Papers and Originals

Rheumatoid Arthritis: Extra-articular Manifestations*

F. DUDLEY HART,† M.D., F.R.C.P.

British Medical Journal, 1969, **3**, 131–136

It is with great pleasure and with a deep sense of the honour done to me that I give this lecture in celebration and memory of the late Dr. Philip Ellman. He was my friend and colleague, and we shared beds in the wards of St. Stephen's Hospital, Chelsea, where he helped to teach our Westminster medical students the rudiments of the art, science, and practice of rheumatology. He was a delightful and inspiring colleague. He specialized in chest disease as well as in the rheumatic disorders, and it was therefore natural that he should describe rheumatoid lung disease with R. E. Ball in 1948. He always preferred the title "rheumatoid disease" to "rheumatoid arthritis," insisting that many tissues of the body were affected, not only the bones and joints. His publications emphasize his wide interest in rheumatology inside medicine, as it were. With Parkes Weber he wrote on arthromyodysplasia congenita (Ellman and Parkes Weber, 1953) simulating the articular manifestations of rheumatoid disease, and on Morquio–Brailsford's disease masquerading as rheumatoid arthritis (Ellman, 1949). In an article entitled "The 'Chronic Rheumatic' and his Pains"—Ellman and Shaw (1950)—he drew attention to the importance of psychiatric factors in the causation of symptoms. It was a tragedy when he died prematurely in 1960 at the early age of 55. In his memory I therefore deliver this lecture on his own particular subject, the systemic manifestations of rheumatoid disease.

There has been considerable interest in, and several publications on, this subject latterly. Progress has been remarkably rapid, as witness the fact that an excellent book devoted to it (Hollingsworth, 1968), published last year, had several major omissions even by the time it was published. Because of the stimulation given by the early work of Ellman and others like him, more is today known of the natural and unnatural, or iatrogenic, variations of rheumatoid disease.

The Heart in Rheumatoid Arthritis

Is there such a thing as rheumatoid heart disease? The answer in broad terms is clinically yes but it is rare, histologically yes and not so rare. At necropsy granulomatous lesions may be seen in the myocardium, valve rings, and root of the aorta; and non-specific aggregates of lymphocytes also. The granulomatous lesions resemble the subcutaneous nodule, but more often have a collagenous rather than a necrotic and fibrinoid core. Marginal palisading of histiocytes and fibroblasts is common, and the edges of the nodule may be serpiginous in outline (Gardner, 1965). Lebowitz (1963), in a study of 62 subjects, found distinct granulomata in the heart of only two, whereas 19% of these rheumatoid subjects showed inflammatory lesions consisting of focal infiltration of the myocardium with plasma cells, lymphocytes, and histiocytes. In only 2 out of 12 patients with this type of lesion was myocardial necrosis seen. A focal myocarditis of this type is found, however, not infrequently in necropsies of patients with advanced rheumatoid arthritis, and has been described by Bayles (1943), Sokoloff (1953), Bevans *et al.* (1954), Levin *et al.* (1955), and Cruickshank (1958). The last author, in a necropsy study of 100 cases, noted valvular lesions in 13, pericarditis in 16, and arteritis of the cardiac vessels in 20. Bywaters (1950), in a clinicopathological study, distinguished rheumatoid heart lesions from rheumatic heart disease associated with chronic post-rheumatic arthritis of the type described by Jaccoud (1869). Amyloid heart disease in rheumatoid arthritis is rare; it accounted for only two of Lebowitz's 62 patients.

Going from the pathology department to the ward, we find that clinical evidence of rheumatoid heart disease is much less in evidence than pathological. These patients may be so restricted by their arthritis that symptoms caused by exertion do not arise: when they do they are in my experience much more likely to be due to ischaemic or hypertensive changes unrelated to their arthritis than to any specific rheumatoid changes. Nevertheless, cases do rarely occur where conduction defects, arrhythmias, and actual failure may be apparently due to rheumatoid cardiac changes. Sinclair and Cruickshank (1956), for instance, found clinical signs of heart disease in 12 out of 16 patients with advanced rheumatoid disease, and Cathcart and Spodick (1962) found an increased incidence of myocardial disease in cases of advanced rheumatoid arthritis as compared with a group of normal subjects. Aortic reflux, a recognized complication of ankylosing spondylitis and Reiter's disease, may also very rarely occur in rheumatoid disease (Weintraub and Zvaifler, 1962).

A patient with a severe debilitating disorder such as rheumatoid disease dies, as it were, by inches. She is usually on several drugs, and often on corticosteroids. Cardiac deaths are common in such a group of extremely ill patients. Very good pathological evidence must therefore be found at necropsy before the diagnosis of rheumatoid heart disease is justified. Epidemiological studies of large numbers of living patients with rheumatoid arthritis by Short *et al.* (1957, p. 283), Egelius *et al.* (1955), and in our unit (Gibberd, 1965) have usually failed to show an increased prevalence of clinically detectable cardiac disease.

Pericarditis is a frequent finding at necropsy in rheumatoid patients, though it is less apparent clinically in life. It may occur early, late, or at any stage in the course of the disease. Although uncommon in any except advanced cases, it may very occasionally cause trouble; Kennedy *et al.* (1966), for instance, reported three cases in which pericardectomy was required for chronic effusions with heart failure. Constrictive pericarditis, occasionally needing operation, has been reported not infrequently (Lange *et al.*, 1965). It remains, however, a rarity, more common in the literature than in the ward. Indeed, it almost amounts to a new Parkinson's Law: "The incidence of rare syndromes and unusual findings in common disorders

* The Philip Ellman lecture delivered at the Royal College of Physicians of London on 1 May 1969.

