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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.

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 *et al.* (1957)	2	1
Sokoloff and Bunim (1957)	1	1
Hart *et al.* (1957)	6	4
Irby *et al.* (1958)	5	1
Mason and Steinberg (1958)	3	3
Vignon and Durant (1958)	1	1
Johnson *et al.* (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.

TABLE III.—*Details of the Five Patients that Died*

No.	Sex and Age at Onset	Duration of R.A. at Onset of Neuropathy	Time between Onset of Neuropathy and Death	Cause
2	F 64	6 years	9 months	Pyrexia and increasing dyspnoea for which no cause could be found. It was decided to withdraw steroids, after which patient died. ? adrenal failure
3	M 71	2 ,,	1 month	Chest pain and dyspnoea. Presumed coronary thrombosis
4	F 64	1 year	2 weeks	Acute bronchopneumonia with multiple abscess formation. Post-mortem: polyarteritis of myocardium, kidney, sciatic nerve
6	M 54	4 years	6 months	Tuberculous bronchopneumonia. Post-mortem: polyarteritis sciatic and femoral nerves
13	M 57	1 year	1 month	Sudden death. Coroner's post-mortem: death due to myocarditis and atherosclerosis

TABLE IV.—*Features of the Neuropathy*

Distribution				Course	
Lower limbs ..	12	Sensory ..	18	Dead	5*
Upper ,, ..	1	Motor:		Recovered ..	1
Upper and lower limbs ..	5	Clinical ..	8	Improved ..	1
Bilateral ..	13	Electrodiagnosis ..	4 more	Progressive or static ..	11
Symmetrical ..	8				18

* Neuropathy improved before death in one case.

Neuropathy, therefore, in rheumatoid arthritis is a serious prognostic finding.

The details of the neuropathy are shown in Table IV. The lower limbs alone were affected in 12 patients, both upper and lower limbs in five patients, and one upper limb alone in one patient. This was a man who had extensive arteritic phenomena affecting the hand, with evidence of sensory loss.

Of the five cases in which both upper and lower limbs were affected, in three the legs were more severely involved and in the other two the involvement appeared to be equal. The condition was bilateral in 13 but strictly symmetrical in only eight of these, for though the same areas, more or less, were always involved, in five the degree of involvement was strikingly different. This was the position at the time of the analysis, for the distribution changed from time to time. Objective sensory changes were present in all the patients. In addition eight patients showed motor weakness.

Electrodiagnosis was performed on four patients who at that time showed no clinical evidence of motor involvement, and in every case there was evidence of a motor neuropathy ; the intensity duration curve showing denervation, or the electromyograph a reduced interference pattern with long-duration polyphasic units. In one case these changes were followed in three months by a severe unilateral foot-drop. Even when motor changes are obvious clinically, electrodiagnostic tests reveal that these may be more extensive than is apparent. In every case sensory symptoms preceded motor symptoms—the latter, when they occurred, following at varying intervals of time. The longest interval in our experience is five months.

All the patients presented with tingling, burning, and numbness of the extremities, the burning sensations being so severe in some cases as to require strong analgesics. These sensations were often the patient's chief complaint. Muscle pain was also present, and, as in other forms of peripheral neuropathy. the calves could be extremely tender. In one patient hyperaesthesia was one of the most severe symptoms. Loss or impairment of sensation to pinprick, temperature, and light touch was present in all cases and more or less followed the paraesthetic areas. The deep reflexes were usually preserved except for the ankle-jerks in seven of the cases. Loss of position sensation was variable, and was usually confined to the toes. Loss of vibration sense, which was often more widespread than other changes, occurred in 10 cases. The sensory changes alone were in some cases sufficient to account for the impaired functional capacity.

When present, motor weakness was definite and was always responsible for some of the symptoms, though they could be overshadowed by the sensory symptoms. In every case the motor changes were confined to the lower limbs. In six these were manifested as foot-drop, either unilateral or bilateral.

