equal. Women who reach the menopause prematurely—particularly those under 40—show a seven-fold increase in the incidence of myocardial ischaemia compared with women who are still menstruating. Premenopausal women have significantly lower total serum lipoproteins and cholesterol levels than men of the same age or women who have reached the menopause. Administered oestrogens will decrease the levels of cholesterol and lipoproteins and most cardiologists regard it as sensible to give oestrogens to women with a premature

menopause. There is at present, however, little reliable evidence that oestrogens given to women in their 50s and 60s will lower the incidence of coronary artery disease. There is also little evidence that oestrogens can prevent the development of osteoporosis in women.

If oestrogens are given carefully and sensibly they can alleviate much discomfort at the time of the menopause. Nevertheless, their use must be part of a comprehensive clinical approach, and they are not a panacea for all ills.

Clinical Problems

Classification of the Arthropathies*

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There are a large number of degenerative and inflammatory conditions which affect bones and joints. In a review in 1969 I listed 179,¹ but my colleagues and I have thought of several more since. Though a handful of conditions cause most attendances at rheumatism clinics many patients with arthropathies due to many other much rarer conditions go to almost every department of a general hospital every day, and with overseas travel so readily available every general practitioner can encounter all or any of the rarer arthropathies from any part of the world at any time. Current classifications of the arthropathies do not allow for this. In Copeman's current *Textbook of the Rheumatic Diseases*² the editor gives the proposed classification of the International League against Rheumatism and a nomenclature and classification tentatively adopted by the American Rheumatism Association. The latter is the more comprehensive and is based, as far as is possible, on aetiological factors. It seems timely, however, to look again at this classification, for many conditions have now been described which do not appear in any of these classifications. I therefore suggest the following, which, though fairly comprehensive, cannot claim to be completely so.

Congenital

Congenital conditions may cause abnormalities of joints by contractions (arthrogryphosis multiplex congenita, Hurler's syndrome); trauma from increased laxity and hyperextensibility of joints (hypermobility syndrome, Ehlers-Danlos syndrome, Morquio-Brailsford osteochondrodystrophy); or from failure to appreciate pain (congenital indifference to pain, familial dysautonomia). In some cases congenital abnormalities lead to premature osteoarthritis (osteodysplasty, hypermobility syndrome, dysplasia epiphysialis multiplex). In others unnatural fragility of tissues predispose to joint effusions, contractions, and subsequent deformities (Ehlers-Danlos syndrome,

osteogenesis imperfecta). In most cases mental development is not significantly affected—Hurler's syndrome and some cases of arthrogryphosis being exceptions to this rule. Apart from the risk of crippling and deformity the general health is usually unimpaired unless there are associated congenital abnormalities of vital structures, as there may be in some cases of Ehlers-Danlos syndrome. There may well be five separate entities under the latter heading, and there seem to be several different subgroups also of the Morquio-Brailsford osteochondrodystrophy.

Degenerative, Traumatic, and Occupational

All people suffer the changes of ageing cartilage and bone, but only in some do symptoms warrant the diagnosis of osteoarthritis. This, in turn, depends on pain and complaint threshold, one man's ache being another man's agony. While women have the reputation of being more stoical than men hospital admissions and outpatient attendances hardly bear this out; women pre-ominate in our experience in both. As a student said in the rheumatism clinic, it seems that women have the symptoms here and men the physical signs. Generalized osteoarthritis is, however, more common in women than in men. Traumatic and occupational syndromes are legion, ranging from base-fiddler's thumb to miner's knee and porter's neck, the last due to the repeated trauma of fish baskets being piled high on the head.

Dietetic

Vitamin deficiency is today rare in this country but for that very reason is more likely to be missed. The danger of missing rickets lies in the resultant deformities, particularly of the pelvis, in girls. Kashin-Beck's disease is a condition noted in the valleys of Siberia and thought to be due to fusarial infection of flour leading to cartilage degeneration and premature osteoarthrotic changes.

Endocrine

Acromegaly, myxoedema, and hyperparathyroidism are all associated on occasion with an arthropathy. Indeed, in the

*Based on a postgraduate lecture given at the Institute of Orthopaedics, Great Portland Street, London W.1. on 30 September 1970.

original description of myxoedema Sir William Gull drew attention to muscle stiffness and joint swelling. Apart from these, however, there is clearly a strong endocrine influence in other disorders—as, for instance, in generalized osteoarthritis, which often comes on about the time of the menopause.

