THE NEUROPATHY OF MULTIPLE MYELOMA*

BY

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Much has been written about disorders of nervous function due to tumours of the plasma cell type (plasmacytoma and multiple myeloma). Detailed discussions of this subject and reviews of the literature are to be found in the monograph of Snapper, Turner, and Moscovitz (1953), and in the comprehensive articles of Geschickter and Copeland (1928), Davison and Balser (1937), Shenkin, Horn, and Grant (1945), and Bayrd and Heck (1947). These writings make repeated reference to several syndromes resulting from compression of neural structures by masses of tumour tissue. By far the best known of these is "myelomatous paraplegia" due to compression of the spinal cord by extradural deposits of myeloma and occasionally by a collapsed vertebra. Similarly, nerve roots and peripheral nerves may be compressed by myelomatous tissue extending from contiguous bone. Cranial nerve palsies may result from myelomatous compression at their foramina of exit at the base of the skull and less commonly there may be neoplastic invasion of intracranial or intraorbital structures. These orbital and intracranial complications of multiple myeloma have recently been reviewed by Clarke (1953, 1954). Herpes zoster is a rare complication of multiple myeloma (Anders and Boston, 1903; von Bomhard, 1914; Wallgren, 1920) and, most recently, median neuritis due to amyloid deposition in the carpal ligament has been described† (Grokoest and Demartini, 1954).

The topic to which we invite attention is a curious and little known affection of peripheral nerves which is only obscurely related to multiple myeloma, for the disease, unlike the aforementioned neurological syndromes, does not in any way depend on compression of nervous structures by tumour tissue.

The literature dealing with this particular neurological complication is meagre and in only one of the reported cases to date can the pathological description be considered adequate (Scheinker, 1938). We therefore feel justified in presenting the clinical findings in five cases which have come under observation in recent years. In three of these post-mortem examinations were performed and in one other appropriate biopsy material was procured.

Review of the Literature

Although the literature on multiple myeloma contains a considerable number of references to peripheral nerve involvement, very few of the reported cases can be accepted as authentic examples of polyneuropathy. This is particularly true in the writings which deal primarily with other than the neurological aspects of multiple myeloma. Here the occurrence of neuropathy is merely mentioned, with little or no description of the neurological signs. Falling into this category are Case 3 of White and Tillinghast (1950) and Cases 6, 8, 10, and 14 of Madonick and Solomon (1953). Snapper *et al.* (1953) recognize a form of a peripheral neuritis in multiple myeloma in which no direct involvement of nerves or nerve roots could be demonstrated. They state that four of their cases developed a "glove-and-stocking" type of peripheral neuritis but provide no further clinical or pathological data to support their statement. The cases mentioned by Levison (1933) and Levison and Møller (1924) and Case 3 of Lawrence and Rosenthal (1949) may have been instances of polyneuropathy with multiple myeloma, but again the clinical and pathological data are so scant that one is reluctant to accept the diagnosis of polyneuropathy. The same criticism applies, in general, to the cases of Neel (1931). However, one of his cases did show, on pathological examination, a disappearance of the myelin sheaths of the peripheral nerves of the lower extremities and to a lesser degree of the upper extremities. Unfortunately, there was also an irregular tumour mass involving the dura, so that it cannot be taken to

*The pathological studies were aided in part by a research grant (M-767) from the National Institute of Mental Health, United States Public Health Service.

†We have also seen a 44-year-old man who developed a bilateral carpal tunnel syndrome in the course of multiple myeloma. The symptoms responded to division of the carpal ligaments, which contained amorphous masses suggestive of amyloid.

represent a pure example of the syndrome under discussion.

Kurnick and Yohalem (1948), Estes and Millikan (1954), and Clarke (1956) have written specifically on the association of peripheral neuropathy and multiple myeloma and have claimed that the neurological changes were not due to direct involvement of nerve tissue. Their evidence was purely clinical, however, for they had no opportunity to verify this impression pathologically. Kurnick and Yohalem described three patients. In their first patient, the signs of neuropathy were practically limited to the right hand. Their second patient showed a symmetrical sensorimotor neuropathy affecting the feet and hands. The authors assumed that there was no invasion or compression of nervous structures by myelomatous tissue in these two patients, despite lack of pathological confirmation and the focal nature of the neuropathy in their first patient. The third patient had signs of a mild neuropathy and nocturnal pain was a prominent symptom. This patient was also diabetic, a state which may have accounted for the symptoms. At necropsy the peripheral nerves were not examined.

Estes and Millikan (1954) have reported the case of a 43-year-old woman whose chief complaints had been extreme weakness and pain in the legs. These symptoms were progressive and were followed by constrictive sensations around the chest. There was weakness of the proximal musculature of the legs and absent knee jerks, as well as a loss of superficial sensation below the level of the second thoracic dermatome. Although there was no clinical evidence of an epidural tumour, an operation or post-mortem confirmation of this fact was not obtained; the discrete sensory level on the trunk would be an unusual finding in our experience in a case of polyneuritis and radiculitis.

The case reported by Clarke (1956) is an undoubted example of multiple myeloma, which, though unverified pathologically, satisfies the clinical criteria for the diagnosis of polyneuropathy. Clarke also cites the case of Berlin (1946) and a case report from the Massachusetts General Hospital as examples of myelomatous neuropathy. Berlin's case is not entirely acceptable. The patient was a severe hypertensive (blood pressure 215/115 mm. Hg) who showed ataxia, foot drop, and absent knee and ankle jerks, but no sensory signs. His symptoms were said to regress with the administration of a vasodilator drug but his ultimate fate was not determined. The Massachusetts General Hospital case was suggestive of polyneuropathy on clinical grounds but post-mortem examination showed no abnormality of the peripheral nerves. We have reviewed the pathological material in this case; it represents an instance

of amyloidosis complicating multiple myeloma and will be commented on further in the discussion.

The most convincing descriptions of the neuropathy under discussion are those of Davison and Balser (1937) and of Scheinker (1938). One of the patients with multiple myeloma reported by the former authors was a 49-year-old woman, who had had a progressive history over two years of parasthesiae, weakness, and wasting of the hands. Post-mortem examination disclosed no myelomatous invasion of the brachial plexuses, although there was, on microscopic examination, demyelination and degeneration of the axis cylinders to be seen in these nerves. The spinal cord, spinal ganglia, and radicular nerves were not examined.

Scheinker (1938) reported a well documented case of a 39-year-old man with a progressive neuropathy of two years' duration. The patient had had signs of both sensory and motor involvement beginning in the legs and later affecting the arms, and there was also a raised cerebrospinal fluid protein level. Necropsy disclosed a solitary plasmacytoma of the sternum. The nervous system was not directly involved by tumour, but nevertheless there was a patchy degeneration of myelin and axis cylinders in the roots and peripheral nerves, including the phrenic nerve. Moreover, the spinal cord sections, stained by the Pal-Weigert and Spielmeyer methods, showed at every level a slight pallor in the posterior columns indicating a loss of medullated fibres. There was also, with Nissl stains, evidence of cellular destruction in the grey matter. Because of the proliferation and thickening of the perineural connective tissue, Scheinker termed this neuropathy "perineuritis interstitialis scleroticans".

