive oedema, especially at the periphery and round bloodvessels, engorgement of bloodvessels, infiltration of the tissue with small round cells and changes in the nerve-cells, especially of the anterior horns. In Case II the structure of the abnormal lymph gland was characterized by lack of definition, diffuse endothelial hyperplasia and the presence of a few large cells closely resembling Dorothy Reed cells. The meninges and the spinal cord showed little abnormal. In neither case was there demyelination or degeneration of long tracts.

In Case I the changes were those of a very acute and active process affecting not only lymph glands and the spinal cord but also the other organs of the body. In Case II they were those of a more chronic process with secondary effects in the kidneys and no obvious end-results of an acute process in the spinal cord. There was a definite contrast between the effects of an acute tissue-response in the lymph glands, spinal cord and other tissues in the one case, and those of a more chronic process in the lymph glands and spleen in the other case. The most remarkable feature was the disparity between the severe clinical effects in both cases and the slight pathological changes in the spinal cord in Case I and the even slighter changes in Case II.

CLINICAL COMMENTARY

The first case was that of a man age 34 years who had not felt well for 18 months and in whom the size of lymph glands had varied for 12 months. Acute symptoms had been present for one week. The total non-protein nitrogen content of the blood was high and changes in the urine indicated functional damage to the kidneys. In the blood 78 per cent. of a white cell count of 18,000 were eosinophil cells—figures which fell 11 days later to 64 per cent. of 12,000. There appeared symptoms and physical signs of damage to nervous tissues; at first spontaneous sensations at the periphery of the upper limbs with diminution or loss of tendon reflexes, diminution of motor power and muscle tone and loss of sensation for pinprick over glove and stocking areas in both upper and lower limbs; and later loss of motor power below the upper dorsal segmental level, diminution of motor power, muscle tone and tendon reflexes in the upper limbs, and loss of sensation for deep pressure, vibration and changes of position in the lower limbs. The cerebrospinal fluid was slightly yellow, clotted on standing, and contained an excess of globulin and six small round cells per c.mm. The patient died 25 days after the onset of acute symptoms.

The histological changes in a lymph gland and the clinical findings were those of Hodgkin's disease. The neurological picture was that of an acute lesion of the lower cervical and upper dorsal segments of the spinal cord with an onset which suggested primary involvement of more peripheral nervous

structures. The changes in the cerebrospinal fluid suggested that the condition was probably inflammatory. The rapid enlargement of lymph glands for three weeks, the rapid lowering of the patient's resistance, the response of the blood with a white cell count of 18,000 and 78 per cent. of eosinophils, findings indicating acute lowering of renal function, the appearance of an acute lesion of the spinal cord with an increase of the globulin and cells of the cerebrospinal fluid, and intense infiltration of a lymph gland and its capsule with eosinophil cells—all pointed to the rapid activation in the body of a pathogenic agent which had already been attacking it in a mild way during the previous 18 months. The spinal cord symptoms would appear to have been the result of direct attack upon the spinal cord as well as upon tissues elsewhere in which the more characteristic response of the disease under consideration was evident.

In Case II the development of the condition and the clinical course were more prolonged. A man of 53 had spontaneous sensations in the lower limbs for three weeks. Submandibular lymph glands were enlarged. Five weeks from the onset there were changes in the lower limbs associated with damage to motor paths in the spinal cord and sensation for pinprick was diminished over the feet. Seven weeks from the onset, submandibular, axillary and inguinal lymph glands were enlarged; motor power and muscle tone were diminished and tendon reflexes were diminished or absent in the upper limbs; and in the lower limbs motor power and muscle tone were diminished, the plantar reflexes were extensor, and sensation for deep pressure, vibration and changes of position was absent. The blood contained 3 per cent. of eosinophils, increasing later to 13 per cent., and the cerebrospinal fluid contained excess globulin and 17 small round cells per c.mm.

