Papers and Originals

Peripheral Neuropathy in Rheumatoid Arthritis

C. A. PALLIS,* D.M., M.R.C.P.; J. T. SCOTT,† M.B., M.R.C.P.

[WITH SPECIAL PLATE]

Brit. med. J., 1965, 1, 1141-1147

Sporadic references to peripheral neuropathy complicating rheumatoid arthritis appeared as long ago as the last century. The early literature is reviewed by Irby, Adams, and Toone (1958) and by Hart and Golding (1960). During the past ten years neuropathy has been mentioned in a number of papers dealing primarily with the vascular complications of rheumatoid arthritis or with treatment of the disease with corticosteroid hormones. A recent comprehensive account of arteritis in rheumatoid disease by Schmid, Cooper, Ziff, and McEwen (1961) reviews these communications in detail.

Hart, Golding, and Mackenzie (1957) were the first to describe a definitive series of patients with neuropathy and rheumatoid disease. Similar publications then followed from Mason and Steinberg (1958), Irby *et al.* (1958), Johnson, Smyth, Holt, Lubchenco, and Valentine (1959), Ansell (1960), Hart and Golding (1960), Steinberg (1960), and Ferguson and Slocumb (1961). The association has become well recognized by those treating large numbers of patients with rheumatoid arthritis, but is perhaps less familiar to neurologists and general physicians. Moreover, certain features of the condition have not yet received adequate attention.

The present paper describes 30 cases of rheumatoid arthritis¹ and peripheral neuropathy personally examined at Hammer-smith Hospital and at the Canadian Red Cross Memorial Hospital, Taplow, during the past two years. These comprise most patients with rheumatoid neuropathy attending the two centres during this period.

Clinical Examination

The examination of patients with rheumatoid arthritis and neurological complications is difficult and time-consuming.

The *history* of arthritis is usually long, the details of its fluctuating course being more or less accurately recorded in voluminous dossiers. Patients often have difficulty in giving accurate information if to their arthritic symptoms are added neuritic ones, which may themselves evolve in a variety of ways. Neuritic pains may be confused with those of arthritis, the distribution of numbness may be difficult to recall, and complaints of weakness are notoriously hard to evaluate. For example, many patients with rheumatoid arthritis complain of weak hands, when what they mean is a combination of stiffness,

pain, and fear of pain. Slight weakness of the intrinsic musculature of the feet may not give rise to much in the way of symptoms. Morning stiffness may be so marked in some of these patients that for a while they are literally unable to use their limbs.

The *examination* itself is also difficult. Impaired movement in these patients is often due to causes other than neuropathy, such as joint disease itself, tendon rupture, or fear of pain. Paresis of the small muscles of the feet may escape detection or its significance be hard to assess. (Testing for power in the toes is not usually part of routine neurological examination, and the limits of normality are not easy to define.) Wasting, when present, is much more often due to the effects of arthritis and disuse than to the presence of neuropathy. Weakness and wasting in parts of the body where the joints have not been involved are therefore of particular interest to the neurologist. Steroids used in treatment may contribute to the weakness by causing a myopathy (Yates, 1963), which will further complicate the neurological picture.

On the sensory side, as will be shown, isolated peripheral nerves or their individual branches may be affected. In the upper limbs at least, the detection of this "digital neuropathy" involves careful testing of both sides of every digit. Not only is this tedious but the results are difficult to interpret because of variations in skin texture and sensitivity.

Many of the patients have locomotor difficulties. These are more usually due to arthritis in the hips, knees, or ankles than to weakness or sensory ataxia. In some patients long confined to bed the Romberg sign is difficult to interpret.

Finally, the frequent occurrence of combined lesions adds to the diagnostic problem. For example, the patient may have a distal neuropathy combined with a lesion of a major nerve trunk, either in the same limb or elsewhere. Again, peripheral nerve lesions may be combined with radicular lesions, and we have seen rheumatoid changes in the cervical spine add signs of cord compression to those caused by lesions of the nerve roots and peripheral nerves.

Types of Neuropathy

Five patterns of neurological involvement were encountered: (I) *Upper limbs*: lesions of major peripheral nerves. (II) *Upper limbs*: digital neuropathy. (III) *Lower limbs*: lesions of major peripheral nerves. (IV) *Lower limbs*: distal sensory neuropathy. (V) *Distal sensori-motor polyneuropathy* of upper and lower limbs.

Although most patients showed signs of more than one type of neurological involvement (see Table), we feel that the different patterns are worth individualizing in view of their differing

* Lecturer in Medicine and Consultant Physician (Neurology), Post-graduate Medical School of London.

† Lecturer in Medicine and Consultant Physician (Rheumatology), Post-graduate Medical School of London.

¹ By rheumatoid arthritis is meant an inflammatory, erosive, and predominantly symmetrical arthritis involving at least four joints, and excluding such conditions as ankylosing spondylitis, psoriatic arthritis, Reiter's disease, and systemic lupus erythematosus. All patients met the criteria laid down by the American Rheumatism Association for definite rheumatoid arthritis (Ropes, 1959).

prognostic significance, and of the possibly different mechanisms whereby symptoms arise in the various groups.

I. Upper Limbs : Lesions of Major Peripheral Nerves

In this group there were 10 patients with obvious lesions of the ulnar, median, posterior interosseous, or terminal (cutaneous) branches of the radial nerves (Cases 1–10).

