to the more recent studies of Ewing, Lacassagne, and Burrows, is briefly described. In recent years I have demonstrated the presence of a growth-promoting factor in inflammatory exudates. This factor offers a reasonable explanation for the mechanism of repair. Its growth properties can be elicited by repeated injections in either the ear or the breast tissue of rabbits. In the latter area a picture resembling that seen in chronic cystic mastitis of humans is frequently obtained as a result of repeated injections of the growth factor in non-pregnant rabbits. In the ear, both epithelial and cartilaginous structures are affected in the form of marked proliferation from the perichondrium as well as pronounced hyperplasia and keratinization on the part of the epithelium.

The growth-promoting factor of exudates is diffusible, and as such it can be obtained by dialysis and subsequent concentration of the diffusate. It is heat-stable. Repeated injections tend to produce a state of irreversibility, so that the enlarged breast fails to regress upon cessation of the course of administration. Nevertheless, the factor *per se* fails to induce an autonomous neoplastic process. It has, however, been demonstrated that the growth factor of exudates behaves as a cocarcinogen when combined with a carcinogenic hydrocarbon—for example, methylcholanthrene. This appears to be the role of inflammation in carcinogenesis—namely, that of a co-carcinogen via the growth-promoting factor, liberated in turn by injured cells at the site of inflammation.

Absorption as well as chromatographic studies support the view that the growth-promoting factor of exudates contains peptide and nucleotide structures involved in its activity. The possibility that the factor is a nucleopeptide is envisaged, and is therefore being considered. Inactivation of the factor by both trypsin and ribonuclease supports such a view.

The problem of carcinogenesis and cellular injury is discussed. It is pointed out that severe cellular injury leads to the development of inflammation, while mild injury tends to produce proliferative activity. Basically, neoplastic formation appears to depend on genetic susceptibility, which, in turn, can be intensified, accelerated, or reinforced by the liberation of the endogenous growth-promoting factor of exudates, acting thus as a cocarcinogen.

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RHEUMATOID NEUROPATHY*

BY

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"Nobody is on my side, nobody takes part with me:
 I am cruelly used, nobody feels for my poor nerves."

—Mrs. Bennett in *Pride and Prejudice*.

A sufferer from rheumatoid arthritis has enough to contend with in attempting to live in rough harmony with his painful, stiff, weak, and swollen joints. The addition of peripheral neurological features may make life even more unbearable for him and may necessitate admission to hospital and a greater degree of disability and crippling in the future. This complication of rheumatoid disease, for so we consider it, was forcibly brought to our notice three years ago, when four out of eight in-patients presented with sensory signs in the legs; one had motor weakness also, being unable to dorsiflex one foot. The fact that half our in-patients with rheumatoid disease at that time had peripheral neuritis was a pure coincidence, for the complication is relatively uncommon, but it started us on our present investigation (Hart *et al.*, 1957).

We have now seen a total of 25 such cases in our own unit and a further 17 in the clinics of colleagues who have kindly allowed us to see their patients and their records. An increasing number of cases have been reported in the last three years in the world's literature, mostly from the United States of America, where steroid therapy has largely been blamed for its emergence as a clinical entity. In this country, however, we have seen several cases which have never received steroids, and a neuropathy in rheumatoid disease was reported as long ago as 1887 by Pitres and Vaillard, in France, and in this country in 1898 by Bannatyne, who, in a book on rheumatoid arthritis, recognized it as a systemic disease and stated, "in a certain number of cases peripheral neuritis has been noticed, but in so far as to negative any idea that this [neuritis] is the cause of the [rheumatoid] disease"; and again, "in the cases where the reflexes are absent it is almost certain that we have to do with a neuritis probably set up by the joint inflammation or by toxins." The late W. H. Allchin (1900) wrote: "Definite peripheral neuritis has been demonstrated in a few cases [of rheumatoid arthritis] though not in the nerves which actually supply the joints."

In the last 30 years increasing emphasis has been placed on the systemic manifestations of rheumatoid arthritis (Fingerman and Andrus, 1943; Bauer and Clark, 1948; Calkins and Bauer, 1955), and a pathological study by Sinclair and Cruickshank (1956) has emphasized the widespread nature of rheumatoid

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arthritis. Various reports appeared concerning the histology of nerves and muscles in rheumatoid arthritis, focal collections of round cells occurring commonly (Freund *et al.*, 1942; Gibson *et al.*, 1945; Morrison *et al.*, 1947), but until recently there was relatively little in the literature regarding neuropathic changes in rheumatoid arthritis, though it was known to occur relatively often in polyarteritis nodosa. Its occurrence in systemic lupus erythematosus is also well recognized (Heptinstall and Sowry, 1952).

