Papers and Originals

Rheumatoid Arthritis: Extra-articular Manifestations.* Part II

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It is a great honour to be asked to give the Stanley Davidson lecture in this famous medical school, where he was regius professor of medicine from 1930 to 1938 and did so much of the work that has made him rightly world-famous. His energy flowed into many fields of general medicine—nutrition, dietetics, and therapeutics, but into haematology and rheumatology perhaps most of all, subjects which his junior colleague Professor J. J. R. Duthie and his unit at Edinburgh continue to explore today. Sir Stanley's energy and enthusiasm were electric and infectious; it was his stimulus that initiated the Empire Rheumatism Council's multicentre gold trial in rheumatoid arthritis, and it was his ruthless editorial pen that led to my rewriting it several times to produce ever shorter and clearer typescripts. I only hope that what I have to say is half as stimulating as he would have been were he standing in this place now instead of me.

Last year in the Philip Ellman lecture at the Royal College of Physicians of London I spoke on extra-articular manifestations of rheumatoid disease (Hart, 1969, Part I). I will endeavour today not to go over again any of the ground covered in that lecture. In a sense what follows is complementary to it. In this common, variable, and extraordinary disease there is no shortage of new material.

Bursitis

The bursae of the body tend to be forgotten; they are the lost souls of rheumatology, but they make their presence unpleasantly obvious all too often. The bursae become inflamed somewhere in the body in almost all cases of rheumatoid arthritis, and contribute greatly to the average clinical picture of the disease: the extensor sheath swelling over the backs of the hands, the sausage fatness of the finger with flexor sheath involvement, the thickness at the wrist due to the involvement of the sheath of extensor carpi ulnaris, olecranon bursitis or "students' elbow," the swollen shoulder due to subacromial bursitis, and many more. These I have mentioned are so widely recognized that they have become diagnostic features of rheumatoid disease; not so familiar is rheumatoid subachilles bursitis (Bywaters, 1954), bursitis between metatarsal heads, iliopsoas bursitis, and many others. Bywaters (1965) pointed out that there are more than 78 bursae on each side of the body, well known to anatomists of the eighteenth century (Monro, 1785, 1799) but since forgotten by most clinicians. One hundred and fifty-six potential areas of inflammation and pain in the body should not lightly be disregarded.

Just as joints and tendons become involved by the inflammatory rheumatoid process, so do bursae and tendon sheaths, and much of the swelling in active rheumatoid arthritis is often periarticular in bursae and tendon sheaths rather than in

the joint itself. In the region of the knee, for instance, anatomy books list the semimembranosus bursa which lies between the semimembranosus and the medial head of the gastrocnemius. This bursa often communicates round the medial border of the gastrocnemius with a bursa which lies between the medial head of the gastrocnemius and the back of the knee joint, and this, in turn, communicates with the cavity of the knee joint. In the patellar region the anatomy books list the subcutaneous prepatellar bursa, the subfascial prepatellar bursa, the subtendinous prepatellar bursa, the suprapatellar bursa, usually communicating with the knee joint, and the subcutaneous and the deep infrapatellar bursa. These bursae are variable and not always present, and in rheumatoid disease may proliferate and enlarge and may in certain cases need local treatment, by intrabursal injections in addition to those given into the knee joint.

Bursae are in a sense miniature joints—small sacs between skin and bone, between tendon and bone, between adjacent ligaments—for example, coracoclavicular—and so on, and the so-called synovial sheaths of the carpal and digital tendons are merely elongated bursae (Barnett *et al.*, 1961). As mentioned above, these bursae may in rheumatoid disease proliferate, and prolongations from joints occasionally appear as bursae a considerable way from the joint, below the elbow, below the shoulder, and below the knee. We have seen this in adults and in children, usually associated with severe inflammatory disease. Rajman (1966), in a study of 490 patients with juvenile rheumatoid arthritis, observed over a 12-year period, noted that six children displayed subcutaneous cystic swellings of the upper arm or near the knee, the result of proliferative tenosynovitis or "bursitis." Such swellings track down and are found below the joint from which they originate. They may disappear spontaneously or fluctuate parallel with the severity of the inflammatory disease. In one of our patients, a boy of 14 years, onset was first in one arm and then the other after haymaking, and was associated with increased disease activity, diminishing greatly on corticosteroid therapy. Though these cystic swellings appeared just above the elbow on one side, there was no communication with this joint; the swellings appeared to come from above.

