RHEUMATOID ARTHRITIS AND POLYARTERITIS NODOSA

BY

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Structural arterial lesions are not usually considered to play an important part in the pathogenesis of rheumatoid arthritis; and in many histological descriptions of necropsy or biopsy material significant arterial lesions are not mentioned even when the vascular system has been carefully scrutinized (Bennett and others, 1940; Baggenstoss and Rosenberg, 1943; Fingerman and Andrus, 1943; Bennett, 1943; Collins, 1949).

In muscle biopsies, Sokoloff and others (1951) found a mild arteritis (in which fibrinoid alteration or fibrosis was not a conspicuous feature) in five of 57 cases of rheumatoid arthritis; and Cruickshank (1952), also examining skeletal muscle, encountered a "subacute arteritis without any necrosis of the vessel walls" only occasionally in a large series of cases. In a recent necropsy study of 72 cases of rheumatoid arthritis, Cruickshank (1954) found arteritis in eighteen. In seven of these there was rheumatic carditis and the arteritis was mainly confined to the heart; in the remainder there was no rheumatic heart disease and the arterial lesions (which in nine were not confined to the heart) were described as "rheumatoid arteritis" and claimed to be distinguishable from polyarteritis nodosa.

On the other hand, Dawson (1940) mentioned in an editorial comment that he had seen three patients with rheumatoid arthritis who were shown to have polyarteritis nodosa at necropsy, and some recent clinical studies draw attention to this type of case. Nyström (1953) described three patients in whom polyarteritis nodosa was detected some years after the onset of progressive rheumatoid disease; and Bauer and others (1952), in a patient diagnosed as suffering from typical rheumatoid arthritis of 2 years' duration, observed the development of eosinophilia, and skin nodules in which biopsy revealed arterial lesions indistinguishable from polyarteritis nodosa. According to Friedman and others (1953), a deforming multiple arthritis, commonly misdiagnosed as rheumatoid arthritis, may herald the onset of polyarteritis nodosa. These authors used the term "pararheumatic arthropathy" to describe such cases, implying, presumably, that the joint changes are based on articular polyarteritis nodosa, though no histological evidence of this is presented in their paper.

Unfortunately, histological studies of the articular tissues in polyarteritis nodosa are extremely rare. Numerous clinical investigations have shown that symptoms referable to the joints are common in this syndrome, but, according to Jones (1942) and Lowman (1952), the disability is of a minor order and "objective evidence of arthritis" is rare. Nevertheless a history of polyarthritis is not infrequently encountered in the published case reports. Rose (1953), using strict clinical criteria, found a polyarthritis indistinguishable from rheumatoid arthritis in eight of 104 histologically proven cases of polyarteritis nodosa; in seven the arthritis preceded and in the remaining case it developed during the course of polyarteritis nodosa. Three further cases of typical rheumatoid arthritis, in which a firm clinical diagnosis of polyarteritis nodosa was made but in which the available pathological material did not provide complete proof, were excluded from his analysis.

It would appear, then, that a small minority of patients classified as suffering from rheumatoid arthritis, and a minority of patients classified as suffering from polyarteritis nodosa, show features of both syndromes. It is the purpose of this communication to describe the clinical and pathological aspects of five cases illustrating this association.

Material and Methods

In addition to the five cases reported here, subcutaneous and tendon nodules from 46 cases of rheumatoid arthritis, and biopsies of the articular tissues in a
further 25 cases, were examined to determine the type and incidence of arterial lesions.

It may be said at once that polyarteritis nodosa was never seen in articular biopsies, and was found (mainly in arterioles) in only four of the 46 nodules, usually in close association with generalized inflammation of the connective tissues.

Tissues were fixed in 4 per cent. formaldehyde in 0-9 per cent. saline and stained in one or more of the following ways: haemalum and eosin; phosphotungstic acid haematoxylin; Lillie's method for reticulin; Van Gieson's stain; various elastic stains; the Masson-Goldner and the periodic acid-Schiff-orange G (Pearse, 1950) trichrome methods.

In all cases various joints were removed in toto, and, after fixation and freezing, they were hemisectioned or cut into slabs with the band saw. Radiographs were taken of selected slabs, which were then double-embedded in low viscosity nitrocellulose and paraffin wax. The heart was routinely examined by taking several blocks after the manner of Gross and others (1930).

In the period during which the present five cases were encountered, fifteen other cases of rheumatoid arthritis were examined without finding arteritis.

### TABLE I

<table>
<thead>
<tr>
<th>Case No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>64</td>
<td>64</td>
<td>62</td>
<td>50</td>
<td>53</td>
</tr>
<tr>
<td>Duration of Illness (yrs)</td>
<td>1</td>
<td>1½</td>
<td>2½</td>
<td>13</td>
<td>1½</td>
</tr>
<tr>
<td>Type of Arthropathy</td>
<td>Rapidly progressive; destructive multiple arthritis</td>
<td>Moderately severe; progressive multiple arthritis</td>
<td>Severe; progressive multiple arthritis</td>
<td>Severe deforming multiple arthritis</td>
<td>Mild transient multiple arthritis</td>
</tr>
<tr>
<td>X-ray Findings</td>
<td>Severe articular erosions</td>
<td>Minor articular erosions</td>
<td>Severe articular erosions</td>
<td>Gross joint destruction with deformity</td>
<td>Juxta-articular osteoporosis only</td>
</tr>
<tr>
<td>Rheumatoid Nodules</td>
<td>Both elbows</td>
<td>Nil</td>
<td>Elbows, sacrum, occiput, scapulae, fingers</td>
<td>Both elbows</td>
<td>Nil</td>
</tr>
<tr>
<td>Skin Rashes</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Differential Sheep Cell Agglutination Test</td>
<td>Positive</td>
<td>Not done</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>White Blood Cells (per c.mm.)</td>
<td>15,000</td>
<td>9,200, 10,000</td>
<td>28,100</td>
<td>3,500, 5,000, 5,600</td>
<td>9,200, 21,600, 19,800</td>
</tr>
<tr>
<td>Treatment</td>
<td>Gold; intravenous iron; aureomycin</td>
<td>Gold; penicillin; radical mastectomy</td>
<td>Gold; antibiotics; anticoagulants; cortisone</td>
<td>Gold</td>
<td>Penicillin; digitalis; cortisone</td>
</tr>
<tr>
<td>Drug Sensitivity</td>
<td>Some distress after iron</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Clinical Diagnosis</td>
<td>Rheumatoid arthritis</td>
<td>Rheumatoid arthritis; polyarteritis nodosa suspected shortly before death</td>
<td>Rheumatoid arthritis</td>
<td>Rheumatoid arthritis</td>
<td>Polyarteritis nodosa</td>
</tr>
<tr>
<td>Pathological Diagnosis</td>
<td>Rheumatoid arthritis and polyarteritis nodosa</td>
<td>Rheumatoid arthritis and polyarteritis nodosa</td>
<td>Rheumatoid arthritis and polyarteritis nodosa</td>
<td>Rheumatoid arthritis and polyarteritis nodosa</td>
<td>Polyarteritis nodosa and rheumatoid arthritis</td>
</tr>
</tbody>
</table>

