sustained: it may well be that the breakthrough will come, not through the study of the overt, hospital case but by the study of those very minor cases which occur often in a *forme fruste* in the general population or in general practice, including what Lawrence and Bennett (1960) have called 'benign polyarthritis'. General practitioners are in a favourable position to study such entities, (if they are entities) since benign polyarthritis has been estimated to occur in about five per cent of the population: these patients seldom appear in hospital clinics, except sometimes under special circumstances, as in the 'doctor's wife syndrome'.

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Differential diagnosis of polyarthritis

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In general, but with some important exceptions, a patient with established rheumatoid arthritis, with deformities and nodules and so on, presents no great exercise in differential diagnosis. Problems in the diagnosis of early rheumatoid arthritis or what may appear to be early rheumatoid arthritis may come to us in the following circumstances. First, the patient may have pain in several joints which is due to a non-inflammatory process or his apparent joint pain may be referred from elsewhere. Second, the patient may have a true polyarthritis which is not rheumatoid arthritis, but whose true character is not diagnosed, either because diagnostic features in other organs or systems are inconspicuous or are slow in appearing. It is not a bad rule to be wary of diagnosing rheumatoid arthritis in the first six weeks of a polyarthritic illness. This is where a hospital doctor sometimes secures an easy success, because in the interval between the making of the outpatient appointment and the arrival of the patient, some diagnostic rash or some other feature develops. Third, the patient may have a polyarthritis complicating a familiar disease and not appreciated as an association. Fourth, the patient has, in fact, got rheumatoid arthritis but the disease is not presenting in the most familiar pattern. I will give you a few examples of these four difficulties.

First, the pain is not due to actual inflammatory disease of the joints. The patient may have the polyarticular type of osteoarthrosis and may have what seem to be spindle-shaped swellings of fingers, but one would be alerted by the presence of Heberden's nodes.

In such a case, you would get some help from radiographs which would show hypertrophy of the joint margins rather than erosive changes, and unless you were unlucky you would find negative serological tests. There are other causes of non-inflammatory polyarticular disease such as infiltration of juxta-articular bone in some cases of hypercholesterolaemia, myeloma or leukemia. Metabolic bone disease, notably osteomalacia causes skeletal pain which may seem to the patient to be joint pain. Occasional errors occur from neuropathy—such as diabetic neuropathy, where the pain may be thought to be articular, and the weakness the accompaniment of arthritis. Pain may be referred from elsewhere, notably the spine. There are occasional difficulties in scleroderma which can cause pain apparently in the joints, with limitation of movement,

and in polymyositis where weakness is due to muscle involvement although arthritis may occur.

Second, the polyarthritis may be a true inflammatory disease of joints but not rheumatoid arthritis, the diagnostic features being inconspicuous or delayed in onset. On the whole we diagnose polyarthritis partly by the look of it, partly by the pattern of the arthritis itself in terms of the joints involved, and partly by the tempo, and whether it is persistent or flitting. Sometimes a diagnosis depends less on the pattern of the disease itself than on the company it keeps, the manifestations which we identify in other systems.

The onset of rheumatoid arthritis is most commonly in the hands. An acute onset is surprisingly common, 46 per cent in our material, though this was somewhat biased by confining the analysis to cases seen within a year of onset. Surprisingly, 38 per cent had in the early stages of their illness a story of brief acute episodes of arthritis usually affecting a single joint and rarely lasting more than 48 hours. Such attacks are acute with immobilizing pain, often affecting a shoulder or hip and inviting in the first attack a variety of diagnoses, such as gout. If the pain is in the hip the patient is liable to be rushed into hospital and put on traction for a month which is unfortunate, if the symptoms subside in 48 hours without treatment. If treated with colchicine the attack will again subside within 48 hours, but this does not prove that the patient has gout. Fortunately, the serological tests are just as often positive in this type of disease as in the more familiar persistent arthritis and can often be of considerable help. Most of these patients quite soon begin to develop signs of persistent arthritis and to fit into the conventional pattern of rheumatoid arthritis.

