Ann. rheum. Dis. (1957), **16**, 471.

NEUROPATHY IN RHEUMATOID DISEASE

BY

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Our attention was focused sharply on the prevalence of neuropathic disorder as part of rheumatoid arthritic disease, when some 12 months ago four out of eight patients in the ward at one time with rheumatoid arthritis complained of sensory or motor changes; on examination signs of a peripheral neuropathy were present in all four. This factor altered the symptomatology, treatment, and prognosis quite considerably. Since this time we have seen further cases, and it now appears to be worth reporting them in some detail and discussing their significance. The eleven cases are listed in the Table.

The literature on the subject is very scanty. In the current textbooks of neurology we see occasional references to "rheumatism" as a cause of peripheral neuritis, but there is no adequate description to give us greater details. Brain (1951) considers the so-called "rheumatic" polyneuritis following exposure to wet and cold to be in all probability the same as, or closely related to, acute infective polyneuritis, very likely of virus origin. The current textbooks of rheumatology are silent on the subject, but an apparently recent increase in polyarteritic features in rheumatoid subjects has been noted by several workers. Since steroid therapy has become

TABLE

PARTICULARS OF ELEVEN CASES

Case No.	Sex	Age (yrs)	Duration of Rheumatoid Arthritis (yrs)	Nodules	Differential Agglutination Test	Relationship to Steroid	Course of Neuropathy	Motor and/or Sensory Involvement	Other Polyarteritic Features
1	M	59	6	+	1/512	14 days after withdrawal	Improved	M + S	+
2	M	44	11	+	1/128	Nil	Improved then relapsed	M + S	—
3	F	59	13	—	1/16	Within a month of gradual withdrawal	Cured	S	+
4	M	61	8	+	1/128	Nil	Cured	S	+
5	F	51	19	—	1/128	Nil	Progressive for 6/12 then unchanged	M + S	—
6	F	57	6	—	—	Nil	Improved	S	—
7	M	80	20	—	1/64	Nil	Unchanged after 3 years	M + S	—
8	F	63	2½	—	1/512	Nil	Unchanged	S	—
9	M	70	6	+	1/2,048	Nil	Improving	S	—
10	M	63	10	+	—	7 days after withdrawal	Rapid recovery in 3 days	M + S	—
11	F	38	1 (Disseminated lupus erythematosus)	—	1/4	7 days after withdrawal	Slow improvement	M + S	+

more widely used such cases appear to have increased, though "polyarteritis nodosa" has been known for some time to occur in rheumatoid arthritis, usually in the later stages, without steroid therapy ever having been given. Neuropathy may be a manifestation of either systemic (disseminated) lupus erythematosus or of polyarteritis nodosa; the question to be answered is whether all such cases may be so explained or whether a true "rheumatoid neuritis" exists.

Case Reports

Case 1, a lorry driver aged 55, developed pain and stiffness in many joints in 1951, beginning with the left shoulder. When first seen at the Westminster Hospital in 1952, he was diagnosed as having rheumatoid arthritis; ulnar nodules and olecranon bursae were present, and all his metacarpophalangeal and proximal interphalangeal joints were swollen and stiff. Advanced radiological rheumatoid changes were present in most of the peripheral joints.

Treatment was by large doses of salicylates, which controlled his symptoms, and he was able to work until September, 1955, when his fingers became increasingly painful and blue, and several developed gangrenous tips.

He was admitted to hospital for 6 weeks rest in bed in October, 1955; salicylates were continued and he showed spontaneous improvement. It was noted at that time that sensation in his fingers and toes was preserved. Polyarteritis nodosa was considered as a diagnosis, especially in view of an episode of left-sided pneumonitis in the following month, but there was no definite clinical evidence to support this. On discharge the tips of his fingers were no longer gangrenous.

His joints became worse during the next few months so that he was hardly able to get about, and prednisolone 5 mg. twice daily was begun in April, 1956. There was a week's initial improvement, but after that he thought that the tablets were making him worse and giving him indigestion, and he stopped them himself abruptly on June 18, 1956. Almost immediately his joints became painful, and a fortnight later he suddenly developed burning pains in both arms and legs of a type he had never experienced before. His legs became weak so that he was unable to walk and in July he was again admitted to hospital.

There he was found to have a peripheral neuropathy. His hands showed only impaired sensation and weak grip, but there was complete anaesthesia of the feet with reduced sensation up to the knees. Bilateral foot drop was complete and all movements at knee and ankle joints were weak; the ankle reflexes were absent.

There was uncertainty at this stage whether the neuropathy was a complication of the rheumatoid arthritis, whether he had developed polyarteritis nodosa, or whether the cause was quite unrelated. A skin biopsy and two muscle biopsies were quite normal, neither showing the least evidence of polyarteritis nodosa, and the Congo red test was negative for amyloid disease. In October, 1956, a section of nerve taken from the cleft between the first and second toes had shown demyelination; an artery removed at the same time was completely normal.

Treatment was begun with corticotropin 40 units daily which gradually had to be reduced because of a moon face and indigestion, and a haematemesis in November, 1956. For 6 months there was no clinical change in the neuropathy, though the patient said that the hands and feet lost the burning pains. Large ulcers developed on the heels and the legs had to be suspended from a Balkan beam. At this time he had several episodes of chest infection, and an attack of paroxysmal auricular fibrillation lasting for 3 hours.

Early in 1957 he was at last beginning to make steady progress, the dose of corticotropin being 10 mg. daily. The signs of neuropathy gradually improved: sensation was normal in his hands and his grip improved. Weak dorsiflexion at the ankle was regained, but there was still reduced sensation over the feet of sock distribution. In March, 1957, he was able to walk a few steps.