### Diagnostic Criteria

The clinical features and course of rheumatoid arthritis vary considerably and in some instances the differential diagnosis from other types of polyarthritis is difficult. Nevertheless the character and distribution of the polyarthritis and the occurrence of subcutaneous nodules and vasospasm, together with characteristic radiological appearances and a positive sheep cell agglutination test (Ball, 1952), enable one to recognize a typical case. Patients presenting clinical or pathological features suggestive of disseminated lupus erythematosus, scleroderma, or dermatomyositis, in which arteritis is sometimes found, have been excluded from the present study.

Rheumatoid arthritis was diagnosed histologically in the presence of an inflammatory erosion of articular cartilage and subchondral bone by pannus, the appearance of which varied from a non-specific granulation tissue to a fibrous nodule depending on the activity and duration of the disease process.

Polyarteritis nodosa was defined as a segmental...
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Destructive inflammatory lesion, characterized, in the acute phase, by a fibrinoid alteration of the vessel wall with or without aneurysm formation or thrombosis and, in the healing phase, by degrees of replacement fibrosis. The cellular infiltration is variable and often pleomorphic though giant cells are exceptional. The lesions most commonly occur in small or medium-sized arteries, but vessels of any calibre may be affected.

General Description of Cases

The principal clinical and pathological findings are presented in Tables I and II. Cases 1 to 4 may be considered together because in general they were closely similar clinically and pathologically. The patients were all elderly subjects who were considered on clinical and radiological grounds to have had typical rheumatoid arthritis for periods varying from 1 to 13 years; only in Case 2, in which peripheral neuritis was first noticed 7 weeks before death, was there a definite suspicion of polyarteritis nodosa in life. Three had rheumatoid cutaneous nodules and the sheep cell agglutination test (D.A.T.) was positive in the three cases tested. None presented clinical evidence of rheumatic heart disease or definite signs of disseminated lupus erythematosus. At necropsy polyarteritis nodosa was found in addition to changes in the joints characteristic of rheumatoid arthritis. Examination of the affected joints showed that the articular vessels were commonly but not always involved, and for this reason (and others which will be discussed later) it was concluded that the arthritis per se was not a direct result of articular polyarteritis nodosa. These four cases are presented as illustrating the occurrence of polyarteritis nodosa as a complication of rheumatoid arthritis.

Case 5 presented an example of polyarteritis nodosa, diagnosed as such in life and confirmed at necropsy. Some time after the onset of the illness, there developed a mild multiple arthritis of rheumatoid type which virtually disappeared 3 months later after the commencement of cortisone therapy for the arthritis. In spite of the transient nature of the arthropathy there was typical histological evidence of rheumatoid arthritis in an inactive phase, the articular vessels being normal.

Table II

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Joints Examined</th>
<th>Rheumatoid Changes</th>
<th>Polyarteritis Nodosa in</th>
<th>Other Lesions</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Joint Capsule</td>
<td>Peri-articular Tissue</td>
</tr>
<tr>
<td>1</td>
<td>1st M.P.</td>
<td>Early severe</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Wrist</td>
<td>Early severe</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Carpus</td>
<td>Early severe</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Elbow</td>
<td>Early moderate</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>1st M.P.</td>
<td>Moderate</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Prox. I.P.</td>
<td>Moderate</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Dist. I.P.</td>
<td>Moderate</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Knee</td>
<td>Moderate</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>1st M.P.</td>
<td>Moderate</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Sternoclavicular</td>
<td>Moderate</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Atlanto-axial</td>
<td>Severe advanced</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Cervical interf.</td>
<td>Early mild</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>Radiocarpal</td>
<td>Advanced</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Sternoclavicular</td>
<td>Advanced</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Cervical interf.</td>
<td>Mild</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>1st M.P.</td>
<td>Early mild</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Prox. I.P.</td>
<td>Early mild</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

M.P. = metacarpo-phalangeal joint
I.P. = interphalangeal joint
+ = found
- = not found
Case Reports

Case 1, a male aged 64, was admitted to another hospital because of generalized pains of recent onset.

Clinical Findings.—Shortly after admission he was seen to develop painful swellings of the wrists, hands, and feet; and during the next 6 months the ankles, elbows, shoulders, and knees became involved despite twenty injections of gold and an unspecified amount of DOCA and ascorbic acid; 11 months after the onset, he was examined in the Out-Patient Department of the Manchester Rheumatism Centre and found to have pale, atrophic skin and subcutaneous nodules on both elbows and ischial tuberosities; the joints of the hands, feet, wrists, knees, and elbows were swollen, painful, and limited in movement; there was ulnar deviation of the hands, flexion deformity of the knees, and slight subluxation of both shoulders. General examination revealed no abnormality apart from slight dullness and diminished movement over the left lower lobe. The blood pressure was 140/80; urine normal; erythrocyte sedimentation rate (Westergren) 81 mm./hr. A month later, on admission to the Centre's Ward, the condition of the joints and other signs of rheumatoid arthritis remained unchanged but there was a mild pyrexia up to 101°F. and a left pleural effusion in which 70 per cent. of the cells were polymorphs, though it was sterile on culture. Radiographs of the chest, both at this time and later when the effusion had subsided, revealed no underlying pulmonary lesion. Radiographs of the hands, knees, hips, and shoulders showed advanced bilaterally symmetrical destructive arthritis of the rheumatoid type. The erythrocyte sedimentation rate was now 90 mm./hr; haemoglobin 70 per cent.; white cell count 15,000/c.mm.; D.A.T. positive. Repeated tests of the urine for albumin and sugar were negative. Intravenous iron was given but discontinued after nine injections because of some attendant distress. The pyrexia persisted, though apparently partially controlled by aureomycin; there was no sign of local sepsis and blood cultures were sterile. The patient's general condition steadily deteriorated and death occurred 3 weeks after admission and some 12 months after the onset of the illness, acute abdominal pain and tenderness being present in the last few days.

