whether men and women respond equally well to the beneficial effects of the potent antiulcer drugs that are now available.

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Drugs and breast-feeding

The doctor asked whether the drug he is prescribing will conflict with breast-feeding will probably feel a little uncomfortable. He may have learnt from irate mothers (or by personal communication from his wife) that absorbable laxatives may have a vicarious and antisocial pharmacological action on the suckling infant,[1] but otherwise his ignorance is likely to be comprehensive. In fact, the question often cannot be answered with any certainty, and the embarrassment properly rests with the whole profession and not with the individual doctor.

It would be quite wrong to dismiss the risk as theoretical or remote. Several drugs, including some with a wide margin between therapeutic and toxic actions in the mother (a "high therapeutic ratio") nevertheless produce adverse effects on the suckling infant. Examples are diazepam,[2] nalidixic acid,[3] ergot derivatives,[4] sulphonamides,[5] phenytoin,[6] phenindione,[7] amantadine,[8] and lithium,[9] and high doses of salicylate[10] or alcohol.[11] On the other hand, breast-feeding may be continued safely while taking some drugs with a low therapeutic ratio (where there is little margin between the therapeutic and toxic effects in the mother)—for example, digoxin[12] or warfarin.[13] Thus a commonsense approach based on the therapeutic ratio of the drug in the mother may lead to adverse effects in some instances and to unnecessary interruption of breast-feeding in others.

The question cannot be tackled readily from first principles, since so many factors have to be taken into account. These include the pharmacokinetics of the drug in the mother; her renal and hepatic function; protein binding of the drug in both plasma and breast milk; the pKa and lipid solubility of the drug; variability in the constituents and the volume of milk; and the high toxicity of some drugs such as sulphonamides, tetracycline, or diazepam to the infant or neonate.[10 14 15]

The doctor may turn to a standard text for help, but if he consults more than one his embarrassment will turn to sheer bewilderment. For example, the *Data Sheet Compendium*[16] and *Martindale*[17] advise that patients taking warfarin should not breast-feed, whereas a recent review[10] suggests that there is no contraindication. The same sources do not give complete or consistent advice on the use of phenytoin, amitriptyline, or propranolol, and none gives guidance about digoxin. Yet these five drugs are all widely used and have been studied in detail. Information is probably less satisfactory (if that is possible) for drugs used less often or introduced more recently.

How, then, can the doctor answer his patient's question? If he can avoid prescribing he should clearly do so. If not, a telephone call to the nearest drug information centre[18] is a sensible move. If the drug in question or a suitable alternative is considered safe, or definitely unsafe, then the correct action will be clear. For many drugs the advice should be that insufficient information is available. To some extent the choice between an attitude of safety first or one that no news is good news is a matter of personal philosophy. Nevertheless, when the benefits of breast-feeding are weighed against the few reports of vicarious drug toxicity, its continuation seems reasonable during treatment with drugs which have a high therapeutic ratio. The mother should be encouraged to report any possible adverse effect on the infant, and the doctor should pass such reports to the Committee on Safety of Medicines.

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Crystals and arthritis

Ten years ago the classification of crystal-deposition arthropathies appeared straightforward. Microscopy of synovial fluids with polarised light[1] had made it possible to identify the urate crystals of gout and to differentiate these from the calcium pyrophosphate dihydrate crystals of "pseudogout" (pyrophosphate arthropathy). Gouty patients were hyperuricaemic; while in those with pyrophosphate arthropathy the joint cartilage was seen to be calcified on radiological examination (chondrocalcinosis). In both conditions symptoms might arise either from episodes of acute crystal synovitis resulting from the phagocytosis of crystals by synovial fluid polymorphonuclear leucocytes[2] or from chronic degenerative changes due to destruction of cartilage and bone. Furthermore, both gout and pseudogout seemed to occur either as primary disorders or secondary to other diseases.

Over the past decade three lines of inquiry have suggested that the relation between crystals and arthritis is more complex than suggested in this scheme. Firstly, hydroxyapatite has been recognised as an additional type of crystal-producing arthritis; secondly, some joints have been found to contain mixtures of crystal types; and, thirdly, there appears to be an association between pyrophosphate deposition and "primary" osteoarthrosis.

Generally, crystals of hydroxyapatite (the chief mineral of bone) are too small to identify by polarised light microscopy. Nevertheless, Dieppe and his colleagues[3] and others[4] have used electron microscopy and other techniques to show that these crystals occur in the synovial fluid, synovial membrane,

and articular cartilage of at least some osteoarthrotic joints. This work is hampered by the difficulty of identifying these very small crystals,[5] but the evidence points towards their reaching the joint by some process other than as ground bone debris. One possible explanation for their occurrence in cartilage is an extension of physiological mineralisation by matrix vesicles.[6] Apatite crystals may cause inflammation[3]: acute calcific supraspinatus tendonitis[7] is probably an example. It is therefore tempting to ascribe the occasional "inflammatory" episodes in osteoarthrotic joints to synovitis due to apatite crystals. More important is the unanswered question of whether apatite crystal deposition may play a causative part in primary osteoarthrosis.