He died suddenly on June 7, 1957, with acute left ventricular failure and pulmonary oedema.

Autopsy Findings.—The body was that of a well-nourished elderly man, showing generalized rheumatoid arthritis which was particularly marked in the joints of the wrists, hands, and ankles. There were two trophic ulcers on the right heel and one on the lateral side of the right foot.

Head and Neck.—The skull and contents, tongue, thyroid, pharynx, larynx, and oesophagus showed nothing of note. The trachea contained frothy mucopus.

Thorax

Heart.—The pericardial sac was almost totally obliterated by a fibrinous pericarditis. When the pericardium was peeled off the whole surface of the heart appeared red and inflamed and a number of tiny nodules were seen along the anterior descending branch of the left coronary artery. The myocardium showed patchy fibrosis consistent with ischaemia and the whole coronary tree showed gross atheroma. There was a tiny nodule on the mitral valve but the valves and endocardium appeared otherwise normal.

Lungs.—There were small bilateral loculated pleural effusions and there were multiple fine adhesions most marked over the left lower lobe. Both lungs appeared rather oedematous and showed chronic bronchitis.

Abdomen.—The peritoneal cavity was dry. The liver weighed 84 oz. and appeared congested and a little fatty. The spleen was also congested and weighed 8½ oz. The kidneys appeared normal macroscopically and weighed 11½ oz. The remainder of the abdominal viscera showed nothing significant.

Histology.—All sections were stained with haematoxylin and eosin and in addition the nerves were stained with Lillie's variant of the Weil-Weigert method for myelin. Selected sections were also stained with Mallory's phosphotungstic acid haematoxylin and Sheridan's elastic stain.

The most important findings concerned changes in the small blood vessels. These were observed in the heart and pericardium, in the lungs particularly the left lower lobe, and in relation to nerve bundles in the peripheral nerves of the right foot. Though the severity of the disease process varied considerably, the essential lesion was an arteritis and periarteritis of the small vessels. The changes were most marked in the pericardium. The milder lesions consisted of little more than perivascular cuffing with lymphocytes, the arterial walls being preserved. In many instances, however, the vessels showed fibrinoid necrosis, an intense periarteritis made up of lymphocytes, plasma cells, and histiocytes (Fig. 1), and aneurysmal dilatation of the vessel walls typical of polyarteritis nodosa. Aschoff bodies were observed in the myocardium of the left ventricle, but the nodule on the mitral valve comprised only a fragment of granulation tissue.

Sections from the right lateral and medial popliteal nerves and from the right posterior tibial nerve showed gross demyelination. The right median nerve appeared normal and acted as a control. The small vessels adjacent to the nerves of the right lower limb showed well-marked arteritis and the demyelination may well have been the result of ischaemia (Fig. 2).

The liver showed gross fatty change and the kidneys a mild degree of chronic pyelonephritis with no evidence of any arterial lesions suggestive of polyarteritis nodosa or of disseminated lupus erythematosus.

Comment.—While on aspirin therapy alone this patient developed the typical necrotic finger lesions described and illustrated by Bywaters (1957, Fig. 22). These left puckered scars but no other disability. There was no sign of a neuropathy then, but presumably an obliterative arteritis must have been present at that time. Later, 14 days after abruptly stopping prednisolone therapy, signs of a neuropathy appeared suddenly in hands and feet. It is likely that the simple "rheumatoid" arteritis had now flared up and become a necrotizing arteritis or polyarteritis nodosa, on which corticotropin had no real effect. It is of interest that, as often happens, biopsies of skin, muscle, and artery were completely negative, though autopsy revealed intensive arterial changes, including those of polyarteritis nodosa (necrotizing arteritis).

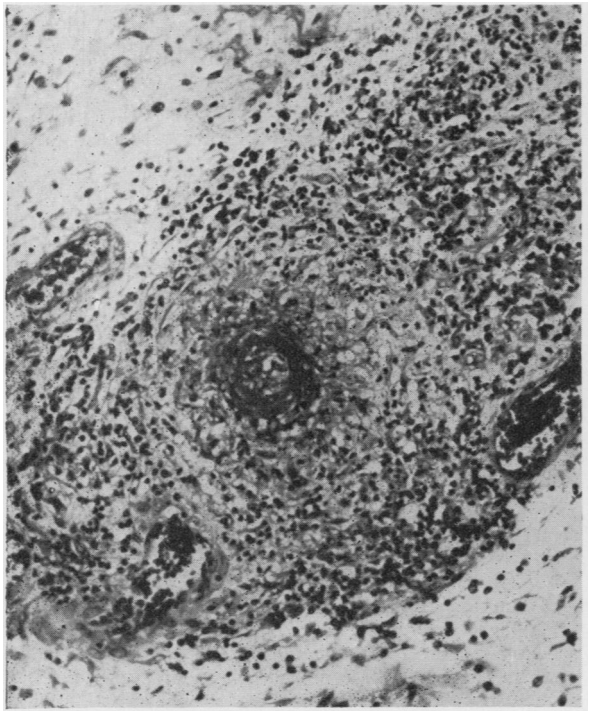


Fig. 1.—Case 1. Fibrinoid necrosis in pulmonary arteriole. Haematoxylin and eosin ×80.