By the time a patient with rheumatoid arthritis first attends a hospital clinic, the feet, hands and wrists are the most commonly affected joints. Among our patients the male-female ratio is four to seven with a peak age incidence at onset of 35 to 64; when first seen, a third of these patients have already developed erosions visible in radiographs.

This pattern can now be contrasted with those of other less common but still important types of polyarthritis. One of these is *hypertrophic pulmonary osteoarthropathy* associated with a bronchial carcinoma. These patients may have pain and swelling in almost any of their joints, often with effusions in the knees; oedema in the ankles and feet is a prominent feature, the pain is severe, and tenderness extends beyond the limits of the joints along the shafts of the adjacent bones. Fortunately for us the diagnosis is almost always revealed by the presence of finger clubbing. The diagnosis is made from the finger-clubbing and from the chest x-ray, but in radiographs of the affected bones you may see a layer of new bone laid down by the elevated periosteum.

Rheumatic fever presents us with more problems in differential diagnosis, in children particularly from Still's disease and in adults from rheumatoid arthritis and the other types of polyarthritis, especially those of acute onset. At the onset the emphasis is on the knees and ankles and the arthritis is characteristically migratory. One has to be careful about this. The point was brought home to me a year or two ago when a young girl developed an acute arthritis of one hip, which lasted two or three days and was succeeded by less severe pain for a shorter period in the other hip; thereafter no further joint symptoms were noticed. This patient shortly afterwards developed severe valvular disease and the diagnosis of rheumatic fever became obvious. So the disease may flit only briefly and in a circumscribed way. Joint involvement may not be prominent, particularly in younger patients. You are fortunate if you are helped towards the diagnosis by the appearance of an erythema marginatum, even more fortunate if you can see a subcutaneous nodule characteristically smaller and more evanescant than those of rheumatoid arthritis. Other things which may point to this diagnosis are the presence

of carditis, and a rise in the antistreptolysin titre, though the latter may come a little late to help you in the difficult early stages of diagnosis.

Another form of arthritis which often causes difficulty in diagnosis is that associated with German measles. This apparently occurs only in certain epidemics of rubella and has a curious predilection for young women. The wrists, fingers and the knees are the most commonly involved joints, and diagnosis is difficult if joint signs precede the rash, though they rarely do this by more than a day or two. One can often get help from finding that rubella has occurred in other members of the family. It commonly produces the *carpal tunnel syndrome*, probably because of the acute involvement of the wrist; Professor Bywaters' group has shown us that the cells in the joint effusions are predominantly mononuclear, and this may be of help in diagnosis. The acute phase rarely lasts more than two weeks, but in my experience these patients tend to have lingering polyarthralgia for quite some time afterwards. Serological test for rheumatoid factors are negative. Arthritis probably occurs in association with many other identified and unidentified viral diseases. It certainly does occur in the pre-icteric phase of infective hepatitis and may present difficulty there because the serological tests for rheumatoid factor may be positive, as of course they commonly are in liver disease without joint involvement. Arthritis may also occur in mumps.

Erythema nodosum. Arthritis in erythema nodosum presents diagnostic difficulty if it occurs—as it commonly does—before the onset of the rash; involvement of the knees and ankles is particularly prominent though the wrists may also be affected. In our material the sex rate was five men to nine women; 85 per cent were between the ages of 20 and 39; 70 per cent occurred in the months of March, April and May, although the textbooks say that there is also a smaller peak in the autumn. This seasonal incidence may be helpful. The commonest cause has been sarcoid, evidenced by bilateral enlargement of the hilar lymph glands; the next most common, streptococcal infection. Tuberculosis comes much lower down as a cause.