Haematological

In any arthropathy a full haematological investigation should be done, but certain disorders may present as an arthropathy which are primarily haematological in origin. Haemarthrosis is not uncommon in haemophilia (factor VII deficiency) and Christmas disease (factor IX deficiency), though rare in von Willebrand's disease. Leukaemia presents not infrequently with haemorrhagic, articular, or periarticular complications and sometimes with flitting pains resembling rheumatic fever. About a quarter of patients with agammaglobulinaemia, congenital or acquired, develop a nonsuppurative arthritis not unlike rheumatoid arthritis, though radiological changes are rare. In sickle-cell anaemia painful crises may occur in bones and joints in adults or children and aseptic necrosis of bone may occur, particularly in heads of humerus or femur.

Idiopathic

Unfortunately, idiopathic arthropathies still occupy a very large section. Though ankylosing spondylitis, Felty's syndrome, Still's disease, Sjögren's syndrome, and palindromic rheumatism can all be considered to be variants of rheumatoid arthritis they all have separate and peculiar features which make them different as regards treatment and prognosis. Many cases, perhaps most, of polymyalgia rheumatica are undoubtedly due to an arteritis but in some no adequate aetiology is discovered.

Infective

In the infective arthropathies the infecting organism is present in the joint tissues. The gonococcus, for instance, in gonococcal arthritis; brucella abortus in abortus arthritis. They may sometimes assume epidemic proportions, as in epidemic Australian arthritis and chikungunya and o'nyong-nyong fever. Rubella arthritis is not uncommon in this country at present, and is an interesting example of a virus-induced disease which may closely resemble rheumatoid arthritis except in its complete and relatively rapid resolution. For some days this infective arthritis may appear to be identical with an early rheumatoid arthritis but it then regresses and does not become chronic.

Postinfective Arthropathies

Reiter's (Brodie's) disease is today probably more common than rheumatic fever. It may follow dysentery, gonorrhoea, or non-specific urethritis. Incomplete forms of the triad (rash, urethral discharge, and arthritis) are common. It may progress to permanent changes of rheumatoid type or spondylitic type and, as in ankylosing spondylitis, may rarely be accompanied by aortic reflux. Rheumatic fever following streptococcal infection is much more rare nowadays. The syndrome seen after coronary thrombosis and prostatectomy are also relatively uncommon.

Metabolic

Amyloidosis may be a complication of arthropathies, notably rheumatoid arthritis but also ankylosing spondylitis and

Reiter's disease. It may also be a primary disorder causing arthritic symptoms which may be confused with other arthropathies. In chondrocalcinosis articularis (pseudo or "calcium" gout) calcium pyrophosphate is thrown down in articular tissue and may cause an acute crystal synovitis in the same way as urate crystals do in true gout. The knees are commonly involved but in some cases symmetrical involvement of many large and medium sized joints occurs. Calcification is common in x-ray films taken some weeks later (unlike uric acid gout, where calcification of tophaceous material is rare). Para-articular deposits of calcium salts also occur in uraemia and in patients treated with dialysis and renal grafting. Such patients may present with considerable effusions in knees, ankles, and other joints. The fluid from such joints and in the blood may give a positive sheep-cell agglutination test. Multicentric reticulohistiocytosis may resemble rheumatoid arthritis in adults as changes occur in fingers and tendons and tendon sheaths but yellow nodules on forehead, ears, and elsewhere suggest the true diagnosis, which is confirmed by biopsy.

Vascular

Avascular necrosis occurs in caisson disease, in fat embolism, and occasionally in chronic alcoholism; hips and shoulders being predominantly affected, knees less often. Giant-cell arteritis accounts for many cases of appreciable morning stiffness in the shoulder and hip joints of the elderly in association with a sedimentation rate of over 80 mm in one hour (Westergren). This same disorder is probably responsible for many, if not most, cases of polymyalgia rheumatica. Polyarteritis nodosa may be triggered off by a number of agents; recently Australia antigen has been incriminated³ and we have recently had such a case under our care. It is of interest that in 1947 Paull reported four cases from an American military hospital and in each instance an inoculation against yellow fever had been given two to four months previously.¹ In three cases the patient had become jaundiced at about the time of onset of the polyarteritis. Rose⁵ has also seen two cases of polyarteritis associated with an illness resembling hepatitis.