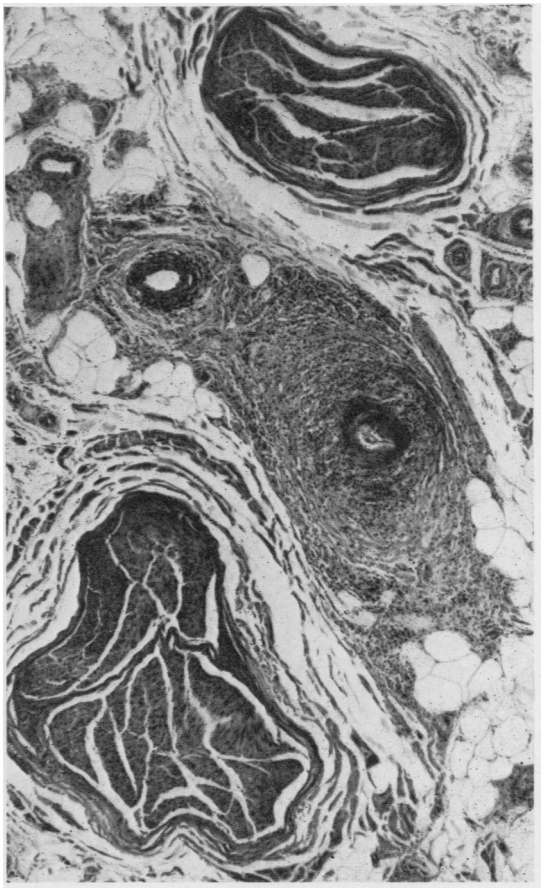


Fig. 2.—Case 1. Demyelination of medial popliteal nerve and periarteritis. Weil-Weigert Myelin Stain ×56.

Case 2, a man aged 44, had an 11-year history of rheumatoid arthritis which caused gross deformities of the hands and feet, but he had been able to get about and continue work as a machine operator. Phenylbutazone (300 mg. daily) was begun in 1953 and continued with good analgesic effect.

In August, 1956, he complained for the first time of a burning pain in the soles of his feet, spreading up the legs to the knees and disturbing him at night. Similar but less troublesome pains appeared at the same time in the hands.

On examination at that time he had advanced and deforming rheumatoid arthritis with ulnar nodules and olecranon bursae. He was hypertensive (Blood Pressure 200/110), but his exercise tolerance was good. The power of his feet was normal but the right ankle reflex was greatly reduced compared with the left. All forms of sensation below the knees were diminished, becoming more severe peripherally. The only sensory change in the hands was to pin prick.

There was a trace of albumen in the urine, but nothing abnormal in the deposit. The sheep cell agglutination test was positive 1 : 128. No evidence of porphyrinuria was found and the Congo red test was negative for amyloidosis. A skin and muscle biopsy from the deltoid region showed no arteritis, but a nerve biopsy from the foot demonstrated demyelination.

The symptoms of neuropathy persisted, making the patient miserable, and walking became difficult. He often stated that the neuropathy was far more unpleasant and more disabling than the arthritis. Prednisolone 10 mg. daily which was begun in April, 1957, had no effect, good or bad, and was discontinued in May.

In July, 1957, the symptoms spontaneously improved and clinical examination a month later could demonstrate no sensory abnormality at all, though the right ankle reflex was still reduced; 6 weeks later, with no change in therapy, foot drop developed abruptly, and this, though improved, has now persisted for several months.

Comment.—In this case signs and symptoms of a peripheral neuropathy developed after 3 years on a regular daily dose of phenylbutazone, without any change in therapy or preceding infection. Prednisolone in moderate dosage had no effect, and spontaneous improvement followed by relapse occurred after its discontinuance.

Case 3, a housewife aged 59, gave a history of severe and progressive rheumatoid arthritis which began in 1944. She was treated with salicylates and physiotherapy, and a short course of corticotropin in 1951 gave temporary benefit. In that year she had an unexplained pyrexial illness with severe pain at both lung bases, more left than right. An *x*-ray film showed bilateral basal mottling and fibrosis. While corticotropin had a profound effect on the arthritic features of the disease, the intractable basal (? pleural) pain was untouched but subsided slowly and spontaneously.

Later in 1952 phenylbutazone was tried, but had to be stopped because of purpura and indigestion. She was admitted to hospital in August, 1955, and long-term prednisolone was started (15 mg. daily). At first she improved, but in a month or two was as bad as ever. Accordingly prednisolone was gradually discontinued between March and July, 1956.

In March, 1956, she had noted that her hands seemed numb and useless, and she was unable to pick up small objects. At night she would be awakened by intense burning pains in both hands and these symptoms persisted. She was, therefore, admitted for further investigation in October, 1956. Sensory and motor signs of peripheral neuropathy were found in both hands, and there was reduced sensation over the toes and distal parts of the feet. She said on direct questioning that she had numbness of the toes but had not mentioned it as her hands were so much worse. Her rheumatoid arthritis was severe, but unchanged from the previous year.

Treatment was by graded rest and salicylates. In the next 6 months symptoms and signs of the neuropathy completely disappeared, astereognosis being the last abnormal feature to disappear. A Congo red test for amyloid disease was negative and skin and muscle biopsies were normal.

Comment.—Symptoms and signs of a peripheral neuropathy affecting hands and feet appeared on reduction of dosage of prednisolone. No form of treatment appeared to have any effect, but improvement took place naturally over a period of some 6 months. An unexplained pain in the lower thorax possibly pleural in origin had been an outstanding feature of this case 5 years previously, and unlike the arthritic features of the disease had not responded to corticotropin given at that time.