† Physician and Medical Officer in charge of the Rheumatism Clinic, Westminster Hospital, London S.W.1.

is usually in inverse relation to their frequency in the world's literature." Rheumatoid nodular involvement of the pericardium is usually unaccompanied by symptoms or signs.

Vasculitis

Changes in the vascular tree are a regular and essential part of severe rheumatoid disease and are common in strongly seropositive cases with many rheumatoid nodules. Ellman and Ball (1948), in their paper on pulmonary manifestations of rheumatoid disease, gave one of the first detailed descriptions of the vascular changes seen in the disorder. In the Empire Rheumatism Council's (1950) inquiry into possible aetiological factors associated with rheumatoid arthritis more of the patients noted sweaty hands and feet, and cold, blue, white, or dead fingers, than did the controls. In 55% of rheumatoid patients, but in only 12% of controls, was some abnormality of peripheral circulation found on examination, and 75% of patients compared with 52% of controls stated that at least one of the specified vascular disorders had been present before the onset of arthritis. This should not be interpreted as a vascular predisposition to rheumatoid disease, but rather as an early pre-arthritic vascular manifestation of the disease in these cases.

Bennett *et al.*, as long ago as 1940, drew attention to vascular injury and thrombosis in the subcutaneous nodes of rheumatoid arthritis, and suggested that connective-tissue necrosis might be initiated by ischaemia. Schmid *et al.* (1961) reported 17 cases with this syndrome, and found reports in the literature of 81 other cases. Christie (1950) emphasized the importance of chronic arteritis in rheumatoid arthritis. Kulka (1966), in an excellent review of vascular derangement in rheumatoid arthritis, stated that the evidence supported the view that a basic capillary vascular derangement characterized by excessive dilatation and leakage might well be the basis of the proliferative reaction in the involved connective tissues, vascular obliteration leading finally to necrosis. Such changes are known to occur in patients untreated by corticosteroids, but Kemper *et al.* (1957) found that the more severe lesions, those of necrotizing arteritis, occurred essentially in the corticosteroid-treated patients. Our own experience is that the severe arteritic lesions are almost entirely confined to corticosteroid-treated patients who have received more than 7 mg. of prednisone or its equivalent daily for periods of many months or years.

Like the increase in clinical porphyria, which reflected the prescribing habits of the population of South Africa at this time (Dean, 1963), the increase in vascular complications of rheumatoid disease in the past 20 years runs parallel with corticosteroid overdosage. Such arteritic lesions have played a large part in earning the ugly reputation of cortisone and its analogues as being dangerous drugs. They certainly are if used in excessive dosage, and this is true of any drug in the *Pharmacopoeia*. Cortisone has a wide range of dosage, depending on the condition to be treated ; what is right for rheumatoid arthritis is lethal for systemic lupus erythematosus. Used excessively in too high dosage, in any condition, corticosteroids are dangerous drugs. Used correctly in more conservative dosage they are often helpful and occasionally life-saving.

My own idea of what goes on in rheumatoid arthritis is that all severe nodular cases have a diffuse vasculitis. With a dose of corticosteroid high enough to suppress normal adrenal function—that is, above 25 mg. of cortisone equivalents daily according to Shuster and Williams (1961)—the natural rise and fall in hormone output in relation to stress and other factors is eliminated. If a vasculitis controlled by a certain dosage of corticosteroids escapes from this control it flares up when dosage is reduced or when insufficiently raised to deal with an exacerbation of disease or a stress situation. This vasculitis affects not only medium-sized and small arteries but also arterioles, veins, venules, and capillaries (Kulka, 1964, 1966). A vasculitis presents not only as small visible lesions in the skin but in a variety of visceral aches and pains scattered through all systems of the body. Gangrene of the fingers or toes may occur ; indeed, after seeing the brachial arteriographs of Scott *et al.* (1961) and of Laws *et al.* (1963) and Laws (1965) one wonders why gangrenous fingers are not the rule rather than the exception in rheumatoid arthritis. Happily, as Bywaters (1957) and Bywaters and Scott (1963) have shown, this digital vasculitis is relatively benign, and most patients run their anticipated clinical course free from major ischaemic features.

The complex picture of complicated rheumatoid disease is essentially that of the underlying vasculitis. Happily the kidney appears to be rarely involved in rheumatoid polyarteritis, the picture being unlike that seen in polyarteritis nodosa or systemic lupus erythematosus, Ferguson and Slocumb (1961), for example, seeing no instance of severe renal involvement in their 64 patients, though 14 had gangrene of skin or digit. Deaths from vasculitis are mostly from haemorrhage into any organ, perforation of stomach or gut, general exhaustion, terminal infection, or coronary occlusion.

Neuropathy

Neuropathic changes may occur in rheumatoid arthritis as part of the disease process. They may also be due to compression of a nerve, as of the median at the wrist, ulnar below the elbow (Osborne's (1957, 1959) syndrome), or branches of the peroneal nerve at the knee. Neuropathic changes may also be due to amyloidosis or to drugs (thalidomide was one in its day). It may also be due to concurrent disease such as pernicious anaemia, diabetes, porphyria, or alcoholism. We described rheumatoid neuropathy 12 years ago (Hart *et al.*, 1957), and Golding and I later reported details of 42 cases (Hart and Golding, 1960) from Westminster Hospital at the same time as Steinberg (1960) published very similar findings from the London Hospital. Later Pallis and Scott (1965) reported similar findings, but, in addition, patchy areas of sensory loss over the fingers, possibly due to digital arteritis ; and in the same year Bennett and Scott (1965) described autonomic neuropathy, as manifested by decreased sweating in association with minor sensory changes.