Pathological Findings

Macroscopic.—There was wasting of subcutaneous fat and limb muscles. Typical subcutaneous rheumatoid nodules were found in the elbow region. All the limb joints showed some degree of subluxation and the joint capsules were thin and atrophic. The right knee, right shoulder, and left hip joint contained much yellowish friable debris, partly lying free and partly attached to the slightly thickened but generally smooth synovial membrane; the biceps psoas and semimembranous bursae were distended with similar material. Both trochanteric bursae were thickened with similar material. The red lining-membrane was mottled with irregular yellowish patches.

The heart (210 g.) and pericardial sac were normal. There was a left pleural effusion, and a thick shaggy fibrinous exudate covered the lower lobe of the left lung (700 g.). On section, a terminal broncho-pneumonia was found in both lungs. Scattered throughout the small intestine were numerous ulcers (0.5-1.0 cm.) with associated recent peritoneal fibrinous exudate; a paraduodenal abscess containing yellow pus communicated with a mucosal ulcer. A solitary deep chronic ulcer was found in the pyloric region of the stomach. The adrenals together weighed 20 g. and appeared normal, as did the spleen, pancreas, and kidneys. The liver (1,240 g.) contained occasional friable bluish areas about 0.5 cm. in diameter. There was slight dilatation of the lateral ventricles. In the region of the optic chiasma there was a localized gelatinous exudate, but the meninges were otherwise normal.

Microscopic

Viscera.—Polyarteritis nodosa was found in the small arteries of the kidneys, pancreas (Fig. 1), stomach, and small intestine, and in the bronchial arteries at the hilum of the left lung. These lesions were all in the acute or early subacute phase. Renal and splenic parenchyma were not notably abnormal. There was an area of pleomorphic cellular infiltration at the base of the posterior mitral cusp, but evidence of either rheumatic carditis or Libman-Sachs endocarditis was not seen. Occasional areas of haemorrhagic necrosis were present in the liver. The left pleura and overlying exudate presented no unusual features. In the region of the optic chiasma the pia-arachnoid contained an indeterminate inflammatory exudate infiltrated with lymphocytes.

Fig. 1.—Case 1, acute polyarteritis nodosa in pancreas. Haemalum and eosin. × 115.
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Articular Tissues.—The fibrous wall of the trochanteric and bicipital bursae contained areas of fibrinoid. In the surrounding muscle and connective tissue occasional acute lesions of polyarteritis nodosa were seen. The wrist joint was partially ankylosed, and subchondral erosions were numerous in the carpal bones. Some of the eroded areas were filled with necrotic debris and lined in parts with oedematous connective tissue scantily infiltrated with lymphocytes; others contained vascular fibrous pannus. There was acute arteritis in the periosteal tissues, but not in the joint capsule. Early pannus erosion of cartilage was found in the knee joint, where arteritis was present in the joint capsule and periarticular tissues.

In the metacarpo-phalangeal joint characteristic erosions by fibrous pannus infiltrated with lymphocytes and plasma cells were evident, but the synovium generally was only moderately infiltrated with lymphocytes. In the synovial recesses fibrinous masses were conspicuous. Acute polyarteritis was present in the peri-articular muscles and periosteal tissues, but not in the joint capsule or synovium (Fig. 2).

The articular histology suggested that a severe rheumatoid process had become relatively quiescent some time before death.

Summary.—Clinically, this patient had a rapidly progressive rheumatoid arthritis of some 12 months' duration. The occurrence of a sterile pleural effusion and failure to respond to bed rest and other supportive measures were the principal clinical features in the last few weeks of the illness, though terminally acute abdominal symptoms developed.

Histological studies revealed polyarteritis nodosa in various internal organs and in the peri-articular tissues, particularly the flexor muscle groups. Though some of the features of rheumatoid arthritis, such as villous synovial hypertrophy and dense inflammatory infiltrates were absent, typical rheumatoid erosions of articular cartilage and subchondral bone were conspicuous. The persistence of joint pain and tenderness in the final stages of the illness, when the arthritis was judged histologically to be relatively inactive, may be explained by the late occurrence of arteritis in the peri-articular tissues and outer parts of the joint capsule.

Case 2, a female aged 64, attended the Infirmary complaining of pains in the joints of 6 months' duration.

Clinical Findings.—Examination revealed tender swelling of the joints of the fingers, wrists, ankles, and knees, and some painful limitation of movement of the shoulders and cervical spine. There was some deafness in the

Fig. 2.—Case 1
(A) Metacarpo-phalangeal joint. White spots indicate sites of arterial lesions.
(B) Outlined area enlarged to show typical rheumatoid erosion of cartilage and subchondral bone.
(C) Acute polyarteritis nodosa in a juxta-articular vessel.
right ear and a slight discharge from a frontal sinus that had been operated on 30 years previously, but otherwise no abnormality was detected on general examination. A diagnosis of early rheumatoid arthritis was made, and 3 months' physiotherapy was followed by a course of gold injections. These were terminated after a further 4 months because of skin irritation which rapidly subsided. A white cell count taken some time later was 9,200/c.mm. and the haemoglobin was 82 per cent.

