Palindromic Rheumatism

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In 1941, Hench and Rosenberg[1] described 34 patients with 'a new and oft-recurring disease of joints' which they called 'palindromic' rheumatism, from the Greek word meaning 'to recur'. The shoulder, knee and small joints of the hand were most commonly involved. Acute synovitis affecting one or several joints recurred at variable and irregular intervals; each joint was usually inflamed for less than three days. Attacks could occur daily or only a few times a year. Some patients experienced 'para-articular' attacks with transient subcutaneous nodules, soft-tissue swellings or patchy erythema. Results of laboratory investigations were normal, apart from a relative lymphocytosis and raised erythrocyte sedimentation rate (ESR) during attacks and increased serum fatty acids in nine out of ten patients tested. A few joint biopsies revealed a non-specific synovitis and radiographs showed only coincidental osteoarthrosis. Food allergy was suspected but exclusion diets were ineffective[1, 2].

Hench and Rosenberg concluded that no treatment was of value and that no joint was permanently damaged despite thousands of attacks. However, many patients thought to have palindromic rheumatism have subsequently developed a chronic seropositive polyarthritis[3-7]. Ginsburg[8] and Boland and Headley[9] were the first to report a favourable response to gold salts. Subsequent reports[5, 6, 10] have confirmed this, although remissions were often incomplete and the follow-up period short. This article summarises the results of a 25 year study of patients with palindromic rheumatism attending the Middlesex Hospital.

Method

Detailed information on 90 patients who had attended the Department of Rheumatology between 1955 and 1979 with palindromic rheumatism as described by Hench and Rosenberg[1] was abstracted from the case-notes. During 1978-1979, 68 of these patients were re-examined. Additional investigations included up-to-date radiographs of chest, hands, feet, knees and sacroiliac joints, and tests for serum RF, ANA, thyroid, gastric parietal cell, smooth muscle and mitochondrial antibodies. A titre of 1/40 RF or ANA was considered positive. Antibodies to desoxyribonucleic acid (DNA) and extractable nuclear antigen (ENA) were sought if the serum ANA was positive. The sera of 41 patients were screened for antibodies to influenza A and B, Coxsackie viruses, measles, mumps, rubella, hepatitis B surface antigen, varicella-zoster, adenovirus, cytomegalovirus, herpes simplex, psittacosis, *Coxiella burnetii* and *Mycoplasma pneumoniae*. Fasting plasma triglycerides and cholesterol were measured on at least one occasion in 50 patients.

Results

Forty-seven women and 43 men were studied. Their age at onset ranged from 18 to 64, with a peak incidence in the fifth decade. Most patients suddenly developed an acute monarticular arthritis, often affecting the shoulder, without obvious cause, although in 11 patients the onset appeared to be closely associated with such varied conditions as viral or bacterial infections, snake bite, minor trauma and the medical treatment of thyrotoxicosis and of teratoma of the testis. Twenty-six patients subsequently experienced only monarticular attacks, although the majority had at least some polyarticular attacks, one joint becoming involved after another. The duration of the arthritis in any one joint varied from a few hours to several days but was never longer than three days in 94 per cent of the patients. The frequency of attacks varied considerably. They might occur only a few times a year but two-thirds of the patients had them at least once a week and at their worst they could occur daily. Joints commonly involved included the wrist, shoulder, knee and small joints of the hand, but almost any joint could be affected at some time (Fig. 1). A typical pattern of attacks is shown in Fig. 2.

Attacks could start at any time of the day, but 39 patients said that they usually came on in the late afternoon or evening and nine had nocturnal attacks. Pain was often severe, preventing sleep, and eight patients were admitted urgently to hospital. Attacks were