As the systemic features of rheumatoid arthritis have been more widely appreciated, so it has become apparent that these three so-called "collagen" disorders have no fixed, firm barriers; changes in serum proteins, positive sheep-cell agglutination tests, or development of L.E. cells in the circulating blood may occur in all on occasion. There seems to be, in fact, a merging pattern of these disorders, and we have come to recognize a clinical picture of "complicated rheumatoid arthritis" short of the full development of polyarteritis nodosa or systemic lupus erythematosus. It is in this complicated group that peripheral neuropathy occurs more commonly. The usual case is of long-standing rheumatoid disease with subcutaneous nodules, high-titre positive differential agglutination test (Rose-Waaler test), features of therapeutic hypercortisonism, marked changes in the serum electrophoretic pattern, and polyarteritic and neuropathic features. Though milder and less serious cases occur we consider that the development of this full clinical picture is of grave prognostic importance. Mason and Steinberg (1958) are of the same opinion. Epstein and Engleman (1959) go further and state that steroids should not be used in this group of patients.

Clinical Study

We now have details of 42 cases, 25 from our own unit. Of these 42 patients, 18 were men and 24 were women, their ages ranging from 36 to 88 years, the large majority being between 40 and 60. 15 had had no steroids within a period of three years from the onset of neuropathy, and 12 had never had steroid therapy at any time prior to the development of the neuropathy. 20 were on a regular dose of steroid and had no history of recent alteration in dosage; in six reduction or withdrawal of steroid therapy had apparently precipitated neuropathic changes. Except in a few cases, steroid therapy had been given continuously for one to five years before the onset of neuropathic changes. Visible arteriopathic changes were present in 6 of the 42 at the time of onset of the neuropathy, in two cases coming on at the same time. Phenylbutazone and gold appeared to play no part in precipitating symptoms in any case. Rheumatoid nodules were present in 24 cases and absent in 15; in 3 the records are inadequate. The D.A.T., or Rose-Waaler test, was not done or recorded in eight cases, but in the other 34 it was negative in 5 and positive in 29, usually in high titres. In almost all cases where neuropathy occurred on regular dosage prednisone or prednisolone was being given at the time of onset, but one case occurred on corticotrophin therapy.

The newer steroids, triamcinolone, methylprednisolone, and dexamethasone, have not yet been used extensively long enough for anything to be said about the relative incidence of neuropathy with the different steroids; it is of interest, however, that a change to a new steroid in comparable dosage appeared to trigger off the neuropathy in three cases—two on changing

from cortisone to prednisolone, one from prednisolone to dexamethasone—and in two further cases manipulation of dosage of different steroids in the preceding few weeks may have played a part. Motor weakness occurred in 18 cases, always when sensory changes were considerable. Marked weakness or absence of dorsiflexion of the foot was the best guide. This was positive in both legs in seven cases, in one leg in seven, and in all four limbs in four, marked weakness in finger movement and grip also occurring. This assessment of muscle weakness had to be carefully done, as rheumatoid changes in joints cause pain and weakness, and this had to be carefully considered in every case. The important point in differentiation lay in the temporal relationship between fresh muscle-weakness and the onset of neuropathic change.

In all cases where muscle power was affected, sensory changes were relatively advanced. In two cases transient unilateral facial hypoaesthesia was noted at the time of development of the neuropathy, but its significance is uncertain. Ankle reflexes were much reduced or absent bilaterally in eight cases, unilaterally in four. The pattern of the neuropathy was symmetrical in 26, asymmetrical in 16. L.E. cells were found in only four patients, but in no case could the diagnosis of systemic lupus erythematosus be seriously considered. In four cases a skin condition variously named livedo reticularis or livedo racemosa, said to be a skin manifestation of polyarteritis nodosa (Ketron and Bernstein, 1939; Talbott and Moleris Ferrandis, 1956), developed during the course of rheumatoid neuropathy.

It may be of significance that arteritis and neuropathy have not to date, to our knowledge, been reported in other conditions treated by steroids, such as asthma or ulcerative colitis, but only in the collagen disorders. This may, however, be due to the fact that few other disorders are treated for such long periods continuously.