Case 4, a porter aged 61, had developed rheumatoid arthritis in 1949, with involvement of many of the peripheral joints. In 1954 a period of rest in hospital helped him; phenylbutazone 400 mg. daily was started and continued with sustained analgesic effect.

He remained reasonably well and at work until August, 1956, when he became disturbed at night by numbness, paraesthesia, and burning pains in the hands and feet, which began to spread proximally up the limbs. His hands became useless because he was unable to feel with his fingers and did not know where they were; he would drop objects and was unable to feed himself or undo buttons. He was emphatic that these symptoms were unlike anything connected with the arthritis that he had previously experienced. Later, in October, 1956, a generalized relapse of the arthritis set in and he was admitted to hospital for treatment.

Clinically, he presented the picture of active rheumatoid arthritis with large axillary and epitrochlear glands, ulnar nodules, and extensor sheath swellings of both wrists. There was reduction of all types of sensation below both wrists and knees, and the distal halves of all fingers were anaesthetic; the deep reflexes were still preserved.

The erythrocyte sedimentation rate varied from 35-52 mm./hr (Westergren). The sheep cell agglutination test was positive, 1 : 138. All other possible causes of peripheral neuropathy were excluded as in the other patients. At no time was there albuminuria.

Phenylbutazone was continued and corticotropin 20 mg. daily was begun. A week before his discharge from hospital the corticotropin was replaced in stages by prednisolone 15 mg. daily. The joints improved and over a month he lost his neuropathic symptoms, though sensation in all fingers was still reduced when he was discharged.

When examined a month later in the out-patient clinic, he was well and at work and there was no evidence of neuropathy whatsoever.

Comment.—This patient, who was in his 3rd year of treatment with phenylbutazone, developed a peripheral neuropathy with sensory but no motor features affecting hands and feet. Treatment with phenylbutazone was continued, and the addition of steroid therapy had no immediate apparent effect though features of the neuropathy gradually disappeared completely.

Case 5, a housewife aged 51, had had rheumatoid arthritis for 19 years, beginning in the wrists and thereafter spreading to the hands and feet. The disease ran a fluctuating but slowly progressive course, and there was no improvement with courses of gold. 6 years ago (in 1951) cortisone therapy was started and has been continued until the present.

In May, 1956, the patient noted that her feet were becoming numb up to the ankles. There was at first associated pain and paraesthesia, but these later passed off. Numbness gradually spread proximally and her feet became weak so that she could walk only with the aid of crutches. In September, 1956, her hands were involved with burning pains and by the time of her admission to hospital (November, 1956) she could not hold a pen or undo buttons.

On examination she was moon-faced, and had advanced but not very active rheumatoid arthritis. Sensation was reduced in the finger ends up to the proximal interphalangeal joints. It was interesting how comparatively slight these physical signs were compared with the striking disability caused by the symptoms.

There was loss of all modes of sensation in the feet as far as the ankles, particularly over the lateral parts of the feet, and vibration sense was much diminished up to the knees. Ankle reflexes were absent and all movements of the feet were weak.

The erythrocyte sedimentation rate was 58 mm. in 2 hours (Westergren), and haemoglobin was 94 per cent. with a normal total and differential white count. There was no albuminuria and no abnormality in the urinary deposit. The Congo red test gave no evidence of amyloid disease. Examinations of the blood were negative for L.E. cells.

In hospital the patient was given corticotropin for a time instead of cortisone, and afterwards cortisone was stopped and then started again. None of these changes made any difference to the neuropathy which was also unaffected by vitamin B and vitamin B_{12}.

Comment.—This mixed sensory and motor peripheral neuropathy of hands and feet came on after 5 years of steroid therapy without any previous change of dosage. The symptoms were extremely incapacitating, though the physical signs were relatively slight. Subsequent changes in steroid therapy make no difference to the clinical picture.

Case 6, a spinster aged 57, gave a 6-year history of rheumatoid arthritis, affecting knees, ankles, hands, and shoulders. When first seen in July, 1957, she stated that for 2 months she had had "hot pins and needles in the feet" and that more recently the feet had become numb; her hands were unaffected. She was taking an average of 6 aspirins daily, together with 400 mg. phenylbutazone; steroids had never been given.

On examination there were classical signs of rheumatoid arthritis in the joints, with enlarged epitrochlear and axillary lymph nodes. Sensation to cotton wool and vibration was absent in the feet in a short sock distribution, and sensation to pin prick was reduced. Power was well preserved in the feet, and the ankle reflexes were present.

Case 7, a man aged 80, who was admitted to hospital for prostatectomy, later had a coronary thrombosis. When seen in the medical ward he gave a history of having had rheumatoid arthritis for many years; he had never had cortisone. He said that for 2 to 3 years he had noticed numbness and loss of control of his hands and feet.

On examination, in addition to advanced changes of rheumatoid arthritis, all modes of sensation were absent in the feet and grossly reduced in both hands.

Case 8, a housewife aged 63, had had progressive rheumatoid arthritis for 2½ years, which had been treated by salicylates and physiotherapy. On admission to hospital she complained that she had lost sensation in the 3rd, 4th, and 5th toes of both feet, and in the dorsum of the first joint proximally.

On examination, she had active rheumatoid arthritis, with swelling and tenderness of the metacarpophalangeal joints and proximal interphalangeal joints, the more proximal joints being stiff and tender. Sensation was absent in the feet in the areas which she had noted were numb.

Case 9, managing director aged 70, gave a 6-year history of rheumatoid arthritis. When first examined in the Westminster Hospital in September, 1956, he was found to have advanced and florid disease with large rheumatoid nodules. There were then no signs of neuropathy. Treatment was begun with 10 mg. prednisolone daily in divided doses.