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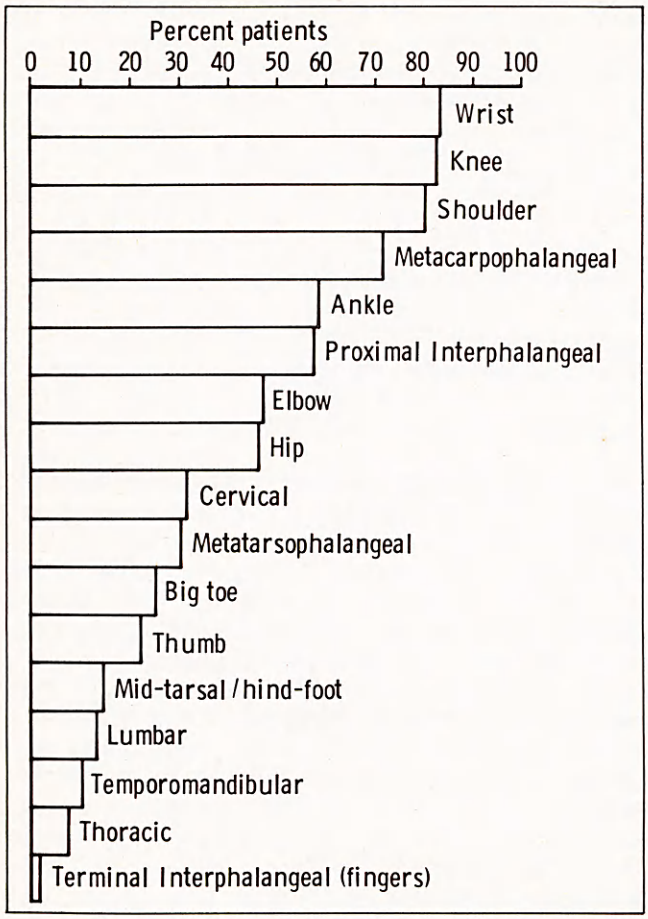
Fig. 1. *Joints affected by episodic arthritis in 90 patients with palindromic rheumatism.*