Mode of Onset

In 13 cases the neuropathy appeared abruptly and painfully, so that the patient could state the day and even the approximate time when symptoms were first noticed; in the remaining 29 cases the onset was more gradual and insidious. In only 3 of these 29 cases was the appearance of the neuropathy at a time of overall exacerbation of the rheumatoid disease. Though in six cases the appearance of neuropathic features was related to reduction or cessation of steroid dosage, one, when started on prednisolone, cleared in a month and one improved when started on corticotrophin. In two cases steroid therapy was abruptly stopped by the patients after the development of the neuropathy, without any alteration in the signs and symptoms.

Progress

The course of the neuropathy has often been difficult to assess. Some cases have remained constant and unchanged over periods of observation up to four years; others have improved, with some residual neurological change; some have fluctuated, improving and worsening at different times; some have disappeared completely. At the time of this review or at death 20 cases appeared relatively constant and unchanged; 14 have improved, sometimes after marked fluctuation in the past; two steadily deteriorated before death; five have apparently recovered completely; and one continues to fluctuate erratically. Of the 15 patients not given steroid therapy

for the previous three years, two have worsened, one has fluctuated erratically, six have remained constant, five have improved, and one has completely recovered within one month of starting prednisolone by mouth. Two patients who developed neuropathy before receiving steroids and who were later started on prednisolone suffered an exacerbation of symptoms and a severe worsening of their neuropathy, one on withdrawal and one on constant dosage. Of the seven fatal cases, four had been on prolonged steroid therapy, two had suffered an exacerbation of symptoms on sudden withdrawal of steroids, and one had not received this therapy. In these fatal cases the neuropathic features worsened prior to death in two cases, improved in one, and remained relatively unchanged in four.

As regards treatment, nothing given has conclusively improved the neuropathy. Occasional fluctuations make assessment difficult, but neither moderate increase in steroid dosage nor vitamin administration or anything else we have tried has appeared to make any real difference. Estimations of the plasma vitamin B₁₂ in the last nine cases have all been entirely normal.

Clinical Picture

The more usual mode of onset was of numbness or "deadness" in toes and feet, or of an intolerable burning pain. The complaint was usually bilateral or symmetrical, though one leg was commonly more extensively involved than the other. The pressure of bedclothes, even socks, was often intolerable to the sufferer. It was in general only in the more severe cases, where sensory changes were marked and extensive in the feet, that fingers and hands were also involved. Excessive sweating was noted in only one case—a male patient under the care of Dr. R. R. Bomford at the London Hospital. In this patient so severe was the hyperaesthesia over the soles of the feet that walking was prevented by this alone. Weakness of foot movements, notably dorsiflexion, or of grip was complained of in the more severe cases with extensive sensory changes in the legs. On examination all modalities were found to be reduced in the affected areas; light touch, pin-prick, two-point discrimination, heat and cold, and vibration sense were usually markedly affected, but position sense usually remained well preserved. If sensory changes were not of the more usual stocking, shoe, sock, or glove distribution in the extremities, lateral (popliteal) involvement was more common than medial in the legs and ulnar than radial in the hands, though in three cases median-nerve compression was considered in the diagnosis. Occasionally there was numbness confined to one foot, with unilateral foot-drop, but in general the neuropathy was of symmetrical pattern, legs and feet being affected more than hands and arms, sensory findings occurring before and in excess of motor changes. The milder cases usually showed sensory changes only, though electromyographic examination in these cases showed a motor weakness also in the few where this investigation was done.

One interesting feature of the neuropathy was that the ankle reflexes were usually present even with extensive sensory loss. In only eight cases of our series were both ankle responses absent; it was striking how in rheumatoid patients with wasted calf muscles the ankle reflexes could normally be elicited with ease. As a rule, the ankle reflex was absent only if there was foot-drop on that side.

The earliest evidence of a neuropathy developing in rheumatoid arthritis is usually the patients' own unsolicited statement that something fresh, new, and unpleasant has happened to their feet, which feel different and are painful in a different way. Their unsolicited and voluntary statement was the earliest evidence of neuropathic change in most instances: in some cases physical signs were much less impressive initially than the patient's own firm statement of abnormality. Those of us who have had mandibular-nerve blocks for dental operations know how odd and abnormal the anaesthetized area feels even though the various forms of sensation can be roughly appreciated in that area. It is sobering to contemplate how often in the past patients must have made complaints almost diagnostic of this complication to their physicians, who, as this disorder was not an orthodox one described in the current textbooks on the subject, turned a deaf ear to them. The patient's account of these sensory changes is so completely unlike the usual one of the pain, stiffness, weakness, and swelling of his arthritis that it is extraordinary that they were ever confused.