During a subsequent admission (March, 1957) it was

noted that the arthritis had progressed despite steroid therapy; he began to complain at that time of numbness and paraesthesia of the feet, and sensation was absent on examination, particularly on the lateral aspects of the feet. These symptoms and signs had developed while he was taking prednisolone and without any reduction of the dose.

The neuropathy is now improving, and there are no objective signs though he still has minor subjective complaints.

Case 10, a man aged 63, developed rheumatoid arthritis 10 years ago, which progressed to involve most of his joints. After 2 years on steroid therapy, prednisolone was gradually and very slowly reduced over a period of 4 months from 15 to 5 mg. daily. For the past 3 weeks he had had paraesthesia over the feet and heels, but one week after discontinuing steroid therapy completely he lost the power of dorsiflexion in one foot, and paraesthesia became more marked, and sensation was diminished over the anterior position of both feet, the lateral aspect more than the medial. After 3 days power returned and the sensory symptoms abated.

Comment.—This appears to be a steroid withdrawal syndrome in miniature, followed by rapid improvement.

Case 11, a married woman aged 38, began to have pains in most peripheral joints in October, 1955, with early morning stiffness. Her symptoms were well controlled by soluble aspirin and she was able to continue all her normal domestic activities. In April, 1956, she was first referred to the Rheumatism Clinic at the Westminster Hospital; the sensitized sheep cell agglutination test was negative, and the erythrocyte sedimentation rate (Wintrobe) was 38 mm./hr. A diagnosis of rheumatoid arthritis was made.

Her condition began to deteriorate, and cortisone 100 mg. daily was begun by her general practitioner. Left lower chest pains occurred at this time with slight tenderness of the chest wall, but no L.E. cells were found in the blood in June, 1956. There was apparently a good response to cortisone for a few weeks.

During August she had a relapse and had to remain in bed with very painful joints, a fever of 100° F., headache and vomiting. Because of these symptoms cortisone was suddenly stopped by her general practitioner, and a week later, her condition deteriorating, she was admitted to hospital as an emergency.

She was ill and in great pain with tachycardia and tenderness, but no swelling of the peripheral joints. Rales were present at both bases and it was noted that both ankle reflexes were absent and that sensation to pin prick over her feet was impaired, although at this time she made no complaint to suggest neurological involvement.

On the day after admission L.E. cells were found in the blood. Intense burning pains of both feet and legs were then present, necessitating large doses of pethidine. Signs of a peripheral neuropathy rapidly progressed so that a week after admission there was complete anaesthesia of both feet with bilateral foot drop. By that time a facial butterfly rash was obvious.

Despite treatment with antibiotics and large doses of steroid, up to 60 mg. prednisolone daily, she remained extremely ill with an irregular fever of up to 104° F., and severe joint, chest, and limb pains; improvement was very slow and she was in hospital for over 5 months.

On October 4, 1956, while she was on a maintenance dose of 60 mg. prednisolone daily routine examination following a complaint of abdominal pain demonstrated a large cystic mass in the abdomen. A fortnight later she passed per rectum a 30-cm. length of complete thickness of colon, with disappearance of the "cyst" and relief of her pain; this was thought to be due to an intussusception.

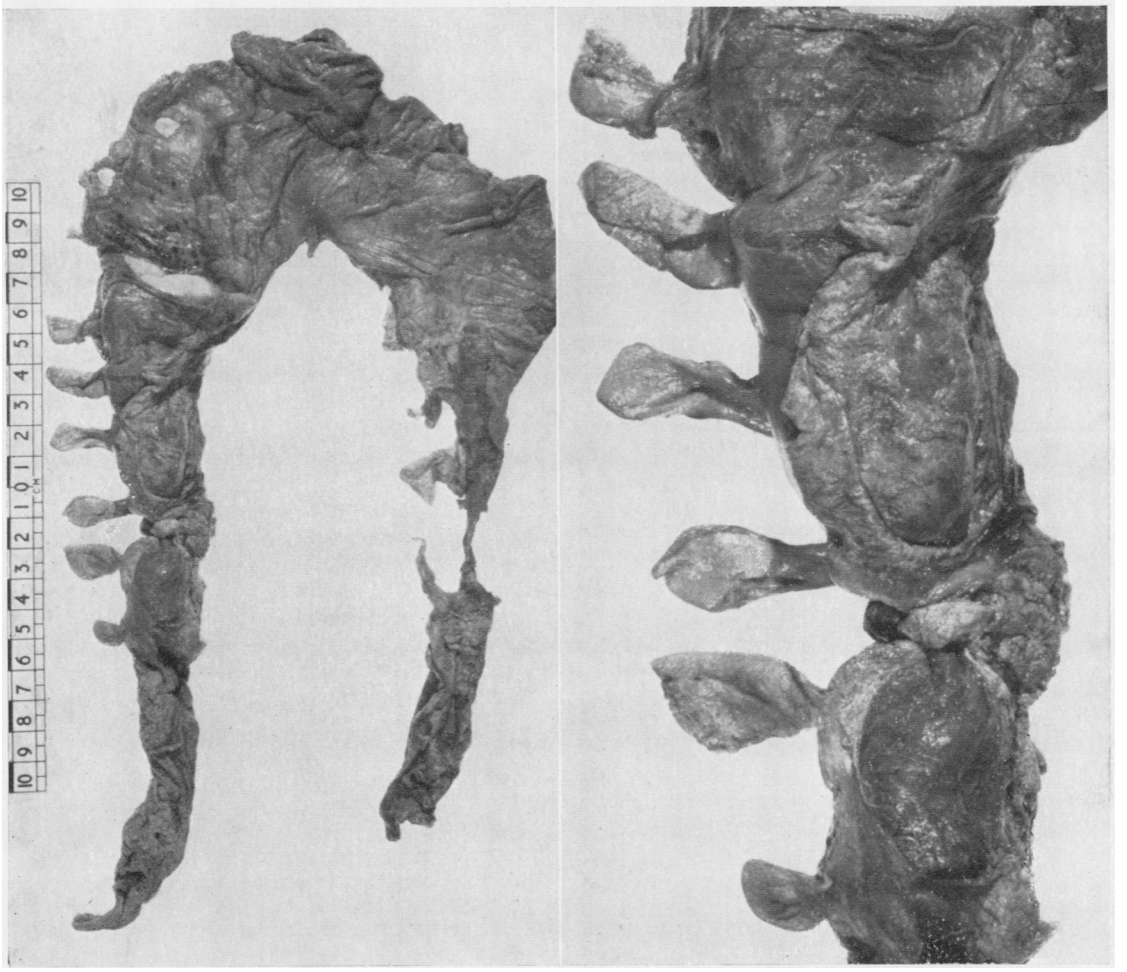
It was possible to let her leave hospital in February, 1957, by which time she was quite well apart from a complete bilateral foot drop; she was then taking 30 mg. prednisolone daily. Sensory signs had improved compared with those present on admission, but power in both legs showed little sign of improvement.