In nine patients the upper-limb lesions were single. Of these, four (Cases 3, 5, 6, and 8) had a median neuropathy due to compression in the carpal tunnel, and in each instance there had been arthritis of the wrist-joint. Three (Cases 1, 4, and 9) had ulnar neuropathy, and in each instance there was clear evidence of recent or old arthritis of the appropriate elbow. A further patient (Case 2) had a lesion of the posterior interosseous nerve due to an effusion in the elbow-joint, which had required repeated aspiration and eventual surgical release. We have also included in this group a single patient (Case 7) with well-defined involvement of the terminal branches of one radial nerve, shown by localized dense sensory impairment over the appropriate area of the dorsum of one hand.

Only once (Case 10) was there involvement of more than one main peripheral nerve in the upper limbs. Over a period of 18 months this patient had developed a median-nerve lesion, first on one side, then on the other, followed by an ulnar-nerve palsy and finally by a distal, symmetrical sensori-motor polyneuropathy (see below).

In Cases 1–4 the neuropathy was attributed solely to the effects of swelling or damage in a neighbouring joint. These patients showed no evidence of neuropathy elsewhere. The other six (Cases 5–10) showed evidence of neuropathy in the lower limbs. In these six cases the articular lesions at the wrist or elbow seemed to be no more than contributory factors in the localization of the neuropathy. Case 7 was the only instance of a major peripheral nerve lesion in the upper limbs, where local joint damage could not be wholly or partly incriminated.

II. Upper Limbs : Digital Neuropathy

The second group consisted of 12 patients with a neurological syndrome not hitherto identified which we have termed "digital neuropathy" (Cases 7, 8, and 11–20).

The symptoms were exclusively sensory. Numbness was the presenting complaint in all cases, developing insidiously and affecting one or more digits of either hand in a random manner, quite unlike the characteristic pattern of an ulnar or median lesion. The numbness was usually confined to the terminal phalanx or at most to the terminal two phalanges of the involved digits. At times it was confined to one side of a digit. The

FIG. 1.—Digital neuropathy: distribution of sensory loss in Case 18. A small cutaneous ischaemic lesion can be seen beside the third left finger-nail.

thumb was rarely involved. Symptoms usually started in one hand, but in 10 cases had become bilateral.

Only three patients experienced paraesthesiae, and these were never severe. One patient, in whom several digits of one hand were densely affected, developed a marked sensory clumsiness. Several patients stated spontaneously that their symptoms were aggravated by cold. The symptoms sometimes ran a self-limiting course of weeks or months, eventually subsiding. In two cases the sensory deficit progressed over a period of months, eventually affecting the whole of one or both hands and even the distal third of the forearm.

Seven of these cases had abnormal findings on sensory examination. These consisted of digital hypoaesthesia and hypalgesia in five patients, vibration loss in three (severe only in one), and postural loss in two (severe in one). Fig. 1 shows the distribution of sensory loss in a typical case.

Of the 12 patients with digital neuropathy, 11 had some additional form of neurological involvement—in nine instances a sensory neuropathy of the lower limbs.

III. Lower Limbs : Lesions of Major Peripheral Nerves

Ten patients had lesions of the larger peripheral nerves of the lower limbs (Cases 7–10 and 19–24).

Seven patients had lateral-popliteal-nerve palsies, and in four instances these were bilateral. Two patients had low sciatic-nerve palsies. In one instance these were bilateral. In one case there was sensory loss confined to both saphenous fields.

Lesions of the lateral popliteal and sciatic nerves had come on rapidly, motor and sensory disturbances of characteristic distribution usually reaching their height within 48 hours. The sciatic-nerve lesions were low ones—that is, distal to the branch to biceps femoris.

With lesions of the sciatic nerves the symptoms and signs were both motor and sensory. In one of the six patients with a lateral-popliteal lesion the symptoms were exclusively sensory (intense paraesthesiae in the appropriate territory, aggravated by pressure over the head of the fibula).

Bilateral lesions usually came on at intervals of several months. The natural history of these palsies was towards slow but incomplete recovery.

Three of the patients with lateral-popliteal palsies had obvious arthritis with effusion of the ipsilateral knee-joint at the time the palsy developed (Cases 7, 20, and 21). In two of these, however (Cases 7 and 20), there was also evidence of neuropathy elsewhere, so that the local effusion was felt to be no more than a contributory cause. In the third patient (Case 21) the lateral-popliteal palsy was the only neurological abnormality. When it developed, however, the patient was passing through a phase of systemic vasculitis with fever, eosinophilia, weight loss, and pericarditis, so that here again the local joint lesion may not have been the only causative factor. None of these three patients had been wearing a plaster cast and none had been recumbent for any length of time—two factors which in other cases (not included in this series) we have seen cause lesions of the lateral popliteal nerve.

The patient (Case 8) in whom a diagnosis of saphenous neuropathy was made complained of burning dysaesthesia confined to an area 5 cm. wide and 15 cm. long above each medial malleolus. The knee-jerks were retained and there was no weakness of the quadriceps. There were hypalgesia and hypoaesthesia confined to the dysaesthetic areas.