Other Types of Neuritis in Rheumatoid Arthritis

In rheumatoid arthritis median-nerve compression in the carpal tunnel may occur, giving the signs and symptoms of this disorder; or large effusions in, or gross derangement of, certain joints may be associated with neuritis distal to them—for example, ulnar neuritis below a severely affected elbow. It is of interest that in one case under the care of Dr. A. G. S. Hill the initial disorder was diagnosed and treated as a carpal-tunnel syndrome with poor therapeutic response, only to be followed two and a half years later, after steroid therapy had been introduced, by a typical symmetrical rheumatoid neuropathy. In retrospect it is hard, on retaking the history, to differentiate the two, and it seems possible that all were manifestations of one disorder—that is, rheumatoid neuropathy. Similarly, in one of our patients a large effusion in the right elbow was associated with an ulnar neuritis on that side, but a more detailed examination on her next attendance revealed symmetrical sensory changes in the feet. Nevertheless, signs in the arm were so much more marked that Mr. David Evans was asked to transplant the ulnar nerve from its usual site to an area anteriorly where it could not be traumatized on the arms of chairs and table tops. At operation the nerve was exposed and explored. No thickening or adhesions were found, but the arcuate ligament between the two heads of flexor carpi ulnaris was thickened. This was incised for $\frac{1}{2}$ in. (1.3 cm.) and nothing more was done. This operation has given immediate and lasting relief and has cured the ulnar neuritis completely in the same way as a successful carpal-tunnel operation relieves the symptoms of median-nerve compression. Though these local causes for neuritis do occur in rheumatoid arthritis, in our experience they are rare, and when they do occur careful search should be made for signs of neuropathy elsewhere at the time and over several months subsequently.

Cervical spondylosis may occur in the more elderly patient and may confuse the picture in rheumatoid disease; for, although rheumatoid involvement of the cervical spine is not associated with narrowing of the foramina of Luschka, the later development of degenera-

tive changes may cause root pain referred down the arm. Though sensory changes may occur in the upper extremities with cervical spondylosis, simulating rheumatoid neuropathy, signs of upper-motor-neurone disease in the legs with extensor plantar response point to the correct diagnosis. Subluxation of one cervical vertebra on another with marked spondylolisthesis is recognized as a cervical complication of rheumatoid arthritis, and the resultant quadriplegia is one of the most unpleasant complications of this disease and one of the hardest to treat. One of our patients, ten years ago, while at convalescent home developed contracture deformities due, not to her rheumatoid disease, but to the insidious development of subacute combined degeneration of the cord. Other conditions which may be encountered are neuritis associated with malignant disease, with alcohol, with diabetes mellitus, or with amyloidosis.

It is worthy of note that although the female: male ratio in rheumatoid arthritis is about 2.5:1 in this country, both in this series and in that of Steinberg (1960) the sex incidence of rheumatoid neuropathy is about unity—that is, more male patients get this complication than do females. It is of further interest that the usual sex incidence in other types of peripheral neuritis is predominantly male. Rose (1960) giving the male:female ratio as 3:2. There seems to be no adequate explanation for this predominance of males in neuropathic disorders.

Pathology

Seven deaths have occurred in this series—four of our own patients, one (Case 5) of Drs. West and Newns in Sheffield, and two of Drs. Mason and Tegner at the London Hospital. These last two cases have already been reported (Mason and Steinberg, 1958). Four necropsies have been done on patients with rheumatoid neuropathy at the Westminster Hospital. Extensive arteritis had been found in one male case, previously reported by us (Hart *et al.*, 1957). The clinical and necropsy findings in five fatal cases are given in the accompanying Table.

Case 1.—This patient was a man of 55 whose clinical course was marked by extensive neuropathy, episodes of left

ventricular failure, and necrotic vascular lesions of the fingertips, as described by Bywaters (1957). During the last four weeks of life the neuropathic symptoms in his hands improved greatly, though he deteriorated in other ways; and, before his death, examination of the hands revealed a diminished vibration sense of the fingers and diminished two-point discrimination as the only abnormalities. At necropsy there was obliteration of the pericardial sac by a fibrinous pericarditis. The surface of the heart was red, and nodules were seen along the anterior descending branch of the left coronary artery. There was atheroma of all the coronary arteries. Histologically, arteritis was found in the small arteries of the heart, pericardium, lungs, and peripheral nerves in the feet. Different grades of arteritis were found: the most mild consisted of perivascular infiltration with lymphocytes, but some vessels showed fibrinoid necrosis, periarteritis with infiltration by different types of cell, and aneurysmal dilatation of the vessel walls typical of polyarteritis nodosa. Section of peripheral nerves in the right leg showed obvious demyelination and arteritis of the vasa nervorum. The right median nerve was apparently normal histologically. It is of interest that, during life, biopsies of skin, muscle, and small arteries did not show any abnormality.