Besides the lesions of erythema nodosum the patient may also have a chronic sarcoid infiltration of the skin easily confirmed by biopsy. There are also patients who show the combination of polyarthritis with enlarged hilar lymph nodes without the skin lesions of erythema nodosum, so that it is sometimes useful in the presence of a polyarthritis of uncertain etiology to have the chest x-rayed.

Reiter's syndrome, which may be increasing in incidence, is an important cause of polyarthritis. It occurs or is diagnosed largely in young men. In women it is more difficult to establish the diagnosis because infection of the genitourinary tract is more common. The three basic features are: (1) Arthritis, rather like the arthritis of erythema nodosum, has a predilection for the knees and ankles and can be quite acute, the pain persisting for about three months and recurring sometimes after several years of freedom. (2) A non-gonococcal urethritis, although it is quite possible that many patients who have a urethritis and from whom gonococci have been isolated do in fact develop Reiter's syndrome. If, as now seems likely, Reiter's syndrome is an infection, patients may have a double infection with the unidentified agent of the syndrome and with the gonococcus. Their arthritis may in fact be due to Reiter's syndrome even if they do have gonococci in their urethra. This has probably distorted in the past the recognized pattern of a true gonococcal arthritis. (3) Conjunctivitis, or less commonly uveitis, may be transient or may not occur at all. Other features include balanitis; the skin rash of *keratoderma blennorrhagica*; ulceration in the mouth; involvement of the sacroiliac joints (fairly common); the development of calcanean spurs; and, of course, long remissions.

Ankylosing spondylitis is the disease in which the longest interval generally elapses between the first symptoms and the making of a diagnosis. This is partly because the young men whom it commonly affects tend to be of the uncomplaining type and partly

because the initial symptoms are apt to be diagnosed as sciatica. The earliest symptom is likely to be that of sacroiliitis, with aching pain in the buttocks and the back and upper thighs, and with stiffness, most marked in the morning and rapidly relieved by exercise. Beware of the diagnosis of bilateral sciatica in young men. Important too as an early feature is involvement of the knees, and a mysterious effusion in one or both knees in a young man should raise the possibility of ankylosing spondylitis. Uveitis appears as an initial symptom in ten per cent in our experience. By the time these patients have been under observation for several years the incidence of uveitis has risen to somewhere in excess of 30 per cent. Some of these patients come to a rheumatology department via departments of ophthalmology.

Gonococcal arthritis. Some material was collected by Dr Verna Wright who surveyed past cases treated at the Johns Hopkins Hospital in Baltimore. He applied to these cases retrospectively the strict criterion that they would only be accepted as cases of gonococcal arthritis if gonococci had been actually isolated from a joint or from a tendon sheath; he excluded cases in which the diagnosis was based only on the isolation of gonococci from the urethra. This produced a pattern which differs from that recognized in textbooks in the past. First of all, gonococcal arthritis was found to be commoner in women than in men. The age incidence was not unexpected, 16 to 25; the onset was acute and monarticular in 60 per cent of patients, occurring about three weeks after the urethritis. Involvement of sternoclavicular joints was not observed. Diagnosis is made first by considering the possibility, then by culture of the organisms from the joint or tendon sheath.

The differential diagnosis of acute *gout* is not difficult except from episodic rheumatoid arthritis; it does produce difficulties later on in chronic tophaceous polyarthritis, which may to some extent mimic chronic rheumatoid arthritis. Seventy per cent of patients are men, and the onset, most commonly in the feet, is usually between the ages of 30 to 49. In women it usually starts after the menopause.

Whipple's disease occurs predominantly in men. The arthritis is acute and episodic, leaving no residual damage—rather like the episodic type of rheumatoid arthritis, though with a greater tendency for reddening of the skin over the joints. It is difficult to diagnose over the many years when its sole manifestation may be recurrent acute attacks of arthritis, and is usually investigated only when the patient begins to lose weight and show signs of malabsorption. At this stage there are often attacks of hypotension which simulate an Addisonian crisis, and signs of malabsorption will be found. A definitive diagnosis can be made by jejunal biopsy. One patient we had been treating for six years as a case of atypical episodic rheumatoid arthritis with negative serological tests began to lose weight; jejunal biopsy showed a vast accumulation of material which stained with the PAS stain in the cells of the submucosa.