IV. Lower Limbs : Distal Sensory Neuropathy

This large group consisted of 19 patients. In 14 (Cases 5, 6, 12–18, 25–29) there were distal and purely sensory symptoms and signs in the lower limbs. In five (Cases 9, 19, 20, 22, and 23)

the picture was complicated by concomitant lesions of the sciatic and lateral or medial popliteal nerves.

The presenting complaint in 13 of the 14 cases with "pure" distal sensory neuropathy was numbness. This usually affected the toes and variable proportions of the foot, rarely extending above the level of the malleoli. The onset was usually insidious, and many patients complained of the symptom being aggravated by cold. Seven patients complained of distal paraesthesiae in the lower limbs, but in only two instances was this severe. Only one patient had a sensory ataxia. At the time of examination these patients invariably had bilateral symptoms and signs, although at the onset their symptoms had sometimes been unilateral.

Loss of vibration sense was always the most obvious abnormality. In a few patients age may have contributed to this finding. Vibration loss at the malleoli was found in all cases, being symmetrical in all but two. Pain loss was found in 11 instances (asymmetrical in three), tactile loss in 10 (asymmetrical in three), and postural loss in the toes in three. Thermal sensibility was not routinely tested. In only one instance was there distal hyperalgesia, manipulation of the toes being intensely unpleasant. In most cases the sensory loss was confined to the toes and distal third or half of the foot, but in a few it extended up to the middle of the calf.

Abnormalities of the reflex pattern in the lower limbs were common in this group and were usually symmetrical. In seven instances both ankle-jerks were absent, and in the remaining six patients one or both ankle-jerks were depressed. One or both knee-jerks were depressed in six cases.

Five patients, already referred to, showed a more complex picture in the lower limbs, attributed to the additive effects of distal sensory neuropathy and of popliteal- or sciatic-nerve lesions. These patients might exhibit, for instance, typical features of a lateral-popliteal-nerve lesion in one lower limb and of distal sensory neuropathy in the other. Or the history might be typical of a lateral-popliteal-nerve lesion but examination reveal, in addition to the expected signs, absent ankle-jerks, impaired vibration sense over the medial malleoli, and impairment of pain sense over the plantar surface of the toes or soles of the feet.

Of these 19 patients considered to have distal sensory neuropathy (either alone or with a concomitant major nerve lesion in the lower limb) it is noteworthy that the dorsalis pedis and posterior tibial pulses were easily felt in all but two cases. The commonest associated lesion in the upper limbs was digital neuropathy. This was present in nine instances.

V. Distal Sensori-motor Polyneuropathy of Upper and Lower Limbs

Three patients had a sensori-motor neuropathy of all four limbs with symmetrical distal weakness, wasting, and impairment of all modalities of sensation (Cases 10, 24, and 30). All three died with widespread visceral ischaemic lesions or infection while under observation.

The clinical picture of this form of neuropathy, when fully developed, was easy to differentiate from that seen in other clinical groups. In its symmetry it resembled polyneuritis of infective or toxic origin. It differed, however, in that the neurological picture had evolved in an irregular, asymmetric, and unpredictable manner—usually over a period of several months.

Two of the three patients (Cases 10 and 24) presented with "mononeuritis multiplex," only later progressing to a distal sensori-motor polyneuropathy. One of these (Case 10) developed a lesion of the right lateral popliteal nerve, followed within a few months by lesions first of the left and then of the right median nerves. Several months later he developed a left lateral-popliteal-nerve lesion, followed within two days by a lesion of the left ulnar nerve. He died a few weeks later of meningitis, having received 40 mg. of prednisolone daily during the last three months of life. Widespread ischaemic lesions were found at necropsy.

In Case 24 the neuropathy presented as bilateral low sciatic lesions, occurring sequentially, within a period of a few weeks. Two months later the patient was found to have symmetrical distal weakness and wasting of the upper limbs, with dense sensory loss over the fingers, affecting all modalities of sensation—a clinical picture quite unlike the digital neuropathy described in group II. The neuropathy was meanwhile progressing rapidly and symmetrically in the lower limbs.

The third patient (Case 30) presented a symmetrical pattern of neurological involvement without, so far as we know, antecedent mononeuritis multiplex. Over a period of about six weeks he developed severe sensory impairment and weakness in the hands and feet.

In Cases 24 and 30 the neurological symptoms and signs progressed rapidly, in each case heralding, by a few weeks or months, the patient's death from the visceral effects of a widespread systemic arteritis.

Correlation of Neurological and Other Findings

Age of Onset of Neuropathy.—The mean age of onset of neuropathy was 55.3 years, range 43–71 years. There was little difference in age between the various clinical groups.

Sex.—There were 17 males and 13 females. All three fatal cases in group V were in men. This incidence differs from that of uncomplicated rheumatoid arthritis, which affects women more often than men.

Duration of Rheumatoid Arthritis at Onset of Neuropathy.—The mean period between the onset of rheumatoid arthritis and the onset of neuropathy was 11.9 years, range 3 months to 47 years. There was no significant difference between the clinical groups.

Erythrocyte Sedimentation Rate (Westergren).—The mean E.S.R. at the time of examination for this study was 48 mm./hr., range 2–100 mm. Only two patients had an E.S.R. of under 20 mm. There was again no significant difference between the clinical groups.