Case 2.—A man aged 43 had clinically a myocardial infarct eight weeks before his death, which was due to bronchopneumonia. He had more gross signs of peripheral neuropathy at death than any other patient in our series. At necropsy the pericardial cavity contained little fluid, but there was no fibrinous pericarditis. An area of fibrosis representing healed infarction was found on the posterior wall of the right ventricle. A little nodule was seen on the artery supplying the infarcted area, which was suggestive but not diagnostic of polyarteritis nodosa. There was a purulent bronchitis and extensive confluent bronchopneumonia. No other significant macrocytic abnormality was seen. Histologically, evidence of arteritis was seen in two of the smaller vessels of the coronary tree. In the first a segment of muscle coat was replaced by fibrous tissue and the internal elastic lamina was fragmented. In the second there was a form of fibrinoid material infiltrated by young fibroblasts and surrounded by granulation tissue. Active and healed arteritis was seen in the liver. It was difficult to be certain whether a form of arteritis in the lungs was due to his rheumatoid disease or to the terminal bronchopneumonia. Arteritis was seen in one small splenic vessel and in one medium-sized artery in the adrenal capsule. Most interesting of all, however, were the nerves: Sections of nine peripheral nerves of arms and legs showed no abnormality, either arteritis or demyelination. An isolated

Clinical and Necropsy Findings in Five Fatal Cases

Case No.	Sex and Age	Duration R.A.	Duration Neuropathy	Nodules	R.W. D.A.T.	Duration Steroid Therapy	Cause of Death	Cardiac Findings	Arterial Lesions	Neurological Findings	General Comments
1	M 59	6 years	9/12	++	1/256	1 year abruptly stopped	Acute left ventricular failure	Nodules on coronary arteries. Fibrinous pericarditis	Diffuse arteritis and periarteritis	Arteritis + and demyelination	—
2	M 43	12 "	15/12	++	1/256	7/12 stopped abruptly	Coronary thrombosis. Bronchopneumonia	Arteritis. Coronary thrombosis	Scattered arteritis	9 nerves from extremities, all normal	Multiple areas of fibrosis suggestive of repair
3	F 58	4 "	2/12	+	1/128	4 years	Complicated R.A. with hypercortisonism	Pan- and pericarditis	Arteritis of 1 peripheral nerve only	Arteritis vasa nervorum in one area	Marked signs of hypercortisonism. Multiple fractured ribs. Collapsed vertebrae
4	F 56	14 "	2/52	+	1/128	7 "	Coronary thrombosis	Right coronary artery thrombosed	Nil	Nil	Previous perforated double peptic ulcer and staphylococcal septicaemia
5	M 46	16 "	2 years	—	—	3 "	Pulmonary artery thrombosis. Intestinal bleeding from peptic ulcer. Bronchopneumonia	Adherent pericardium only	"	"	Pyæmia

arteritic lesion could easily have been missed, but it might be thought that demyelination would have been demonstrable distally.

Case 3.—A woman aged 58, a nodular rheumatoid case, developed mild sensory neuropathy of the legs only a few weeks before her death. Again an adherent pericarditis was found, with a few haemorrhages immediately below the visceral layer of the pericardium. The lung bases and liver were congested. Pancarditis was shown histologically, with changes of activity and healing in different areas. The myocardium was infiltrated with chronic inflammatory cells and contained numerous small paravascular areas of acellular collagen. The coronary vessels themselves were normal. One section of a small cutaneous nerve of the foot showed a grossly thickened wall of its nutrient artery, with narrowing of the lumen. The wall was infiltrated with lymphocytes; this was the only example of a true arteritis seen in all the sections examined.

Case 4.—The death of this patient occurred half an hour after a large coronary thrombosis. She had developed symptoms and signs of sensory peripheral neuropathy on the lateral border of the right foot two weeks previously. At necropsy, careful examination of her viscera failed to demonstrate any evidence of arteritis, though the right coronary artery was completely plugged by thrombus. The nerves in the leg were dissected out from the sciatic nerve via the lateral popliteal nerve and then down through the cutaneous nerves to their many small ramifications. Examination of 50 sections from largest to smallest nerves failed to show either arteritis or demyelination.

Case 5.—The findings in this case are similar to those in Case 4. The patient had marked signs of motor and sensory neuropathy in the feet and legs, and died after pulmonary thrombosis and intestinal bleeding from a gastric ulcer. No organ, including sections of nerves, showed any arteritis, apart from some perivascular round-celled infiltration in the dermis.