In Case II the clinical picture was established in six weeks, whereas in Case I it was completely established within one week from the onset of the acute phase. In the former the changes in the blood were less pronounced, those in the glands were of a more chronic type and the changes in the spinal cord developed more slowly. During the first year physical signs in the upper limbs improved considerably, those in the lower limbs improved slightly, and symptoms of interference with bladder-controlling paths appeared for short periods. During the first two months the percentage of eosinophil cells in the blood again fell to 6, that of basophil cells rose to 4, and changes were still present in the cerebrospinal fluid. At the end of 18 months there were no changes in the cerebrospinal fluid, the percentage of basophil cells in the blood had risen to 16, and the neurological condition was stationary.

The clinical picture and changes in the lymph glands were those of lymphadenoma. The neurological picture was that of a lesion affecting the lower cervical and upper dorsal segments of the spinal cord, and changes in the cerebrospinal fluid favoured a lesion of an inflammatory type. There was evidence of activity in this lesion during the first three or four months, and after that the clinical effects of the lesion gradually subsided with

occasional waves of activity. At the end of 18 months there was no evidence of an inflammatory reaction, and thereafter the clinical course was largely that of a permanent neurological disability with intercurrent infections.

In Case II the complete clinical picture was a response less acute, more prolonged, and developing and subsiding more gradually than in Case I. The neurological aspect developed with moderate activity and subsided slowly with occasional waves of slight renewal of activity. Widespread tissue reaction was less evident than in Case I. In Case I there had been increasing waves of activity of the disease during 18 months and the final acute phase with neurological symptoms developed on that background; whereas in Case II the condition began apparently on a background of normal health only three weeks before admission to hospital. If, as seems probable from the tissue and clinical reaction in Case I, a pathogenic agent had become suddenly active or the defences of the patient lowered, the modifications in the clinical course and tissue reactions in Case II would be due to either less activity on the part of the pathogenic agent or more enduring resistance on the part of the patient. In both cases the phase of the disease which brought the patient under attention was much more acute than is usual with the disease. In Case I the patient died early, though paralysis of respiratory movements probably hastened that event, while in Case II a position was reached in which the process was checked at least temporarily except in the lymph glands themselves.

DISCUSSION

Gordon and van Rooyen have shown that intracerebral inoculation of rabbits with emulsions of lymphadenomatous tissue is followed by characteristic nervous lesions in the animal. After an incubation period of three or four days the animal develops signs of ataxia, incoordination, muscular spasms, head retraction and generalized encephalomyelitis, and usually dies. Some animals which are affected in a lesser degree survive and pass into a chronic condition of which general emaciation and progressive atrophy of muscles are the chief features. The duration of the condition thus produced in the rabbit varies from three days to a month or more. According to Gordon, 'post-mortem examination of the rabbits that die shows generally a pronounced degree of marasmus but no naked-eye lesion of any kind, except occasionally for some slight congestion of the meninges. . . . In spite of the striking clinical picture, sections of the earlier rabbits showed, as in the case of rabbits that die after cerebral inoculation with dermovaccine, a scarcity or absence of infiltrative lesions; but with the more active lymphadenoma material that killed the rabbits in four days, definite lymphocytic meningitis was present and a proportion of the bloodvessels in the cortex and elsewhere were seen to be surrounded with a perivascular cuff of lymphocytes.' These effects cannot be produced by the intracerebral inoculation of lymph glands affected with lymphosarcoma, leukæmia, carcinoma, tuberculosis or syphilis.

These conclusions have been confirmed by Gordon, Ogilvie and van Rooyen, Gow, and van der Hoelden and Hulst. The nature of the pathogenic agent is, however, undetermined. Gordon suggested that its behaviour is analogous to that of certain viruses in man and animals, whereas van Rooyen concluded that the effects produced in the rabbit neither confirm the possibility of their being the result of a specific toxic activity nor exclude them from being due to the action of a filterable virus. Friedemann and Elkeles produced similar effects in rabbits by intrathecal injection of sterile bone-marrow emulsions; and subsequently Friedemann showed that they may also be produced by the inoculation of emulsions of normal splenic tissue, bone-marrow and normal leucocytes. Similar material from cases of acute leukæmia and pernicious anæmia yielded characteristic effects. Mackenzie and van Rooyen showed that the encephalitogenic agent in lymphadenomatous glands is not identical with the proteolytic enzyme extracted by Jochmann and Lockemann from leucocytes, splenic tissue and bone-marrow, nor with several proteolytic enzymes described by other workers, and found it still impossible to define the pathogenic agent in lymphadenomatous glands.

