RA-like and erosive) and fibrosing alveolitis (reviewed in [9]). One feature of the syndrome is said to be 'mechanic's hands' which consists of hyperkeratosis of the fingers associated with cracking and fissuring of the skin overlying the finger pulp. When it was definitively demonstrated that the Jo-1 antigen was histidyl-tRNA synthetase, other tRNA synthetases, including alanyl- and threonyl-tRNA synthetase, were also described as less common autoantigens in polymyositis-associated overlap syndromes. The clinical features of all of these syndromes are similar so that they are often grouped together as the tRNA synthetase syndromes.

Antibodies to PM/Scl are part of a complex of precipitin reactions originally termed PM-1. Although the PM-1 antibody was originally regarded as a marker for polymyositis, anti-PM/Scl was found in ~15% and appeared to be associated with a polymyositis/scleroderma overlap syndrome [8]. The clinical features are very similar to those of other myositis-associated overlap syndromes with a high frequency of Raynaud's phenomenon, arthritis, myositis and interstitial lung disease [10]. Every patient studied to date is DR-3 positive. The PM/Scl antigen is nucleolar, and hence serum samples contain anti-nucleolar antibodies by immunofluorescence.

The clinical features of the three myositis-associated overlap syndromes are remarkably similar and would challenge the use of the word 'distinct' to describe MCTD. It would be difficult to guess the serology of an individual patient on clinical examination alone. However, there are subtle differences which can be appreciated when larger groups of patients are seen. All three are essentially SLE/scleroderma/polymyositis overlap syndromes with MCTD tending more to the SLE end of the spectrum. The PM/Scl syndrome veers towards scleroderma and the Jo-1 syndrome towards systemic sclerosis with more prominent lung disease and less skin involvement, although it may occasionally present as RA. Of the three, Jo-1 syndrome probably has the worst prognosis and requires the most aggressive treatment, and MCTD the least. Whether or not these syndromes can be classified as 'entities' awaits the demonstration of aetiology. If each antibody were shown to be induced by a different but specific aetiological agent, then the use of antibodies for diagnosis would be justified and the use of the word 'disease' substantiated. Until such time, it is probably best to maintain the term 'overlap syndrome' for all three, including MCTD.

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THE DIAGNOSIS OF GOUT AND CPPD CRYSTAL ARTHROPATHY

GOUT generally presents to the clinician as an episodic, self-limited inflammatory arthritis. Identification of monosodium urate (MSU) crystals in a synovial fluid sample obtained from the inflamed joints during an attack, or from tophi at any time, is pathognomonic of the disease, providing a precise and simple diagnostic test. When the relationship between MSU crystals and gouty inflammation was originally established, it was assumed that crystal seeding in the joint cavity, or perhaps their de novo formation, was the cause of the gouty attacks, which tend to subside spontaneously in a few days or weeks. It was then supposed, despite occasional observations suggesting the contrary, that crystals were absent from the joint cavity between attacks, thus the clinician would have to wait for a new attack to make a diagnosis through crystal identification. During the last 15 yr, it has become apparent that crystals can be found in synovial fluid samples obtained from asymptomatic metatarsophalangeal [1] and knee joints [2] of these patients. The presence of MSU crystals in the synovial fluid is very regular in those joints previously inflamed in patients whose serum uric acid has not been lowered by treatment [3]. MSU crystals were also found in
joints which have never been inflamed in the same untreated patients. Those joints containing crystals have a mild subclinical inflammation of uncertain local consequences [4]. All these data indicate that after depositing in a joint, MSU crystals remain in it indefinitely and can be found in its synovial fluid. Probably, crystals only disappear from the joint and its fluid, similarly to tophi, if they are dissolved as a consequence of a long enough reduction of the serum uric acid [3]. A practical consequence of these findings is that a precise diagnosis of gout can be made long after the attack has subsided only if the serum uric acid has not been lowered long enough to dissolve the crystals.

Despite the existence of such a simple and accurate diagnostic test, and probably based on tradition, to diagnose gout on clinical grounds seems a common practice and an approach which may appear supported by the use for diagnostic purposes of the classification criteria for gout of the ACR (which were published almost 20 yr ago) [5]. Such an approach is plagued with possible errors; among others, the following should be noted: frequently the disease does not begin with podagra (its most characteristic manifestation) and podagra may be due to other causes [6]; when inflammation appears in other less typical locations, the possibilities of clinical misjudgement increase. Hyperuricaemia is most frequently asymptomatic and must not be confused with gout: only 0.9 people/1000/year among those whose serum uric acid is between 7 and 7.9 mg/dl will present with gout. The proportion rises to 4.1/1000/year when the serum uric acid is between 8 and 8.9 mg/dl, and to 49/1000 with serum uric acid concentrations >9 mg/dl [7]. Some of the items included in the ACR diagnostic criteria are quite non-specific, such as culture-negative synovial fluid, X-ray asymmetrical swelling of a joint, suspected tophus (when just aspirating it with a regular intramuscular needle the diagnosis can be made certain!), maximum inflammation in 1 day or monoarticular arthritis. Classification criteria are undoubtedly of great aid in recruiting patients for studies, and provide reasonable assurance that those included have the disease. Also, the diagnostic use of criteria based on combinations of non-specific clinical and laboratory features, in conditions in which a specific finding does not exist, seems very reasonable: such are the cases of rheumatic fever or systemic lupus erythematosus. However, in diseases in which a simple and accurate diagnostic test is at hand, such as gout, the use of diagnostic criteria based on indirect findings has little sense. Identification of MSU crystals should always be required for the diagnosis of gout.