In our first description of these cases we found the peripheral neuropathy to be essentially symmetrical, the lower limb being more affected than the upper, sensory changes more than motor, fibular (outer) and ulnar areas rather than tibial (inner) and radial. We found no close relation to severe involvement of adjacent joint or concurrent administration of drugs, nor did Good *et al.* (1965) in a later study. We found no relation to duration of disease, but in both our and Steinberg's series several cases followed reduction or manipulation of steroid dosage. While a few cases in these two series had never received corticosteroids, the vast majority were on this form of therapy, and it has seemed to us that, like vasculitis, the incidence of neuropathy has rapidly diminished parallel with reduction in corticosteroid therapy, far fewer patients being started on this form of therapy latterly, and these few in more conservative dosage. We feel that, like vasculitis, and probably usually stemming from it, this complication was in great part the result of indiscriminate corticosteroid overdosage. We regard this complication, as did Steinberg, to be of serious prognostic importance in most cases.

Dr. Golding has recently given me his latest figures. He had now seen 64 cases, 28 male and 36 female. (This relatively large percentage of male patients in almost all published series with this and other extra-articular manifestations of rheumatoid arthritis is of great interest.) Of Golding's patients 28 were dead, 26 alive, and 10 untraced. Ten had never received steroids, 36 were on constant dosage, 11 had had changes in dosage, and 7 had had changes of type of steroid ; 12 of those on constant dosage had suffered stress immediately before development of the neuropathy. Of the 28 patients who have

died, the average survival time from date of diagnosis to death was in 12 males two weeks to three years, averaging about one year, and in 12 females two weeks to seven years, averaging roundly two years. In four patients details were inadequate for analysis.

In our own series of 42 cases there were 10 deaths ; necropsy examinations were carried out in all of them ; all had been on corticosteroid therapy. Three died of myocardial infarction, but, though nodules were present on the epicardium, in no case did they cause occlusion, the infarction being apparently unrelated. One died of haematemesis and melaena and terminal pneumonia, and in four others pneumonia or broncho-pneumonia played a major part in causing death. In five cases a widespread arteritis was found involving viscera and other tissues, in four a patchy arteritis involving only certain tissues, and in one no arteritis was found. Of the four cases with patchy arteritis one involved many nerves diffusely, one involved one nerve only, one fingers only, and one muscles and dermis. In such a disorder, however, the more complete the histological examination the more is found, and it is likely that in general a greater number of lesions are present than are reported even after a careful necropsy. While it is likely that the majority of cases of neuropathy are based on underlying arteritis, I am not satisfied on the evidence that this is the one and only cause.

Rheumatoid Lymphadenopathy

Chauffard and Ramond (1896) are credited with the first description of lymphadenopathy occurring in patients with rheumatoid arthritis, and it has been commented on by many authors since. Lymphadenopathy is a well-recognized feature of Still's disease and Felty's syndrome, but little had been done to find how regular a feature of adult rheumatoid disease it was as compared with similar normal subjects of the same age groups. Short *et al.* (1957, p. 311), in their classic study of rheumatoid arthritis, made such a comparison in Boston, Massachusetts, and found that 29·4% of rheumatoid patients, as compared with 8·9% of their control subjects, had significant lymph-node enlargement, the condition being more common in males than in females.

At Westminster (Robertson *et al.*, 1968) we compared 100 patients with active rheumatoid arthritis with 100 non-rheumatoid subjects of the same age and sex groups attending outpatient clinics at the same time. We found that lymph-node enlargement was significantly more common and more marked in the rheumatoid patients than in the control subjects in axillary, epitrochlear, and inguinal regions, but not above the clavicles. Generalized lymph-node enlargement was relatively rare, in most cases the localization being essentially in anatomical relation to actively inflamed joints. Lymph-node enlargement was significantly greater and more common in males than in females in both rheumatoid and control groups. Node enlargement was greater with Waaler–Rose-positive than -negative cases, and with active rather than inactive disease. Occasionally node enlargement may be so pronounced that a reticulosis is suspected, as in two of our cases and in several of an excellent study by Motulosky *et al.* (1952). Histologically the features are of a severe follicular hyperplasia. Secondary germinal centres appear and may reach a large size, the centres becoming almost confluent, suggesting giant follicular lymphoma. In our lymphographic studies we found a non-specific inflammatory picture not pathognomonic of rheumatoid disease. Lymph vessels in calves, thighs, and arms appeared normal in our series, contrary to the findings of Kriegel *et al.* (1961).

Chronic Oedema of One Hand and Forearm

A rare but interesting finding in patients with rheumatoid arthritis is chronic oedema of one hand and arm, or forearm. We have observed this in two cases in the past three years, and in one case in both hands and forearms. Kalliomäki and Vastamäki (1968), in Turku, Finland, have studied this condition in two female patients. It is a diffuse chronic oedema, apparently unrelated directly to the arthritic condition present, and unresponsive to treatment which relieves the other symptoms. They studied the condition with lymphoscintigraphy, giving subcutaneous injections of colloidal gold isotope ^{198}Au. This enters the lymph ducts and is absorbed by the regional lymph nodes, only little passing into the blood (Sage *et al.*, 1964). In the normal subjects active accumulation is always seen in the axillary lymph nodes, and Virkkunen *et al.* (1967) found the same concentration in regional lymph nodes after intra-articular injections of radio-gold suspensions. No such localization occurred in the two cases of chronic oedema ; there was very little drainage of lymphatics from the swollen hand, unlike the normal hand in the same two subjects, which gave the normal lymphographic picture. This would suggest a local peripheral lymphatic blockage in these cases. In our bilateral case the condition has gradually improved over the past four years since it first appeared early in the course of the active disease, and is now hardly apparent. Unfortunately no lymphographic studies were made in this case.