Duration of Neuropathy at Time of Examination for this Study.—This ranged from a few days to seven years. In most (19) of the patients the onset of neuropathy had been within two years of the present assessment.

Rheumatoid Nodules.—These were present in 23 of the 30 patients. They were absent in all four patients with isolated pressure neuropathy in the upper limbs (Cases 1–4).

Digital Vascular Lesions.—Small infarcts on the nail-bed, nail-fold, or finger-pulp of the type first described by Bywaters (1957) were observed at some time or other in 10 of the 30 patients, and again they were absent in all four patients with isolated pressure neuropathy.

Types of Neurological Involvement

Case No. :	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Group I ..	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Group II ..																														
Group III ..																														
Group IV ..																														
Group V ..																														

Other Cutaneous Lesions.—Seven patients had purpura, usually of the feet and ankles. Two additional patients had larger ecchymotic lesions, mainly on the forearms and hands, of the type associated with steroid therapy. Ischaemic ulceration of the legs occurred in three patients (Cases 5, 24, and 30). In addition to purpura, one patient, (Case 19) showed over a period of some years several other types of cutaneous lesion associated with arteritis (Bywaters and Scott, 1963; Case E.D.).

Other Clinical Features of Systemic Disease.—Episcleritis was seen in Cases 6, 19, and 30. Cases 5, 21, and 25 showed clinical and electrocardiographic evidence of pericarditis. Case 5, in addition to rheumatoid arthritis, had the other features of Sjögren's syndrome—namely, dryness of the eyes and mouth. Case 26 developed a pleural effusion a few weeks before the onset of peripheral neuropathy. The onset of rheumatoid arthritis in Case 27 had coincided with symptoms of thyrotoxicosis, for which thyroidectomy was carried out: the histology was that of Hashimoto's thyroiditis. Cases 15 and 16 both had well-documented but transient hypertension a year or so before the onset of neuropathy, and in Case 15 this had been of the malignant type with papilloedema. Case 19 underwent laparotomy because of acute cholecystitis, and histological evidence of healed arteritis was found in mesentery attached to the gall-bladder. Two patients (Cases 24 and 30) died of mesenteric arteritis and its complications, and one (Case 10) died of meningitis while receiving 40 mg. of prednisolone daily.

Differential Agglutination Titre (D.A.T.).—The D.A.T. or Rose-Waaler test (Rose, Ragan, Pearce, and Lipman, 1948) was positive in 26 of the 30 patients with neuropathy. The four patients with negative tests—that is, with titres of less than 1:16—were the four with isolated peripheral nerve lesions in the upper limbs, attributed solely to local pressure (Cases 1–4). Excluding these four, therefore, all the patients had a positive D.A.T. This is to be compared with an incidence of 71% in 248 in-patients with rheumatoid arthritis in Hammersmith Hospital between 1958 and 1961.

L.E. Cells and Antinuclear Factor.—L.E. cells were looked for in 27 of the 30 patients and were found in two (Cases 5 and 27). Antinuclear factor (Holborow, Weir, and Johnston, 1957) was looked for in 23 patients and was found in nine.

Brachial Arteriography.—We have recently been using brachial arteriography to study the peripheral circulation in rheumatoid arthritis (Scott, Hourihane, Doyle, Steiner, Laws, Dixon, and Bywaters, 1961; Laws, Lillie, and Scott, 1963). Arteriography was attempted in 26 of the 30 patients in the present series. In six cases it was not possible to visualize the vessels of the hand and fingers either because the procedure was technically unsatisfactory or because of vascular spasm. Of the 20 successful arteriograms, 18 showed widespread vascular occlusions (Special Plate, Fig. 1). The other two successful arteriograms, although not completely normal, showed blockage only in the distal segment of a single digital vessel, contrasting strongly with the widespread vascular lesions in the other cases. Both of these arteriograms were of patients with isolated ulnar-nerve lesions attributed solely to the effects of pressure from a damaged elbow-joint (Cases 1 and 4). (In the other two patients with isolated pressure lesions the arteriograms were technically unsatisfactory.)

Corticosteroid Treatment

Of the 30 patients, 16 were receiving steroids when the neuropathy started. The proportions were similar in groups I, II, III, and IV. The three patients with distal sensori-motor polyneuropathy (group V) were all receiving steroids. Of the 16 taking steroids, 10 had been on the drugs for more than a year before the onset of neuropathy. The development of neuropathy did not appear to be related to changes in dose.

In six patients the onset was more closely related in time to starting steroids.

Case 6.—Prednisone treatment had been started because of haemolytic anaemia a year before the patient came under our care. Dosage had been 20 mg. daily, falling gradually to 15 mg. daily. The onset of neuropathy, initially misdiagnosed as subacute combined degeneration of the cord, occurred insidiously about the same time as prednisone was started.

Case 10.—Three years after the onset of increasingly severe rheumatoid arthritis, prednisolone was started in a dosage of 15 mg. daily, the dose being reduced and the drug stopped three months later. The following year prednisolone 15 mg. daily was again started, with subsequent reduction of dosage. Eleven months later, while the patient was taking 5 mg. daily, neuropathy appeared with paraesthesiae in the feet.

Case 14.—Symptoms of neuropathy developed three months after prednisolone 10 mg. daily had been started because of active rheumatoid arthritis. Signs of peripheral vascular disorder, however, had first appeared about two years before, in the form of transient blanching of various fingers.