A common site of synovial cysts is posterior to the knee, the so-called Baker's cyst or popliteal effusion. Burleson *et al.* (1956) confirmed the anatomical relationship to the gastrocnemius-semimembranosus bursa quoted above, finding communication in 65% of cases. Doppman (1965), using radiographic contrast media, found such communication in 50% of the cases examined, flexion of the knee driving the fluid posteriorly and relaxing the neck of the bursa. It is relatively common to find these popliteal cysts sealed off from the rest of the knee joint, and they may cause considerable discomfort and some disability. In time they may dissect inferiorly and appear between the two heads of gastrocnemius or even as low as the Achilles tendon (Kogstad, 1965). Hall and Scott (1966) and Hench *et al.* (1966) also reported dissection superiorly into the posterior thigh. Though these dissecting lesions usually occur slowly and insidiously,

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they often appear quite suddenly (Hollingsworth, 1968). In such cases one must consider the likelihood of joint rupture having occurred.

Synovial Rupture

It is extremely common in flexing affected joints in rheumatoid arthritis to see synovial bulgings through weakened periarticular structures. These may masquerade as "soft nodules" around the finger joints, but one of the commonest sites, as mentioned above, is posteroinferiorly in the knee. It has recently become clear from the work of Dixon and Grant (1964), Tait *et al.* (1965), and Hall and Scott (1966) that such protrusions may rupture; the rheumatoid joint fluid tracking down the calf produces an inflammatory reaction, the general appearance being very similar to a popliteal thrombophlebitis. There is no doubt that in the past most of these cases have been misdiagnosed as thrombotic complications, for Homan's sign is present and the area tense, woody, and hot. This complication is common enough for almost all rheumatologists to have seen several instances below the knee and some elsewhere, below elbow or shoulder. It is more than likely that many of the so-called synovial protrusions reported remote from joints are, in fact, walled-off cysts of fluid from a ruptured synovial sac.

Kogstad (1965), in his study of Baker's cysts, noted that a normal bursa is lined with synovial cells, but the dissecting cysts have no such lining, being merely fibrous connective tissue sacs containing inflammatory cells. This makes it seem very likely that these "ruptured cysts" may well be the rule and elongated synovial protrusions the exception. It is of interest that normal joint fluid does not have this inflammatory reaction. Dixon and Grant (1964), having injected knees with 30-40 ml. of fluid, found that pressure rose as high as 1,000 mm. Hg/cm. in the posterior knee joint on full knee flexion; two normal volunteers ruptured their synovial capsules during this manoeuvre but without suffering the inflammatory reaction in the calf seen in rheumatoids.

Rheumatoid Disease: Psyche or Soma

When aetiology is unknown, Confucius might well have said, psychiatric causes are always available and ready to hand. Every physician has taken case histories where it has seemed clear that psychological factors precipitated the onset of rheumatoid arthritis. In the Empire Rheumatism Council (1950) study, however, no such relationship could be shown. In a study of 292 patients with rheumatoid arthritis compared with an equal number of subjects without this disorder, no difference was shown between the two groups.

In a disease which affects over 3% of the population in this country, it would be surprising if psychiatric and psychogenic aspects did not become evident in a disorder which may affect 50 joints for 50 years without remission, with systemic ill-health, anaemia, hypoproteinaemia, and much else. Depression and anxiety are built-in constituents of any chronic disorder, and are very much part of the clinical rheumatoid picture. MacDonald Scott (1969) showed that even when psychiatric overtones are not evident, antidepressants improve a large number of patients with rheumatoid arthritis. The argument is still essentially whether such psychogenic factors are primary or secondary. Geist (1966) found that as a result of an analysis of the Minnesota Multiphasic Personality Inventory "rheumatoid arthritics have weak egos, repress their hostility, express their psychopathology in physical symptoms and are likely to go into a psychotic state (under emotional stress), this state being schizophrenogenic with homosexual implications." He found, however, that emotional trauma was not

present at the onset of the disorder in most cases. I personally find it hard to believe that psychic features are anything but secondary in these patients. A disease which may strike children aged 2 years or adults aged 92, in one or in a large number of joints, suddenly or insidiously in a variety of ways in patients of all psychological and physical dispositions, does not appeal to me as a psychosomatic disorder. Evidence quoted in these studies does not appear to me adequate to form the basis of any aetiological hypothesis.