Pulmonary Lesions

In 1948 Ellman and Ball published their paper on lung changes in three patients with rheumatoid disease. These patients had fibrosing pneumonia with fibrinoid vascular necrosis of the small pulmonary vessels. *X*-ray films showed progressive bilateral reticular change. Ellman *et al.* (1954) later reported granulomatous pleural lesions, and Emerson (1956) recorded pleural effusions associated with and attributed to rheumatoid arthritis. Since then a spate of publications has occurred, and the literature is heavy with what in some instances are probably coincidental associations of common disorders. Short *et al.* (1957, p. 281), in their extensive 20-year clinical study of patients with rheumatoid arthritis, found relatively little lung disease, though Bauer and Clark (1948) had previously commented on rheumatoid lung disease. Surveys by Aronoff *et al.* (1955) (253 patients) and, in our own unit, by Gibberd (1965) (406 patients) failed to show any significant connexion between lung disease and rheumatoid arthritis, and Talbott and Calkins (1964) found no difference in necropsy studies of 37 patients with rheumatoid arthritis compared with 37 control cadavers matched for age and sex as regards pulmonary changes, though they found a higher incidence of pleural involvement.

Two recent papers, however, do report an increased incidence of pleuro-pulmonary involvement in rheumatoid sufferers. Walker and Wright (1967) compared 516 patients with definite or classical rheumatoid disease with 301 patients with degenerative joint disease. Their findings were as follows:

	Rheumatoids			Osteoarthrosis		
	Male	Female	Total	Male	Female	Total
Episodes of pleurisy ..	28%	18%	21%	6%	13%	12%
Pleural effusions ..	7·9%	1·6%	3·3%	2 patients only		

This shows not only that there is an increased incidence of pleurisy in the rheumatoids as compared with the controls, but that there is a male preponderance. There was nothing to suggest any other aetiology, and smoking habits did not explain the differences. Pleural biopsies were helpful in 42% of cases. Sievers *et al.* (1964), in Finland, found radiological evidence of abnormality in 23% of 126 seropositive rheumatoids as compared with 7·9% of 114 seronegative arthritics and 7·4% of a third control group of patients.

Patterns of Lung Lesions

Lung lesions occur in the following patterns (Petty and Wilkins, 1966): (1) chronic fibrosing pneumonitis, as described by Ellman and Ball (1948); (2) diffuse interstitial fibrosis (Stack and Grant, 1965); (3) nodular lung disease; (4) rheumatoid pneumoconiosis (Caplan's (1953) syndrome); and (5) miscellaneous pulmonary syndromes.

Without positive histological evidence many of the cases reported as being rheumatoid must remain not proved. Groups 3 and 4 contain many histologically proved cases, the others many possibles and some probables. We have had two patients with large apical pleural rheumatoid nodules, one causing erosion of the adjacent ribs which was removed surgically as a possible carcinoma of the bronchus. Such lesions occur, but are rare. Pulmonary rheumatoid nodules may occasionally cavitate, become infected, or rupture with development of pneumothorax or pyopneumothorax, but they are more likely to be associated with a simple effusion. Diffuse interstitial fibrosis may be associated with rheumatoid factor in the serum more often than with rheumatoid arthritis (Turner-Warwick and Doniach, 1965). The picture is usually a non-specific one of fibrosis with or without some degree of lymphocytic and plasma-cell infiltration (Hollingsworth, 1968). Caplan's syndrome may occur in association with other pneumoconioses than coal miners—for example, in workers with asbestos and gold, in iron-founding, in tile-making, and in chalk-mining and boiler-scaling. Similar lesions occur rarely without pneumoconiosis or exposure to irritating dusts. The miscellaneous group includes pulmonary amyloidosis (Cohen, 1967) and idiopathic pulmonary haemosiderosis (Karlish, 1962; Ognibene and Dito, 1965; Smith, 1966). Because of the presence of rheumatoid factor and other abnormalities in the serum of patients with pulmonary disease, it has been suggested that precipitation of these complexes in pulmonary vessels may play a part in causing fibrosis and other lung lesions.

Last year, in the Philip Ellman lecture at the Royal Society of Medicine, Scadding (1969) reviewed the whole question of lung involvement in rheumatoid arthritis. He classified such lesions as (1) nodules having a histological structure similar to that of rheumatoid arthritis; (2) pleural effusions sometimes associated with pleural nodules or plaques; and (3) widespread diffuse chronic inflammatory peripheral changes leading to fibrosis—that is, a fibrosing alveolitis. In the first two groups he considers a causal relationship likely, in the last not proved. It is an excellent and critical review, well worthy of close study.

One other paper should be mentioned here, that of Wagner and McCormick (1967). With both rabbit and human gamma-globulins the highest titres of rheumatoid factor occurred in cases of Caplan's syndrome, though 26% were negative at all titres with human reactant and 43% with rabbit reactant. In most of the remainder the tests were positive at titres of 1/640 or above in both systems. Specific staining for rheumatoid factor in the tissues was positive in 8 out of 10 cases of histologically proved Caplan's syndrome and in 10 out of 15 cases of progressive massive fibrosis with vasculitis, but in only 3 out of 16 cases of non-specific progressive massive fibrosis, in 7 out of 35 cases of simple pneumoconiosis, and in none out of six cases of silicosis and six cases of tuberculosis.