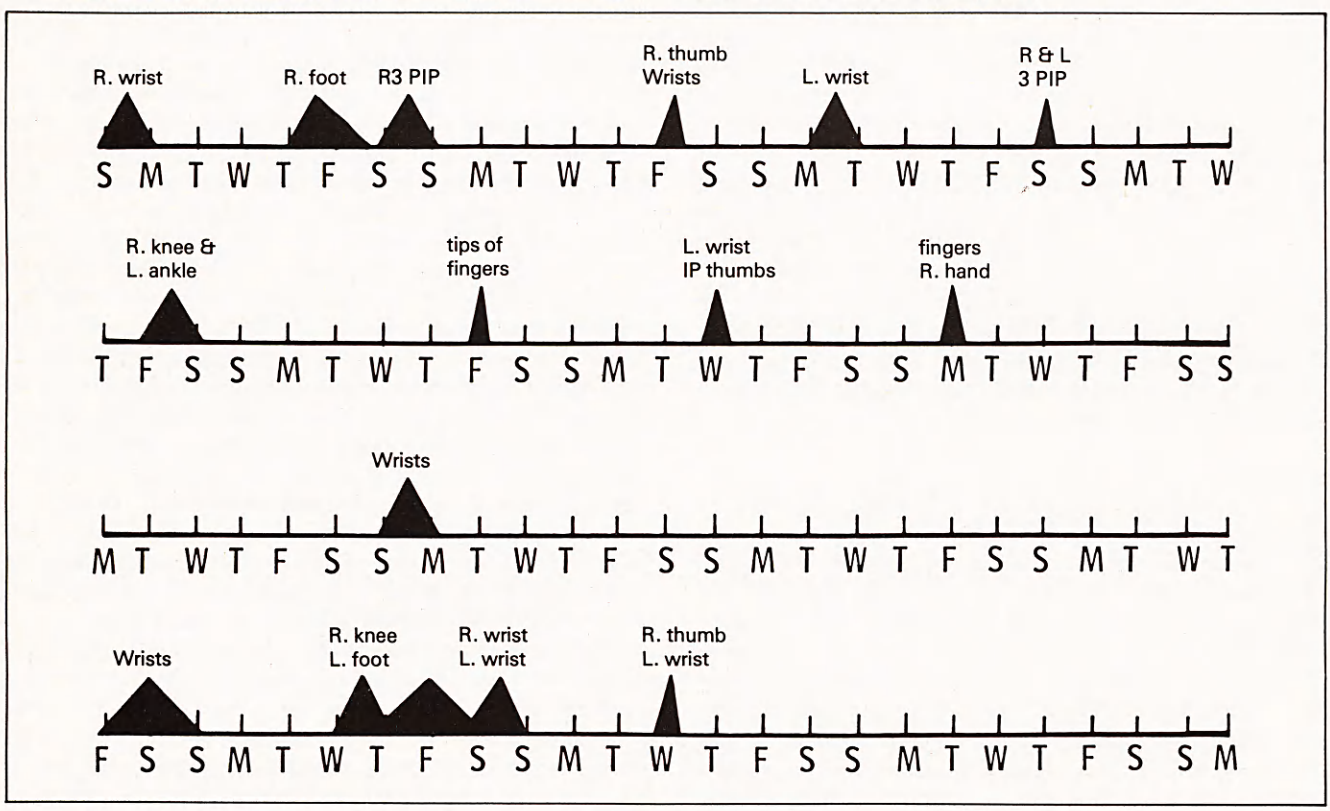


precipitated by over-use or minor injury in 30 patients, emotional stress in 28 and exposure to cold in twelve. Five seronegative patients attributed them to the ingestion of specific food or drink. Although a third of patients described redness of the skin overlying inflamed joints, only a few mentioned other para-articular manifestations. These included transient lip and peri-orbital oedema (2), painless finger and elbow nodules (3), and patchy erythema or soft-tissue swellings on the forearms (3) usually lasting about 48 hours. Four patients were feverish during attacks.

Outcome

Thirteen patients were followed-up for over 20 years and 63 for a minimum of ten years (Fig. 3). Two groups could be distinguished at follow-up: those who were seropositive for rheumatoid factor and those who were seronegative (Table 1). However, both presented with a similar episodic arthritis. When last seen, 21 patients were in spontaneous remission, 51 appeared to be in remission due to drugs and 18 still had episodic arthritis. However, drug remissions were often incomplete, the patient experiencing occasional mild attacks. Forty-one of 45 seropositive patients had developed rheumatoid arthritis compared with only five seronegative patients. Nine others in the seronegative group had a pauci-articular arthritis, psoriatic arthropathy, gout or systemic lupus

Fig. 2. *The pattern of acute attacks over a three month period in a patient with palindromic rheumatism, showing joints affected, the duration of attacks and the variable interval between them.*



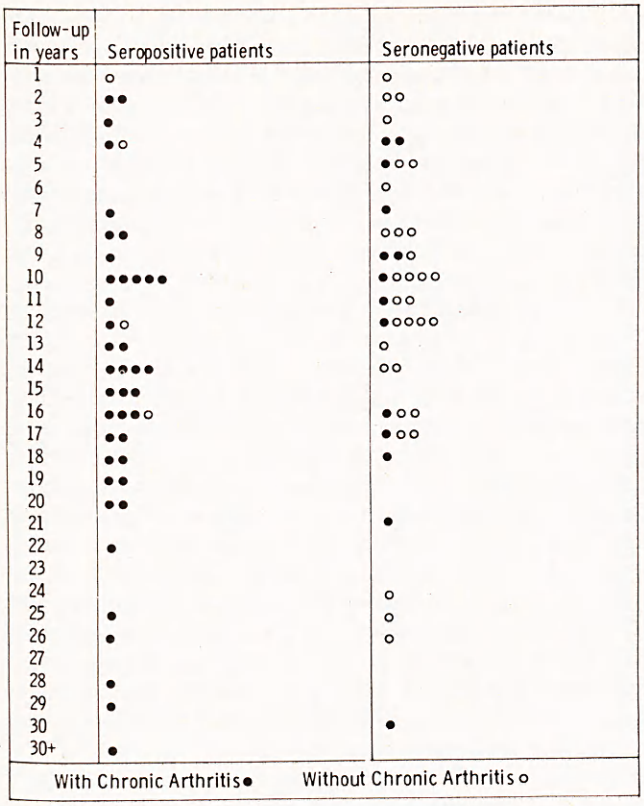


Fig. 3. *Duration of disease at follow-up in 90 patients with palindromic rheumatism.*