The arthritis continued to be active and 4 months after cessation of gold therapy and following a rapid deterioration in her general condition she attended hospital again. There was a mild pyrexia (101°F.), obvious loss in weight, and severe polyarthritis. The blood pressure was 110/60, and white cell count 10,000/c.mm. A small scirrhous carcinoma was found in the left breast and radical mastectomy was performed the following week. After operation the wound broke down and there was a persistent pyrexia which was unaffected by penicillin; 7 weeks after the operation a peripheral neuritis developed and 5 weeks later, following a steady deterioration in the general condition, the patient died. The total duration of the illness had been 20 months.

Pathological Findings.—There was severe general wasting and large sores over the sacrum. Apart from a slight spindling of the fingers there was no obvious joint deformity. There was a recent mild pericarditis and the flabby myocardium contained occasional small haemorrhagic foci; no valvular or endocardial abnormality was found in the heart (260 g.). The loops of the small intestine were bound by numerous focal adhesions and there was superficial ulceration of the mucosal surface. The liver (1,140 g.) contained several small haemorrhagic areas.

The spleen, pancreas, kidneys, adrenals, brain, stomach, and large intestine were apparently normal.

Post-mortem X rays of the right index finger and cervical interfacial joints revealed slight reduction in joint space and several small erosions of rheumatoid type.

Microscopic

Viscera.—There was a mild non-specific fibrinous pericarditis, but no definite evidence of rheumatic heart disease. Polyarteritis nodosa, mainly in the subacute or healed phase, was found in the myocardium, limb muscles, liver, kidneys, periaridrenal fat, serous coat of small intestine, and sciatic and median nerves (Figs 3 and 4). Renal and splenic parenchyma presented no definite abnormality. The pituitary contained rare groups of polar bigranulate cells (Pearse, 1953).

Articular Tissues.—The joints of the right index finger and one knee joint were examined histologically and typical rheumatoid erosions of the marginal articular cartilage and subchondral bone were found in them all (Fig. 5, opposite); the synovial tissue and pannus formations were moderately infiltrated with lymphocytes and plasma cells. The arthritic process was judged to be relatively mild in comparison with Case 1. Subacute and healed lesions of polyarteritis were present in the periarticular muscle and joint capsule of the metacarpophalangeal joint and in the intercondylar fossa of the right knee joint; but no vascular lesions were detected in the proximal and distal interphalangeal joints, where the rheumatoid process was equally advanced.

Summary.—For some 17 months a female aged 64 presented the typical features of a rheumatoid arthritis of...
A course in stiffness of the some painful swelling made recurred and symptoms clinical process. owing was clinical and rheumatoid arthritis organs, nodosa. were found and the left shoulder a 1950. affected male were superimposed. Thus the evidence suggests that the left ventricle was healed lesions of polyarteritis. The knees, hips, shoulders, and cervical spine. The only abnormal sign on general examination was a slight sensory impairment in the left leg and both feet. Changes indicative of old coronary infarction were present in the electrocardiograph. X rays showed extensive articular erosions of rheumatoid type. The blood pressure was 160/85-100; urine normal; haemoglobin 80 per cent.; albumin-globulin ratio 0-8; D.A.T. positive.

One week after admission another coronary attack occurred for which anticoagulant therapy was given for 3 weeks. At this time ulceration occurred over the subcutaneous nodules, and antibiotic therapy was instituted to control secondary infection. Blood cultures were sterile and there was never a severe pyrexia; the highest white cell count was 28,100/c.mm., and the blood urea reached 76 mg. per cent. The general condition steadily deteriorated and a month after admission he had another attack of severe retrosternal pain and dyspnoea. Death occurred 3 weeks later, 1,100 mg. cortisone having been given in the last 7 days.

Pathological Findings

Macroscopic.—There was general wasting and ulcers were present over most pressure points. The olecranon bursae were enlarged and thickened, and typical fibrinoid nodules were found in the subcutaneous tissue along the ulnar border. There was ulnar deviation of the hands and a flexion deformity of the knees. The heart (550 g.) was enlarged and there was fibrinous pericarditis; the posterior wall of the left ventricle contained an infarct and the proximal 2 in. of the right coronary artery were completely occluded by firm thrombus. Both coronary arteries were severely atheromatous. Two of the aortic valves were firmly adherent but otherwise the heart valves and endocardium were normal. There was pneumatic consolidation of the lower zones of both lungs which were adherent posteriorly. A deep ulcer (1 cm. diam.) was present in the first part of the duodenum and smaller superficial ulcers were scattered throughout the small and large intestine. There was some distortion of the cortical pattern in both kidneys, and the right contained an old infarct. Two red infarcts were present in the spleen (90 g.) which was otherwise normal. The portal tracts in the left lobe of the liver (1,150 g.) were unduly prominent.

Microscopic

Viscera.—Many of the larger renal arteries showed focal destruction of elastic and muscle layers and partial or complete fibrous occlusion of the lumen (Fig. 6, overleaf).

Some of the smaller vessels resembled endarteritis moderate severity. She died 3 months after a radical mastectomy; and the occurrence of a peripheral neuritis 5 weeks before death was the first sign of polyarteritis nodosa. Subacute and healed lesions of polyarteritis were found in the peripheral nerves and various internal organs, and in the peri-articular vessels of most but not all of the affected joints in which changes typical of rheumatoid arthritis of a severity compatible with the clinical observations were present. Thus the evidence both clinical and pathologically strongly suggests that the arthritis was superimposed on an established rheumatoid process.

Case 3, a male aged 62, developed pain in the left shoulder early in 1950. This was followed, in a few weeks, by painful swelling of the joints of the hands and feet. Within 6 months the knees, hips, and cervical spine became involved and he had lost a stone in weight. A course of gold injections was given, and by April, 1951, he had returned to work, the only residual disability being some stiffness of the left hand. Five months later the symptoms recurred and he was again treated with gold, but after six injections the treatment was discontinued owing to an attack of coronary thrombosis from which he made a good recovery; he had had a similar episode 10 years previously. During the next 9 months the arthritis became gradually worse and he was admitted to the Infirmary in June, 1952.