The literature on myelomatous neuropathy contains a number of reports of other neurological syndromes in which no contiguous or invasive myelomatous lesions of the nervous system were evident. Frequently quoted in this connexion are the reports of Senator (1899) and of Nonne (1921), who, lacking anatomical proof that tumour had impinged on nerves or spinal cord, ascribed the neurological symptoms to a toxic state. The data in these reports are quite incomplete, and one cannot be certain that the patient suffered only from myeloma and that pathologically, tumour had not involved the nervous system. In the case of Kreuzer (1926), the author states that the spinal cord was in no way compressed by the tumour; nevertheless, there was an epidural plasma cell tumour extending from the fourth to seven thoracic segments and extravasation of blood in the underlying cord. The case of Lindeboom and Mulder (1941) is the most convincing of this group. They described a patient with multiple myeloma who rapidly developed an asymmetrical paraplegia

with a sensory level on the trunk. Pathologically there was no evidence of compression of the spinal cord by myeloma, but there was degeneration, evident with myelin stains, of all the funiculi of the cord.

Case Reports

Case 1.—Y. S., a Portuguese 45-year-old mother of seven, was first admitted to the Massachusetts General Hospital on June 26, 1953. Her illness had begun one year previously with mild pain in the lower back and in the right hip, often radiating along the outer aspect of the leg to the foot. Shortly thereafter she developed dependent swelling of both ankles, a feeling of "pins and needles" in the toes and feet, and weakness of the legs. The latter symptoms progressed in severity, so that by March, 1953, she was unable to walk without support. At that time an x-ray examination disclosed a lesion of the sacrum and she was admitted to another hospital, where she remained until her transfer to the Massachusetts General Hospital. Three weeks before the latter admission she began to have pain in the forearms and weakness of the hands. She had lost 30 lb. weight in a year.

Physical examination in June, 1953, disclosed striking evidence of weight loss. There were no abnormalities of the heart, lungs, or breasts. The liver edge was palpable 6 cm. below the right costal margin. Pelvic examination was normal excepting for the presence of a cystocele and rectocele.

The patient's mental state was considered normal, as were the cranial nerves. There was a great loss of motor power, affecting all the muscles of the trunk and the limbs. She was unable to sit unsupported and could barely retract her head. All movements of the upper limbs were freely performed. There was no voluntary movement in the toes or feet, and only the slightest degree of flexion and extension was possible at knees and hips. The limbs were flaccid and somewhat wasted. The deep tendon reflexes were absent and the plantar response was neutral. There was no sensory loss in the upper limbs. In contrast, vibratory sense was lost in the toes, and diminished at the ankles, knees, and iliac crests. Position sense was impaired in the toes and intact at the ankles. Painful, thermal, and tactile sensibility was impaired but not lost over the dorsal and ventral aspects of the feet and to a level just below the knees. The sensory impairment was symmetrical and much more severe in the distal than in the proximal parts of the legs.

Laboratory examination on admission disclosed the following: Haemoglobin 11.8 g.; W.B.C. 8,400 (65% polymorphonuclears, 9% lymphocytes, 6% monocytes); total protein 5.6 g. with an albumin-globulin ratio of 3.7 to 1.9. The blood serology was negative. Alkaline phosphatase was 3.2 Bodansky units (normal 0-5). Urine showed a specific gravity of 1018, but no albumin or other abnormalities. Radiological examination of the lumbar spine and pelvis revealed an extensive area of bone destruction and new bone formation. The lesions involved the upper part of the body and greatest part of the right wing of the sacrum. The sacro-iliac joint appeared pre-

served. Areas of increased density were also seen in the upper end and shaft of the left femur, in the left ischium and in the right ischium. There was also a sclerotic area in the anterior portion of the right sixth rib. It was thought that these lesions represented bony metastases of a mixed osteolytic and osteoblastic type. The remainder of the bony skeleton showed no focal involvement and there was no generalized osteoporosis. The stools were negative for blood and a barium enema revealed no abnormalities. The spinal fluid was under an initial pressure of 200 mm. of water; dynamics were normal, there were no cells but the protein content was 195 mg. %. Because of this finding the lumbar puncture was repeated several days later, at which time the protein was 210 mg. %. Spinal fluid dynamics were again normal, as were lumbar, thoracic, and cervical myelograms. By July 13 the spinal fluid protein was 260 mg. %. Samples of marrow from the sternum and the iliac crest were not considered abnormal; the plasma cells were 2% in number and of the adult type.

On July 17 a biopsy of the sacrum was taken. A destructive lesion was encountered which had eroded through the outer cortex in several spots, especially near the right sacro-iliac joint. The tissue within the lesion was friable, grey, gelatinous, and homogeneous in appearance. It did not bleed. The microscopic examination revealed masses of loosely arranged cells supported by fibrous bands which were rich in capillaries. The cells were generally oval or polyhedral and varied considerably in size. The cytoplasm was moderately basophilic, and whereas the majority of the nuclei were round or oval, others were elongated or bilobed. The nuclei were generally eccentrically located and contained a coarse network of chromatin. Many binucleated cells were seen. There were collections of eosinophilic material around the blood vessels suggesting amyloid, but Congo red staining was negative. This tumour was considered to be a myeloma.

On August 4, 1953, treatment with cortisone was begun. One week later a course of x rays to the sacrum was instituted, 300 r per day for six days. The neuropathy remained unaffected, although pain was alleviated. On August 11, the spinal fluid protein level had risen to 340 mg. %. Films of the skeleton and skull were repeated but no lesion other than those originally reported could be seen. A Congo red test was done on August 12 and repeated on September 29; they showed that in the serum 57% and 50% of the dye was retained respectively.

Electrophoretic fractionation of the serum and the spinal fluid was carried out. The serum pattern was 44% albumin, 6% α_1 globulin, 13% α_2 globulin, 13% β_1 globulin, 15% β_2 globulin, and 9% γ globulin. This was interpreted as showing an increase in the β_2 component, the corresponding percentages for a normal control subject being 55, 5, 9, 13, 7, and 11 respectively. Electrophoretic fractionation of the spinal fluid disclosed values of 71, 10, 3, 7, 1, and 8 respectively; these figures are within normal limits.

Gradually and slowly the neuropathy progressed. By early November, 1953, only slight movement was possible at the shoulders and none in the arms and legs. By this time, sensory loss had become prominent in the arms.

Position sense was lost in the fingers and impaired at the wrists; vibration was barely perceived at the elbow; painful, thermal, and tactile sensation was impaired symmetrically in the hands and arms up to the elbow. As in the legs, the sensory affection was most severe in the distal portions. Repeated radiographs up to the time of death showed no change in the skeletal lesions. The diaphragms moved poorly. On December 20, 1953, the temperature rose to 104° F., respirations to 40 per minute, and signs of consolidation appeared in the right lower lobe. The patient died on December 27, 1953.

General Pathological Findings.—The necropsy was performed eight hours after death. There was less than the normal amount of subcutaneous fat. Numerous enlarged axillary and inguinal lymph nodes were palpable. There were numerous soft lymph nodes, 1-2 cm. in diameter, in the mesentery and around the bronchi. The lower lobes of both lungs were firm and congested and sections of these portions of the lung showed numerous small areas of consolidation. The heart was not remarkable excepting for a brownish discoloration of the sectioned muscle. The liver weighed 1,850 g. The surface and cut sections showed diffuse yellow markings. A survey of the vertebrae and ribs revealed no bony lesions, with the exception of the sacrum and right iliac bone, which contained numerous foci in which bone was replaced by pinkish-grey friable tissue.

Microscopically the sacral tumour mass was identical with the biopsy material. No amyloid was seen. A section of rib marrow disclosed masses of tumour cells similar to those in the sacral tumour. Also the sinusoids of the spleen and many of the lymph nodes were filled with poorly differentiated plasma cells.