It is important to consider the steroid history of these patients. Only three had never been on steroids, and these had minimal signs ; five were on continuous steroid dosages ; and in 10 there appeared to be a definite relationship to either initiation or alteration of steroid therapy.

TABLE V.—*Relationship to Steroids*

Case 1. Prednisolone 15 mg. daily 1 year. Neuropathy 3 months after withdrawn
,, 3. Cortisone 75 mg. daily 1 year. Changed to prednisolone 20 mg. daily 4 months. Abruptly withdrawn 3 months before onset
,, 4. A.C.T.H. 40 units daily 1 week, then stopped. Neuropathy within 4 weeks
,, 6. Cortisone 75 mg. daily 1 year. Prednisolone 15 mg. daily for 2 months before onset
,, 7. Prednisolone 10 mg. daily 10 months. Changed to triamcinolone 8 mg. daily 3 months before onset
,, 8. A.C.T.H. 1 year, followed by triamcinolone for 6 months, interrupted for 7 days. Prednisolone for 4 days before onset
,, 9. Prednisolone acetate 100 mg. weekly for 2 months prior to onset
,, 11. Prednisolone 15 mg. daily 1 month before onset
,, 13. A.C.T.H. 80 units for 3 days, reduced to 60 units. Reduction accompanied by neuropathy
,, 18. Cortisone 50 mg./25 mg. alternate days for 7 years. Withdrawn under A.C.T.H. cover. Neuropathy within 3 days of stopping cortisone. Still on A.C.T.H.

Table V shows this relationship. Thus in Cases 1, 3, and 8 the neuropathy followed the interruption of prolonged steroid therapy; in Cases 9 and 11 it followed the introduction of steroids in Cases 6 and 7 a change in steroids, in Case 4 A.C.T.H. initiation and withdrawal, in Case 13 A.C.T.H. initiation and reduction; and in Case 18 it followed cortisone withdrawal under an A.C.T.H. cover while still on A.C.T.H.

Thus 15 out of 18 patients were or had been on steroids and in 10 there appeared to be a direct connexion with such therapy. This does not preclude a connexion between the other five on continuous steroid dosage. This association of neuropathy with steroid therapy has been noted in other series, but it is by no means constant. Robinson *et al* (1953) showed four cases of rheumatoid arthritis that developed neuropathy ; only one had never received steroids or A.C.T.H. Neither of the two cases described by Ball (1954) was on cortisone before the onset of the neuropathy ; all cases of Kemper *et al.* (1957) had been, as had the two described by Sokoloff and Bunim (1957), one of which was a case of cranial neuropathy. Five of the 10 cases of Hart *et al.* (1957) had never received steroids, but in three the neuropathy developed within one month of discontinuing them.

In three series described by Irby *et al.* (1958), Johnson *et al.* (1959), and Epstein and Engleman (1959)

all the patients were, or had been, on steroids. In eight of Johnson's 17 patients neuropathy followed interruption or cessation of steroid therapy; all of his patients showed evidence of hypercortisonism prior to the onset of the neuropathy. Evidence of hypercortisonism was not prominent in this series; one patient had evidence of mild osteoporosis of the spine, one had pathological fractures of the humerus and femur one year before neuropathy, and one developed purpuric haemorrhages at the time of the neuropathy. Apart from this the other patients showed some mooning of the face or gain in weight.

TABLE VI.—*Associated Features*

Lupus erythematosus cells	3
Digital arteritis	5
Other evidence of arteritis	1
Lung changes	4
Other systemic disturbance (i.e., fever, splenomegaly, albuminuria)	4

Table VI shows the associated features of these patients. L.E. cells were detected in the serum of three patients at one time or another. All three were males. In one they were found on two occasions three years prior to the onset of the neuropathy; in one, a year after the onset of the neuropathy (this patient also had evidence of digital arteritis); and in the third they were found after the neuropathy had remitted, but at a time when he was having fresh digital arteritic phenomena. This patient also had *x*-ray changes of the rheumatoid lung. Five patients had evidence of digital arteritis as described by Bywaters (1957). The time relationship of the onset of the digital arteritis to the neuropathy was very variable. One patient had post-mortem evidence of polyarteritis nodosa affecting the kidney and myocardium. Four patients had *x*-ray changes in the lung fields thought to be due to the rheumatoid disease.