Case 21.—A right foot-drop suddenly occurred 10 weeks after prednisolone 40 mg. daily had been started, the dosage meanwhile having been gradually reduced to 20 mg. The drug had been given because, on a background of chronic rheumatoid arthritis of 19 years' duration, the patient showed evidence of rapidly progressive systemic disease (fever, weight loss, eosinophilia, and pericarditis). Vasculitis was suspected but never proved.

Case 22.—After a 17-year history of rheumatoid arthritis prednisolone 25 mg. daily was started because of progression of the disease. A foot-drop developed four months later.

Case 30.—This man had suffered from rheumatoid arthritis for five years before treatment with prednisolone 10 mg. daily was started because of increasing activity of the disease. About six months afterwards he developed a sensori-motor peripheral neuropathy in all four limbs, together with episcleritis and leg ulceration. He later died from mesenteric arteritis.

Prognosis

These patients have been followed for periods ranging from a few months to several years. It is not yet possible to chronicle the eventual outcome in every instance. Some differences in prognosis between the various clinical groups are, however, already apparent.

Group I.—Improvement occurred in Cases 1–4, where the neuropathy was thought to be exclusively due to local pressure from a damaged joint. In three of these (ulnar, posterior interosseous, and median nerve lesion in the carpal tunnel) there was improvement after surgical exploration. In one (with an ulnar lesion) improvement occurred spontaneously. Of the six patients in whom there were additional neurological lesions (in the lower limbs) three had carpal-tunnel syndromes improving after surgery; one had a persisting ulnar neuropathy with severe arthritis of the elbow; and one a terminal radial-nerve lesion which has gradually improved over 18 months.

Group II.—The symptoms here ran variable courses in many ways comparable to those of the vascular lesions of the fingers seen in rheumatoid arthritis (Bywaters and Scott, 1963). In some patients symptoms persisted for a few weeks only, in others they persisted either intermittently or continuously for much longer periods. Patients in whom this type of neuropathy was found varied from Case 11—where there had been barely discernible impairment of sensation of one and, later, another finger for about seven years with no other evidence of neuropathy or ischaemia—to Case 19, where digital sensory loss was accompanied by severe vascular insufficiency of the fingers, one of which became gangrenous.

Group III.—The tendency of these lesions was towards gradual improvement after a rapid onset. Cases 7 and 9 have shown almost complete recovery over a period of about two years. Case 19 improved considerably despite evidence of widespread systemic vasculitis, which had apparently passed from an active necrotizing phase into one of healing. Where local pressure was a contributory feature, its relief was followed by

improvement—for example, when the initial foot-drop in Case 20 rapidly improved after aspiration of a swollen knee. In contrast to the not unfavourable prognosis of the other nine patients in this group, Cases 10 and 24 progressed to a distal sensori-motor neuropathy, death occurring some months later.

Group IV.—In 9 of the 19 patients with distal sensory neuropathy of the lower limbs there was associated digital neuropathy in the hands. The prognosis of the two groups appears to be similar. As with digital neuropathy, the symptoms of lower-limb sensory neuropathy have varied in severity and duration. Complete recovery has been unusual. Patients with this purely sensory type of lesion have not progressed to serious systemic disease.

Group V.—As already stated, the three patients in this category deteriorated rapidly and died.

Pathology

Biopsy of digital arteries had been carried out on a number of these patients (Cases 8, 12, 14, 16, 18, and 25) in connexion with an earlier study of brachial arteriography in rheumatoid arthritis (Scott *et al.*, 1961; Laws *et al.*, 1963). These all showed a bland intimal thickening, at times amounting to complete occlusion, as previously described.

A detailed pathological study of the peripheral nerves was carried out in a single case. The patient (Case 12) had both digital neuropathy and a distal sensory syndrome in the legs, which had started asymmetrically but which had eventually become symmetrical. Neurological symptoms and signs had been present for at least five years. He died of a gastric carcinoma.

The right sciatic nerve and its branches were dissected out as far as the foot and fixed in 10% formalin within a few hours of death. Sections were taken from the following sites: (a) the upper and lower thirds of the sciatic nerve itself, (b) the lateral popliteal nerve, near the head of the fibula, (c) the musculocutaneous nerve, just distal to the branch to peroneus longus, (d) the anterior and posterior tibial nerves (in both their upper and lower thirds), and (e) the lateral plantar nerve.

After embedding in paraffin, transverse and longitudinal sections were stained with haematoxylin and eosin, van Gieson's stain, Gomori's aldehyde-fuchsin, and Verhoeff's stain for elastin; periodic-acid-Schiff reagent, Congo red, Weil's and Heidenhain's stains for myelin; and Davenport's silver-impregnation method for axons. Some specimens were stained *en bloc* for 24 hours with 1% osmium tetroxide, and the sections counterstained with van Gieson's stain or light green.