Her general condition has remained satisfactory and the dose of prednisolone has been gradually reduced to 15 mg. daily. Now, for the first time for a year, there is slight dorsiflexion at the ankle and coarse sensation is present over both feet.

Comment.—This patient, probably a case of systemic lupus erythematosus from the commencement of her symptoms, did not show the L.E. cell in the blood until prednisolone had been abruptly terminated by her general practitioner. This biological shock to the system caused a flare-up, and apparently produced the L.E. cell and precipitated a neuropathy. A high dosage of prednisolone was necessary to control her symptoms; while she was on 60 mg. daily, a silent intussusception occurred and she passed 30 cm. of her colon (Figs 3 and 4, opposite). This relieved the abdominal symptoms, and now over a year later, treated conservatively on a continued but lower dosage of prednisolone, she is in better general condition than since the onset of symptoms, though some signs of the neuropathy persist. She has no residual abdominal symptoms.

Discussion

A point to emphasize in all these cases was the obvious clinical significance of the neuropathy; in most cases this new group of symptoms was a prominent complaint. These, far from being elicited by direct questioning, were often from the patients' point of view the major disability. Adjusted and used to some degree to their chronic rheumatoid complaints, they found these new superimposed symptoms doubly distressing and demoralizing. All these cases of peripheral neuropathy occurred in long-standing advanced rheumatoid arthritis, but they did not occur in periods of



Figs 3 and 4.—Case 11. Intussuscepted colon from case of disseminated lupus erythematosus. The patient was on 60 μg. prednisolone daily at the time. No operation was performed and the patient remains well 1 year later.

natural exacerbation or relapse. In the two worst (Case 1 and Case 11), severe motor and sensory changes occurred within 2 weeks of abruptly stopping steroid therapy; as in all such cases sensory changes preceded motor changes, the former being the more common. Two further cases occurred within 4 weeks of discontinuing steroid therapy; four out of eleven cases thus appear to have been precipitated by steroid withdrawal. Once the neuropathy had occurred, therapy appeared to be of no help; vitamins, steroids, and physiotherapy caused no improvement in the condition which, if it was going to improve, did so without regard to the clinician's therapeutic endeavours. Natural recovery occurred in 4 days (Case 10) and after 10 months (Case 2); the latter case relapsed soon afterwards. It is of interest to compare these cases with the acute infective polyneuritis described by Graveson (1957) which responded very satisfactorily to steroid therapy within 1 to 2 weeks in seven out of eight cases.

The sensory changes occurring in rheumatoid arthritis were symmetrical as compared with the frequent asymmetry of the neuropathy seen in polyarteritis nodosa unrelated to rheumatoid arthritis (Talbott and Ferrandis, 1956). As stated above, sensory always preceded motor changes; if the feet only were affected the outer part of the foot showed more marked changes than the inner. Three of these ten rheumatoid cases had fibrotic changes in

the lungs not explicable in terms of any other pathological process. Blue, cold, moist hands, common in early rheumatoid arthritis, were not particularly apparent in these cases; there seemed to be no correlation between a poor peripheral circulation and the development of a neuropathy. In Case 1 small black areas, of the type described and well illustrated by Bywaters (1957), occurred when there were no signs of peripheral neuropathy, sensory and motor changes taking place many months later when the discoloured necrotic areas had healed. It would seem that the milder arterial changes present earlier were responsible for these lesions which flared into a florid polyarteritis on steroid withdrawal.

Unlike disseminated lupus erythematosus, rheumatoid arthritis rarely involves the kidneys, except by amyloid disease (Muehrcke, Kark, Pirani, and Pollak, 1957). In these ten cases no renal abnormalities were noted, nor did hypertension appear in any case. Other causes for a neuropathy, such as porphyria, amyloidosis, avitaminosis, diabetes mellitus, and subacute combined degeneration of the cord were looked for, but no signs of these disorders were present. No cases occurred during or after gold therapy. None of the rheumatoid cases was highly febrile, though fever was present in the case of disseminated lupus erythematosus (Case 11). The development of the neuropathy was not heralded or accompanied by fever or systemic upset, or by any particular elevation of sedimentation rate or sudden alteration in the pattern of plasma proteins. Skin and muscle biopsies in four cases were unhelpful and a nerve biopsy showed only a non-specific demyelination. An arterial biopsy showed no abnormality in Case 1, who later at autopsy had widespread changes of polyarteritis nodosa. Eosinophilia was not present in any case.