No treatment seemed to affect the course of the neuropathy in these patients, and this is the view also expressed in other series. Steroids did not control the condition, though in two patients who were not on steroids at the onset of neuropathy this did improve when they were employed. It would appear wiser, however, to avoid too violent a fluctuation in the steroid dosage when a neuropathy does occur.

Aetiology

The evidence seems to suggest that neuropathy in rheumatoid disease is secondary to arteritis. In two cases that came to necropsy in this series there was evidence of polyarteritis nodosa affecting the peripheral nerves.

This finding of an arteritis has been noted in all the series so far reported, but the exact changes appear to cover a wide spectrum. Thus Robinson *et al.* (1953) found arterial changes which differed qualitatively from classical polyarteritis nodosa; Ball (1954) found evidence of polyarteritis nodosa; in the one case of Hart *et al.* (1957) that came to necropsy there was widespread arteritis, including fibrinoid necrosis; and Johnson *et al.* (1959) found post-mortem evidence of arteritis in three cases, in one of which the changes were those of classical polyarteritis nodosa. Further support for a vascular basis of the neuropathy is that five of our patients also had evidence of digital arteritis. This again has been the experience with other series. On the other hand, it must be remembered that arteritis is seen in the absence of neuropathy and may simply be a feature of rheumatoid disease. Thus Cruikshank (1954) found the nerves to be one of the most common sites of arteritis; and Sokoloff and Bunim (1957) detected arteritis of the nerves in two patients (Nos. 3 and 5) in in whom there was no clinical evidence of neuropathy.

Discussion

It is important to discuss neuropathy in rheumatoid disease against the wide background of vascular changes that may occur. It seems more than likely that there has been a true increase in these changes over the last few years, and this has coincided with the introduction of steroid therapy. Clinically they were hardly mentioned and post-mortem evidence of arteritis was equally rare. It is of course possible that they were present but were missed; and we know, once something is described, how obvious its presence is to all of us.

Freund *et al.* (1942), who reported characteristic changes in the perineurium, calling the condition nodular rheumarthritic polyneuritis, made no reference to any vascular change. Baggenstoss and Rosenberg (1943), reporting on 30 post-mortem cases, found no changes in the blood-vessels though these were looked for.

What is the relationship between steroid therapy and arteritis, and hence neuropathy? In most patients steroid therapy has been used, but these changes may occur in the absence of steroids. Though none of the post-mortem cases described by Cruickshank (1954) had been on steroids, the changes appear to be more severe in the steroid-treated cases. Kemper *et al.* (1957), reporting on 52 post-mortem cases, found evidence of vasculitis in 12. Four of these who had received cortisone had changes similar to polyarteritis nodosa. He concluded that in certain susceptible patients with rheumatoid arthritis cortisone may precipitate a diffuse necrotizing arteritis.

Epstein and Engleman state that the association of rheumatoid arthritis, subcutaneous nodules, and the presence of large amounts of rheumatoid factor in the serum may constitute a relative contraindication to the use of adrenocortical steroid therapy.

It may be that the fact that most of these cases were on steroid therapy is an indication of the severity of the rheumatoid process rather than the cause of the arteritis and neuropathy. It seems that these manifestations may be provoked by sudden changes in steroid therapy, and Slocumb (1953) drew attention to the panangiitic and panmesenchymal reactions which may occur after cortisone reduction.

Summary

Eighteen cases of rheumatoid arthritis with peripheral neuropathy are described. In 15, steroids or A.C.T.H. had been used, and in 10 there appeared to be a direct association between changes in such therapy and the onset of the neuropathy. Five patients died within one year of the onset of the neuropathy, and all were on steroids or A.C.T.H. No treatment appeared to affect the course of the neuropathy. Digital arteritis occurred in five patients, and there was post-mortem evidence

of arteritis of the peripheral nerves in two cases. A diffuse arteritis may be the cause of the neuropathy.