Infections in Rheumatoid Patients

Rheumatoid patients appear to be more susceptible to bacterial infections than normal subjects. They are usually anaemic and hypoproteinaemic and often debilitated, and in the case of the so-called Felty's syndrome, neutropenic also. This last group is notoriously prone to purulent complications, and splenectomy is often life-saving. The diseased disorganized rheumatoid joint is unduly liable also to pyarthrosis, Kellgren *et al.* (1958) noting that bacteria from the blood stream tended to seep out into such joints. When corticosteroids are given this risk is even greater. Not only joints but any other tissue may be affected, and in our own unit we have seen empyema, lung abscess, purulent pericarditis, peritonitis, perinephric abscesses, bacterial endocarditis, abscesses under the skin and between muscles, infected gangrenous feet, osteomyelitis, and a subdural abscess (see Table). Rimoin and

Infections, Excluding Pyarthrosis, Seen in Rheumatoid Arthritics in Westminster Hospital Since 1950

Subdural abscess	1	Perinephric abscess	3
Cerebral abscess	1	Abscesses under skin and between	
Pneumonitis with abscess formation	2	skeletal muscles	6
Pneumonitis without abscess formation	2	Empyema gall bladder	1
Empyema	1	Pelvic abscess	1
Purulent pericarditis	2	Actinomycosis	1
		Retroperitoneal abscess	1

Wennberg (1966) reviewed 32 reported cases, only 10 of which were on corticosteroid therapy at the time. Fever and leucocytosis were not always present and proved to be poor indices of septic arthritis. Bacteria were isolated from the blood stream in 15 of the 32 patients, staphylococci predominating, though coliforms, streptococci, pneumococci, and *Haemophilus influenzae* were also reported. Just under 50% of the patients died as a result of their infection. It has long been a rule in our unit that an exacerbation of one joint only, with swelling and other signs of inflammation, should not be regarded as a localized exacerbation of the disease or due to trauma until aspiration and culture had excluded pyarthrosis. Even so we have missed some cases.

Case 1

A 54-year-old painter had nodular rheumatoid arthritis complicated by arteritis, Sjögren's syndrome, fibrosing alveolitis, myocardial infarction, and terminal pyarthroses and empyema. He presented in 1964 with an 18-month history of joint pains, initially in the knees and feet, later affecting hands, elbows, and shoulders.

Examination showed early rheumatoid changes, clubbing of the fingers, and rheumatoid nodules. The diagnosis was supported by a strongly positive Rose-Waaler test (1 in 2,048) and typical x-ray films. One year later arteritic lesions were noted on the fingers, and shortly after this he began to complain of shortness of breath. Chest x-ray films showed the appearances of fibrosing alveolitis. Eighteen months after presentation he sustained a myocardial infarction complicated by shock and cardiac failure, but he made a good recovery. Over the years his arthritis progressed steadily with the development of typical deformities. He was admitted to hospital in 1968 because of increasing breathlessness; lung function tests confirmed the presence of a transfer factor defect without evidence of airways obstruction. Lung biopsy showed interstitial round cell infiltration and moderate fibrosis consistent with fibrosing alveolitis, but there was no definite evidence to

support the diagnosis of rheumatoid lung. He was discharged from hospital but deteriorated and was readmitted in cardiac failure with a right pleural effusion; this was tapped and revealed sterile blood-stained fluid. He remained breathless and was not improved by a three-week course of tetracosactrin (Synacthen); apart from this he received no steroid therapy. He continued to deteriorate and died.

Necropsy showed unsuspected bilateral pyarthroses of the shoulders and an empyema which was about to ulcerate through the skin of the anterior chest wall. Swabs from these sites grew *Staphylococcus aureus*. Blood counts and temperature charts had never suggested an infective process.