The heart, pancreas, and adrenal were normal. In the lungs there was severe congestion and oedema throughout the parenchyma. Many of the bronchioles were dilated and filled with an exudate consisting chiefly of polymorphonuclear leucocytes. Many alveoli contained a similar exudate. There was a slight to moderate congestion throughout the liver parenchyma and the sinusoids were generally dilated. The architecture of the kidney was well preserved. There were small focal areas of subcortical fibrosis and round cell infiltration. Some tubules contained hyaline casts, others contained a bluish-purple material suggesting calcium.

Neuropathological Findings.—The brain weighed 1,350 g. and appeared entirely normal. The spinal cord was removed in its entirety, and there was no evidence of compression at any point. The dura, cord, roots, and ganglia were grossly normal. The nerves of the legs were followed from their origin to their termination and showed no evidence of infiltration or compression. They were of approximately average size. All the skeletal muscles were light red and atrophic. The muscles in the extremities were more affected than those in the trunk. Coronal sections of the brain after fixation in formalin were normal.

Microscopic examination of the cerebrum and brainstem was normal excepting for a mild and questionable swelling and chromatolysis in the gracile and cuneate nuclei in the medulla. Blocks of tissue from the spinal

cord, roots, ganglia, peripheral nerves, and muscle were fixed in formalin and embedded in celloidin or paraffin. Representative sections were prepared also by the frozen section technique. The stains employed were cresyl violet, haematoxylin and eosin, phosphotungstic acid, haematoxylin, oil red O, Congo red, periodic-acid-Schiff, and crystal violet; appropriate sections were also stained by the methods of Spielmeyer, Loyez, Cajal, Bielschowsky, Bodian, and Van Gieson.

At all levels of the spinal cord a change in the posterior funiculus was evident. It was characterized by a loss of myelinated fibres and by gliosis in the columns of Goll and Burdach (Fig. 1b). The anterior horns showed an axonal reaction, most prominent in the lumbo-sacral and cervical regions. Most of the cells were swollen and chromatolytic with eccentric nuclei and a few of them had been replaced by glia (Fig. 2a).

There was marked disintegration of myelin in both the anterior and posterior roots, more prominent in the former and more in the distal than in the proximal portions (Fig. 3). The large fibres were more severely affected than the small ones. These changes, like the axonal reaction, were most marked in the lower lumbar and sacral roots, next in the cervical and upper thoracic roots, and least in the lower thoracic and upper lumbar roots. The myelin destruction was patchy in distribution and in these areas there was interruption of axis cylinders and invasion by macrophages. There was a mild lymphocytic infiltration here and there in both anterior and posterior roots. No plasma cells were seen in the nerves.

In the dorsal root ganglia there was a moderate degree of cell loss. Some of the ganglion cells were replaced by nests of cells with either oval or pleomorphic nuclei, the residual nodules of Nageotte. The oval or polyhedral cells in these clusters seemed to have been derived from proliferating satellite cells (amphicytes). Some of the surviving ganglion cells were frayed or angular in appearance and around them the satellite cells had increased to a marked degree. Between these cells there was a mild lymphocytic infiltration. These cellular changes were most marked in the sacral ganglia but were present to some extent in all. Many of the medullated nerve fibres and axis cylinders in the central parts of the ganglia had disappeared and numerous fatty macrophages were present (Fig. 2b).

All of the peripheral nerves studied showed degeneration of the medullated fibres. In general, the affection was more severe in the nerves of the extremities than in those of the trunk and more severe in their distal than in their proximal segments, just as it was in the roots. The large fibres were more affected than the smaller ones. Here, however, rather few fatty macrophages were seen in the areas of myelin disintegration, presumably because of the chronic nature of the process. Many of the axis cylinders had disappeared in the areas of myelin degeneration and many of those remaining were fragmented. In the sciatic nerve, both in the distal and proximal parts, not a single large fibre could be seen. The changes in the ulnar nerve were not as severe as those in the sciatic or femoral, but degeneration of the large fibres was prominent. In the ulnar nerve, masses of disintegrating myelin in the form of ovoids were invaded by macrophages;

FIG. 1A

FIG. 1B

FIG. 1.—A. Case 2. A section from the tumour of the first lumbar vertebra. The tumour is composed of a homogeneous mass of mature plasma cells. Hematoxylin and eosin stain. $\times 380$.

B. Case 1. A transverse section of the sixth dorsal segment of the spinal cord, showing pallor of the columns of Goll. Loyez myelin stain. $\times 18$.

FIG. 2.—A. Case 1. Spinal cord at the C2 level, showing swelling, chromatolysis, and eccentricity of nuclei in the anterior horn cells. Cresyl violet stain. $\times 60$.

B. Case 1. Spinal ganglion at C7 segment showing loss of cells and an occasional "residual nodule of Nageotte". Vascuolated cell is seen in the lower left corner. Loyez myelin stain. $\times 45$.

FIG. 2A

FIG. 2B

FIG. 3A

FIG. 3B

FIG. 3.—Case 1. The first sacral posterior root (A., $\times 70$) and anterior root (B., $\times 300$), showing the patchy destruction of myelin. Spielmeier myelin stain.

FIG. 4A

FIG. 4B

FIG. 4.—Case 2. A. A posterior root (Spielmeier myelin stain. $\times 100$) and B., an anterior root (oil red O stain. $\times 380$). In both of these sections the segmental degeneration of myelin is evident.

FIG. 5A

and some of these ovoids contained particles of axoplasm—so-called digestion chambers. Here and there in sections of nerves stained by the Bodian method, numerous small, delicate strands were seen which were taken to be regenerating axones. In the cross sections of nerve, an interesting change was seen involving veins, arterioles, and small arteries. The vessels walls were thickened, and the lumina were narrowed by intimal hyperplasia but all were patent. Occasional vessels were surrounded and infiltrated by lymphocytes and mononuclear cells. In numerous sections stained by Congo red, P.T.A.H., crystal violet, iodine, and periodic-acid-Schiff methods, no amyloid could be identified.

All the muscles of the extremities, and to a lesser extent of the trunk, showed the picture of far advanced neural atrophy (Fig. 5B). The muscle fibres were reduced to thin ribbons of sarcoplasm and the sarcolemmal nuclei were relatively increased. In some places the fibres had disappeared entirely, and only darkly stained

FIG. 5B

FIG. 5.—A. Case 3. A section of the right common peroneae nerve, showing a loss of some fibres and others undergoing degeneration. Spielmeyer myelin stain. $\times 300$.

B. Case 1. A section of the vastus lateralis muscle showing an advanced degree of neural atrophy. Hematoxylin and eosin stain. $\times 200$.

cells were found in rows within the thin sarcolemmal tubes. In places, even the tube was absent and small groups of dark nuclei appeared to lie within the fibrous tissue. The blood vessels showed the same changes as described in the blood vessels of the nerves.

Case 2.—W. E. McD., a 48-year-old linotype operator and former parachutist, was admitted to the Boston Veterans Administration Hospital on August 18, 1952. About nine months before he had noted weight loss, he became easily tired, and had low back pain. Examination at that time disclosed the presence of haemorrhoids and in December, 1951, a haemorrhoidectomy was performed under caudal anaesthesia. His post-operative course was uneventful, although his general symptoms failed to improve. About one month after the operation there was a gradual onset of numbness and weakness of the legs. These symptoms progressed rapidly and by April, 1952, he was unable to stand or walk unaided.