Neoplastic

Metastatic malignant disease usually causes pain and swelling of bone and para-articular tissues rather than the articular tissues themselves, but in pseudohypertrophic pulmonary osteoarthropathy the joints themselves become involved, knees and ankles usually being swollen in association with definite clubbing and periosteal new bone deposition. The underlying lesion is usually malignant disease of the lung, but other conditions such as congenital cyanotic heart disease are occasionally responsible. Two interesting cases were reported from Philadelphia.⁶ Clubbing was present in two women in association with, in one case, juvenile polyposis of the colon and, in the other, congenital heart disease. During pregnancy the full picture of pseudohypertrophic pulmonary osteoarthropathy occurred at the end of the third month. Acute symptoms settled a few days after delivery leaving only residual clubbing.

New growths may occasionally involve the joint directly. The benign osteoid osteoma may, though not truly an arthropathy, cause diagnostic confusion, as the pain it causes is often worse at night and after movements, starting as an intermittent pain and becoming more severe. There are no physical signs, though typical radiological changes may be present, usually in the femur or tibia.

Neuropathic

Median nerve carpal tunnel compression may be an early manifestation of rheumatoid arthritis: it may also, however, occur in other conditions such as pregnancy, myxoedema, acromegaly, and multiple myeloma. Other compression neuropathies are usually unrelated to arthritis, through ulnar and digital nerves may be affected in rheumatoid arthritis, the former as it passes around a grossly disorganized elbow or just below as it passes under the arcuate ligament (Osborne's syndrome).⁷ Neuropathic (Charcot) joints may occur in syphilis and syringomyelia owing to loss of sense of pain, but the arthropathy seen in diabetes mellitus is more complex, with superadded infective and ischaemic features. Neuropathic arthropathy has also been reported with meningomyelocoele, spinal cord injury, paraplegia leprosy, congenital indifference to pain, and a number of other conditions. In paraplegia osteoporosis, finger-clubbing, persistent oedema, and decubitus ulcers may all occur, as may formation of new bone and pyarthrosis and narrowing of the sacroiliac joints. In the shoulder-hand syndrome trophic changes may follow injury to the shoulder or occur some weeks after a coronary thrombosis: a similar syndrome has been reported in patients on antituberculous therapy with isoniazid⁸ but in many cases no precipitating cause is evident.

Therapeutic

Myopathy associated with alcoholism has been reported by Klinkerfuss *et al.*⁹ and Perkoff *et al.*,¹⁰ but alcoholics are also more likely to sustain fractures and they are more prone to septic arthritis and avascular necrosis of bone. Patients on prolonged corticosteroids are also more liable to develop fractures, septic arthritis, osteoporosis, and vertebral crush fractures, and in some patients gross changes occur in rheumatoid joints used excessively under cover of the drug. Many drugs may be associated with the systemic lupus-like condition, the so-called hydralazine syndrome, but procaineamide appears to be the most common offender. Acute haemarthrosis occurring in patients on anticoagulant therapy may be mistaken for gout.

Miscellaneous

Every classification must finish with a rag-bag of what cannot be fitted in elsewhere, and to those items listed in the Appendix must be added any others which will not fit into the earlier categories. The xiphoid syndrome, for instance, is caused by subluxation and undue painful mobility of the xiphisternum causing pain or discomfort in the region of the epigastrium. Fibrous knuckle pads may coexist with Dupuytren's contraction, which in turn (though rarely) may be found with Peyronie's disease. Acute pains in and around joints may occasionally be rapidly relieved by removal of a septic focus; such rare cases probably gave rise to the belief, common in the 1920s, that removal of septic foci would cure or improve cases of rheumatoid arthritis, which is very seldom the case.

Conclusion

This list of arthropathies cannot be inclusive: every two to three months of medical publications brings one or two new arthropathies to light. The above classification serves only to show the size of the field in rheumatology and the extent to which it derives from all parts of medicine. Although some 10 conditions contribute most patients seen in a rheumatic unit, the diagnostic range covers all of medicine. Rheumatology, diagnostically speaking, is very much a part

of general medicine: it is a specialty in that in the management and treatment of so many of the community special skills, knowledge, and application and special units are required, to cope with the many patients involved.