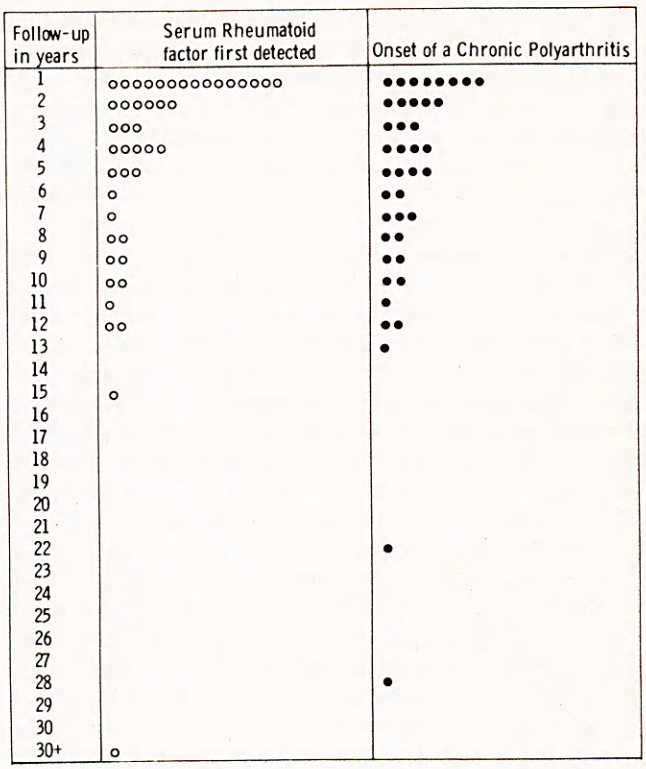


Fig. 4. *Duration of disease in 45 seropositive patients with palindromic rheumatism (a) when serum rheumatoid factor was first detected and (b) at onset of chronic polyarthritis.*

Table 1. Outcome at follow-up in 90 patients with palindromic rheumatism.

Diagnosis at Follow-up	Patients Seropositive	Seronegative
Rheumatoid arthritis		
highly active disease	6	0
moderately active disease	11	0
inactive disease	24	5
Pauci-articular arthritis	0	3
Psoriatic arthropathy	0	3
Gout	0	1
Systemic lupus erythematosus	0	2
Episodic arthritis only	4	31

Table 2. Functional grading of 90 patients with palindromic rheumatism at the time of follow-up.

Degree of Disability	Patients Seropositive	Seronegative
Grade I		
No disability and normal activities	23	43
Grade II		
Moderate restriction of activities but normal employment or housework	17	2
Grade III		
Partly dependent on other people and light work only	5	0
Grade IV		
Confined to bed or wheelchair	0	0

erythematosus (SLE), while 35 patients still had normal joints. Patients who became seropositive usually did so during the first ten years, developing a chronic polyarthritis at about the same time (Fig. 4). The average length of follow-up was 14.1 years for seropositive and 11.7 years for seronegative patients. Three from each group gave a family history of palindromic rheumatism.

There were 24 men and 21 women in the seropositive group compared with 19 men and 26 women who remained seronegative. There was little difference between the sexes in the severity of their arthritis or the degree of disability[11] but the seropositive patients were more disabled, although none was confined to bed or wheelchair (Table 2). They required 38 hospital admissions for medical treatment or surgery compared with only seven admissions for seronegative patients, and the complications of their disease included sensory neuropathy (3), cutaneous vasculitis (2), lung fibrosis (2) and pleural effusion (1). Twelve seropositive patients needed long-term steroid therapy (average 10.2 years) compared with five seronegative patients (average 4.5 years), two of whom had SLE. A patient from each group died during the period of follow-up, one from bronchial carcinoma and the other from ischaemic heart disease.

Soft-tissue lesions were more common in seropositive patients and included subcutaneous or tendon nodules

(15), olecranon or popliteal bursitis (12), tenosynovitis and tendon rupture at the wrist (12), palmar tendinitis (10) and carpal tunnel syndrome (5). Only a few seronegative patients had tendon nodules (2), bursitis (2), palmar tendinitis (2) or carpal tunnel syndrome (2).