Case 2: Felty's Syndrome

A married woman aged 63 developed rheumatoid arthritis in one finger at the age of 39. In 1950 it spread to knees, feet, and ankles, and after a dental extraction in 1953 it further spread to hands and other large joints. Prednisolone was started in 1957 with great benefit. In 1958 peripheral neuropathy, many nodules, and lymph node and slight splenic enlargement occurred. In 1961 leucopenia became apparent (730 total neutrophils per cu.mm.) and the spleen was two to three fingerbreadths enlarged. Recurrent pyogenic skin infections with persistent neutropenia now became a major trouble and her condition became critical. Mr. Frank D'Abreu removed her spleen and a splenunculus in 1962. At this time she developed an ulcer on the right shin unrelated to trauma. This healed on resting the limb for several weeks, but a year later a similar ulcer appeared on the left shin, also responding to bed rest. In 1966, four years after splenectomy, she became less well and neutropenia recurred. It was felt she might have grown a fresh splenunculus, but after some four months of vague ill-health signs of a perinephric abscess appeared. When this was drained, neutrophils rapidly reappeared and her white blood cell count returned to normal. In 1967 a right shin ulcer recurred, and in 1968 she developed a staphylococcal pneumonitis and large lung abscess, which responded to conservative measures. In 1969 the ulcer returned over her right shin. She is now in 1970 recovering from uncomplicated influenza. This history illustrates well two features of Felty's syndrome: the tendency to develop shin ulcers and to pyogenic infection.

Case 3

A married woman aged 58 was admitted to Westminster Hospital in 1964. She had had seropositive rheumatoid arthritis in severe form since 1945 with Sjögren's syndrome. She was severely ill, temperature 104° F. (40° C.). Blood cultures were positive for *Staph. aureus* and as cloxacillin therapy was started an aortic reflux murmur appeared. She made a steady recovery, but later in 1964 developed a pyarthrosis of the right knee, and after this an abscess reappeared in that area. She remained a frail, crippled person but without obvious pyarthrosis, and her cardiac condition was quiescent. Since 1963 she has been on conservative doses of prednisolone, averaging latterly 3-4 mg. daily. In the last year crops of nodules have appeared, breaking down over pressure points; sacral sores are now her major concern.

Anaemia

I was taken to task (Calin, 1969) for omitting to refer to anaemia as an extra-articular manifestation of rheumatoid disease. I did not do so as it is so well recognized and reported, the Edinburgh school alone having contributed greatly to the subject. Their series of articles on the nature of anaemia in rheumatoid arthritis started in 1955 (Roy *et al.*, 1955) and is still going strong, number 11 of the series appearing in May last year (Mowat *et al.*, 1969).

Anaemia is the rule in any but mild or inactive cases of rheumatoid arthritis. Usually normochromic and normocytic microcytosis and hypochromia may be present. The major factor in the aetiology of the anaemia appears to be the

increased uptake and failure of release of iron by the hyperplastic reticuloendothelial system and the phagocytic cells of the proliferated synovial tissue of a patient with active rheumatoid arthritis. Minor factors include a mild impairment in absorption of iron from the gastrointestinal tract, a mild extracorporeal haemolysis, a small increase in plasma volume, a failure of the bone marrow to increase red cell production, and possibly in some cases blood loss from salicylate and other drugs used in therapy. Also, in the presence of a low serum albumin, incorporation of iron into new red cells is impaired, there is an increased rate of degradation of transferrin, and a diminished release of endogenous iron from senescent red cells (Mowat, 1969). Most of these abnormalities of iron metabolism correlate well with disease activity, and it has been postulated (Whittingham *et al.*, 1967; Mowat *et al.*, 1969) that the serum iron level is the best indication of rheumatoid disease activity. If the active disease in rheumatoid arthritis is controlled, the hypochromic normocytic anaemia is corrected without additional haematinics, but correction may also occur if large quantities of parenteral iron are given, as this allows sufficient iron to bypass the overactive synovial and reticuloendothelial tissues.