About this time similar symptoms appeared in the hands. Examination in April, 1952, revealed evidence of advanced neuropathy. The hip musculature had only about 50% of normal power, the thigh muscles somewhat less, and the lower leg muscles were completely paralysed. There was a slight weakness of the para-spinal muscles, and in the arms the only weakness was in the hands. The affected muscles were atrophic and tendon reflexes were abolished. Painful and tactile sensibility was impaired in the hands and feet.

In May, 1952, he suffered an attack of severe abdominal pain and a cholecystostomy was performed at another hospital. Recovery was delayed by the drainage of bile from the operation site.

By the time of his final hospital admission in August, 1952, he had lost 40 lb. in weight. Examination at this time disclosed a severe degree of muscle wasting and a fistula at the upper end of the cholecystostomy scar. The skin over the lower legs and sacrum was shiny and erythematous and the remainder of the skin appeared tanned. There were no abnormalities in the mental sphere or in cranial nerve function. All the muscles of the lower limbs were paralysed and extremely atrophic with contractures at the knees and ankles. The intrinsic muscles of the hands were atrophic, those of the forearm less so, and there were flexion contractures of the fingers and wrists. Only weak movements of flexion and extension were possible at the elbows and of abduction and adduction at the shoulders. The deep reflexes were absent throughout and the plantar responses were neutral. Superficial sensation was lost over the feet and was impaired to some extent as high as the hips. Vibration and position sense were lost in the hands, in the lower limbs, and in the ankles, knees, and hips.

Laboratory examination disclosed the following: Haemoglobin 13.5 g. %; W.B.C. 7,500 with a normal differential count; the urine was normal except for occasional red cells in the sediment; the cerebrospinal fluid pressure and dynamics were normal and showed 3 lymphocytes, sugar 75 mg. %, chlorides 120 mEq. per litre, total protein 90 mg. %, and a normal colloidal gold reaction; the blood and cerebrospinal fluid Wassermann reactions were negative. There was free acid in the gastric aspirate. The total protein of the blood was 5.1 g. %, but otherwise the blood chemistry was normal.

Shortly after the patient's admission to the Veterans Administration Hospital a chest film revealed an infiltration in the left lower and mid-lung fields. He was treated with penicillin and intravenous fluids, but he continued to have fever, dyspnoea, and increasing signs of pulmonary consolidation. Bronchoscopy was performed but no obstruction was found. The patient became afebrile on large doses of penicillin and streptomycin, but because of the large amount of secretions and the inadequacy of his cough he required almost continuous bronchoscopy. He died on October 1, 1952, of respiratory failure.

General Pathological Findings.—There was a marked depletion of fat in the omentum and mesentery; the serosal surface of the small bowel presented a spotty, dull, granular appearance; four greyish, firm, retroperitoneal nodes measuring 1.5 cm. in diameter and several similar nodules in the mesentery of the small

bowel were seen. There were adhesions between the duodenum, transverse colon, and the gall bladder, and a small pocket of pus beneath these. Approximately 140 ml. of greenish-yellow fluid was found in the left pleural cavity, and there were firm fibrous adhesions between the left lung base and the diaphragm. The right lung weighed 500 g., the left 650 g. The trachea and main stem bronchi contained a considerable amount of purulent, tenacious, greenish-white material and the bronchus leading to the left lower lobe was completely occluded by this material. The left lower lobe was firm and not aerated; on section it was purple, and the bronchi exuded purulent material.

Microscopically, the alveoli contained numerous macrophages and occasional polymorphonuclear cells. The alveolar walls appeared thickened. Other sections showed emphysema and atelectasis. The heart and valves were essentially normal. In the abdominal aorta there were scattered atheromatous plaques. The spleen weighed 240 g. The capsule was wrinkled, dull grey, and adherent to the diaphragm. On section, it was soft and the corpuscular markings were accentuated. The liver weighed 2,100 g. but was otherwise normal. The gall bladder was adherent to its bed and contained two cholesterol stones measuring 2.5 and 1.8 cm. in diameter. The cystic duct was occluded by dense fibrous adhesions. The other portal structures were normal. The pancreas, adrenals, gastro-intestinal tract, genito-urinary system, and the thyroid were all normal.

Filling almost the whole body of the first lumbar vertebra was a well-circumscribed, soft, pink-white tumour mass measuring 2.7 cm. in diameter. It was delimited peripherally by a paper-thin, bony shell with a smooth grey lining. The tumour did not extend beyond the normal limits of the body of the vertebra, and compression of the cord by the tumour or by vertebral deformity could not be made out. Microscopic examination disclosed a homogeneous well-vascularized mass of mature plasma cells (Fig. 1A). There were only occasional cells with multiple nuclei; mitoses were lacking. There was a narrow zone of collagen around the capillaries. Unfortunately no other sections of the bone marrow were taken.

Neuropathological Findings.—No areas of rarefaction were seen in the calvarium. The brain, which weighed 1,300 g., was examined after fixation in formalin. The dural sinuses were negative. In the fronto-parietal regions bilaterally the leptomeninges were thickened and of opaque whitish appearance. There was some slight generalized atrophy of the frontal lobes as indicated by narrowed gyri and widened sulci. The cerebral vessels showed minimal atheromatous changes. On serial sections of the brain, no abnormalities could be seen.

The dura over the spinal cord was somewhat thickened. There were no adhesions between the dura and arachnoid, and the inner surface of the dura and the surfaces of the spinal cord and roots were of normal appearance. The blood vessels in the cauda equina were rather large but not increased in number. A few roots of the cauda equina seemed unusually grey and thin. On sectioning the cord, no areas of softening, discoloration, or other abnormalities were found.

The most striking abnormalities were seen in the peripheral nerves. There was a loss of a large proportion of the medullated fibres, predominantly of the large ones and a relative increase in connective tissue. In the areas undergoing degeneration one could also see changes in the Schwann cell syncytium, with clumps of Schwann cells and fibroblastic nuclei and rare fatty macrophages. Here and there the peripheral nerve was infiltrated with mononuclear cells, mainly lymphocytes, but no plasma cells were seen. In the cross sections of the nerve, the blood vessels appeared slightly thickened; however, their lumina were patent. No amyloid could be demonstrated.

In the spinal nerve roots there was definite evidence of disease, somewhat more in the posterior than in the anterior ones (Fig. 4). The large fibres and some of the medium-sized ones had disappeared, whereas most of the smaller fibres were well preserved. In addition, small clusters of very thin, poorly medullated or non-medullated fibres were embedded in small clumps of connective tissue. There was little evidence of Wallerian degeneration. Some of the intact fibres were abnormal, in that their myelin sheaths had disappeared in segments for distances of 150 to 200 μ , leaving bare axis cylinders. In places where medullated fibres had disappeared the axis cylinders were also fragmented or were no longer visible. Ellipsoids and ovoids of myelin were still present. In the cauda equina both in the anterior and posterior roots there was a diffuse infiltration of mononuclear clear cells, predominantly lymphocytes.

In the sensory ganglia some of the cells were round and pale, and there were large numbers of fibroblasts and many fat-containing histiocytes. Some cells had disappeared completely and were replaced by the "residual nodules of Nageotte".

In many of the anterior horn cells of the spinal cord there was an axonal reaction, especially in the more laterally placed cells of the lumbar and cervical segments. At the cervical level, the columns of Goll showed a slight loss of large fibres, with an increase in astrocytes in this region. Microscopically, there was no evidence of arachnoiditis.

The muscles of the limbs showed a marked denervation atrophy. No abnormalities were observed in the microscopic sections of the brain.