Investigations

Radiographs of hands and feet revealed evidence of chronic arthritis in 43 patients, 38 of whom were seropositive. Twenty showed minimal changes such as soft-tissue swelling, juxta-articular osteoporosis, minor erosions or subluxations; 15 patients had marked subluxation of the metatarsophalangeal joints or erosions confined to a few joints, while eight had a widespread erosive arthropathy. Chest X-rays were usually normal but lung lesions seen in seropositive patients included: active pulmonary tuberculosis (2), pleural effusion (1), nodules (2), basal fibrosis (2), bronchial carcinoma (1).

At follow-up only six patients were anaemic, with a haemoglobin of less than 12.0 g/dl. Most had a normal white cell count throughout their illness and at no time did any patient have a relative lymphocytosis. When last seen the ESR was over 40 mm/1 hour in 16 but normal in 59 patients. Only six seropositive and 25 seronegative patients had never had a raised ESR. Most seropositive patients had had an RF titre of less than 1/320 but it exceeded 1/5000 in three. Nine seropositive and 12 seronegative patients, mostly women, had positive tests for serum ANA; the titre had seldom exceeded 1/160 but was greater than 1/1000 in two patients, one of whom had SLE. She was the only patient to have serum anti-DNA antibodies. None had a positive ENA test. Few other auto-antibodies were seen. Eleven women and one man had thyroid antibodies and two developed myxoedema. Only one woman had mitochondrial antibodies and she was found to have biliary cirrhosis on liver biopsy. No smooth muscle antibodies were found. None of the six women with gastric parietal cell antibodies had pernicious anaemia. No patient, except one man with a history of Coxsackie meningitis, was considered to have a significantly raised titre of viral antibodies when compared with the normal population.

Only one patient with diabetes and another with myxoedema were found to have a high fasting plasma triglyceride or serum cholesterol level. One man had gouty arthritis and four other seronegative men had a persistent low-grade hyperuricaemia and may have had gout, although their acute attacks never lasted longer than three days and they failed to respond to allopurinol or uricosuric therapy.

Synovial biopsy of joint or tendon sheath in five patients revealed a non-specific inflammation with infiltration by lymphocytes and plasma cells. Biopsy of a nodule in four seropositive patients showed the typical histological appearance of a rheumatoid nodule.

Treatment

While acute attacks were often relieved and sometimes aborted by full doses of anti-inflammatory drugs, analgesics were usually ineffective. Few drugs, other than gold, seemed to suppress the recurrent attacks of arthritis. Prednisolone in a dose of 10-15 mg daily was only effective in 9 of 17 patients, hydroxychloroquine sulphate 200-400 mg daily in 4 of ten and penicillamine 250-1000 mg daily in 2 of four. Seven of 23 patients given 75-125 mg indomethacin or 500-1000 mg naproxen daily also went into remission. However, patients usually relapsed when the dose was reduced or the drugs were withdrawn.

Sixty-two patients were given a total of 107 courses of intramuscular sodium aurothiomalate (Myocrisin). Doses ranged from 5-50 mg given at intervals of one to four weeks for periods of up to 14 years. The initial maintenance dose varied with the prescriber; 34 patients were given 20 mg Myocrisin a week or less, while 18 received 50 mg weekly. Subsequent maintenance doses were largely determined by the high incidence of minor adverse effects and were often reduced to as little as 5-10 mg a week. Common adverse effects, such as pruritus, minor rashes or stomatitis, were frequently transient and gold injections could be resumed after a few weeks. However, two patients developed a persistent proteinuria lasting many months; one man had a severe thrombocytopenia, and a woman developed an exfoliative dermatitis; both required long-term steroid therapy.

Chrysotherapy appeared to suppress or modify acute attacks in 53 patients, 32 responding to a total dose of less than 100 mg Myocrisin. Attacks frequently recurred when gold injections were stopped for a few months or even when the interval between injections was extended to more than two weeks; 48 patients responded well to 10-20 mg Myocrisin given weekly but many relapsed if 50 mg were given at intervals of 3 to 4 weeks. Chrysotherapy, therefore, was often continued indefinitely in low doses and 18 patients had been on gold injections for over five years when last seen. The total length of remission from acute attacks was very variable, but 14 had had a remission lasting more than nine years and 27 patients were still in remission at follow-up.