We are indebted to Drs. Clara Margolies and P. K. Thomas, of the Maida Vale Hospital for Nervous Diseases, for the following report:

"Vessels: Within the epineurium the lumen of several arterioles and medium-sized arteries was reduced in size as a result of either fibrous intimal thickening or medial muscular hypertrophy. Fig. 2 (Special Plate) shows a small artery from the proximal third of the posterior tibial nerve with segmental destruction of half its circumference throughout the whole thickness of the vessel wall and replacement with fibrous tissue. Only a scant amount of elastic tissue was identified beneath the intima in one area, close to the junction of the thickened fibrous part of the vessel wall and the thinner part where the muscle cells were still preserved. Another section from the lateral plantar nerve showed considerable irregular disruption of the elastica (Special Plate, Fig. 3). A medium-sized artery in a section from the lateral popliteal nerve showed a damaged media with new capillaries growing in from the adventitial surface and a certain amount of scarring of the wall. Organizing thrombi were seen within the lumina of two arteries in sections from the lateral plantar nerve.

"Within the perineurium as well as within the fascicles there were occasional thick hyalinized arterioles with small lumina. No

amyloid was demonstrated in any of the vessels. There was possibly a mild excess of endoneurial collagen in sections from the lateral popliteal nerve, and to a greater extent in the lateral plantar nerve.

"Axons and Myelin Sheaths: Sections from the sciatic, lateral popliteal, and anterior and posterior tibial nerves showed numerous axons, but there may have been some axonal loss in the distal part of the lateral plantar nerve. There was probable loss of myelin sheaths in both the lateral popliteal and the lateral plantar nerves (Special Plate, Fig. 4), although the lack of adequate quantitative data on normal material makes interpretation difficult.

"A single fascicle from the lateral popliteal nerve (taken from a point 3 cm. below the point of separation from the medial popliteal nerve) was stained for 24 hours in 1% osmium tetroxide. The fascicle was then teased apart in glycerin by the method described by Thomas (1955) to obtain single nerve fibres. The fascicle showed an oval-shaped area, elongated in the length of nerve and 2–3 mm. long, where the nerve fibres showed evidence of having undergone segmental demyelination and subsequent remyelination with preservation of axonal continuity. When nerve fibres passing through this region were isolated the thickness of the myelin sheaths was seen to become reduced and the internodal length shortened, myelin thickness and internodal length being normal above and below the region. Elsewhere in the fascicle the fibres appeared normal apart from occasional widening of the nodal myelin gaps.

"Conclusions: The vascular changes consisted mainly of intimal thickening and medial muscular hypertrophy of the small and medium-sized arteries. The segmental destruction of one small artery and the medial damage with scarring of a medium-sized artery were reminiscent of healed lesions of polyarteritis nodosa type. Segmental demyelination of the lateral popliteal nerve was demonstrated. The axons were generally well preserved."

No evidence of visceral arteritis was found in this patient. In Cases 20 and 22 death occurred from atheromatous myocardial infarction, and no visceral arteritis was found at necropsy. In Cases 10, 24, and 30 (group V), however, there were widespread vascular lesions in the viscera: the sciatic nerve of Case 10 was examined but no significant abnormality was found.

Discussion

Although patients in this study illustrate the various peripheral neurological complications of rheumatoid arthritis, the numbers in each group may not reflect too closely the true relative incidence of the different syndromes. For example, only a few patients with median-nerve compression by a tendon-sheath effusion at the wrist (either alone or in combination with other neurological disorders) have been included in this series, although this is probably the commonest neurological complication of rheumatoid arthritis. Neither are we in a position to comment on the overall incidence of neurological complications in rheumatoid arthritis.

Apart from isolated nerve lesions due to local pressure, peripheral neuropathy in rheumatoid arthritis has generally been attributed to occlusion of the vasa nervorum by the arteritis which occasionally complicates the disease (Schmid *et al.*, 1961). Evidence comes from three main sources.

Firstly, there is a high incidence of nodule formation and a positive D.A.T. both in patients with neuropathy and in patients with arteritis. Of the 26 patients in the present series (excluding the four with pressure neuropathy only), 23 had nodules and all had a positive D.A.T. In contrast, of the four with pressure neuropathy none had nodules or a positive D.A.T.

Secondly, patients with neuropathy sometimes show clinical evidence of vascular disease, such as ischaemic changes in the digits. Ten of our patients had digital ischaemic lesions.

Thirdly, arteritis has been found histologically in patients with neuropathy, both in the vasa nervorum and elsewhere (Kemper, Baggenstoss, and Slocumb, 1957; Sokoloff and

Bunim, 1957; Irby *et al.*, 1958; Schmid *et al.*, 1961; Case 12 of the present series). Such changes are not always seen, however: of the five patients of Hart and Golding (1960) studied at necropsy, two showed neither vasculitis nor demyelination of peripheral nerves, and one had a vascular lesion in one nerve only, despite a careful histological search and widespread clinical neuropathy during life.

We can now add further evidence associating neuropathy with peripheral vascular occlusion. Twenty patients in the present series had a technically satisfactory brachial arteriogram, and severe widespread occlusion of digital vessels was seen in 18 of them. No data are available about the overall incidence of digital vessel occlusion in rheumatoid arthritis. In a previous account of brachial arteriography in selected patients with this disease (Laws *et al.*, 1963) it was shown that abnormal arteriograms were found in 14 out of 15 patients with associated neuropathy (most, but not all, included in the present series), but in only 12 out of 23 patients without neuropathy. This almost invariable association of neuropathy with digital vascular occlusion strengthens the concept of a vascular cause for the neuropathy. In a patient with rheumatoid arthritis and neurological signs an abnormal brachial arteriogram does not necessarily imply that the neuropathy is related to the arthritis; a normal arteriogram, however, would strongly suggest another cause for the neuropathy.