Clinical Findings.—On examination the hands were cold and moist, and typical subcutaneous nodules were present over the elbows, scapulae, sacrum, and occiput, and in the fingers. There was painful swelling of the joints of the hands and feet, and painful limitation of movement in the elbows, hips, shoulders, and cervical spine. The only abnormal sign on general examination was a slight sensory impairment in the left leg and both feet. Changes indicative of old coronary infarction were present in the electrocardiograph. X rays showed extensive articular erosions of rheumatoid type. The blood pressure was 160/85-100; urine normal; haemoglobin 80 per cent.; albumin-globulin ratio 0-8; D.A.T. positive.

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Some of the smaller vessels resembled endarteritis moderate severity. She died 3 months after a radical mastectomy; and the occurrence of a peripheral neuritis 5 weeks before death was the first sign of polyarteritis nodosa. Subacute and healed lesions of polyarteritis were found in the peripheral nerves and various internal organs, and in the peri-articular vessels of most but not all of the affected joints in which changes typical of rheumatoid arthritis of a severity compatible with the clinical observations were present. Thus the evidence both clinical and pathologically strongly suggests that the arthritis was superimposed on an established rheumatoid process.

Case 3, a male aged 62, developed pain in the left shoulder early in 1950. This was followed, in a few weeks, by painful swelling of the joints of the hands and feet. Within 6 months the knees, hips, and cervical spine became involved and he had lost a stone in weight. A course of gold injections was given, and by April, 1951, he had returned to work, the only residual disability being some stiffness of the left hand. Five months later the symptoms recurred and he was again treated with gold, but after six injections the treatment was discontinued owing to an attack of coronary thrombosis from which he made a good recovery; he had had a similar episode 10 years previously. During the next 9 months the arthritis became gradually worse and he was admitted to the Infirmary in June, 1952.

Clinical Findings.—On examination the hands were cold and moist, and typical subcutaneous nodules were present over the elbows, scapulae, sacrum, and occiput, and in the fingers. There was painful swelling of the joints of the hands and feet, and painful limitation of movement in the elbows, hips, shoulders, and cervical spine. The only abnormal sign on general examination was a slight sensory impairment in the left leg and both feet. Changes indicative of old coronary infarction were present in the electrocardiograph. X rays showed extensive articular erosions of rheumatoid type. The blood pressure was 160/85-100; urine normal; haemoglobin 80 per cent.; albumin-globulin ratio 0-8; D.A.T. positive.

One week after admission another coronary attack occurred for which anticoagulant therapy was given for 3 weeks. At this time ulceration occurred over the subcutaneous nodules, and antibiotic therapy was instituted to control secondary infection. Blood cultures were sterile and there was never a severe pyrexia; the highest white cell count was 28,100/c.mm., and the blood urea reached 76 mg. per cent. The general condition steadily deteriorated and a month after admission he had another attack of severe retrosternal pain and dyspnoea. Death occurred 3 weeks later, 1,100 mg. cortisone having been given in the last 7 days.

Pathological Findings

Macroscopic.—There was general wasting and ulcers were present over most pressure points. The olecranon bursae were enlarged and thickened, and typical fibrinoid nodules were found in the subcutaneous tissue along the ulnar border. There was ulnar deviation of the hands and a flexion deformity of the knees. The heart (550 g.) was enlarged and there was fibrinous pericarditis; the posterior wall of the left ventricle contained an infarct and the proximal 2 in. of the right coronary artery were completely occluded by firm thrombus. Both coronary arteries were severely atheromatous. Two of the aortic valves were firmly adherent but otherwise the heart valves and endocardium were normal. There was pneumatic consolidation of the lower zones of both lungs which were adherent posteriorly. A deep ulcer (1 cm. diam.) was present in the first part of the duodenum and smaller superficial ulcers were scattered throughout the small and large intestine. There was some distortion of the cortical pattern in both kidneys, and the right contained an old infarct. Two red infarcts were present in the spleen (90 g.) which was otherwise normal. The portal tracts in the left lobe of the liver (1,150 g.) were unduly prominent.

Microscopic

Viscera.—Many of the larger renal arteries showed focal destruction of elastic and muscle layers and partial or complete fibrous occlusion of the lumen (Fig. 6, overleaf).

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fibrosa, but clinically there was no evidence of hypertension and hypertensive glomerular changes were absent. Subacute or healed lesions of polyarteritis nodosa were seen in the portal tracts (Fig. 7), spleen, pancreas, and duodenum. In the kidneys the lesions were associated with groups of fibrosed glomeruli and atrophic tubules but otherwise the renal parenchyma was not remarkable. In addition to myocardial fibrosis, there were recent and old infarcts in the left ventricle, but no evidence of polyarteritis nodosa, the coronary arteries showing only severe atheroma. Where secondary infection was minimal or absent, it was clear that the skin ulcers had developed by subepidermal extension of subcutaneous fibrinoid with consequent sloughing of the epidermis. Rare groups of polar bigranulate cells and occasional Crooke-Russell cells were present in the pituitary.

**Articular Tissues.**—Typical rheumatoid marginal articular erosions were found in the sternoclavicular joints, the disks of which contained areas of fibrinoid change; arthritis was not encountered in the joint capsule or peri-articular tissues in several sections. Similarly there was a moderately severe destructive arthritis in the metacarlo-phalangeal joint and terminal interphalangeal joint of the right index finger without articular polyarteritis nodosa. The anterior and posterior atlantoaxial joints were largely replaced by pannus at various stages of maturity, and remnants of synovial tissue presented typical rheumatoid changes; areas of fibrinoid were seen in the apical and alar ligaments (Figs 8 and 9, opposite).

No polyarteritis was found in sections of this region. All of three cervical interfacetal joints showed typical
marginal rheumatoid erosions; though vascular lesions were found occasionally in the intervertebral foramina, the vessels in the joint capsules were not involved.