Eighteen patients also experienced relief of chronic joint symptoms on gold injections; at follow-up, seven had normal joints and eight had an inactive low-grade polyarthritis.

Discussion

Although less than 400 cases have been reported so far, palindromic rheumatism is not a rare condition, as it affects 1-2 per cent of new patients attending our clinics with an inflammatory arthritis. Yet it is frequently unrecognised and often misdiagnosed. Although 36 of our patients were thought initially to have rheumatoid arthritis, 14 remain seronegative, with normal joints; 19 were wrongly diagnosed as having gout and only 2 of eight patients thought to have SLE have so far developed that disease.

Although Hench and Rosenberg[1] believed that palindromic rheumatism never damaged joints, half their 34 patients were followed-up for less than five years. A third of those who subsequently attended the Mayo Clinic

developed rheumatoid arthritis[4]. This progression has been reported elsewhere[3, 5-7, 12]. Our study confirms that a large number of patients with palindromic rheumatism develop a chronic polyarthritis within ten years of onset. Those who are seropositive have higher ESRs, more soft-tissue lesions and greater joint damage on X-ray; they require more drugs, hospital treatment and surgery than seronegative patients and tend to become more disabled, although relatively few of our patients were severely handicapped at the time of follow-up. Both groups of patients presented with a similar episodic arthritis.

Only four seropositive patients had normal joints at follow-up: two had experienced an episodic arthritis for over 12 years; one man with a short history was found to have active pulmonary tuberculosis and may have been a case of tuberculous rheumatism. The 31 seronegative patients with normal joints at follow-up included six women with persistently raised titres of serum ANA (1/80 to 1/160) without other manifestations of SLE, one woman with biliary cirrhosis, one man with Crohn's disease and four men with a persistent low-grade hyperuricaemia who may have mild gout. Although some of these patients have remained seronegative for over 20 years, they could still become seropositive and arthritic. Seven seronegative patients who presented at hospital with an early low-grade polyarthritis had normal joints at follow-up after chrysotherapy. The effect of such treatment on the course of the disease cannot be discounted.

Patients with so-called palindromic rheumatism are a heterogeneous group including those with episodic rheumatoid arthritis, seronegative arthritis, SLE, tuberculous rheumatism[13], sarcoidosis, gout, chondrocalcinosis, type II hyperlipoproteinaemia[14], allergic arthritis[15] or familial Mediterranean fever[16]. In most cases the cause of the episodic arthritis is unknown. Chronic viral infection has been suspected[17] but our patients had normal viral antibody titres. Attempts to demonstrate circulating immune complexes during acute episodes have so far failed[7, 18]. Although Hench and Rosenberg[1] reported raised serum fatty acid levels in nine of ten patients tested, we have failed to demonstrate a common disturbance of lipid metabolism. Some of our seronegative patients seem to have food allergies and are being studied further. At least one case of palindromic rheumatism has been attributed to the ingestion of sodium nitrate[19] and the possible role of food additives should not be forgotten.

In order to obtain an accurate picture of the frequency, severity and site of attacks, patients should be asked to keep a diary recording the date and duration of attacks and the joints involved. The course of the disease and its response to treatment can thus be more easily assessed.

Acute attacks are best treated by large doses of anti-inflammatory drugs; if they recur frequently, the drugs should be given regularly. If they are not effective, gold injections, chloroquine[20] or penicillamine[21] may reduce the frequency and severity of the attacks. Many of our patients thought chrysotherapy was the most effective treatment they had been given, which is perhaps not surprising in view of its proven value in the treatment of rheumatoid arthritis[22]. The weekly maintenance dose should not exceed 20 mg of Myocrisin, and 10 mg may be adequate. Serious adverse effects are rare on this dosage. The interval between injections should not exceed two weeks and, to avoid relapse, they must often be continued indefinitely.

It has been suggested that the diagnosis of palindromic rheumatism should only be made retrospectively to describe those patients who do not develop a chronic arthritis. However, this implies a prolonged follow-up and, in the meantime, the patient goes from doctor to doctor and from hospital to hospital in search of a diagnosis and treatment. Until more is known about arthritis, the term 'palindromic rheumatism' aptly describes the characteristic episodic arthritis, whatever its outcome.

Acknowledgements

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