Case 3.—Mrs. S. G., a 58-year-old woman, was first admitted to the First (Tufts) Medical Service of the Boston City Hospital on June 27, 1952. She had been well until four months before, when severe and persistent pain in the shoulders, chest, low back, and legs began. Over the four-month period she had suffered from general weakness and night sweats and had lost 20 lb. in weight. Other symptoms included frequency and burning pain on urination, lightheadedness, and exertional dyspnoea, all of which had become progressively worse until the time of her admission to the hospital.

Examination disclosed an obese and somewhat dyspnoeic woman. The vital signs were normal and the blood pressure 130/60 mm. Hg. There was a mild dorsal kyphosis, and slight tenderness over the right scapula

and over the right lower chest anteriorly. The heart, lungs, and abdomen were essentially normal. There was no loss of muscle power or atrophy. Reflexes were brisk and equal throughout; the plantar responses were flexor, and no sensory loss could be discerned.

Radiographs disclosed multiple, rounded areas of radiotranslucence in the bones of the skull, fractures of several ribs, and diffuse destruction of the bones of the spine, pelvis, and upper femurs. The urine showed a constant albuminuria and occasionally red cells, white cells, and granular casts in the sediment. No Bence-Jones protein could be detected. A blood count on June 27, 1952, was as follows: R.B.C. 3.44 million; haematocrit 34; haemoglobin 10.5 g. %; W.B.C.s 8,250 with a normal differential. The blood serology was negative. The total protein level was consistently elevated, up to 9.8 g. on one occasion, with an albumin-globulin ratio of 4 to 5.8. The serum calcium level was 6 mg. %, phosphorus 9 mg. %, and the alkaline phosphatase was 4.7 units. The non-protein nitrogen was consistently elevated, fluctuating between 136 and 240 mg. %. The sternal marrow contained clumps of atypical plasma cells, many of them showing the characteristics of the "myeloma cell".

Treatment with urethane was instituted, but the patient was unable to tolerate this drug, and it had to be discontinued. However, she improved spontaneously and was discharged on August 30, 1952. On September 8, 1952, she returned to the hospital because of the manifestations of tetany. The symptoms responded well to treatment with intravenous calcium gluconate and sodium bicarbonate, and she was discharged on September 16, 1952.

The patient returned to the hospital for the last time on April 11, 1953. For several months preceding this final admission she had suffered from generalized pains and persistent vomiting. In addition she had noted a specific weakness of the legs, progressive in nature, so that she was unable to walk for any distance and was finally confined to bed. Examination on this admission, in addition to the abnormalities previously noted, revealed a softened area in the right frontal bone measuring about 4 cm. in diameter, and an enlarged liver, the edge being palpable 4 cm. below the right costal margin. The patient was alert, cooperative, and well orientated. The cranial nerves were judged to be entirely normal. There was an advanced degree of atrophy of the legs, more marked on the left, and weakness of dorsiflexion, eversion, and plantar flexion of the feet, also more marked on the left. Muscle power in the arms was adequate. There was a fine tremor of the extended hands. The tendon reflexes were brisk and equal throughout, excepting at the ankles, where they were absent bilaterally. The plantar responses could not be interpreted accurately because of withdrawal responses. Below the knees, there was a diminution of tactile, pain, and vibratory sensations, and position sense was impaired in the toes. The patient was now markedly anaemic; the non-protein nitrogen was 220 mg. %, and the CO_2 -combining power was 25 vol. %. The cerebrospinal fluid pressure and dynamics were normal; the fluid contained 4 lymphocytes and a total protein of 45 mg. %. The colloidal gold was normal. Despite

transfusions of whole blood the patient died on April 17, 1953.

General Pathological Findings.—A necropsy was performed 19 hours after death. The marrow of the ribs, sternum, vertebrae, and iliac bones was pale, with light tan, soft, fatty areas scattered throughout. The mitral and aortic valves showed many small calcified nodular areas. The lungs were increased in weight (right 800 g.; left 600 g.). On section, both lower lobes showed a lack of crepitation and a deep reddish appearance and they were slightly greasy to the touch. The kidneys each weighed 300 g., and the cut surfaces showed marked pallor and poor corticomedullary demarcation. In the para-aortic area there were eight to 10 firm, greyish-white lymph nodes, 1.5 cm. in length.

Microscopically, the heart muscle showed marked fatty infiltration throughout. The liver cells were poorly preserved, with fat-containing vacuoles of varying size in their cytoplasm. Throughout the lungs, but mainly in the lower lobes, many of the alveoli were collapsed, others contained macrophages, and the vessels in the alveolar walls were congested with red cells. In the kidneys, many of the tubules were filled with granular casts, and in many areas these tubules were surrounded by foreign body giant cells and small numbers of neutrophils. Many of the glomeruli and tubules were absent and replaced with fibrous tissue. Sections through the sternal, costal, vertebral, and iliac bone marrow all showed varying degrees of infiltration with cells of the plasma cell type. These cells had eccentric nuclei and some had two nuclei. The basi-chromatin of the nuclei was arranged in clumps. The cytoplasm stained a lavender colour with haematoxylin and eosin, and often the perinuclear zone was lighter in colour than the remainder of the cytoplasm.

Neuropathological Findings.—Because of restrictions placed on the post-mortem examination, the brain was not examined. The spinal cord and roots appeared grossly normal, with no evidence of compression or infiltration by tumour. There was a haemorrhage which appeared to be of recent origin in the right common peroneal nerve.

In the spinal cord there was a slight loss of myelinated fibres in the columns of Goll and Burdach, with a slight increase of astrocytes in this region—a replacement gliosis. In the lumbo-sacral region of the cord, the more laterally placed anterior horn cells showed a typical axonal reaction, about one-third of the cells being affected in this manner.

In both the anterior and posterior lumbo-sacral roots the myelin sheaths were conspicuously altered. The larger myelin sheaths were fragmented and some of these fragments were expanded or ballooned, and at the nodes of Ranvier there was extensive retraction leaving gaps in the sheathing and a short stretch of naked axis cylinder. In some fibres the myelin disintegration could be followed for a considerable extent, in others it involved only short segments. In the areas of myelin disintegration there was also some loss and destruction of axis cylinders.

In the dorsal root ganglia there was only a mild degree of abnormality of the cells. Some cells had evidently

disappeared and had been replaced by residual nodules; others appeared swollen and chromatolytic, with an increase of satellite cells in the subcapsular space. Histiocytes, some of which contained fat, were seen in the residual nodules and here and there in the centre of the ganglia. The axis cylinders within the ganglia were tortuous and dilated.

In the more proximal parts of the femoral, peroneal, and tibial nerves, there was relatively little change in some places except for isolated fibres which were undergoing degeneration (Fig. 5A). In some of these fibres, the myelin degeneration could be followed for a considerable extent, in others it was circumscribed. In the intact fibres, except for minor alterations in the myelin sheath and a slight increase in the number and size of the Schwann cells, there was little change of importance. In the right common peroneal nerve the haemorrhage had undergone fibroblastic organization; in this area the walls of the blood vessels were infiltrated with inflammatory cells, mainly polymorphonuclear leucocytes. In general the arteries and arterioles in and around the nerves were hyperplastic, their lumina were narrowed, and a few of the vessel walls appeared hyalinized. However, there was no evidence of infiltration with amyloid. Muscle tissue was not available for microscopic examination.