Mowat *et al.* (1969), giving 20 i.u. of corticotrophin daily to 13 rheumatoid patients, found a very rapid correction of low plasma iron values which was maintained during the period of administration, the mean rise in haemoglobin ratio being 2.05 g./100 ml. after 14 days' treatment without the addition of haematinics. A similar improvement is seen with effective oral corticosteroid therapy.

To revert to the question of iron absorption, Boddy and Will (1969) measured absorption of oral iron in patients with rheumatoid arthritis and in control subjects by whole-body monitoring; no significant difference was found. The mean absorption of hypochromic rheumatoid patients was twice that of normochromic patients, but non-rheumatoid patients with iron-deficiency anaemia had a significantly higher mean absorption than rheumatoid patients with hypochromic anaemia of comparable severity. Gibberd (1966), working in our unit at Westminster Hospital, in a study of 533 patients with definite rheumatoid arthritis found in 148 males that the haemoglobin level was normal, but that the average level in 385 females was low and fell during the course of the illness. Increasing the daily dose of iron above 200 mg. did not produce a more rapid rise in haemoglobin level, though iron deficiency appeared to be the cause of the low haemoglobin level, which was unaffected by salicylates, phenylbutazone, or corticosteroids.

Partridge and Duthie (1963) found an increased incidence (1.38%) of macrocytic anaemia in rheumatoid arthritis. Most of their 35 patients had primary Addisonian anaemia or vitamin-B₁₂ deficiency secondary to surgery, but seven patients were found to have a megaloblastic anaemia with normal absorption of vitamin B₁₂ and folic acid. Such cases have not been described elsewhere. Folic-acid-deficiency anaemias have been reported in rheumatoid arthritis (Gough *et al.*, 1964) but are uncommon.

Liver Disease

As Hollingsworth (1968) truly says, no evidence exists for histologically definable liver disease as a facet of generalized rheumatoid arthritis, and though changes in plasma proteins may be evident and bromsulphthalein excretion impaired (Castenfors *et al.*, 1964), there is no primary evidence of hepatic disturbance and the serum aspartate aminotransferase levels are normal in rheumatoid arthritis (Nettelbladt, 1960). Recently Blendis *et al.* (1970) investigated 12 patients with Felty's syndrome; six were anaemic, owing to a considerable increase in plasma volume, the red cell mass being either normal or increased. In eight patients some liver function

tests were abnormal and in five of these where aspiration biopsies and necropsies were done, liver histology showed lymphocytic infiltration of the sinusoids and portal tracts together with portal tract fibrosis. One patient later was found to have a macronodular cirrhosis, and in others a nodular appearance without true cirrhosis was seen. In uncomplicated rheumatoid arthritis, however, such changes are rare, Lefkovits and Farrow (1955) finding only 2 of their 15 patients with histological changes and Movitt and Davis (1953) only slight to moderate fatty infiltration in 4 out of 17 rheumatoids examined by liver biopsy.

Ankle Oedema

Ankle oedema is common in rheumatoid disease even when there is no cardiac, renal, or amyloid cause for it. These patients often move less than normal subjects and sit for hours with legs dependent and minimal muscle movements. The oedema is rather reminiscent of that seen in the London population in the Blitz during the last war, where so many slept all night in sitting positions in the shelters. Hypoalbuminaemia may play a part in its causation in some cases (Wilkinson *et al.*, 1965). Gandy *et al.* (1965) and Conşden and Smith (1965) found a higher protein content (1.6 g.) in the oedema fluid of patients with active than in those with quiescent rheumatoid disease (0.7 g.). Bywaters (1948) had previously found a higher protein content in the neighbourhood of the swollen and inflamed joints of rheumatoid arthritics: the tissue fluid clotted and contained over 2 g. of protein per 100 ml. as compared with less than 1 g./100 ml. in cardiac or renal oedema. Park and Swinburne (1964) did not confirm these findings; they found less than 1 g./100 ml. in the oedema fluid and considered it to be a transudate.