Summary.—A 62-year-old male, who had suffered from severe rheumatoid arthritis for over 2 years, died of atheromatous coronary disease. The only unusual clinical sign was the occurrence of sensory impairment in the lower limbs late in the course of the illness. Histological studies confirmed the diagnosis of rheumatoid arthritis and also disclosed healed polyarteritis nodosa of various internal organs; the articular vessels, however, were not involved in most of the affected joints, so that there can be little doubt that the arthritis was pathogenetically independent of articular polyarteritis nodosa. It is difficult to date the onset of the arteritis, though this is the probable explanation of the sensory impairment noted 7 weeks before death.

Case 4, a male aged 50, was admitted to the Manchester Rheumatism Centre because of severe polyarthritis. His illness had started 13 years previously with painful swelling of the joints of the feet; 4 years after the onset, the hands, knees, and cervical spine became involved, and subcutaneous nodules appeared on the elbows. During the succeeding 9 years all the affected joints became increasingly deformed and though there was no great constitutional disability the patient had lost 4 stones in weight.

Clinical Findings.—The skin was found to be atrophic and the hands were cold, moist, and cyanotic. Typical rheumatoid nodules were present in the flexor tendons of the hands and in the elbow and sacral regions. The joints were deformed, tender, and swollen. General examination revealed no abnormality. The blood pressure was 160/95; urine normal (and remained so throughout); E.S.R. (Westergren) 90 mm./hr; D.A.T. positive; haemoglobin 82 per cent.; white cell counts 3,500 and 5,000/c.mm.; lupus erythematosus cells looked for but not found; albumin/globulin ratio 0.7.

X-rays showed gross rheumatoid changes in hands and feet, lateral subluxation of the atlas, and normal sacroiliac joints. A course of gold injections was started and 2 weeks after admission the patient was transferred to the Devonshire Hospital, Buxton, where a collar was applied to the neck. At this time the patient was confined to bed because of general malaise associated with slight buccal ulceration; white cell count 5,600/c.mm.; temperature normal apart from occasional rises to 100°F. He collapsed and died suddenly 11 days after admission.

Pathological Findings

Macroscopic.—There was gross deformity of the limb joints and typical subcutaneous nodules over both elbows. Both lungs were severely congested, but the pleural cavities were normal. There was a shaggy pericarditis and an abundant haemorrhagic pericardial effusion. The coronary arteries were patent but atheromatous, and there was severe myocardial fibrosis. The valves and endocardium were normal. Small (1-3 mm.) nodules were scattered throughout the liver which was adherent to the
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diaphragm. There was an old adherent peri-
splenitis but otherwise the spleen appeared
normal. The brain and cervical cord were
not remarkable apart from a small haemor-
rhagic lesion in the membranes in the region
of the second cervical vertebra.

Microscopic

Viscera.—Subacute or healed lesions
of polyarteritis nodosa were readily found
in the pancreas, liver, spleen, kidneys, stomach,
and intestine (Fig. 10), and in the auricular
and ventricular myocardium. There was
no evidence of rheumatic heart disease, and
the pericarditis presented no unusual features.
There was some peri-arteriolar hyalinosis
in the spleen, but the renal, hepatic, and splenic
parenchyma were not remarkable. No
definite abnormality was seen in the pituitary.

Articular Tissues.—The sternoclavicular joint,
wrist joint, and carpus all showed a severe destructive
but quiescent arthritis of rheumatoid type with some
secondary osteo-arthritis (Figs 11 and 12). Polyarteritis
nodosa was present in the capsule and peri-articular
tissues of the wrist and carpal joints, but no arterial
lesions were detected in several sections of the sterno-
clavicular joint. Vascular lesions were also found in the
muscles and intervertebral foramina in the vicinity of the
-cervical interfacetal joints in which minor rheumatoid
changes were evident.

Summary.—Clinically there was no reason to suspect
that the patient was suffering from anything but advanced
rheumatoid arthritis of some 13 years' duration. Death
was probably due to haemorrhagic pericarditis and myo-
cardial failure associated with myocardial polyarteritis
nodosa; arteritis was also present in various other organs.
Histologically the joint changes were typical of advanced
rheumatoid arthritis of long duration.
Case 5, a female aged 53, was admitted to the Infirmary complaining of cough, breathlessness, and loss of weight of 2 months' duration.

Clinical Findings.—Investigation revealed a mild pyrexia, a sterile right-sided pleural effusion, mitral stenosis, a mild anaemia (haemoglobin 76 per cent.), a white cell count of 9,200/c.mm., and sterile blood cultures. The pyrexia gradually subsided following penicillin therapy, but in spite of comprehensive studies no satisfactory explanation of the pleural effusion was found. The pleural effusion was considerably reduced in size 6 weeks after admission, and the patient was discharged. She was subsequently seen at intervals as an out-patient, but after 3 months was readmitted because of increasing breathlessness, fatigue, and pain and stiffness in the arms, legs, and back. There was painful limitation of movement in the hands, feet, wrists, ankles, shoulders, and spine. X rays of the hands showed juxta-articular porosis but no bony erosions. Weight loss was obvious, but the temperature, pulse, and blood pressure were normal. Salicylates were given, but the patient remained unwell, and shortly after admission developed bouts of pyrexia and auricular fibrillation which was controlled with digitalis; the blood cultures were sterile. A Wasserman reaction at this time was positive but no other evidence of syphilis was found; erythrocyte sedimentation rate 43 mm./hr; urine contained albumin, a few red and white blood cells, and granular casts; blood urea 58 mg./100 ml.; haemoglobin 64 per cent., and persistent polymorphonuclear leucocytosis, the count rising as high as 21,600 c.mm.; albumin/globulin ratio 0.9; tests for amyloid and lupus cells and D.A.T. negative.

A diagnosis of polyarteritis nodosa was made and 100 mg. cortisone daily was given for 23 days, being stabilized after a 12-day interval at 25 mg. on alternate days. From the start of cortisone therapy there was a considerable and steady improvement in her general condition and when she was discharged some 3½ months after admission the joint symptoms had disappeared.

However, 3 weeks after discharge and whilst still taking cortisone, she was readmitted as an emergency because of increasing oedema, cough, breathlessness, and lassitude. On examination there was pyrexia, pulmonary oedema, ascites, and oedema of the ankle, but no distension of the neck veins; blood pressure 106/56; blood urea 58 mg./100 ml.; white cell count 19,800/c.mm. (92 per cent. polymorphs). There were no symptoms or signs of joint disease. Death occurred 2 days after admission.