Case 4.—C. D., a 47-year-old man, was first seen on the First (Tufts) Medical Service of the Boston City Hospital on September 22, 1947, complaining of numbness of the hands, burning sensations of the feet, and drawing pains in the legs of about six months' duration. In addition he had lost 25 lb. in weight in the year preceding admission. The physical examination at that time was normal in a general sense, although he was mildly anaemic (R.B.C.s 3.91 million, haemoglobin 72%). On neurological examination, forward bending of the neck was slightly limited, this movement producing pain and paresthesiae in the arms and back. There was slight tenderness over the seventh cervical spine. Tactile sensation was impaired over the fingers. Position sense was defective but not lost in the toes, and vibration sense was diminished below the level of the first lumbar vertebra. Deep reflexes were normally active, and the plantar response was flexor bilaterally. A lesion of the cervical cord was suspected, but none could be found despite a careful search. Radiographs of the spine and skull were normal. Lumbar puncture disclosed clear and colourless cerebrospinal fluid. The initial pressure was normal as was the response to jugular compression. Seventy-two cells were reportedly found, predominantly lymphocytes. Total protein was 222 mg. % and the colloidal gold curve was 0122333332. The Wassermann reaction in the cerebrospinal fluid was negative. Lumbar puncture was repeated on October 6. The protein was 174 mg. %, but no cells were found on this or subsequent examinations. A cervical myelogram performed on this occasion was normal.

During the next several months there may have been a slight degree of spontaneous improvement in the numbness and tingling of the extremities, and a gain in weight; certainly the disease did not progress. The patient

remained in this state until February, 1948, when, because of a worsening of the paresthesiae and the onset of a constrictive abdominal sensation, he was readmitted to the hospital. The neurological examination was the same as previously, except that on this occasion forward flexion of the neck did not result in paresthesiae of the arms and legs.

Laboratory examination revealed many new abnormalities. There was a consistent albuminuria and occasional white and red cells in the urinary sediment. The blood proteins were elevated, on one occasion as high as 9.25 g. %, with an albumin-globulin ratio of 4 to 5.25. The cerebrospinal fluid protein was 200 mg. %, and the dynamics were normal on two separate tests. The findings in the blood were: R.B.C.s 3.86 million, haematocrit 37%, haemoglobin 11.4 g. %, with normocytic indices.

An aspiration of the sternal marrow disclosed 19% plasma cells, many of which were multinucleated and characteristic of "myeloma cells". A sternal marrow biopsy also disclosed an increased number of plasma cells, many in clumps. Finally, on March 31, 1948, Bence-Jones protein was discovered in the urine. A diagnosis of multiple myeloma was made and urethane therapy, 3 g. daily, was instituted.

For the following two years the patient was admitted to the hospital many times, mainly for readjustment of the urethane dosage, and on one occasion for an illness presumed to be infectious hepatitis. In May, 1948, he received a series of injections of stilbamidine, 150 mg. every second day, to a total dosage of 1,300 mg. In October, 1948, he developed facial paresthesiae, which gradually receded over the ensuing months. Throughout this two-year period he continued to complain of severe constricting pains around the lower costal margin, and of cramping pain in the thighs. In the course of this time blood values returned to normal, but the neurological signs remained unchanged, and the cerebrospinal fluid protein level ranged between 133 and 174 mg. %.

The patient was readmitted to the hospital on March 16, 1950, because of increasing stiffness of the legs and difficulty in gait and persistence of the girdling sensations of the lower chest and abdomen. On examination it was noted for the first time that his gait was unsteady and "high stepping" in character. There was marked weakness of dorsiflexion of both feet, and a moderate degree of wasting of the anterior tibial and peroneal muscles of both legs. Ankle jerks were depressed. There was also a mild, distal blunting of pain sensation in the legs, and a diminution in vibratory sensation at the iliac crests and below. Once again the spinal fluid dynamics were normal, but the protein was 95 mg. %. A radiological survey of the lumbar vertebrae and other parts of the skeleton revealed no bony lesions of significance. He was given a course of intravenous urethane therapy, but the weakness of the feet increased, and the ankle jerks were lost entirely. In May, 1951, urethane therapy was discontinued, never to be resumed. Between May and October, 1952, he received x-ray treatment to the spinal column, in the belief that the myeloma had seeded itself along the lumbo-sacral roots. Nevertheless, weakness increased and his gait deteriorated progressively. By

October, 1952, he required a cane to get around. He was unable to rise on his toes, nor could he rise from a squatting position. There was now a marked weakness of both the flexor and extensor muscles of the feet and moderate weakness of the knee and hip musculature. The ankle jerks were absent and the knee jerks could barely be obtained with reinforcement. The plantar responses were neutral. The wasting of the calf and anterior tibial muscles was more pronounced than previously. Position sense was lost in the toes and vibration sense was lost at the iliac crests and below. There was also a symmetrical loss of painful and tactile sensations over the feet. Motor, sensory, and reflex functions were entirely normal in the upper limbs. Once again the spinal fluid dynamics were normal and the protein content was 103 mg. %.

The patient has been seen periodically, the last time in April, 1957. Over a six-year period the neuritic signs have progressed only slightly. In general he feels well and the blood constituents are maintained at normal levels. In January, 1952, a compression fracture of the fourth lumbar vertebra was discovered radiologically. There were no new neurological signs, however, and subsequent films of the lumbar region and the entire skeleton have failed to disclose any further bony changes.

In January, 1952, a biopsy was taken of the left superficial peroneal nerve and neighbouring muscle. The operation this nerve seemed to be larger than normal, 3-4 mm. in diameter. It appeared greyish and "watery" in colour. Manipulation of this nerve during the section did not provoke the pain that one is accustomed to experience in such manoeuvres.

Microscopically, only a few medullated nerve fibres remained in the nerve. There was degeneration of both the myelin and axis cylinders of most of the fibres, with fibrous tissue replacement. Most of the muscle fibres were small but there were isolated groups of normal-sized fibres as well. There was a relative increase in connective tissue.

Case 5.—W. R., a 54-year-old man, a patient of Dr. William C. Maloney, was admitted to the Cambridge City Hospital, Cambridge, Massachusetts, on March 25, 1947, complaining of pains in all the joints of the extremities of one year's duration. Two weeks before this admission he developed a particularly severe pain in the right shoulder, with radiation into the hand and the right side of the chest. He had suffered from a chronic, slightly productive cough, but otherwise his past and family histories contributed nothing. Examination disclosed a generalized muscular tenderness and evidence of bronchopneumonia at the bases of both lungs. The laboratory examination showed the following abnormalities: Haemoglobin 9 g. %, R.B.C.s 2.7 million, W.B.C.s 4,500, with a normal differential count; marked albuminuria; total protein 7.2 g. with an albumin-globulin ratio of 2.6 to 4.6. The skull film was typical of multiple myeloma; there were multiple small round areas of radiance scattered throughout the fronto-parietal and occipital regions and the skull tables in general appeared decalcified. There were also small radiant defects in the ribs. About 40% of the sternal marrow cells were of the

plasma-cell type. The majority of these exhibited an eccentrically placed nucleus, deeply staining blue cytoplasm and vacuoles in the cytoplasm. Many of the cells were undergoing mitosis and a few contained nucleoli.

The blood Wassermann reaction was negative. Repeated testing of the urine failed to reveal Bence-Jones protein. A lumbar puncture showed normal cerebrospinal fluid pressure and dynamics, a total protein of 50 mg. % and a flat colloidal gold curve.