The Kidney in Rheumatoid Arthritis

It is probably true in general to say that there is no such thing as primary rheumatoid renal disease. Although this organ may be affected by amyloid disease, by an arteritis, and by drugs such as compound phenacetin tablets and gold salts, the primary uncomplicated disorder does not seem to cause renal manifestations. Amyloidosis has been shown to occur in 3 to 60% of post-mortem studies (Missen and Taylor, 1956), but clinical studies have shown a rather low incidence. Fearnley and Lackner (1955) found that 24 out of 183 patients with rheumatoid arthritis had proteinuria, and in seven of these amyloidosis was demonstrated histologically. Proteinuria may not always occur in amyloidosis, however, and in the two series reported by Teilum and Lindahl (1954) and Arapakis and Tribe (1963) about half the patients with amyloidosis had no proteinuria. The latter authors, using rectal biopsy as a screening and diagnostic test, found amyloid in 6 out of 115 patients with rheumatoid arthritis of more than three years' duration, only three of whom had proteinuria at the time of biopsy. Tribe (1966) gave the incidence of amyloidosis in rheumatoid arthritis as probably between 5 and 10%, Kenney and Calkins (1965) as 20%.

From the pathological viewpoint Gardner (1969) stated that secondary amyloidosis is found in 13 to 17% of patients dying with rheumatoid arthritis; in a study of 142 patients with rheumatoid arthritis dying in hospital he found 17 (12%) had amyloidosis and 11 (8%) renal papillary necrosis. Amyloidosis is not a big problem, therefore, in rheumatoid arthritis, but it is by no means uncommon, and renal amyloidosis is a recognized cause of death in these unfortunate patients, though according to Hollingsworth (1968) in no more than 2 to 3% of adult patients. It should be emphasized that primary amyloidosis can occur in joint tissue and occasionally masquerades as rheumatoid arthritis (Kenney and Calkins, 1965).

Drug Toxicity

As regards drug toxicity I will not enter the lists for or against phenacetin as a renal poison except to say that in 1953 we dropped it from our Westminster Hospital tab. codeine co. This was, I regret to say, largely because it saved us £100 a year, though I disliked the drug because of its causing, at least, enterogenous cyanosis. Since then the patients have gone on taking it equally happily without the phenacetin, and Reckitts have now produced their modified phenacetin-free soluble tab. codeine co. on the same lines (and I do not anticipate their sales will decline as a result). It has been pointed out that it is the compound analgesic tablet that has been proved guilty of renal toxicity rather than phenacetin, but as the latter drug is never prescribed alone the case against it on clinical grounds is in English law, as it were, not guilty, and in Scottish non-proven. There seems, in any event, no particular reason to retain it as an analgesic.

Two recent papers should be mentioned here. Saker and Kincaid-Smith (1969) in Melbourne found that a proprietary aspirin, phenacetin, and caffeine preparation given to Wistar rats, in a dose equivalent to that taken by patients with analgesic nephropathy, over a period of more than six months produced papillary necroses in 55% of cases; no such lesions were seen in rats receiving twice as much phenacetin, nor in the untreated control group over the same period. Also from Melbourne, Green *et al.* (1969) injected a single intravenous dose of 20–60 mg. of *p*-aminophenol hydrochloride, a compound closely related to phenacetin. This produced necrosis of the terminal third of the proximal convoluted tubule. As the tubules regenerated a chronic inflammatory reaction set in in the interstitial tissues and extended beyond the original zone of injury this they considered to be toxic in nature rather than ischaemic. Although it is a long jump from rat to rheumatoid, these findings are of great interest.

Nephrotoxic changes occur as a result of administration of gold salts, but delayed chronic irreversible changes are today unknown from this drug. Lawson and Maclean (1966) reviewed the clinical and necropsy records of 61 patients with rheumatoid arthritis: 72% had significant renal disease and 21% renal papillary necrosis. Of these patients 34% died in renal failure, and the authors conclude that drugs, particularly phenacetin, contributed to this renal disease. Sørensen (1961,

1966), however, thought that analgesic drugs do not play a significant part, and while he agreed that on histological grounds there is no such thing as rheumatoid renal disease, he felt that the arthritic disorder itself might lead to a form of interstitial nephritis, often with papillary necrosis. Most of us find the evidence for this inadequate, and the case against phenacetin is considerable, even if not completely proved.

To conclude, we agree with Gardner (1965) that in spite of inactivity, crippling, anaemia, poor nutrition, and often the presence of various complications, the chronic rheumatoid sufferer shows less active renal infection at necropsy than one would expect. Even with widespread arterial disease as part of a rheumatoid vasculitis, death in uraemia is uncommon.

Gastrointestinal Disorders

While these are common in patients with rheumatoid arthritis, there is no doubt that therapy causes or aggravates the gastrointestinal tract in many cases. Is the rheumatoid population more dyspeptic and more ulcer-prone than the rest of the community? In the Eighteenth Rheumatism Review (1968) peptic ulcers were found to be twice as common in rheumatoid sufferers as in the general population, but the Editors (p. 644) think that this is probably related to therapy, particularly salicylates. Gibberd (1966), in our unit, found the incidence of dyspepsia in over 500 rheumatoids to increase from 3·4% before the advent of arthritis to 15·9% after onset of the disorder. As there is no such thing as an untreated rheumatoid, and as almost all so-called antirheumatic drugs can cause dyspepsia or ulceration, this question must remain open. Most clinicians have the impression that peptic ulceration is more common in steroid-treated rheumatoids than in similarly treated asthmatics, but once again other drugs taken concomitantly probably play a part, salicylates in particular. There seems to be no evidence that hepatic or biliary complications are part of the rheumatoid syndrome.