These differences are almost certainly due to the fact that multiple causes operate in all cases; involvement of ankle or knee (where a gross effusion may slow venous return), gross anaemia, varicose or thrombosed veins, muscle wasting, and salt and water retention caused by drugs such as phenylbutazone, corticotrophin, or the corticosteroids. There is usually no evidence of lymphatic obstruction, though this may be a factor in a few cases. Short *et al.* (1957) noted that oedema which could be regarded as a manifestation of rheumatoid arthritis was found in about 5% of their patients. Almost all these patients were over 40 years of age and had active arthritis in the adjacent joints. Varicose veins occurred more often in the control patients than in the rheumatoids. Of the many factors involved in the production of ankle oedema, active arthritis in adjacent joints and immobility of the legs are probably of the greatest importance.

Osteoporosis and Fractures

Areas of bone adjacent to joints enclosed in synovium and capsule affected by the inflammatory rheumatoid process show localized periarticular porosis. This is in fact the earliest and often the only radiological sign in rheumatoid disease of short duration. Osteoporosis of the spine and of other bones occurs frequently in severe prolonged rheumatoid arthritis, partly from immobility and disuse, partly from poor nutrition and excessive protein catabolism, partly from corticosteroid or corticotrophin therapy, and partly from advancing age. Dent and Watson (1966) emphasized that the pain in an osteoporotic spine comes essentially only after recent crush fractures; as these settle down, though the initial pain may be severe and may even occur on complete bed rest, the pain goes, and, though radiographs look worse than before, the pains are less or are absent. Spinal cord compression is extremely rare in such cases, as is renal stone formation. McConkey *et al.* (1965) described a 78% correlation between skin transparency and osteoporosis in 102 women over the

age of 40 with rheumatoid arthritis. The prevalence of transparent skin in women who had or who had not had corticosteroids did not differ significantly, but radiological osteoporosis was more common in those who had received corticosteroids, all those with fractures being in this group. Rheumatoid arthritis is therefore one of the brittle bone diseases, whether the patient has been on corticosteroids or not.

One of my patients had an apparent local flare-up in an elbow, which proved to be due to a fracture of the radius and ulna that occurred as he buttoned his trousers at the back; he was not on corticosteroids. Another male on 10 mg. of prednisolone a day broke his tibia as he got out of bed in the morning. A third, a woman aged 55, with no apparent major trauma, and not on corticosteroids, fractured her pelvis throughout the whole width of the ilium on one side. Crush fractures of dorsal or lumbar vertebrae and of ribs are relatively common, particularly in women over the age of 50 on corticosteroids, and fractures in metatarsals may even be overlooked; just as infection should always be suspected in a one-joint exacerbation, so should injury when sudden pronounced disability and pain appear locally in bony structures.

Coronary Arteritis

Vasculitis and cardiac disease in rheumatoid arthritis was discussed in the Ellman lecture (Hart, 1969) of last year, but I did not touch on rheumatoid coronary arteritis except to mention that Cruickshank (1958), in a necropsy study of 100 patients, noted arteritis of the cardiac vessels in 20. How common is rheumatoid coronary vasculitis and how often does it cause coronary occlusion and myocardial infarction?

Most studies to date have not shown an increased incidence of myocardial infarction in rheumatoid patients (Lebowitz, 1963; Gibberd, 1965) and Cobb *et al.* (1953) produced some evidence that the disabled arthritic might be less prone to this complication. Cathcart and Spodick (1962), however, reported an increased incidence of definite and probable coronary artery disease in 240 sufferers from rheumatoid arthritis compared with a control group of subjects; all of five patients so diagnosed in life had coronary artery sclerosis at necropsy. Karten (1969) examined the necropsy records of patients with rheumatoid arthritis who had died between 1941 and 1968. In seven patients with myocardial infarction there was no evidence of coronary arteritis in the histological sections available. In 102 patients with rheumatoid arthritis admitted consecutively to the Goldwater Memorial Hospital, New York, for inpatient treatment, he found six who developed diffuse vasculitis; two of these had myocardial infarctions. One of these patients survived; in the other definite evidence of coronary arteritis was found at necropsy. This patient had a peripheral neuropathy in all four extremities, multiple decubitus ulcers, cachexia, a staphylococcal pyarthrosis, and a terminal ileus with haemorrhage from extensive ulcers in stomach and small intestine, but nothing clinically suggestive of coronary occlusion, the necropsy findings being entirely unexpected.