On May 12, 1947, urethane therapy, 3 g. daily, was instituted. Within two weeks the pain was markedly less, and in the ensuing months he was symptom free except for a mild, inconstant ache in the joints. By December, 1947, the blood values had returned to normal with the exception of the protein which was 8.3 g. with an albumin-globulin ratio of 3.8 to 4.5. The skull films showed the same abnormalities, but those in the ribs seemed to have cleared. The plasmacytosis of the sternal marrow was no longer present. Urethane therapy was stopped in September, 1949.

The patient was seen again on October 26, 1954, with complaints of tingling and "pins and needles" feelings in the hands and feet. He was unsure of the exact time of onset of the symptoms, but they had been constant for several years. Examination on this date revealed evidence of a mild but definite sensory loss, affecting the distal parts of the limbs in a symmetrical fashion. There was impairment of vibratory sensation in the toes and finger tips. Using a Von Frey hair, a weight of 20 mg. was required before the patient first perceived a touch stimulus at the mid-leg and at the metacarpophalangeal joints. With 40 mg. he was able to detect touch at the ankle and over the middle of the digits. A defect of pain and temperature sensation was also demonstrable. The sharpness of a 6 g. pin was not appreciated until points above the mid-forearm and above the mid-leg were reached. The impairment of temperature sensation corresponded to that of pain. Motor power was intact in the limbs, reflexes were sluggish, but all were present and equal. The plantar responses were flexor. An examination in April, 1955, disclosed very much the same abnormalities. A lumbar puncture done on this date showed the cerebrospinal fluid to be under an initial pressure of 130 mm. water and a final pressure, after the removal of 10 ml. of fluid, of 100 mm. water. The cerebrospinal fluid dynamics on jugular and abdominal compression were normal, there were no cells, and the protein level was 16 mg. %.

A biopsy was not performed.

Discussion

Reviewing briefly the salient clinical features of our cases it will be noted that three were males, two were females, and their ages at the onset of the illness ranged from 44 to 58 years. These figures reflect the age incidence and the predominance in males generally found in this disease. Three of our patients (Cases 3, 4, and 5) showed the classical features of multiple myeloma; their symptomatology was characterized by varying degrees of bone pain, anaemia, osteolytic lesions, hyperglobulinaemia,

Bence-Jones proteinuria, and the presence of myeloma cells in the marrow. In Cases 3 and 5, these features were present from the onset of the illness, whereas in Case 4 they were only recognized six months after the onset of a perplexing neurological problem. In two patients (Cases 1 and 2) the symptoms of polyneuropathy dominated the clinical picture and the characteristic symptoms of multiple myeloma were either minimal and obscured (Case 1) or entirely unrecognized during life (Case 2). These two patients showed a number of other distinctly unusual features. Hyperglobulinaemia and Bence-Jones proteinuria were absent in both, although the serum electrophoretic pattern of Case 1 showed an elevation of the β_2 globulin. Repeated radiological and sternal marrow examination did not reveal evidence of disseminated myeloma. Neither of these cases, however, could be accepted as examples of a solitary plasmacytoma. In Case 2 a careful post-mortem examination of the marrow, aside from the lumbar vertebrae, was not made. In Case 1 post-mortem examination disclosed the presence of disseminated lesions in the form of masses of tumour cells in the rib marrow, as well as the presence of undifferentiated plasma cells in the sinusoids of the lymph nodes and the spleen. A most unusual feature of Case 1 was the radiological appearance of the sacral lesion: it was osteoplastic as well as osteolytic. Osteoplastic lesions are distinctly rare in this disease, and we are aware of only one report of a similar case (Krainin, D'Angio, and Smelin, 1949).

Two patients (Cases 4 and 5) have experienced a remarkable remission in symptoms. In these patients the symptoms of multiple myeloma have been present for over nine years, and at the time of writing both patients are well in so far as the symptoms of multiple myeloma are concerned, although the neuropathy is stationary or progressing very slowly. Since the average duration of life after the onset of symptoms is between 18 and 24 months (Snapper, 1952; Geschickter and Copeland, 1928), the long survival in these patients has proved of considerable interest and has formed the subject of a special report by Kenney and Moloney (1956). These authors point out that the patients who survive for many years have certain features in common, namely, the relatively small myeloma cell population in the bone marrow, myeloma cells of the mature type, and minimal renal, blood protein, and bone abnormalities. Although the cases reported by these authors were treated with urethane, they attribute the benign and chronic course to the natural history of the disease rather than to drug therapy.

The polyneuropathy, although varying in severity, took a characteristic form in four of our patients.

Essentially, it was a symmetrical, atrophic, areflexic, sensorimotor affection of the legs, and, in two cases, of the arms. In our first two cases the sensorimotor neuropathy affected all the limbs, and later the trunk as well. It was severe and progressive in nature and was responsible for the patients' deaths. In two other patients (Cases 3 and 4), the neuropathy was less severe in degree and more sharply limited to the legs. In Case 2, in which the myeloma was only discovered at post-mortem examination, the clinical picture was similar to that described by Scheinker (1938), in which a plasma cell tumour of the sternum was discovered at necropsy in a patient who had suffered from a progressive neuropathy for two years. Another patient (Case 5) presented a mild sensory polyneuropathy which has remained stationary for about six years.

There was a striking lack of parallelism between the symptoms of neuropathy and those of myeloma. In Cases 1 and 2 the clinical pictures were essentially of severe and ultimately fatal polyneuropathy, and the usual symptoms of myeloma were lacking. In these two cases the diagnosis of multiple myeloma was only established by the biopsy of an unsuspected bone lesion and by post-mortem examination respectively. In Case 3, the symptoms of neuropathy were restricted and relatively mild, and had developed in the course of a rapidly advancing multiple myeloma. In Case 4 the neurological symptoms antedated the recognition of the myeloma; in Case 5 a mild sensory neuropathy became evident three or four years after the onset of a moderately advanced form of multiple myeloma. In both Cases 4 and 5, the symptoms of neuropathy were arrested or perhaps progressing very slowly, whereas the symptoms of myeloma had visibly regressed.

The total protein level in the cerebrospinal fluid was elevated in four of our patients. It ranged from 50 to 340 mg. %, and was greatest in the patients with the most severe degrees of neuropathy. There was no obstruction to the flow of cerebrospinal fluid to explain this abnormality. Nor could the neuropathy itself be accepted as an adequate explanation, since an elevated spinal fluid protein level has been described in patients with multiple myeloma and without neurological complications (Degenhardt and Sheehan, 1949; Madonick and Solomon, 1953). The latter authors stated that there was no consistent relationship between the serum proteins and cerebrospinal fluid proteins. Their conclusions were based on estimates of total proteins obtained by standard fractionation methods, and did not take into account the possibility that abnormalities of globulin fractions could be present with little or no alteration of the total protein. Labhart, Schweizer, and Staub (1951), on the basis of electrophoretic studies in

three patients with multiple myeloma, claimed that the changes in the cerebrospinal fluid protein fractions were simply a reflection of the abnormal serum fractions. This view was not substantiated by the study of the serum and spinal fluid electrophoretic patterns in one of our patients (Case 1). Serum electrophoresis showed an increase in the β_2 globulin component; the cerebrospinal fluid protein level was raised, but electrophoretic patterns were normal. It is apparent that more studies are necessary before an authoritative statement can be made regarding the cerebrospinal fluid protein elevation in multiple myeloma.