The Eye

In the past the inclusion of cases of ankylosing spondylitis in American papers on rheumatoid arthritis led to much confusion, not least in relation to anterior uveitis, now known to be common in ankylosing spondylitis and Reiter's disease and uncommon in rheumatoid arthritis. This was brought out by Short *et al.* (1957) when they divided up their 293 cases into those with and those without spondylitis: 19% of the former had iritis, but only 1·6% of the latter. Much of the literature on the ocular complications of rheumatoid arthritis is bedevilled by untidy diagnosis, the cases of "arthritis" being often of different types, only some being true rheumatoid. Thompson and Eadie (1956) found keratoconjunctivitis sicca in 14·3% of a series of 210 patients. They considered it the commonest ocular complication of rheumatoid arthritis, largely confined to female patients; Stenstam (1947) had previously reported its incidence in rheumatoid arthritis as 11%. Only 3·5% of Thompson and Eadie's 210 cases showed evidence of active or old uveitis. Ellman *et al.* (1951) had previously noted it to be uncommon, and reported the case history and necropsy findings in a patient in whom eye symptoms preceded arthritis by several years.

Four Groups

Duke-Elder (1965), under the title "Necrotizing Inflammation," described four types of scleral inflammation associated with the collagen disorders and rheumatoid arthritis in particular, the essential pathological change being an alteration in the connective tissue, particularly its mucopolysaccharide ground substance, with an infiltration of chronic inflammatory cells and the development of fibrinoid necrosis, as is seen in the rheumatoid nodule. These four groups are: (1) nodular episcleritis, (2) necrotizing nodular scleritis (necroscleritis nodosa), (3) scleromalacia perforans, and (4) massive granuloma of the sclera.

In the first group, nodular episcleritis, small areas only a few millimetres in diameter appear as raised patches of inflammation surrounded by intense hyperaemia. It is associated with discomfort and resolves gradually without ulceration over a period of several weeks or months, leaving a faintly pigmented area where the conjunctiva remains adherent to the sclera.

The second group, necrotizing nodular scleritis, starts acutely and painfully, unilaterally or bilaterally, usually progressing to areas of widespread necrosis, attacks of acute scleritis recurring with marked local hyperaemia followed by the appearance of raised nodules with yellow centres on the scleral surface which are extremely tender. The yellow centre may necrose and slough or break down to exude pus. Resolution then tends to occur without perforation of the eye, but with disappearance of large areas of the sclera, the underlying uvea shining through with an astronautical blue-black colour, the whole process taking several months.

Scleromalacia perforans, the third group, Duke-Elder described as being of insidious onset and slow progression, with few or no symptoms in its early stages. The yellow necrotic nodule, after some six months or more, sloughs, leaving a scleral defect varying from a shallow depression to a deep ulcer right down to the uvea. There may be several such areas, which may fuse together. The prognosis is bad, most cases progressing to loss of the eye from rupture of the globe, though some cause iritis, vitreous opacities, cataracts, glaucoma, or panophthalmitis.

In the fourth group, massive granuloma of the sclera, proliferation is more in evidence than necrosis. Although starting as a nodule with a central area of fibrinoid necrosis, so much surrounding granulomatous infiltration with chronic inflammatory change occurs that the sclera becomes greatly thickened, often forming a tumour-like mass.

These scleral manifestations of rheumatoid disease are rare, Sevel (1965) giving the incidence of rheumatoid nodule of the sclera, the term proposed by Ashton and Hobbs (1952), as 1 in 3,000 cases of rheumatoid arthritis. Though rare, the complications are real—keratitis, cyclitis, episcleritis, choroiditis, choroidoretinitis, retinal detachment, cataract, secondary glaucoma, and perforation. Loss of vision may rarely be more disastrous for the patient than loss of mobility.

Skin and Subcutaneous Structures

The wasted tight skin over the rheumatoid shin, splitting readily with minimal trauma, is well known to any experienced physician. It is fatal to attempt to suture such areas, as the sutures pull out of the tissues as through wet blotting-paper. Leg ulcers may occur (1) from trauma, particularly in cortico-steroid-treated patients; (2) from simple stasis and poor venous return, aggravated by reduced mobility caused by the disease; (3) associated with Felty's syndrome; (4) as part of a generalized vasculitis; and (5) as idiopathic "rheumatoid" ulcers, described by Allison and Bettley (1957) and Wilkinson and Kirk (1965).

It is doubtful if this last group should be given a separate heading; many will probably fall into one of the other four categories. As Professor Bywaters asked at a meeting of the Heberden Society, Is there such a thing as a rheumatoid pile? What makes a haemorrhoid in a rheumatoid sufferer a rheumatoid one in the absence of characteristic histology? In these skin ulcers there is no characteristic histological change. Such patients are often wasted, usually anaemic, sometimes malnourished, usually have atrophic changes of the skin and subcutaneous tissues, particularly if they have been on cortico-

steroid therapy for years, and are usually unable to use their legs and leg muscles normally. In addition some cases have vascular and/or neuropathic changes. Their healing powers and resistance to infection are often diminished. It is small wonder that leg ulcers occur in the more-crippled subjects.

Another troublesome lesion is the ulcerated rheumatoid nodule, situated inevitably over a pressure point, usually elbow or buttock. Nodules may vary in size from a small pea to a Jaffa orange, and the bedsores which occur when they break down constitute a major challenge to medical and nursing staff. Healing is literally painfully slow; in ill bedfast patients they may never heal, and can contribute to a fatal outcome.