It will be noted that three of these five fatal cases died cardiac deaths—two from coronary thrombosis and one from cardiac failure. It is ironic that the first two patients had been reasonably well for some years on aspirin but later worsened, were transferred to steroid therapy, and deteriorated after its sudden withdrawal in each case. Cases 3 and 4 were active progressive patients with hypercortisonism, the latter having perforated a gastric ulcer and been cured of staphylococcal septicaemia previously. In all five cases steroid therapy clearly contributed to the general condition and downhill course. The scanty or absent findings in the peripheral nerves in the last three cases are of interest, for these patients all showed abundant clinical evidence of neuropathic disorder at the time of their death.

Discussion

In a search for other causes for the neuropathy we found no evidence in our cases of any other aetiological agent such as amyloidosis, porphyria, diabetes, avitaminosis, intercurrent infection, or heavy metal poisoning. On the existing evidence most authors feel that the neuropathy is probably due to vascular lesions, which are commonly seen to co-exist. Johnson *et al.* (1959) found that 14 out of 138 patients treated in 1957 with adrenocortical steroids developed peripheral neuropathy. Of these 14, 11 had subcutaneous rheumatoid nodules; the D.A.T., or Rose-Waaler, test was positive in 13 and the L.E. cell absent in the 13 cases where this test was performed. In six cases steroid therapy had been uninterrupted, five had occurred one to five months after it had been discontinued, and in three cases it had

been stopped and restarted. In their three fatal cases polyneuropathy preceded gangrene and multiple systemic manifestations, being more severe and extensive than in the survivors.

Epstein and Engleman (1959) reported nine cases of typical rheumatoid arthritis in which severe vascular occlusive lesions and peripheral neuropathy developed. All nine patients were receiving steroids, usually prednisone or prednisolone, and had been on such therapy for from one and a half to five years. All had severe rheumatoid disease, subcutaneous nodules, large amounts of circulating rheumatoid factor, and ischaemic skin change. In four cases an arteritis was seen in biopsy specimens, in four it was not. Sokoloff and Bunim (1957), Mason and Steinberg (1958), Steinberg (1960), and others have also reported similar cases. Irby *et al.* (1958) reported 6 cases that were on, or had been receiving, steroid therapy. All were long-standing severe cases. Examination of the cerebrospinal fluid was made in all cases and was normal except for an elevated protein (90 mg.) in one. Radnai (1953) emphasized the importance of vascular changes in the development of neuropathy in rheumatoid arthritis, and Slocumb (1953) drew attention to the "panangiitic and panmesenchymal reactions" which occurred on reduction of steroid dosage in this disorder.

Kemper *et al.* (1957) reported that of 52 rheumatoid patients studied at necropsy 38 had received no cortisone. None of these developed generalized lesions of polyarteritis nodosa, whereas of the cortisone-treated patients four did so, three showing signs of neuropathy. In reviewing the literature on this subject they consider that the vascular changes observed in rheumatoid arthritis fall into three groups: (1) perivascular or adventitial accumulation of leucocytes, plasma, or other cells, with no noticeable necrosis; (2) subacute arteritis with histiocytic and lymphocytic infiltration through all layers of the vessel wall, without necrosis, but possibly with some exudation of fibrin and swelling of collagen; and (3) lesions of acute arteritis with cellular infiltration and necrosis of the vessel wall—a necrotizing angitis. These workers thought that this suggested that in certain susceptible patients with rheumatoid arthritis the administration of cortisone might precipitate changes in the third group, and there is a good deal of secondary evidence that this may occur. The fact, however, that approximately one-third of our patients had had no steroid therapy at the time of the development of the neuropathy suggests that this may and does occur as a true primary or "rheumatoid" neuropathy. We may therefore postulate three groups:

1. Rheumatoid neuropathy occurring in the absence of steroid therapy or any other known agent.
2. Neuropathy occurring after reduction or cessation of steroid dosage. In this case it is possible that a polyarteritis may flare up and occlusive lesions occur in relation to nervous tissue.
3. Neuropathy occurring with constant steroid dosage. In these cases fluctuations in the underlying disease activity, or additional trauma or other aggravating factors, may well play a part. In several of the case-histories some traumatic experience did occur within a few weeks of development of the neuropathy. In this last context the following case-history is of interest.