The clinical manifestations of the arthropathy associated with calcium pyrophosphate dihydrate (CPPD) crystals are less clear cut than those of gout. Generally affecting older people, its manifestations range from acute episodes of arthritis, generally in large or medium-sized joints, to diverse, more chronic presentations, such as osteoarthritis with mild inflammatory episodes, a symmetrical polyarthritis mimicking RA or a destructive arthropathy. Radiology is of great help for the diagnosis of the condition, by showing a characteristic calcification of structures (cartilage, ligaments or menisci) located in the radiological joint space. CPPD arthropathy may occur without radiological chondrocalcinosis and this presentation may not be uncommon. The absence of radiological calcification may be due to smaller CPPD deposits or to the presence of other pathological changes—generally osteoarthritis or a destructive arthropathy—which may obscure the calcific deposits; cartilage and menisci degraded and taken away from the joint space in the osteoarthritis knee joint may take along the crystal deposits.

Although the identification of CPPD crystals in synovial fluid obtained from inflamed joints permits an accurate diagnosis, quite likely the diagnosis is often based only on clinical and radiological grounds. It should be remembered that radiological chondrocalcinosis is a frequent finding in healthy aged people (15% between 65 and 74 yr; 36% between 75 < 84 yr; 44% > 85 yr [8]). Any joint pain in patients of this age group may be easily mislabelled in these bases. Synovial fluid analysis offers the definitive proof of the presence of CPPD crystals in the synovial fluid. As is the case in gout, besides being present in the synovial fluid obtained from inflamed joints, CPPD crystals are also regularly found in uninflamed joints [9] offering the possibility of an accurate diagnosis during asymptomatic periods, or in clinically uninflamed joints.

Synovial fluid analysis for MSU or CPPD crystal identification is a very simple procedure: only an ordinary microscope provided with polarized filters and a first-order red compensator is needed. Observation of a fresh synovial fluid sample with polarized filters, but without the compensator, allows the strongly birefringent needle-shaped MSU crystals to be seen very easily, showing nearly all the crystals the same amount of birefringence. The use of the first-order red compensator shows their characteristic negative elongation which helps to differentiate them from other crystal types (morphologically, CPPD crystals are so different from MSU crystals that the possibility of confusion by a trained observer is small [10]; the first-order red compensator is very useful on those occasions in which both MSU and CPPD crystals coincide in the same synovial fluid sample, since some CPPD crystals are needle-shaped). The possibility of either steroid crystals from previous intra-articular injections or birefringent artefacts, which are so common in preparations being observed with the polarized microscope, as sources of error must be remembered, although easily recognized by experienced observers.

The identification of CPPD crystals may be more tricky: they have different shapes, from needle-shaped (morphologically similar to MSU crystals) to parallelepipedic and rhomboid; often they are very minute and intracellular, and better seen with a 1000 x oil lens, or even better at 1000 x with a phase...
microscope. Some authors consider that CPPD crystals are better seen with polarized filters, and others with ordinary light [11], and this is my strong feeling too. It may lead to confusion that many of these crystals do not show birefringence (only ~20% of them show it in our experience [12]; whether this percentage may vary with polarized microscopes of different characteristics or qualities is an open question). For anyone interested in the subject, it may be worth examining under a 400× lens, or a 1000× oil lens, a fresh synovial fluid sample containing CPPD crystals, which often are abundant, frequently intracellular, and very well seen at the higher magnification, locating and counting the crystals with ordinary light in a field, and then crossing the polarized filters to check how many of them shine. Contrary to gout, not all the crystals show the same degree of birefringence and in very few the birefringence is very strong. A more definitive identification is provided by their positive elongation when observed with polarized filters and a first-order red compensator. The definitive identification of crystals requires method unavailable in hospitals, such as X-ray diffraction.

It is uncertain what percentage of rheumatologists feel confident in establishing the diagnosis of gout and CPPD arthropathy only on clinical grounds, but this is likely a common practice. Crystal arthropathies are an important part of the core of rheumatology and although other physicians may feel happy with their clinical diagnosis (a feeling strengthened by rheumatologists' own content with such approach), rheumatologists should always require for diagnosis the definitive proof, which is in their hands. Obtaining synovial fluid from inflamed joints is a standard procedure, and the technical skill required for tapping asymptomatic knee of first MTP joints (which can be entered from above, lateral to the extensor tendon, while pulling the toe to open up the joint space—local anaesthesia and an insulin syringe may help) is small in physicians used to arthrocentesis and infiltration. Crystal identification should be an essential part of rheumatology training programmes, and truly became a routine bedside practice, enriching a specialty in which the use of techniques is scanty. Rheumatologists should become as skilled in crystal identification as haematologists are in the morphological recognition of the different blood and bone marrow cells. Crystal arthritides may appear simple diseases, but their sufferers are likely to have lifelong trouble and may need lifelong treatment, characteristics which undoubtedly merit an accurate diagnosis.

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