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A List of the Arthropathies compiled by F. Dudley Hart, R. T. Taylor, and E. C. Huskisson

Congenital:	Diphtheria
Achondroplasia	Erysipelas
Arthrogryphosis multiplex congenita	Glands
Camptodactyly	Gonococcal arthritis
Congenital indifference to pain	Haverhillia
Dysplasia epiphysealis multiplex	Kala-azar
Ehlers-Danlos syndrome	Leprosy
Familial dysautonomia (Riley Day syndrome)	Meningococcal fever
Hurler's syndrome (Gargoylism)	Mycoplasma pneumoniae (Eaton's agent)
Hypermobility syndrome	Pneumococcal
Marfan's syndrome	Pseudomonas pseudomallei
Morquio-Braillford osteochondrodysplasia	Rat-bite fever
Osteodysplasty	Secondary syphilis
Osteogenesis imperfecta	Subacute and acute bacterial endocarditis
Degenerative, Traumatic, and Occupational:	Tuberculosis
Ankylosing vertebral hyperostosis	Typhoid and paratyphoid fever
Osteoarthritis	Weil's disease (<i>Leptospirosis icterohaemorrhagica</i>)
Traumatic syndromes, e.g. traumatic haemarthrosis	Yaws
Occupational syndromes, e.g., porter's neck, wicket-keeper's fingers	
Dietetic:	Infections due to fungi:
Kashin-Beck disease	Actinomycosis
Rickets	Aspergillosis
Scurvy	Blastomycosis
	Coccidioidomycosis
	Cryptococcosis (torulosis)
	Histoplasmosis
	Madura foot (mycetoma pedis)
	Sporotrichosis
Endocrine:	Infections due to protozoa:
Acromegaly	Amoebiasis
Cretinism and myxoedematous arthropathy	Infections due to worms:
Hyperparathyroidism	Chylous arthritis
Thyroid acropachy	Dracunculosis (guinea worm arthritis)
	Filariasis
	Trichiniasis
Haematological:	Infections due to viruses:
Agammaglobulinaemia	Bechet's syndrome
Haemophilia and allied disorders	Cat-scratch fever
Leukaemia	Chikungunya
Sickle-cell disease	Echo virus infection
	Epidemic Australian arthritis
Idiopathic:	Glandular fever (infective mononucleosis)
Ankylosing spondylitis	Infective and serum hepatitis
Caplan's syndrome	Influenza
Crohn's disease	Lymphogranuloma venereum
Dermatomyositis and polymyositis	Measles
Erythema multiforme (Stevens-Johnson syndrome)	Mumps
Familial Mediterranean fever and other periodic disorders	O'Nyong-nyong fever
Felty's syndrome	Psittacosis
Intermittent hydrarthrosis	Rubella
Osteochondritis Dissecans	Smallpox
Osteochondrosis	
Palindromic rheumatism	Postinfective and Postinflammatory:
Pigmented villonodular synovitis	Jaccoud's arthritis
Polymyalgia rheumatica	Osteitis pubis (post-prostatectomy syndrome)
Psoriatic arthropathy	Postcoronary thrombosis syndrome
Relapsing polyarthralgia	Postdysenteric arthropathy
Rheumatoid arthritis	Postscarlatinal arthropathy
Sarcoidosis	Reiter's (Brodie's) syndrome
Schönlein-Henoch (anaphylactoid) purpura	Rheumatic fever
Scleroderma	Subacute pancreatitis
Sjögren's syndrome	
Still's disease	Metabolic:
Systemic lupus erythematosus	Amyloidosis
Ulcerative colitis	Angiokeratoma corporis diffusum (Fabry's disease)
Whipple's disease (intestinal lipodystrophy)	Biliary cirrhosis (hypercholesterolaemia)
	Calcinosis circumscripta
Infective:	Calcinosis uraemica
Infections due to bacteria, spirochaetes, and mycoplasma:	Chondrocalcinosis articularis
Anthrax	Disseminated lipogranulomatosis (Farber's disease)
Brucella abortus and Melitensis arthritis	Familial lipochrome pigmentary arthritis
Clutton's joints	Gaucher's disease

Gout
Haemochromatosis
Lipoidosis
Multicentric Reticulohistiocytosis
(Lipoid Dermatoarthritis)
Myositis ossificans
Ochronosis
Osteomalacia
Osteoporosis
Renal transplant syndrome
Xanthomatosis (primary hypercholesterolaemia)

Vascular:
Avascular necrosis (fat, caisson, etc.)
Giant-cell arteritis

Polyarteritis nodosa
Takayasu's (pulseless) disease
Wegener's granulomatosis

Neoplastic; Arthropathies associated with benign and malignant tumours:
Chondrosarcoma
Haemangioma
Left atrial myxoma
Metastatic malignant disease
Multiple myelomatosis
Osteoid osteoma
Paget sarcoma
Pseudohypertrophic pulmonary osteoarthropathy
Synovioma

Neuropathic:
Carpal tunnel median nerve compression
Charcot's joints, tabetic or syringomyelic
Diabetic arthropathy (neuropathic and infective)
Osborne's syndrome (ulnar nerve compression and other compression neuropathies)
Paraplegia syndrome
Shoulder-hand syndrome