Conclusions

One can only touch on some aspects of this large subject. A disease affecting some 3% or more of the population at some time in their lives, lasting usually many years, and often the rest of the patients' lives, merits considerable study. Nevertheless, only relatively recently has a proper study been made of the natural history of this disorder and the wide variety of its manifestations, articular and non-articular; very much more study of the natural history of the disease is required.

We are grateful to people like Philip Ellman, not only for their pioneer work on the subject but also for their attitude in regarding the disease as one of the whole patient rather than the locomotor system alone.

References

Allison, J. H., and Bettley, F. R. (1957). *Lancet*, **1**, 288.
Arapakis, G., and Tribe, C. R. (1963). *Annals of the Rheumatic Diseases*, **22**, 256.
Aronoff, A., Bywaters, E. G. L., and Fearnley, G. R. (1955). *British Medical Journal*, **2**, 228.
Ashton, N., and Hobbs, H. E. (1952). *British Journal of Ophthalmology*, **36**, 373.
Bauer, W., and Clark, W. S. (1948). *Transactions of the Association of American Physicians*, **61**, 339.
Bayles, T. B. (1943). *American Journal of Medical Science*, **205**, 42.
Bennett, G. A., Zeller, J. W., and Bauer, W. (1940). *Archives of Pathology*, **30**, 70.
Bennett, P. H., and Scott, J. T. (1965). *Annals of the Rheumatic Diseases*, **24**, 161.
Bevans, M., Nadell, J., Demartini, F., and Ragan, C. (1954). *American Journal of Medicine*, **16**, 197.
Bywaters, E. G. L. (1950). *British Heart Journal*, **12**, 101.
Bywaters, E. G. L. (1957). *Annals of the Rheumatic Diseases*, **16**, 84.
Bywaters, E. G. L., and Scott, J. T. (1963). *Journal of Chronic Diseases*, **16**, 905.
Caplan, A. (1953). *Thorax*, **8**, 29.
Cathcart, E. S., and Spodick, D. H. (1962). *New England Journal of Medicine*, **266**, 959.
Chauffard, A., and Ramond, F. (1896). *Revue de Médecine*, **16**, 345.
Christie, G. S. (1950). In *Studies in Pathology presented to Peter MacCallum*, edited by E. S. J. King, T. E. Lowe, and L. B. Cox. Jubilee, Victoria, Melbourne University Press.
Cohen, A. S. (1967). *New England Journal of Medicine*, **277**, 522.
Cruickshank, B. (1958). *Journal of Pathology and Bacteriology*, **76**, 223.
Dean, J. G. K. (1963). *The Porphyrias*. London, Pitman Medical.
Duke-Elder, S. (1965). *System of Ophthalmology*, vol. 8, part 2, p. 1036. London, Kimpton.
Egelius, N., Göhle, O., Jonsson, E., and Wahlgren, F. (1955). *Annals of the Rheumatic Diseases*, **14**, 11.
Eighteenth Rheumatism Review (1968). *Arthritis and Rheumatism*, **11**, 547.
Ellman, P. (1949). *Annals of the Rheumatic Diseases*, **8**, 267.
Ellman, P., and Ball, R. E. (1948). *British Medical Journal*, **2**, 816.
Ellman, P., Cudkowicz, L., and Elwood, J. S. (1954). *Journal of Clinical Pathology*, **7**, 239.
Ellman, P., and Shaw, D. (1950). *Annals of the Rheumatic Diseases*, **9**, 341.
Ellman, P., and Weber, F. P. (1953). *Annals of the Rheumatic Diseases*, **12**, 261.
Ellman, P., Weber, F. P., and Goodier, T. E. W. (1951). *Quarterly Journal of Medicine*, **20**, 33.
Emerson, P. A. (1956). *British Medical Journal*, **1**, 428.
Empire Rheumatism Council (1950). *Annals of the Rheumatic Diseases*, **9**, Suppl., 49.
Fearnley, G. R., and Lackner, R. (1955). *British Medical Journal*, **1**, 1129.
Ferguson, R. H., and Slocumb, C. H. (1961). *Bulletin on Rheumatic Diseases*, **11**, 251.
Gardner, D. L. (1965). *Pathology of the Connective Tissue Diseases*, p. 96. London, Edward Arnold.
Gardner, D. L. (1969). In *Textbook of the Rheumatic Diseases*, edited by W. S. C. Copeman, 4th ed., p. 122. Edinburgh, Livingstone.
Gibberd, F. B. (1965). *Acta Rheumatologica Scandinavica*, **11**, 62.
Gibberd, F. B. (1966). *Acta Rheumatologica Scandinavica*, **12**, 112.
Good, A. E., Christopher, R. P., Koepke, G. H., Bender, L. F., and Tarter, M. E. (1965). *Annals of International Medicine*, **63**, 87.
Green, C. R., Ham, K. N., and Tange, J. D. (1969). *British Medical Journal*, **1**, 162.
Hart, F. D., and Golding, J. R. (1960). *British Medical Journal*, **1**, 1594.
Hart, F. D., Golding, J. R., and Mackenzie, D. H. (1957). *Annals of the Rheumatic Diseases*, **16**, 471.
Hollingsworth, J. W. (1968). *Local and Systemic Complications of Rheumatoid Arthritis*, p. 71. Philadelphia, Saunders.
Jaccoud, F. S. (1869). *Leçons de Clinique Médicale faites à l'Hôpital de la Charité*, 2nd ed. Paris, Delahaye.