Pathological Findings

Macroscopic.—The skin, subcutaneous tissue, and joints presented no definite abnormality. The heart weighed 470 g.; there was recent pericarditis, an old stenosis of the mitral valve, and slight aortic sclerosis, but no recent endocarditis. Both lungs were bound down by easily separable adhesions. There was a rubbery consolidation of the mid-zone of the left lung (740 g.), the cut surface being moist and purple in colour; in the surrounding areas there was congestion and oedema only. The right lung showed congestion and oedema. The peritoneal cavity contained about 0.5 l. sero-fibrinous fluid. There was passive congestion of the liver (1,350 g.) and spleen (350 g.) and an adherent perisplenitis. The kidneys were not enlarged, but occasional haemorrhagic or scarred areas were found in the cortex. The brain was normal.

Viscera.—Acute and subacute polyarteritis nodosa was found in the liver, kidneys (Fig. 13), intestine, pancreas, adrenals, and omentum. The renal lesions were associated with areas of haemorrhage and fibrosis but otherwise the kidney was not remarkable. In the area of consolidation in the left lung, the alveoli were lined by swollen endothelial cells and contained masses of fibrinous material, some of which were being organized; the alveolar septa were thickened partly by oedema and partly by fibrous tissue. The appearances were similar to those often described as "rheumatic pneumonia". In the pituitary there was an obvious reduction in the staining of the basophils with the periodic acid-Schiff method; Crooke-Russell cells were easily found, but polar bigranulate cells were rare.

![Fig. 13.—Case 5, polyarteritis nodosa in small renal artery. Haemalum and eosin. × 150.](http://ard.bmj.com/AnnRheumDis:10.1136/ard.13.4.277)
Articular Tissues.—The right metacarpo-phalangeal joint and first interphalangeal joint were examined. Both showed unmistakable rheumatoid erosions of the marginal articular cartilage in an inactive stage (Fig. 14). Numerous sections of these parts were scrutinized without finding polyarteritis nodosa.

Fig. 14.—Case 5, metacarpo-phalangeal joint showing marginal erosion of articular cartilage and subchondral bone by pannus in a quiescent phase. Haemalum and eosin. × 75.

Summary.—The combination of rheumatic heart disease, unexplained pleural effusion and leucocytosis, weight loss, mild arthropathy, and a urine containing albumin, red cells, and casts, suggested polyarteritis nodosa in life, and this was confirmed at necropsy. Unlike the previous cases the arthropathy was never a feature of major clinical importance. Nevertheless the joint changes were histologically typical of the rheumatoid process and occurred in the absence of articular polyarteritis nodosa.

This case clearly illustrates that, in patients apparently suffering primarily from polyarteritis nodosa, a typical rheumatoid arthritis may occur, the joint changes being independent of arterial lesions and analogous to the non-specific pericarditis commonly found in this disease.

Discussion

The diagnosis of rheumatoid arthritis in Cases 1 to 4 was clearly justified on clinical, radiological, and serological grounds; moreover, until shortly before death, there was no indication of the fatal outcome. The final stages were characterized mainly by a steady deterioration in the general condition. Only in Case 2 were there definite signs of polyarteritis nodosa in life, but in Cases 1, 3, and 4 there were terminal visceral or neurological episodes which in retrospect could be interpreted as clinical evidence of a disseminated arteritis. In three of the cases polyarteritis nodosa was probably a major contributory cause of death; the remaining patient (Case 3) died of atheromatous coronary thrombosis, and in this case the lesions of periarteritis nodosa had healed. In Case 1 the arterial lesions were probably of recent origin, being in the acute phase and contemporaneous (an unusual finding in polyarteritis nodosa), whereas the arthritis had been present for nearly a year; and in Cases 2 and 3 suggestive signs of disseminated arteritis were first detected shortly before death. In Case 4, progressive rheumatoid arthritis had been present for 13 years without unusual symptoms or signs, until death occurred unexpectedly from heart failure.

Histologically, there was a typical rheumatoid process in the joints; in addition, arteries in the peri-articular tissues were commonly involved by polyarteritis nodosa, but the smaller capsular and synovial vessels were unaffected in most instances. Nor did the synovial tissues contain focal granulomatous lesions such as may be encountered in polyarteritis nodosa and have been ascribed to capillary involvement (Ball and Davson, 1952). And in all but Case 1 there were occasional joints with rheumatoid changes but without peri-articular arteritis. Thus, in Cases 1 to 4, clinical and histological evidence favours a double diagnosis, in the sense that the arteritis was superimposed on a true rheumatoid arthritis. It is possible, however, that the peri-articular arteritis was responsible, at least in part, for the persistent joint symptoms in those instances in which the arthritis appeared to be relatively inactive histologically.

The studies of Sokoloff and others (1951) and of Cruickshank (1954) indicate that in certain rare cases of rheumatoid arthritis an arteritis may occur, in which mural necrosis or fibrosis are inconspicuous, and which may therefore be reasonably regarded as different from polyarteritis nodosa. It is noteworthy, however, that among the group of eleven cases described by Cruickshank (1954) as having "rheumatoid arteritis", a fairly wide range of appearances were encountered in the affected vessels; and in two (Cases 8 and 17) the lesions, though remarkably similar to classical acute polyarteritis nodosa, were distinguished from it because there was neither...
aneurysm formation nor thrombosis and because the lesions were not widely disseminated in the viscera. Both these criteria seem open to question, for it is generally acknowledged that many cases of polyarteritis nodosa do not show aneurysm formation, and the distribution and frequency of the lesions are well known to vary widely from case to case. There is an interesting parallel here with the arteritis found in some cases of rheumatic fever: this was regarded by Von Glahn and Pappenheimer (1926) as specific to this syndrome, for reasons similar to those advanced by Cruickshank regarding rheumatoid arteritis. But, in the cases of rheumatic fever described by Friedberg and Gross (1934), the arterial lesions were considered to be typical of polyarteritis nodosa, and it was suggested that the differences between these authors' cases and those of Von Glahn and Pappenheimer might be quantitative rather than qualitative. Similar difficulties may apparently also arise in the interpretation of the arterial lesions that occur in some cases of disseminated lupus erythematosus (Bauer and others, 1952). The available evidence suggests that the distribution, frequency, and morphology of arterial lesions in rheumatoid arthritis are variable, ranging from a mild indeterminate arteritis to classical polyarteritis nodosa.