The onset of peripheral neuropathy is of poor prognostic import in rheumatoid disease.

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SOME OBSERVATIONS ON THE AETIOLOGY OF BREAST ABSCESS IN THE PUERPERIUM

BY

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The purpose of this paper is to shed light on the ways in which breast abscesses arise in mothers who suckle their infants. The observations were made in a busy modern obstetric department throughout a period in which there was a rising incidence of infection with an unusually virulent type of staphylococcus (phage-type 80).

In 1957 an outbreak of breast abscesses occurred in epidemic form. Owing to the geographical position of Southampton all mothers who developed a breast abscess needing incision were seen either at the General Hospital or at the casualty department of the only other hospital in the city. These circumstances provided, therefore, an unusual opportunity to follow up infections which developed after mothers had been discharged from the maternity wards.

Much evidence has been produced of the early colonization with *Staphylococcus aureus* of babies born in maternity hospitals, and it has been shown that there is little correlation between the type of organisms found in the nares or vagina of mothers and in the nares of their infants (Barber *et al.*, 1953 ; Cook *et al.*, 1958). Reports have been made on the particular aspects of the mechanism of this colonization, and it was found that all full-term babies were colonized with staphylococci in the first few days of life unless protective measures were adopted (Hurst, 1957 ; Cook *et al.*, 1958). It appeared also that most infants acquired their staphylococci from the nursing staff or from other babies rather than from their mothers (Knott and Blaikley, 1944 ; Edmunds *et al.*, 1955).

Duncan and Walker (1942) noted that *Staph. aureus* of the same type was isolated both from the milk of nursing mothers and from the rectum and throat of their babies in a high percentage of cases. They suggested that staphylococci were deposited on the mothers' breasts by the babies' noses. Sensitivity tests showed that in most cases babies' noses and mothers' breasts bore like staphylococci.

Further evidence supporting this theory was provided by Cook *et al.* (1958). They investigated the acquisition of *Staph. aureus* by newborn babies and acquitted the mothers as a possible source of infection.

Duncan and Walker postulated a continuous process of infection from baby to baby via the ward environment and thence transference, through suckling, to the breasts of mothers. The staphylococcus then multiplied in the breast milk and was returned again to the baby, sometimes in massive doses though apparently of low pathogenicity. They also found that breast milk was infected after 24 hours of the puerperium but not before delivery. In the milk of the mothers of 28 stillborn infants who did not suckle there was a much smaller incidence of staphylococci. Thus there seemed to be a definite correlation between suckling and milk infection.

More evidence of the importance of the babies themselves as carriers was provided by Colbeck (1949), who investigated 160 cases of breast abscess in Winnipeg hospitals in 1949, taking nose and throat swabs from the babies. He stated that it is possible that infected nasal secretions may pass to the back of the throat and into the baby's mouth and so be regurgitated into the terminal mammary ducts during suckling. Infection of the mothers' nipples by babies' nasopharyngeal organisms is inevitable if breast-feeding is practised. No "breast toilet" can prevent this, and the customary nipple treatment is more likely to introduce a further infection to the mother and infant than to eliminate it. Colbeck thought that if a mother developed a breast abscess, breast-feeding should be stopped. He raised the possibility of lung abscess occurring in the infant through aspiration of infected milk.

Wysham *et al.* (1957) showed that the infants themselves were the major source and reservoir of pathogenic staphylococci. They reported their investigations on 117 mothers and their babies and postulated that staphylococci from babies' mouths may be aspirated into the mammary ducts during feeding when the negative pressure which is created within the ducts at suckling is released. They showed that staphylococci in the throats of babies could pass through the hole in a rubber teat and contaminate the contents of a bottle during normal feeding.