Kalliomäki, J. L., and Vastamäki, M. (1968). *Annals of the Rheumatic Diseases*, **27**, 167.
Karlish, A. J. (1962). *Proceedings of the Royal Society of Medicine*, **55**, 223.
Kemper, J. W., Baggenstoss, A. H., and Slocumb, C. H. (1957). *Annals of Internal Medicine*, **46**, 831.
Kennedy, W. P. U., Partridge, R. E. H., and Matthews, M. B. (1966). *British Heart Journal*, **28**, 602.
Kenney, J. D., and Calkins, E. (1965). In *Progress in Clinical Rheumatology*, edited by A. St. J. Dixon, p. 281. London, Churchill.
Kriegel, F., Málek, P., Belán, A., and Kolc, J. (1961). *Časopis Lékařů Českých*, **100**, 65.
Kulka, J. P. (1964). *Annals of the New York Academy of Sciences*, **116**, 1018.
Kulka, J. P. (1966). In *Modern Trends in Rheumatology*, edited by A. G. S. Hill, p. 49. London, Butterworth.
Lange, R. K., Weiss, T. E., and Ochsner, J. L. (1965). *Arthritis and Rheumatism*, **8**, 403.
Laws, J. W. (1965). In *Progress in Clinical Rheumatology*, edited by A. St. J. Dixon, p. 246. London, Churchill.
Laws, J. W., Lillie, J. G., and Scott, J. T. (1963). *British Journal of Radiology*, **36**, 477.
Lawson, A. A. H., and Maclean, N. (1966). *Annals of the Rheumatic Diseases*, **25**, 441.
Lebowitz, W. B. (1963). *Annals of Internal Medicine*, **58**, 102.
Levin, M. H., Kaplan, L., Marcus, S., Weinberger, H. J., and Patterson, J., jun. (1955). *Annals of the Rheumatic Diseases*, **14**, 430.
Missen, G. A. K., and Taylor, J. D. (1956). *Journal of Pathology and Bacteriology*, **71**, 179.
Motulosky, A. G., Weinberg, S., Saphir, O., and Rosenberg, E. (1952). *Archives of Internal Medicine*, **90**, 660.
Ognibene, A. J., and Dito, W. R. (1965). *Archives of Internal Medicine*, **116**, 567.
Osborne, G. V. (1957). *Journal of Bone and Joint Surgery*, **39B**, 782.
Osborne, G. V. (1959). *Postgraduate Medical Journal*, **35**, 392.
Pallis, C. A., and Scott, J. T. (1965). *British Medical Journal*, **1**, 1141.
Petty, T. L., and Wilkins, M. (1966). *Diseases of the Chest*, **49**, 75.
Robertson, M. D. J., Hart, F. D., White, W. F., Nuki, G., and Boardman, P. L. (1968). *Annals of the Rheumatic Diseases*, **27**, 253.
Sage, H. H., Sinha, B. K., Kizilay, D., and Toulon, R. (1964). *Journal of Nuclear Medicine*, **5**, 626.
Saker, B. M., and Kincaid-Smith, P. (1969). *British Medical Journal*, **1**, 161.
Scadding, J. G. (1969). *Proceedings of the Royal Society of Medicine*, **62**, 227.
Schmid, F. R., Cooper, N. S., Ziff, M., and McEwen, C. (1961). *American Journal of Medicine*, **30**, 56.
Scott, J. T., *et al.* (1961). *Annals of the Rheumatic Diseases*, **20**, 224.
Sevel, D. (1965). *Transactions of the Ophthalmological Society of the United Kingdom*, **85**, 357.
Short, C. L., Bauer, W., and Reynolds, W. E. (1957). *Rheumatoid Arthritis*. Cambridge, Massachusetts, Harvard University Press.
Shuster, S., and Williams, I. A. (1961). *Lancet*, **2**, 674.
Sievers, K., Aho, K., Hurri, L., and Perttala, Y. (1964). *Acta Tuberculosea Scandinavica*, **45**, 21.
Sinclair, R. J. G., and Cruickshank, B. (1956). *Quarterly Journal of Medicine*, **25**, 313.
Smith, B. S. (1966). *British Medical Journal*, **1**, 1403.
Sokoloff, L. (1953). *American Heart Journal*, **45**, 635.
Sørensen, A. W. S. (1961). *Acta Rheumatologica Scandinavica*, **7**, 304.
Sørensen, A. W. S. (1966). *The Kidney in Rheumatoid Arthritis*. Copenhagen, Munksgaard.
Stack, B. H. R., and Grant, I. W. B. (1965). *British Journal of Diseases of the Chest*, **59**, 202.
Steinberg, V. L. (1960). *British Medical Journal*, **1**, 1600.
Stenstam, T. (1947). *Acta Medica Scandinavica*, **127**, 130.
Talbott, J. A., and Calkins, E. (1964). *Journal of the American Medical Association*, **189**, 911.
Teilum, G., and Lindahl, A. (1954). *Acta Medica Scandinavica*, **149**, 449.
Thompson, M., and Eadie, S. (1956). *Annals of the Rheumatic Diseases*, **15**, 21.
Tribe, C. R. (1966). In *Modern Trends in Rheumatology*, edited by A. G. S. Hill, p. 121. London, Butterworths.
Turner-Warwick, M., and Doniach, D. (1965). *British Medical Journal*, **1**, 886.
Virkkunen, M., Krusius, F. E., and Heiskanen, T. (1967). *Acta Rheumatologica Scandinavica*, **13**, 81.
Wagner, J. C., and McCormick, J. N. (1967). *Journal of the Royal College of Physicians*, **2**, 49.
Walker, W. C., and Wright, V. (1967). *Annals of the Rheumatic Diseases*, **26**, 467.
Weintraub, A. M., and Zvaifler, N. J. (1962). *Arthritis and Rheumatism*, **5**, 327.
Wilkinson, M., and Kirk, J. (1965). *Scottish Medical Journal*, **10**, 175.