Since 1941 at least 75 instances of coronary arteritis in patients with rheumatoid arthritis have been mentioned in the literature (Karten, 1969), almost all being first detected at necropsy, where arteritis was also seen in other organs. Clinical myocardial infarction occurred in only 18 out of 55 with detailed records—that is, in only one-third of those with coronary arteritis—this group included a relatively larger number of patients with necrotizing arteritis and a relatively greater number on corticosteroid therapy. The diagnosis of coronary arteritis is made, it would seem, more often on pathological than on clinical grounds, ischaemic symptoms usually being absent. When there is clinical evidence of coronary occlusion or angina pectoris in a rheumatoid patient the underlying morbidity usually appears to be atherosclerotic.

Thyroid Disease

When Gibberd (1965) in our unit did a survey of 406 cases of severe active classical rheumatoid arthritis according to the modified criteria of Kellgren *et al.* (1963), he found that in women only dyspepsia, non-toxic goitres, and thyrotoxicosis were more commonly associated with rheumatoid arthritis than expected, no other co-existent disorder being particularly evident. Dyspepsia is probably largely due to the therapy given, but Short *et al.* (1957) had already noted an approximately twofold increase in thyroid disease in rheumatoids as compared with controls. Becker *et al.* (1963) found a tenfold increase in the incidence of rheumatoid arthritis in patients with Hashimoto's thyroiditis, and Buchanan (1965) also noted an association between the two conditions on clinical and serological autoantibody studies. Masi (1965), Masi *et al.* (1965), and Mulhern *et al.* (1966), doubted if Hashimoto's thyroiditis was autoimmune in nature and were doubtful if the association between rheumatoid arthritis and thyroiditis was a true one. Likewise Hijmans *et al.* (1961), though they found that thyroid antibodies of low titre occurred three times as often as expected in systemic lupus erythematosus, did not observe an increased incidence in rheumatoid arthritis. Nevertheless, it is not uncommon to find hyperthyroidism or a simple goitre in patients with rheumatoid disease, and it has been noted that after thyroidectomy there may be exacerbation of the arthritis. Gardner (1969), in a pathological study of 142 patients with rheumatoid arthritis dying in hospital, found 17 (12%) with evidence of thyroiditis; he stated that thyroiditis and thyroid fibrosis are frequent findings in elderly rheumatoids.

Mortality in Rheumatoid Arthritis

As I noted in the Ellman lecture, a severe rheumatoid arthritic dies, as it were, by inches and it is hard in such crippled, ill, anaemic, hypoproteinaemic patients to say which of several factors have been the major ones in causing death. Such a patient may take many years to die, her condition slowly and insidiously worsening over a long period, the terminal pneumonia or coronary occlusion merely striking down one already, as it were, on her knees. Cobb *et al.* (1953) reviewed the mortality data of 583 rheumatoid patients followed for an average of almost 10 years before corticosteroids were in general use. They found a higher mortality rate than in the rest of the local population, and patients who developed rheumatoid disease before the age of 50 had a higher mortality rate than those with onset after this age. The rheumatoid fared better as regards accidents and possibly hypertension and coronary artery disease, worse as regards infections, renal disease of different kinds, pulmonary embolism, and valvular heart disease. Duthie *et al.* (1964) gave comparable figures in Edinburgh in a study of 307 patients, the fewer deaths being probably due to availability of antibiotics. Reah (1963) followed 200 patients for 13 years and considered that 7 out of 28 men and 27 out of 52 women died as a result of their arthritis. Kellgren and O'Brien (1962) reported a significantly greater mortality in seropositive than in seronegative rheumatoid sufferers. This was also noted by Bywaters *et al.* (1961), who reported 131 deaths in 250 rheumatoids followed up for over 10 years, 76 dying within the 10-year period. Males did better than females, and those with fewer joints involved fared better than those with more diffuse arthritis. Death when it occurred was not so much due to specific complications of the disease as from all the usual causes, though at an earlier age.