Routine polarised-light microscopy of synovial fluids taken from patients with crystal synovitis shows numerous apparently homogeneous crystals. Recently, however, more careful analysis has shown some heterogeneity in the types of crystals present.[8] Furthermore, careful searching of fluids from arthropathies believed to be unrelated to crystal deposition—such as rheumatoid arthritis—sometimes shows a few crystals of one or another type. This heterogeneity of crystal types and the appearance of occasional crystals in other types of synovitis remain to be explained.

Clinical studies of patients with radiological evidence of pyrophosphate deposition (chondrocalcinosis) have shown an unexpected association with apparently primary osteoarthrosis,[9] suggesting that deposition of pyrophosphates may play a part in its causation. Alternatively—and recent evidence points more in this direction—the association may be the other way round. The concentrations of inorganic pyrophosphate are raised in the synovial fluid not only in joints affected by pyrophosphate deposition but also in osteoarthrotic joints.[10] The source of this pyrophosphate is probably the articular cartilage chondrocyte,[11] and turnover studies suggest that raised concentrations reflect increased synthesis rather than local dissolution of crystals.[12] Chondrocyte activity is increased in osteoarthrotic cartilage.[13] Further, the observation that (immunoreactive) parathyroid hormone concentrations tend to be raised both in osteoarthrosis and in pyrophosphate arthropathy[14] suggests that mild parathyroid overactivity may be a feature in the development of osteoarthrosis in some patients, whose joints then progress to secondary pyrophosphate deposition.[15] This speculation must be viewed against the observations that pyrophosphate deposition is common in the elderly,[16] that it is sometimes familial,[17] and that it is associated with some other diseases[18]—all suggesting that it may represent the common end result of a variety of predisposing factors.

There are, then, several indications that deposition of crystals may be relevant to our understanding of a wider range of joint diseases than was first thought when the term "crystal deposition arthropathies" was introduced. Further advances may depend on the development of more effective techniques for identifying small crystals in biological specimens. Fortunately these uncertainties seldom cause confusion in a clinical context, for both polarised-light microscopy of synovial fluid and radiological screening for chondrocalcinosis remain extremely valuable diagnostic aids.

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Loose bodies in the knee

Loose bodies in the knee joint often worry doctors and patients but they only occasionally interfere with knee function and require treatment. They may consist of bone or cartilage or fragments of soft tissue derived from injured menisci or cruciate ligaments, or rarely hypertrophic synovium.[1]

There are four causes of bony or cartilaginous loose bodies in the knee—osteoarthrosis, osteochondritis dissecans, osteochondral fracture, and synovial osteochondromatosis. Loose bodies in the osteoarthrotic knee originate from osteophytes which have fractured and become free in the joint or from fragmentation of the joint surface, as may occur after collapse of a degenerate cyst.[2] In patients with osteochondritis dissecans an avascular fragment of subchondral bone with its overlying cartilage separates from the joint surface, most commonly from the lateral aspect of the medial femoral condyle. It is the avascularity of the bone which distinguishes the fragment from an osteochondral fracture,[3] which may occur when a tangential force is applied across the joint surface, as in twisting injuries or patella dislocation.

Loose bodies occurring in the knees of patients with synovial osteochondromatosis may be chondromas or osteochondromas and may be present in large numbers. They arise from proliferation of undifferentiated stem cells in the stratum synoviale.[4] The nodules grow, become pedunculated, and may drop free into the joint cavity. Some may be resorbed before they separate from the synovium, and loose bodies may be present with or without active synovial disease.

Once formed, loose bodies change their shape as a result of the action of chondrocytes. The angular margins of a fragment are rounded off by peripheral chondrocytes; these then revert to fibroblasts and proliferate to form fibrocartilage. The more central chondrocytes show degenerative changes.[5] Most loose bodies in the knee give rise to no symptoms and are of little clinical importance. Those causing symptoms, such as locking or instability, require treatment, usually removal. Difficulties may arise in diagnosis with cartilaginous loose bodies which are not visible on routine *x*-ray films. Air contrast or double contrast arthrography may be helpful, but even with these techniques the fragment may remain invisible if it has fallen into the intercondylar area or some other inaccessible part of the joint.[6] Arthroscopy may help to localise the position of a loose body immediately before removal, and small fragments may be removed through the instrument. An *x*-ray film taken when the patient is on the operating table may show the position of a radio-opaque loose body before arthrotomy.