Peripheral occlusion in rheumatoid arthritis appears to affect mainly digital vessels rather than larger arteries. For this reason the dorsalis pedis, posterior tibial, radial, and ulnar pulses are usually easily palpable in this disease even in the presence of obvious ischaemia in the fingers. The digital pulses themselves may be obliterated, but clinical assessment of pulsation at this level is often difficult.

A distinction between pressure neuropathy and the polyneuropathy due to vascular disease in rheumatoid arthritis has been clearly appreciated (Ansell, 1960; Hart and Golding, 1960). What has not been stressed is that both factors may operate in a given patient or even in a given lesion. Three of our patients with lateral popliteal palsies showed evidence of such a dual aetiology. It is interesting to relate these observations to the experimental findings of Gilliatt and Wilson (1954). These authors showed that artificially induced ischaemia (by tourniquet) produced more rapid sensory failure in patients with pre-existing lesions of peripheral nerves than in normal controls. The effects of ischaemia and of other factors interfering with neural function were often additive.

Many authors have commented on the association between the onset of neuropathy and the administration or withdrawal of corticosteroids. Of the 42 patients with rheumatoid neuropathy described by Hart and Golding (1960) 20 were on a regular dose of steroid. In six others the authors considered that reduction or withdrawal of therapy had precipitated the neuropathy. Ferguson and Slocumb (1961) found that whereas there was no close relation between sensory neuropathy and corticosteroid therapy, 44 out of 48 patients with motor deficit had received previous treatment with steroids. Most had received high doses and showed signs of hypercorticism. In our smaller series there were nine patients with objective motor loss attributed to ischaemic neuropathy. Of these, six were receiving steroids—four in a dosage of more than 10 mg. daily of prednisolone or its equivalents. None showed clinical signs of gross hypercorticism when the neuropathy developed. The other three patients with polyneuropathy and motor signs were not receiving steroids.

In six patients the onset of neuropathy occurred within a year of starting steroids. Treatment was, however, being given because of active disease and cannot necessarily be implicated as a cause of the neuropathy. The hypothesis of Kemper *et al.* (1957) that corticosteroids may precipitate necrotizing arteritis in susceptible patients with rheumatoid arthritis is difficult either to prove or to refute: the only certain fact is that vascular

lesions (with or without necrotizing arteritis) and neuropathy can occur in the absence of steroid treatment, as shown by our own experience and that of others (Ball, 1954; Bywaters, 1957). In none of our patients had steroids been recently withdrawn. We have, however, seen a number of patients suddenly stop taking steroids without developing neuropathy.

The clinical classification of rheumatoid neuropathy has an important bearing on prognosis. This was emphasized by Ferguson and Slocumb (1961), in whose experience extensive mononeuritis multiplex was a manifestation of systemic necrotizing arteritis and carried a mortality of nearly 50%. Less extensive neurological involvement implied a better prognosis. Our experience is not at variance with theirs, although most of our personally studied patients seem to have suffered from a less severe type of disease. In their retrospective study milder cases may have escaped attention. Of the five neurological syndromes here described, the first four carry a variable but on the whole benign prognosis, in sharp distinction to the patients with a generalized distal sensori-motor polyneuropathy, all of whom died with systemic arteritis soon after the onset of neuropathy.

Necrotizing arteritis occurring in rheumatoid disease is indistinguishable histologically from polyarteritis nodosa. Neuropathy is common in classical polyarteritis, taking the form either of symmetrical distal sensori-motor polyneuropathy or of mononeuritis multiplex (Baker, 1962; Bleehen, Lovelace, and Cotton, 1963). To our knowledge, neither digital neuropathy nor a purely sensory neurological syndrome in the lower limbs has been described in polyarteritis nodosa. However, the occurrence of digital neuropathy in this disease would not be surprising, since the digital vessels may become occluded (Laws *et al.*, 1963).

The peripheral neuropathy of rheumatoid arthritis has also to be distinguished from other forms of peripheral neuropathy, such as those occurring in diabetes mellitus, pernicious anaemia, and carcinoma. It resembles these in that it is mainly sensory. It differs in that the fingers are frequently, and often predominantly, involved, in that superficial modalities of sensation are often more affected than deep, and in that the distribution of sensory loss, at least in the digits, is often characteristically patchy (see Fig. 1). The diagnosis is sometimes helped by finding signs of digital ischaemia. Two of our patients (Cases 24 and 27) had concurrent diabetes. Case 24 followed a rapidly progressive course, as described, and the neuropathy was clearly associated with his rheumatoid disease. The distal sensory neuropathy in Case 27, however, may have been due to long-standing diabetes, and there is no way of settling the point. In Case 12 the patient died of gastric carcinoma and, although the course of his disease leaves little doubt that his neuropathy was of rheumatoid aetiology, it is just possible that the cancer contributed to its terminal deterioration.

No treatment is known to influence the course of rheumatoid neuropathy. Many of the patients are on steroid therapy, and it is probably wise to avoid rapid changes of dosage because of the possibility that this may aggravate the condition. It is important to treat loss of muscle power by appropriate support and physiotherapy, because our experience shows that the weakness is often temporary and that, unless contractures are prevented by splinting, the deformities often become permanent.