Although the various syndromes comprising the collagen diseases are usually fairly well defined clinically and pathologically, cases showing features of more than one syndrome are frequently encountered; and arteritis more or less typical of polyarteritis nodosa has been found in association with rheumatic fever, disseminated lupus erythematosus, scleroderma, and dermatomyositis (Friedberg and Gross, 1934; Banks, 1941; Klemperer and others, 1941; Bevans, 1945; Klemperer, 1948; Bauer and others, 1952). It would appear that the same can be said of rheumatoid arthritis, which is, however, a relatively common disease. Nevertheless, there is suggestive evidence that the association of rheumatoid arthritis and polyarteritis nodosa is more than coincidental. Thus, the incidence of rheumatoid arthritis in the general population has been variously estimated at 1 per cent. (Blécourt, 1953) and 2.4 per cent. (Kellgren and others, 1953), whereas its incidence in polyarteritis nodosa is probably 8 per cent. according to Rose (1953).

The implication is that, in the presence of any of the syndromes mentioned above, there is an increased susceptibility to arterial disease of the polyarteritis nodosa type. But, since only a small proportion of patients with rheumatoid arthritis become hospital in-patients and few of these die, it is obvious that polyarteritis is a rare complication of this syndrome and one likely to be seen mainly in hospital practice. It is clinically important, not because of its frequency, but because it may be fatal and may not readily be recognized as such when superimposed upon the picture of severe rheumatoid arthritis.

The personal study of a considerable amount of biopsy material in rheumatoid arthritis confirms previous opinions that polyarteritis nodosa is a very rare feature of rheumatoid pathology; and the appearance of vascular lesions in the present cases is presumably dependent on pathogenetic factors not usually operative in this form of polyarteritis. Conversely, histological evidence of a rheumatoid process (in the absence of articular arteritis) may be found in cases of polyarteritis nodosa in which joint disability is not a presenting feature (Case 5).

Cases 1 to 4 were carefully reviewed without discovering any common factor which could be regarded as causally significant in relation to the arteritis. There was, for instance, no evidence clinically of a hypersensitivity state; and visceral granulomata, which sometimes accompany polyarteritis nodosa (Wegener, 1939) and to which Zeek and others (1952) attach an allergic significance, were not encountered in the present cases. However, McManus and Hornsby (1951) have recently described necrotizing arteritis and granulomatous glomerulo-nephritis following polyarteritis, and I have seen this Wegener type of polyarteritis nodosa develop in a typical case of ankylosing spondylitis with peripheral joint involvement.

The occurrence of disseminated arteritis in patients under treatment with cortisone has aroused considerable interest. According to Slocumb (1953), attempts to withdraw cortisone therapy may be attended by a "panmesenchymal and panangiitic reaction" which carries all the risks of polyarteritis nodosa or acute disseminated lupus erythematosus; and he makes the further interesting statement that among various patients treated with cortisone, a panangiitic reaction was seen only in those with rheumatoid arthritis. Two of 33 cases of rheumatoid arthritis described by Levin and others (1953) died of polyarteritis nodosa which developed after withdrawal of cortisone; but these workers point out, as do West and News (1953), that this complication may also begin during the period of administration of the hormone. It is evident from all these reports that before being given cortisone therapy the cases developing arteritis were not distinguishable from those that did not; and it has been suggested that the treatment was at least partly responsible for the development of the arteritis. It is, however, clear that a similar sequence of events may arise in the absence of ACTH or cortisone therapy.
Summary

Clinical and necropsy findings are presented in five cases, illustrating the association of rheumatoid arthritis and polyarteritis nodosa.

In four of these, disseminated arteritis apparently complicated an established and typical rheumatoid process, the pathogenesis of the arthritis being essentially independent of the arterial lesions. In one case the arteritis was an incidental finding, in the others it was a major contributory cause of death. Only one of the four cases had received cortisone; none had received ACTH.

In the fifth case a short arthritic episode occurred in an illness diagnosed clinically and histologically as polyarteritis nodosa; at necropsy the joints showed typical rheumatoid changes in the absence of articular arthritis.

It is suggested that, though polyarteritis nodosa is a rare complication of rheumatoid arthritis, the association of these two conditions is more than coincidental. The available evidence suggests that the distribution, frequency, and morphology of arterial lesions in rheumatoid arthritis are variable, ranging from a mild indeterminate arteritis to classical polyarteritis nodosa.

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Arthritis reumatoide y poliarteritis nodosa

SUMARIO

Se presentan los hallazgos clínicos y de autopsia en cinco casos que ilustran la asociación de la artritis reumatoide con la poliarteritis nodosa.

En cuatro de ellos la arteritis diseminada aparentemente complicaba un proceso reumático establecido y, típicamente, la patogenia de la artritis es esencialmente independiente de las lesiones arteriales. En un caso la arteritis fue un hallazgo casual, en los demás constituyó una causa contribuyente mayor de la muerte. Un solo de los cuatro casos había recibido la ACTH o la cortisona.

En el quinto caso un breve episodio artrítico ocurrió en el curso de una enfermedad diagnosticada clínicamente y histológicamente como poliarteritis nodosa; en la autopsia encontraríase en las articulaciones alteraciones reumáticas típicas, la arteritis articular siendo ausente. Se sugiere que, aunque la poliarteritis nodosa sea una complicación rara de la artritis reumatoide, la asociación de estas dos lesiones es más que coincidente. Los datos disponibles sugieren que la distribución, la frecuencia y la morfología de las lesiones arteriales en la artritis reumatoide son variables, yendo desde la arteritis benigna indeterminada hasta la poliarteritis nodosa clásica.