It is generally accepted that nodular, high titre positive differential agglutination titre cases, particularly with vasculitis and neuropathy, fare worst, and most of these in our experience have been treated with corticosteroids. The complications of high dosage—that is, over 7 mg. of pred-

nisolone daily or its equivalent of another corticosteroid, given for many months or years—have undoubtedly added to the mortality in this disease. Occasionally deaths may be due to other drugs—for instance, aspirin, gold, or phenylbutazone—but in the years 1950 to 1962 high-dosage corticosteroids undoubtedly complicated the clinical picture and added to the mortality considerably, though it is true that it was usually the worst cases that received these drugs. Rheumatoid arthritis is not a notifiable disease, and even if it were the picture is such a complicated one that death would usually be attributed to one of the common causes, though undoubtedly contributed to in many cases by coexistent rheumatoid disease and its treatment. It behoves those of us in clinical practice to keep in mind the words of Modell (1967), who said that if the surgeon can be said to have been fathered by the barber, the modern pharmacotherapist is the direct descendant of the Borgias. Rheumatoid disease is complicated and serious enough without additional therapeutic overtones, as was frequently emphasized by Sir Stanley in the past.

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Autoimmunization with Irradiated Tumour Cells in Human Malignant Melanoma

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Summary: Thirteen patients have been immunized with their own irradiated melanoma cells on one or more occasions. Following these autografts tumour-specific cytotoxic antibodies were produced, the longest response lasting 14 days. This procedure had no apparent effect on the course of the disease in these patients.

Introduction

Antibodies cytotoxic to the patient's own malignant melanoma cells are present in most patients who have localized disease but absent in those with widely disseminated tumour (Lewis, 1967; Lewis *et al.*, 1969). We have previously shown in individual patients that as the disease progresses the antibodies disappear from the blood (Lewis *et al.*, 1969). For this reason we decided to immunize patients, who did not have antibodies, with their own irradiated malignant cells to determine whether they were capable of forming antibodies if challenged in this way.

Patients and Methods

Clinical Assessment of Patients.—For the purposes of this study the patients were classified in three grades: Grade 1, Malignant melanoma confined to the primary anatomical site; Grade 2, Invasion of regional lymph nodes with or without local satellite nodules; and Grade 3, Tumour spread beyond

the regional lymph nodes. Three patients with Grade 2 and 10 with Grade 3 disease were given one or more autografts of their own irradiated tumour cells.

Preparation of Autografts.—The tumour was received fresh from operation and minced with scissors and scalpel to obtain a cell suspension in tissue culture medium 199. No enzymes were added. Between 60 and 500 × 10⁶ cells in 6 ml. of TC 199 were irradiated in a glass Petri dish with 12,000 rads. The cell suspension was then transferred to a sterile syringe, and 1-ml. portions were injected subcutaneously at six sites—the outer aspects of both arms, each side of the anterior abdominal wall, and the outer aspect of both thighs. This was preceded in every case by an intradermal test dose of 0.1 ml. of cell suspension, any local skin reaction being noted. The remainder of the cell suspension was concentrated in a mixture of TC 199, 20% fetal bovine serum, and 10% dimethylsulphoxide, and cooled at 1° per minute to –20°C before being placed in liquid nitrogen. Informed consent for these procedures was obtained in each case.

Tests for Detecting Autoantibodies.—Three separate techniques were used to detect the presence of autoantibodies: (1) the complement-dependent cytotoxicity test using a method modified from Pulvertaft; (2) the complement-dependent inhibition of R.N.A. synthesis; and (3) indirect membrane immunofluorescence. These three techniques have already been described in detail (Lewis *et al.*, 1969), the only modification being that, on thawing, the cells stored in liquid nitrogen were washed very thoroughly in TC 199 before being tested for membrane immunofluorescence, as dimethylsulphoxide interferes with this reaction. When titrations of the sera were undertaken, an end-point of > 1:16 was regarded as being significant. The end-point was taken at the last dilution to show 25% of cells with positive speckled membrane reactions.

Results

A total of 18 patients were given autografts, but in five of these the detection of antibodies proved impossible owing to the poor viability of the frozen melanoma cells when they were thawed. In the remainder satisfactory preparations were obtained, and a total of 25 autografts were given to 13 patients. The results are summarized in Table I.

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