Summary

Thirty patients with rheumatoid arthritis and peripheral neuropathy have been personally studied and five patterns of neurological involvement defined: (I) upper limbs: lesions of major peripheral nerves; (II) upper limbs: "digital neuropathy"; (III) lower limbs: lesions of major peripheral nerves; (IV) lower limbs: "distal sensory neuropathy"; and (V) distal sensori-motor polyneuropathy of upper and lower limbs.

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FIG. 1.—Case 7. Brachial arteriogram showing widespread occlusion in the digital vessels.

FIG. 4.—Case 12. Lateral plantar nerve showing loss of myelin sheaths. (Osmium tetroxide and light green. $\times 125$.)

FIG. 2.—Case 12. Artery within epineurium of right posterior tibial nerve showing segmental destruction of the wall and fibrous intimal thickening encroaching on the lumen. (H. and E. $\times 125$.)

FIG. 3.—Case 12. Artery (seen in longitudinal and transverse sections) within epineurium of right lateral plantar nerve. Irregular disruption of elastica. (Verhoeff and van Gieson. $\times 125$.)

In the first four groups the tendency of the neurological lesion was towards recovery, and the prognosis regarding life was usually good. The patients with distal sensorimotor polyneuropathy, however, all died with widespread vasculitis.

In most patients the neuropathy was thought to be due to occlusion of the vasa nervorum by the arterial disease sometimes associated with rheumatoid arthritis. This view was supported in our cases by clinical and histological evidence and by the finding, on brachial arteriography, of occlusive lesions in the digital vessels in the majority of instances. In a few patients the neuropathy was attributed to local pressure from a damaged or swollen joint. In others both pressure and vascular disease were thought to operate.

It is confirmed that patients with rheumatoid arthritis and ischaemic neuropathy have a positive differential agglutination titre and a high incidence of nodule formation. They often show evidence of vasculitis elsewhere. This is not necessarily so where pressure alone is the cause of the neuropathy.

Many of the patients were receiving steroids, but no clear evidence emerged that this therapy was directly related to the development of neuropathy.

It is a pleasure to acknowledge the co-operation of Professor E. G. L. Bywaters and Dr. J. W. Laws in this study.

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Femoro-popliteal Endarterectomy

W. T. IRVINE,* M.D., CH.M., B.S.C., F.R.C.S., F.R.C.S.ED.; E. J. WILLIAMS,† M.B., B.S., F.R.C.S.
 S. N. PLESSAS,‡ M.D.

[WITH SPECIAL PLATE]

Brit. med. J., 1965, **1**, 1147–1149

With the introduction of endarterectomy for occlusive vascular disease it soon became apparent that such arterial reconstructions below the inguinal ligament were much less successful than similar procedures on the aorta and iliac arteries. This led to the introduction of the femoro-popliteal bypass grafts (Kunlin, 1951), and the end-to-side anastomosis allowed by this technique ensured longer anastomoses in these small arteries. There was a far higher primary success rate, but longer assessment has shown the life of cloth grafts below the inguinal ligament to be depressingly short, and adequate saphenous veins for use as grafts were often not present (Irvine, Kenyon, and Stiles, 1963). These late failures have led to the reintroduction of endarterectomy below the inguinal ligament. This has received added impetus from the introduction of arterial strippers which allowed long lengths of artery to be cleared through multiple short arteriotomy incisions, though many surgeons still prefer arterial clearance by open arteriotomy incisions (Edwards, 1962). The second technical advance which has improved the primary results of endarterectomy in small vessels has been the use of vein or Dacron patches at the time of closing the arteriotomy to avoid narrowing the lumen (Cannon, Barker, and Kawakami, 1958; Edwards, 1962).

This report deals with a group of patients having multiple or single endarterectomies below the inguinal ligament. Some of them had, at the same operation, extensive endarterectomy above the inguinal ligament.

Clinical Material

This paper is based on the study of 37 patients (35 male and 2 female), and reports the results of endarterectomy below the inguinal ligament in 38 limbs. All patients suffered from atherosclerosis, and had thrombosis or stenosis of the femoral or popliteal artery. In addition, some patients had thrombosis or stenosis of the aorto-iliac vessels. The mean age of the patients was 55 years. The incidence of related disease has been assessed with regard to those conditions that are known to be associated with peripheral arteriosclerosis. One patient suffered from diabetes; six of the 37 patients had E.C.G. changes of past myocardial ischaemia; 10 had a diastolic blood-pressure greater than 95 mm. Hg. Routine serum cholesterol estimations were carried out in all patients, and in 10 it was 300 mg. or more.

Selection of Patients.—The indications for operation in this series were intermittent claudication, rest pain, or gangrene. The distribution of patients in these groups is shown in the Table. In the majority of cases the claudication distance was 100 yards (90 metres) or less (80%), and in 16 of these the

* Professor of Surgery, Surgical Unit, St. Mary's Hospital, London.

† Assistant Director, Surgical Unit, St. Mary's Hospital, London.

‡ Clinical Assistant, Surgical Unit, St. Mary's Hospital, London. Present appointment: Senior Registrar, King Paul's Hospital, Athens.