In general, 8 per cent. of the cases of lymphadenoma with spinal symptoms analysed by Weil and, in particular, the cases described by Forrest and the present writers show many features in common with the clinical and histological effects produced by inoculation of rabbits with emulsions of lymphadenomatous tissue.

Under experimental conditions the tissue reaction in the central nervous system develops in the neighbourhood of the original inoculation; and in the clinical cases it appears in that portion of the central nervous system adjacent to the most pronounced response in lymph glands lying along the vertebral column. This selective localization of lesions in the central nervous system would appear to depend upon some local factor in addition to the general response in the nervous tissues and the body as a whole suggested in Case I. Extension along nerve-roots and especially the lymph channels associated with them may be the local factor concerned. This has been suggested as the route of extension in those cases in which lymphadenomatous deposits have been found outside and inside the dura mater, and some evidence has been adduced in support. With local lymph stasis, local extension of a pathogenic agent from affected lymph glands and in addition rapid activation of the agent itself or rapid lowering of the resistance of the body, that portion of the nervous tissue associated with development of the local factor would be most vulnerable to attack.

Both in the experimental animals and in the clinical cases described there was a decided disparity between the severe clinical pictures produced and the paucity of findings on anatomical and histological examination. In the animals, naked-eye examination showed only slight congestion of the meninges; in the human subject only in the acute case did naked-eye examination reveal œdema of the substance of the spinal cord and congestion

of the meninges. In the clinical case there was in addition excess of globulin and cells in the cerebrospinal fluid. In the more acute animal cases definite lymphocytic meningitis was present and some bloodvessels in the cortex and elsewhere were surrounded with a cuff of lymphocytes. In the more acute clinical case similar infiltration of the tissues in the neighbourhood of bloodvessels was seen in the affected parts of the spinal cord. In the more chronic animal cases, the animal recovered except for marasmus and muscular wasting, and anatomical examination revealed a scarcity or absence of infiltrating lesions. In addition, some of them were found when recovery was complete to be immune to a second dose of the same material administered in the same way though effects were produced in a control animal. In the more chronic clinical case the activity of the neurological lesion gradually subsided and, after occasional waves of slight renewal of activity, disappeared and left a stationary neurological disability. In spite of the progress of the disease in the lymph glands and spleen, there appeared no further renewal of activity in the spinal cord lesion. Detailed examination of the affected parts of the spinal cord revealed no obvious changes.

The resemblance of the effects in the experimental animal to those in the human subject is at least striking. While the data available leave it undetermined whether the encephalitogenic agent in lymphadenomatous tissue is the essential pathogenic agent of lymphadenoma, the association in the human subject of similar neurological findings and effects with active lesions of lymphadenoma suggests the presence of a factor common to both and the identification of it with a pathogenic agent.

SUMMARY AND CONCLUSIONS

1. The available information indicating the frequency and distribution of neurological lesions with lymphadenoma is summarized.
2. The methods by which spinal symptoms are produced by lymphadenoma are reviewed; and consideration is given to involvement of the vertebral column and its effects, epidural infiltration with lymphadenomatous tissue, extension of this tissue inside the dura mater, involvement of nerve-roots, obstruction of bloodvessels and compression of the spinal cord.
3. In 8 per cent. of cases of lymphadenoma with spinal symptoms the latter appear without compression of the spinal cord or any of the factors indicated under (2).
4. The clinical and pathological features of two cases of lymphadenoma with spinal symptoms are described.
5. The clinical and pathological findings favour the presence in lymphadenoma of a pathogenic agent which may be responsible under suitable conditions for the appearance of lesions in the tissues of the central nervous system.

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