How common are these lesions? We have no exact figure to answer this question. After the first four cases were found, 100 consecutive cases of rheumatoid arthritis attending the Unit as outpatients were carefully examined for this complication, but none was found. Nevertheless, though rare, it is certainly not excessively rare, and it is our impression that the incidence is greater since steroid therapy was introduced.

Freund, Steiner, Leichtentritt, and Price (1942) reported characteristic pathological lesions located in the perineurium in three out of five cases of rheumatoid arthritis. They commented that the sharply nodular and peculiar granulomatous morphology were features of a disease-specific appearance, but made no particular point of any vascular changes; no such changes were seen in our cases. Radnai (1953), however, emphasized the importance of vascular changes in the development of a neuropathy in rheumatoid arthritis:

> " . . . we have arrived at the conclusion that in the muscles and nerves of patients suffering from rheumatoid arthritis the continuous influence of some injury of unknown nature gives rise to constantly relapsing acute vascular changes of small intensity for years or even for decades. Healing of such lesions brings about complete or partial obstruction in more and more arterioles, thus leading to a permanent or transitory functional disturbance."

Slocumb (1953) drew attention 4 years ago to the "panangiitic and panmesenchymal" reactions which occurred on reduction of steroid dosage in rheumatoid arthritis. Four of our eleven cases of peripheral neuropathy were seen within 4 weeks of stopping such treatment.

Kemper, Baggenstoss, and Slocumb (1957) also reported that, of 52 rheumatoid patients studied at autopsy, 38 had received no cortisone. None of these developed generalized lesions of polyarteritis nodosa, whereas of the fourteen cortisone-treated patients four developed these lesions. In reviewing the literature on the subject they consider that the vascular changes observed in rheumatoid arthritis fall into three groups:

(1) Perivascular or adventitial accumulation of leucocytes, plasma, and other cells without 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.
(3) Lesions of acute arteritis with cellular infiltration and necrosis of the vessel wall, a necrotizing angiitis.

These workers consider that their findings suggest that in certain susceptible patients with rheumatoid arthritis the administration of cortisone may precipitate changes of the third group.

Bywaters (1957) has described arteritis in ten patients with rheumatoid arthritis and states that a bland intimal proliferation of fibroblasts and mucoid material, sometimes with secondary fibrin clots on it, not unlike changes noted previously in scleroderma, is typical, Cruickshank (1953) found evidence of an arteritis, past or present, in eighteen of 72 fatal cases of rheumatoid arthritis. He states that this arteritis of rheumatoid arthritis was encountered most often in heart, muscles, and nerves, and that the incidence is probably considerably higher than these figures suggest. Arterial changes in the lung in this condition have been

mentioned by Ellman and Ball (1948) and have been well illustrated by Price and Skelton (1956).

Ball (1953) and Sokoloff and Bunim (1957) have drawn attention to the wide spectrum of changes that may be seen in blood vessels in rheumatoid arthritis. It is noteworthy that in many articles on this subject the illustrations show changes varying from early inflammatory involvement of vessels to a fully-developed necrotizing arteritis histologically indistinguishable from polyarteritis nodosa.

As has been remarked before, the majority of such lesions in life are probably in silent areas and give no outward sign or symptom of their presence; should they occur in the nervous system, however, and in particular in the peripheral nerves of hands or feet, the picture of a neuropathy rapidly becomes evident. That they did occur before the advent of steroid therapy is certain, but it seems likely that they are occurring more commonly and dramatically now that a large number of patients are receiving this form of treatment. It may be that a mild diffuse arteritis is suppressed by such treatment, on withdrawal of which the condition flares into more florid form, as seen in two of our cases where therapy was abruptly terminated.

Is the neuropathy entirely a feature of an arteritis or is there a rheumatoid neuropathy apart from this? Against the latter are the following considerations:

(*a*) The absence of such a neuropathy in the active florid early case of rheumatoid arthritis. Patients with neuropathy are mostly relatively advanced rheumatoids of long standing, and the disease is not particularly active at the time of development of the condition; a withdrawal of steroid suppressive treatment seems more likely to be followed by a peripheral neuropathy than does a natural relapse.

(*b*) High-dosage suppressive steroid therapy does not improve the neuropathy as it does other features of the arthritis. Of interest here is the finding that in Case 3 the acute lower chest pain from which she suffered and which appeared to be associated with a lower zone pulmonary fibrosis was also completely untouched by steroid therapy, which removed at the time all other symptoms and signs of the disease.

However, as the neuropathy appears to be due to an arteritis which is part of the rheumatoid disease process, one is in fact dealing with a real complication of rheumatoid arthritis. The condition is in fact a "rheumatoid neuropathy", unless considered entirely a polyarteritic complication of steroid therapy. Against this is the fact that five of our patients had never had steroid therapy. The demyelination seen is merely a feature of ischaemic change and is a non-specific finding.

Summary

(1) Ten cases of peripheral neuropathy in rheumatoid arthritis are described and for comparison one case of systemic lupus erythematosus. Of these eleven cases, five had never received steroids, but in four the neuropathy developed within one month of discontinuing such therapy. The two worst cases occurred within 7 and 14 days of abruptly stopping treatment with prednisolone.