A married woman aged 35 had for some years been performing on the music-halls as a contortionist. The onset of acute rheumatoid arthritis necessitated a change in the act, and she became an assistant to her husband as

he performed as conjurer. She was by now on prednisolone, 15 mg. daily, and was keeping relatively well on it, when she heard that a medically unqualified hypnotist was curing patients by hypnotizing them out of their arthritis. Unhopeful, but persuaded by a friend (of the hypnotist), she submitted herself to the process; but the hypnotist, unable to procure a hypnotic trance, proceeded to give her "trilene" anaesthesia on three separate occasions. Her arthritis became rapidly worse, and one and a half hours after the third unsatisfactory anaesthetic she became febrile and ill. Next day she felt completely exhausted and noticed numbness of her fingers. Her feet and ankles felt numb and "prickly," but were also unduly sensitive and painful. In her act, that night, she fumbled with the playing-cards and could not properly use her right thumb. When examined 11 days later her hands had returned to normal, but sensory changes remained over short-sock distribution in both feet.

We have seen other transient cases of this nature. It is possible that traumatic factors flared up a latent arteritis which under ordinary conditions and under suppressive steroid therapy had remained quiescent. The following case-history demonstrates the same transient type of neuropathy, in this instance precipitated by withdrawal of steroid therapy.

A man aged 63 had severe active chronic progressive rheumatoid arthritis of 10 years' duration. After two years on steroid therapy, prednisolone was very gradually reduced over a period of four months from 15 to 5 mg. daily. He then developed paraesthesiae over feet and heels. Prednisolone was discontinued completely three weeks later, and one week afterwards he lost the power of dorsiflexion in one foot, paraesthesiae became more pronounced, and sensation was impaired over both feet. Three days later power returned and the sensory symptoms gradually abated.

This case appears to be a steroid-withdrawal syndrome in miniature followed by rapid improvement. Such transient cases are undoubtedly more often missed than noted; in this particular instance the patient was an in-patient and, because of steroid withdrawal, was under particularly close daily supervision.

Why peripheral neuropathy occurs in rheumatoid arthritis is still unknown, and before accepting it as due to an inflammatory arteriopathy one might consider the evidence against this thesis. If we compare the type of neuropathy seen in our rheumatoid patients with that described by Lovshin and Kernohan (1948) in polyarteritis nodosa we find the following differences:

<i>Polyarteritis Neuropathy</i>	<i>Rheumatoid Neuropathy</i>
1. Usually asymmetrical ..	Usually symmetrical
2. Essentially motor ..	Essentially sensory
3. None sensory only ..	Many sensory only
4. If clinically present histological findings invariably present ..	No histological findings in some cases clinically severely affected

If rheumatoid neuropathy were entirely due to an arteritis one might perhaps expect a greater similarity in these two groups. Mononeuritis multiplex occurs in rheumatoid arthritis as it does in idiopathic polyarteritis nodosa, and then it tends to be in ulnar or lateral popliteal distribution. This is also the more common distribution in symmetrical rheumatoid neuropathy, suggesting that the asymmetrical pattern of the one is merely a milder variant of the other, the disease being, as it were, "spread thin." We have seen several cases progress from the patchy type to the more symmetrical over a period of several months. Why rheumatoid neuropathy tends to be symmetrical if it be due to an

arteritis is obscure; it suggests a very diffuse low-grade silent involvement of vessels picking off the longest nerve fibres. The work of Lewis *et al.* (1931) demonstrated that the sensory fibres are more sensitive to ischaemic changes. The alternative explanation is that the neuropathy occurs as part of the rheumatoid illness and is not directly due to an arteritis.

It is of interest here to compare diabetic and rheumatoid neuropathy. Both were overlooked for many years, and both were then ascribed to vascular damage; now the cause of diabetic neuropathy is admittedly unknown. Both affect feet more than hands, are sensory rather than motor, and are symmetrical rather than asymmetrical, with vibration sense much impaired; but there the similarities cease. It is in our experience rare for diabetes and rheumatoid arthritis to coexist, considering how common both conditions are.

Summary and Conclusions

Peripheral neuropathy occurring in rheumatoid arthritis is reported in 42 cases (18 male and 24 female). This relatively high incidence in males has been noted in other reported series of cases, and is in line with the incidence in other types of peripheral neuritis.

Of these 42 patients, 15 had had no steroid (cortisone) therapy within three years of onset of the neuropathy and 12 had never previously received such therapy at any time. We consider the condition a part or a complication of rheumatoid arthritis and have therefore termed it "rheumatoid neuropathy."

The worst cases and all the fatal ones with one exception were treated with steroid, as were the great majority of the reported cases in the world's literature. Sudden withdrawal or changing of steroid treatment may precipitate this complication.