Polyarthritis as a complication—the patient with a familiar disease who has a polyarthritis which is not at first regarded as an association.

Patients with *ulcerative colitis* have a higher than expected incidence of ankylosing spondylitis, a much higher than expected incidence of x-ray changes in the sacroiliac joints and produce acute effusions which settle without leaving residual features. Nobody is quite sure of the relationship of these three phenomena, or whether these patients are unusually liable to ankylosing spondylitis with its peripheral joint features. The general feeling is that there is a specific type of arthritis, called colitic arthritis, usually seen between the ages of 15 and 45. It never precedes the onset of ulcerative colitis, though those patients who develop what seems to be typical ankylosing spondylitis may do so before they develop colitis. Colitic arthritis is equally common in men and women, but ankylosing spondylitis is more common in men.

Arthritis associated with *psoriasis* can be roughly divided into three groups; (1)

Those with predominant but never exclusive involvement of the terminal finger joint, usually associated with changes in the nail of the same finger; they are serologically negative. There may be a swollen finger with loss of the skin markings—a sort of dactylitis, again serologically negative. (2) Those with a much more severe process which produces loss of movement in the spine and changes in the sacroiliac joints much the same as those in ankylosing spondylitis; unlike ankylosing spondylitis, it produces severe deformity often with ankylosis in peripheral joints. Many of the finger joints become deformed and ankylosed. (3) Those cases indistinguishable from rheumatoid arthritis although the majority are sero-negative.

The *Stevens Johnson* syndrome produces acute effusions, particularly in large joints. It is sometimes associated with the rash of *erythema multiforme*, always with ulceration in the mouth and genital tract; the mouth ulcers are accompanied by sloughing, unlike those of Behçet's syndrome which we come to next.

Behçet's syndrome, originally described as a combination of orogenital ulceration with relapsing iritis, is now expanded to include skin lesions, other eye lesions, lesions of the central nervous system, thrombophlebitis migrans, and arthropathy (occurring in 64 per cent). The onset is acute, often affecting only a single joint and settling without residual trouble.

Choice of drugs in the treatment of rheumatoid arthritis

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There are many potential drugs for the treatment of rheumatoid disease, but what are we treating in this disorder? Pain in rheumatoid arthritis is but one of the symptoms. There is also a psychological or spiritual illness and a deep depression, with feelings of hopelessness in seeing no future and feeling thwarted, of incapability to work or play adequately, and of anxiety concerning the future. In addition to the pain in many joints, this attitude covers and colours the whole picture.

Patients get an overall feeling of illness with rheumatoid arthritis; they are systemically ill as well as arthritically ill; they ache all over, feel weak and feeble, have no drive and have certain features slightly suggestive of an Addisonian or pseudo-Addisonian state. Fever and tachycardia are present and their libido is absent or diminished.

In addition, local pain may be felt in nearly all the joints, and these can be referred widely so that the pain in an elbow can fan up to the shoulder and down to the wrist; the important triad is weakness, swelling and stiffness with pain in a given area. Analgesics help this local pain, but they may not help other features much. Antidepressants may help the depressive aspect and corticosteroids help as antiflammatory agents but not as analgesics. We recently asked 100 patients what they thought of alcohol in terms of their rheumatoid arthritis; some said it made them feel worse and they never touched it, but the majority found that the occasional drink helped. It has always been of interest to me that there are so few alcoholic arthritics, although there is nothing to stop an alcoholic becoming arthritic.

Relief of pain

The relief of pain and drug administration is only one part of the general management. Of the analgesics at your disposal, the first to try are the salicylates. We put