Therapeutic:
Alcoholism
Corticosteroid arthropathy

Hydrallazine syndrome (procaine amide, oral contraceptives, etc.)
Anticoagulant therapy
Isoniazid shoulder-hand syndrome
Serum sickness

Miscellaneous:
Acro-osteolysis syndrome
Degos' syndrome
Dupuytren's contracture
Knuckle pads (Hale White's syndrome)
Paget's disease of bone
Periostitis deformans (Soriano)
Septic focus syndrome
Xyphoid syndrome

Today's Drugs

With the help of expert contributors we print in this section notes on drugs in current use

Treatment of Myasthenia—II

Severe weakness leading to paralysis may result from either a deficiency (myasthenic crisis) or an excess (cholinergic crisis) of acetylcholine at the neuromuscular junction. The differential diagnosis between these two conditions is often difficult, and the results of giving 10 mg edrophonium intravenously may provide crucial information. This drug produces improvement in a myasthenic crisis but not in a cholinergic crisis—which may, indeed, become slightly worse. Nevertheless, the drug has such a short duration of action that for a patient in cholinergic crisis any deterioration due to increased anticholinesterase activity is unlikely to have serious consequences.

Edrophonium Test

For these reasons the edrophonium test is invaluable in diagnosing paralytic problems in myasthenic patients. It may have to be resorted to repeatedly in titrating a patient's requirements of parenteral neostigmine. Even so, in employing this test it is important that the response of essential (respiratory and bulbar) muscles should be examined rather than that of non-essential (limb or ocular) muscles. This precaution is mandatory, because the same patient may have weakness in some muscle groups because of inadequate acetylcholine and simultaneous paralysis of muscle groups because of an excess of acetylcholine.¹ In other words, a cholinergic and myasthenic crisis may coexist in the same patient at the same time.

Myasthenic Crisis

The myasthenic crisis is a medical emergency requiring immediate availability of artificially assisted respiration. Tracheostomy may prove necessary. A crisis may develop as a spontaneous deterioration in the natural history of myasthenia gravis, or it may be precipitated by infection, by exertion (as in childbirth), or by surgery. Drugs which exacerbate myasthenia gravis may also provoke a crisis. These include agents which impair neuromuscular condition (such as streptomycin or neomycin), substances which reduce the excitability of muscle membrane (such as quinine or quinidine), and drugs which depress respiration (such as morphine or barbiturates). It has also been claimed that menstruation, emotional stress, and thyrotoxicosis can precipitate rapid paralysis.

A myasthenic crisis can usually be corrected by administration of an anticholinesterase. A dose of 0.5 mg neostigmine may be given by subcutaneous or intramuscular injection, repeating this every 20 minutes with frequent edrophonium tests. As previously mentioned, atropine (0.3-0.6 mg) should be administered to control the muscarinic effects of parenteral neostigmine.

Cholinergic Crisis

Like the myasthenic crisis, the cholinergic crisis is a medical emergency. Facilities must be available for tracheal intubation and positive pressure respiration. Anticholinesterases must, of course, be withheld and excessive muscarinic activity should be blocked by giving large doses of atropine. In these circumstances it is reasonable to give 2 mg atropine parenterally every hour until this treatment itself produces toxic effects. Cholinesterase reactivators have been produced as antidotes for poisoning by certain organophosphorus insecticides and "nerve" gases, and such agents—for example, pralidoxime—may be useful in cholinergic crises. A dose of 1-2 g of pralidoxime may be given by slow intravenous injection over two to four minutes. This may be repeated after 20 minutes if the response is transient or inadequate. Anticholinesterase drugs should not be started again until two successive edrophonium tests have given a "myasthenic" type of response.

Treatment Failures

As already mentioned, failure to respond to anticholinesterases may be due to overdosage (cholinergic crisis). In some cases the cause of the development of "neostigmine insensitivity" is more obscure. For example, patients may respond to edrophonium with increased muscle power but function in the corresponding muscles does not improve when longer-acting anticholinesterase agents are administered. Furthermore, the edrophonium test may be difficult to interpret, particularly if carried out within a short time of giving neostigmine. Problems of this kind are especially likely to be encountered in patients with fulminating myasthenia gravis with severe bulbar involvement, who readily develop respiratory distress. Neostigmine resistance may occur at the beginning of treatment, or it may develop at any stage after starting therapy. Patients with this type of difficulty, or with