(2) Sensory changes preceded motor in all cases in which both occurred. In six cases sensory changes only were present.

(3) The development of a neuropathy led all these patients to make fresh complaints. The weakness and discomfort superadded to their usual articular symptoms often proved particularly distressing and demoralizing.

(4) Therapy had no effect on the nervous lesion: high steroid dosage, vitamins, and physiotherapy made no difference to the nervous signs and symptoms. A major spontaneous improvement or complete recovery occurred in all cases in periods varying from 3 days to one year, but signs persist to some degree in all but two cases, and one case has relapsed after partial recovery.

(5) There was no connexion in these cases with gold or phenylbutazone therapy. None had received the former and the latter apparently played no part in the three cases in which it was given.

(6) The unusual complication of intussusception and sloughing of 30 cm. of colon is reported in a patient with severe systemic lupus erythematosus who was receiving 60 mg. prednisolone daily. She made a good recovery without operation and still remains well 12 months later.

(7) The concept of a diffuse arteritis as part of the rheumatoid disease best explains these cases of peripheral neuropathy; withdrawal of steroid therapy, particularly if abrupt, may precipitate more florid changes.

Our thanks are due to Dr. William S. Tegner for permission to report the case histories of two of his patients, to Dr. Peter Hansell and the Department of Medical Photography, Westminster Medical School, for their help with the illustrations, and to Professor D. H. Collins and Dr. Bruce Cruickshank for their helpful comments in Case 1.

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Neuropathie dans l'arthrite rhumatismale

RÉSUMÉ

(1) On décrit dix cas de neuropathie périphérique dans l'arthrite rhumatismale et, pour comparaison, un cas de lupus érythémateux généralisé. Parmi ces onze cas, cinq n'avaient jamais reçu de stéroïdes, mais chez quatre autres, la neuropathie survint dans le mois qui suivit l'interruption de cette thérapie. Les deux cas les plus graves se produisirent entre 7 et 14 jours après l'arrêt soudain du traitement à la prednisolone.

(2) Les phénomènes sensoriels précédèrent toujours les moteurs; dans six cas ceux-ci furent absents.

(3) Le developpement de la neuropathie provoqua des plaintes renouvellées des malades. La faiblesse et le malaise s'ajoutant à leurs habituels symptômes articulaires se révélèrent déprimants et démoralisants.

(4) La thérapie n'eut aucun effet sur la lésion nerveuse; l'administration de stéroïdes à haute dose, les vitamines et la physiothérapie n'amenèrent aucun changement dans les symptômes nerveux. Une amélioration importante spontanée ou une complète guérison se produisirent dans tous les cas en des périodes variant de trois jours à un an, mais certains signes persistèrent dans tous les cas, sauf deux, et un cas rechuta après guérison partielle.

(5) Dans aucun cas n'y avait-il de lien avec la chrysothérapie ou la phénylbutazone. Aucun des malades ne reçut de première; la seconde, administrée à trois d'entre eux apparemment ne joua aucun rôle.

(6) La complication rare d'invagination et de sphacèle de 30 cm. de colon est signalée chez une malade atteinte de lupus érythémateux généralisé sévère et recevant 60 mg. de prednisolone par jour. Elle guérit sans opération et se porte toujours bien, 12 mois plus tard.

(7) Le principe d'une artérite diffuse formant partie de la maladie rhumatismale offre la meilleure explication de ces cas de neuropathie périphérique; l'interruption de la thérapie stéroide, surtout si elle est faite brusquement, peut précipiter des altérations assez spectaculaires.

Neuropatía en la artritis reumatoide

SUMARIO

(1) Se describen diez casos de neuropatía periférica en la artritis reumatoide y, para comparar, un caso de lupus eritematoso generalizado. De estos once casos, cinco nunca recibieron terapia esteroide, pero en cuatro otros la neuropatía ocurrió dentro del mes que siguió la interrupción de tal terapia. Los dos casos más graves se produjeron entre 7 y 14 días después de la interrupción repentina del tratamiento con prednisolona.

(2) Los fenómenos motores, ausentes en seis casos, fueron siempre precedidos por las manifestaciones sensorias.

(3) El desarrollo de la neuropatía trajo quejas repetidas de los enfermos. La debilidad y el malestar vinieron a añadirse a los síntomas articulares habituales con un efecto penoso y desmoralizador.

(4) Terapia fué sin efecto sobre la lesión nerviosa; administración de esteroides en dosis altas, vitaminas y fisioterapia no produjeron cambio alguno en los síntomas nerviosos. Una mejoría importante espontánea o una cura completa se produjeron en todos los casos en períodos de 3 días a un año, pero ciertas manifestaciones permanecieron en todos casos, salvo dos, y en un caso hubo una recaida después de una cura parcial.

(5) En ningún caso se vió un lazo con sales de oro o la fenílbutazona. Ningún enfermo había recibido los primeros; la segunda, administrada en tres casos, no pareció haber desmpeñado papel alguno.

(6) Se señala la complicación rara de invaginación y esfacelo de 30 cm. del colon en una enferma con lupus eritematoso generalizado grave, recibiendo 60 mg. de prednisolona diaria. Recobró sin operación y aún está bien, después de doce meses.

(7) El concepto de una arteritis difusa formando parte de la enfermedad reumática ofrece la mejor explicación de estos casos de neuropatía periférica; la interrupción de la terapia esteroide, en particular repentina, puede precipitar alteraciones algo asombrosas.