The neuropathy is usually symmetrical and is primarily sensory, motor findings occurring in the more severe cases. Feet and legs are more often affected than hands and arms.

Rheumatoid neuropathy occurs more commonly in patients with nodules and advanced rheumatoid disease, usually with a high-titre D.A.T. (Rose-Waaler test). Vascular necrotic finger lesions may co-exist.

In some cases the finding of a diffuse arteriopathy at necropsy suggests that the probable cause is an arteritis of the vasa nervorum, and at present this is generally accepted as the most likely explanation. It fails, however, to explain adequately all cases coming to necropsy in our series nor the essential differences in the clinical pictures of these cases and those previously reported with neuropathy as part of idiopathic polyarteritis nodosa.

Though mild cases do occur, many recovering spontaneously, rheumatoid neuropathy should in general be regarded as a serious complication and one carrying a bad prognosis. No form of therapy has to date been found to be effective.

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Twenty cases of rheumatoid arthritis with peripheral neuropathy have been observed at the London Hospital or Chase Farm Hospital. Two of these were included by Hart *et al.* (1957) in their series, and are not discussed here. Six were previously reported elsewhere (Mason and Steinberg, 1958), but the survivors have been followed up and all are included in the present series.

Clinical Details

All 18 patients are classified as definite by American Rheumatism Association criteria (Ropes *et al.*, 1956), though L.E. cells have been demonstrated in three at one time or another.

Table I gives brief clinical details of these patients. The sex incidence is equal. Though different series show varying ratios, nine other series, totalling 56, show roughly equal sex incidence when added together

TABLE I.—Clinical Data of 18 Patients with Rheumatoid Arthritis who Developed Neuropathy

Sex	Males, 9; females, 9	Active disease	18
Age	27-71 years (average 55)	Nodules	7
Duration	1-17 " (" 5)	Serology positive	14
		Associated with flare	12
Present Condition			
Dead	5 (within 1 year of onset)		
Bedbound	5		
Varying degrees of disability	8		

TABLE II.—Sex Incidence of Neuropathy in Various Series

	Males	Females
Ball (1954)	1	1
Kemper <i>et al.</i> (1957)	2	1
Sokoloff and Bunim (1957)	1	1
Hart <i>et al.</i> (1957)	6	4
Irby <i>et al.</i> (1958)	5	1
Mason and Steinberg (1958)	3	3
Vignon and Durant (1958)	1	1
Johnson <i>et al.</i> (1959)	5	12
Epstein and Engleman (1959)	3	5
	27	29

(Table II). This is in contrast to the rest of rheumatoid patients, where females predominate by at least two to one.

The ages of the patients ranged from 27 to 71 years, with an average of 55. Disease duration was from one to 17 years, with an average of five. All the patients were suffering from active disease at the time of the onset of the neuropathy. Nodules were present in seven (39%). This is in contrast to Johnson *et al.* (1959), who found an incidence of 71% and Epstein and Engleman (1959), who found 100%. Either the Rose or the latex test was positive in 14 (77%). It is not possible to draw any conclusions from the titres, as the two tests are different, more than one laboratory was involved, and the technique was changed during this period. Epstein and Engleman (1959), however, noted that all their eight patients had very high titres with the F.II haemagglutination test. The neuropathy was associated with a flare in 12 cases (66.6%). This in itself may not be significant, because the flare may bring the patient under closer observation and be responsible for changes in therapy.

At present five patients are dead, all within one year of onset, and three within one month. All of these patients were on steroids or A.C.T.H. (see Table III). Five are more or less bedbound owing to the neuropathy; the remaining eight are a mixed group, but it must be stated that for five it is still early days.

NEUROPATHY IN RHEUMATOID DISEASE

BY

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Over the past few years it has become increasingly obvious that rheumatoid arthritis is a generalized disease, and during this time the systemic manifestations have been described with increasing frequency. In the past six years at least ten communications have described patients with rheumatoid arthritis in whom there was evidence of a neuropathy usually peripheral. Previous to this, clinical reports of neuropathy were rare, and the present increase appears to have coincided with the introduction of steroid therapy. Pitres and Vaillard (1887) found pathological changes in the peripheral nerves of three rheumatoid patients at necropsy. Bannatyne (1898) noted peripheral neuritis in a number of cases and described pathological changes involving the blood-vessels of the nerves. Freund *et al.* (1942) reported changes in the peripheral nerves in five patients seen at necropsy, and Morrison *et al.* (1947) found similar changes in 26.