The pathological changes in the nervous system were similar in our three necropsied cases, varying only in degree. In none was there any evidence of compression of neural structures by myeloma or vertebral deformity. Microscopically, no plasma cells were seen in the nerves or roots. The most striking feature was the degeneration of the peripheral nerves, and to a lesser extent of the anterior and posterior roots, always more in the distal segments than in the proximal ones. Both the myelin sheaths and the axis cylinders were destroyed, the former more than the latter. There were also segments which showed a loss of myelin and bared axis cylinders, the segmental demyelination of Gombault. Only a moderate number of dorsal root ganglion cells were lost, even in cases in which the posterior roots and posterior columns of the spinal cord had degenerated. The alteration of anterior horn cells was most likely secondary to the axis cylinder damage in the anterior roots and peripheral nerves. The thickening of blood vessels was probably a reactive change; it could hardly be responsible for the neural changes.

Despite a careful survey of our pathological material, no amyloid was seen in the endoneurium or contiguous blood vessels. This was surprising, in view of the high incidence of amyloid in cases of myeloma and the fact that the amyloidosis complicating myeloma tends to be of the "primary" type, that is, of the type that is located in the heart, gastro-intestinal tract, and blood vessels. It has been estimated by Bayrd and Bennett (1950) that multiple myeloma is attended by primary amyloidosis in about 15% of instances. Large series of cases have been reported by Atkinson (1937), Lichtenstein and Jaffe (1947), Dahlin and Dockerty (1950), and by Snapper (1952) and Snapper *et al.* (1953). However, in none of these reports is affection of the peripheral nerves mentioned, either clinically or at necropsy. In Cases 8 and 14 of Madonick and Solomon (1953), there was said to be amyloid of the tongue and generalized amyloidosis respectively. These cases were also said to have neuropathy, but

no further statement was made regarding the relationship of the amyloidosis and the neuropathy. The case from the Massachusetts General Hospital, cited by Clarke (1956), was undoubtedly an instance of multiple myeloma with primary amyloidosis; however, it is not at all certain clinically that the patient suffered from neuropathy, and at necropsy the peripheral nerves that were examined appeared normal.

Involvement of the peripheral nervous system by amyloidosis is rare but well documented. Some authors (Kernohan and Woltman, 1942) regard the neuropathy as secondary to amyloidosis of small vessels; others (deNavasquez and Treble, 1938; Findley and Adams, 1948; Ritama and Björkstén, 1954) describe actual involvement of the nerve trunks and perineurial connective tissue by amyloid. Under any circumstance, none of the described cases of amyloid neuropathy were associated with multiple myeloma. The idea that amyloidosis is responsible for myelomatous neuropathy, though theoretically entertaining, lacks pathological confirmation.

No other explanation for the neuropathy has suggested itself. Under-nutrition was not a factor in the commonly accepted sense. All our patients appeared adequately nourished at the outset of the neurological illness, and all received large amounts of vitamins without the symptoms being affected. Two patients (Cases 4 and 5) were treated for long periods with urethane, but in neither case was there a discernible relationship between the drug therapy and the neurological symptoms. In Case 4 the symptoms of neuropathy antedated treatment; in Case 5 the neuropathy developed several years after cessation of urethane therapy. Furthermore, polyneuropathy has not been reported as a complication of urethane therapy despite the many cases in which it has been used in leukaemia and lymphoma. For the same reasons it would be unlikely that cortisone (Case 1) and stilbamidine (Case 4) were causally related to the polyneuropathy.

Any discussion of neuropathy with neoplasia brings to mind the carcinomatous variety delineated in a series of papers by Denny-Brown (1948), Lennox and Prichard (1950), Elkington (1952), Kremer and Pratt (1952), Dodgson and Hoffman (1953), Henson, Russell, and Wilkinson (1954), and Heathfield and Williams (1954). From these writings we learn that most of the patients had carcinoma of the lung, a few of other organs. The neuropathy may be predominantly sensory or motor, or mixed sensory-motor in type. The main affection is of the limbs, in a distal symmetrical distribution, but occasionally the trunk and face may also be involved. The neuropathy may have an insidious onset and steady progression, or it may evolve in a subacute

manner and then undergo spontaneous arrest or remission for several months to a year or longer. The symptoms of neuropathy and of carcinoma may evolve together, but more often the neuropathy is recognized earlier. There is frequently a striking lack of parallelism in the severity of the neuropathy and the extent of the carcinomatosis; in some instances the neuropathy may represent the entire clinical picture, the carcinoma only being discovered at necropsy. Remissions in the symptoms of neuropathy are frequent and seem to be independent of any treatment undertaken for the carcinoma. Usually the cerebrospinal fluid protein level is raised, and rarely there may be a slight lymphocytic pleocytosis.

It will be readily discerned that in this description of carcinomatous neuropathy are embodied the main clinical features of the neuropathy encountered in our patients with multiple myeloma. Of special importance is the fact that the neurological symptoms may precede or entirely dominate the neoplastic ones, so that in patients with obscure neuropathies a careful search should be made for carcinoma and multiple myeloma.

Pathologically, the analogy between the neuropathy of carcinoma and of multiple myeloma is less striking. This is particularly so in relation to sensory carcinomatous neuropathy, in which degeneration of dorsal root ganglion cells is the most prominent change. In the mixed sensory-motor type of carcinomatous neuropathy, however, the pathological changes cannot be distinguished from those of myelomatous neuropathy. The various other neuropathological changes that have been described in carcinoma, such as cerebellar degeneration, myopathy, and primary degeneration of the spinocerebellar and pyramidal tracts, were not encountered in our material.

Inasmuch as carcinoma accompanied by neuropathy in the absence of secondary deposits in the nerves is loosely referred to as carcinomatous neuropathy, it might be appropriate to refer to the condition we are describing as myelomatous neuropathy. It would appear that in both of these neoplastic states some toxic or metabolic abnormality is created in the peripheral nervous system, but the mechanism remains as obscure as that of neoplasm itself.

Summary

Multiple myeloma may be associated with a polyneuropathy which does not depend on compression of nervous structures by tumour tissue. The clinical findings in five such cases are presented; in three of these post-mortem examinations were performed.

The polyneuropathy, although varying in severity, took a characteristic form in four patients. Essentially, it was a symmetrical, atrophic, areflexic, sensorimotor affection of the legs, and in two cases of the arms. The fifth patient presented a mild sensory polyneuropathy. The cerebrospinal fluid protein level was raised in four patients. In three patients the symptoms of polyneuropathy preceded those of the multiple myeloma and completely dominated the clinical picture. In two patients there was a prolonged remission of both the neuropathy and the myeloma.

The neuropathy of multiple myeloma bears a close resemblance to that of carcinoma, of the type unrelated to direct involvement by neoplasm. It is emphasized that in patients with obscure neuropathies, a careful search for both carcinoma and multiple myeloma should be made.

Pathologically, there was no evidence of compression of neural structures by myeloma or by vertebral deformity. Microscopically, no plasma cells were seen in the nerves or roots. The most striking feature was the degeneration of the peripheral nerves, and to a lesser extent of the anterior and posterior roots, always more in the distal segments than in the proximal ones. Both the myelin sheaths and the axis cylinders were destroyed, the former more than the latter. Relatively few dorsal root ganglion cells were lost. No amyloid was seen in the endoneurium or in the contiguous blood vessels.

We wish to thank Dr. Joseph M. Foley, of the Neurological Unit, the Boston City Hospital, for the opportunity to study the pathological material in Case 3, and the biopsy material in Case 4; Dr. John Houghton of the Veterans Administration Hospital, Boston, for the pathological material in Case 2; Dr. William Dameshek of the New England Center Hospital, Boston, for permission to examine his patient with the carpal tunnel syndrome complicating myeloma; and Dr. William C. Moloney of the Boston City Hospital for allowing us to examine Case 5.

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