patients were elderly women (aged 63-90) with a long history of moderately painful shoulders.¹² Examination showed limitation of movement in all four and an effusion in two. The radiological findings included periarticular calcification, rupture of the rotator cuff, and advanced degenerative changes in the glenohumeral joint. Synovial fluid was aspirated from the shoulder in each case¹³; it was viscous and had a low cell count with a predominantly mononuclear distribution—the type of fluid that is sometimes erroneously called a “non-inflammatory” effusion. Spheroid-shaped masses of hydroxyapatite crystals were found in the fluids, and collagenase and neutral protease activities were high; collagen fibrils and degradation products were also present. A synovial biopsy specimen, obtained in only one patient,¹⁴ showed evidence of osteochondromatosis with crystals in superficial areas and evidence of crystal phagocytosis by cells of the synovial lining. This combination of a destructive arthritis in the presence of hydroxyapatite deposition and activated collagenase and neutral protease in the synovial fluid prompted the authors to designate it as a new syndrome, which they termed “Milwaukee shoulder.”

The shoulder joint is the commonest site of periarticular calcification (which is usually in the rotator cuff) and acute calcific periartthritis.¹⁵ Damage to the cuff may precede crystal deposition, and shedding of crystals is the likely explanation of the sudden, acute episodes of inflammation.¹⁶ The glenohumeral joint, however, is an unusual site for advanced osteoarthritis of the sort found in Milwaukee shoulder. The authors speculate on the possible relation between periarticular calcification, rupture of the rotator cuff, and the degenerative changes, though unfortunately the sequence of events cannot be deduced from these four cases alone.

Severe joint destruction, a relatively “non-inflammatory” fluid containing mononuclear cells in the joint, and crystals in the synovium or synovial fluid have been described before.^{7 15} Indeed, this combination is common in advanced osteoarthritis and in chronic pyrophosphate arthropathy, and has been found in a variety of joints, including the shoulder.¹⁶ It may be fairly common in the elderly, especially in their knee joints. The unique finding in Milwaukee shoulder is the presence of activated collagenase and neutral protease, capable of disrupting articular cartilage, in a benign-looking synovial fluid. Cultured synovial lining cells may release these enzymes *in vitro*,¹⁷ and it is suggested that the condition arises from crystal phagocytosis that triggers their release. Crystals may pass from the site of deposition (damaged cartilage, perhaps) to synovium via synovial fluid. Such passage of crystals may be aided by rupture of the rotator cuff in the shoulder and result in phagocytosis of lining cells, release of destructive enzymes, and subsequent damage to the joint.

The importance of the cases described by McCarty and his colleagues lies not in the clinical syndrome, which may be neither unique nor common, but rather in the suggested mechanism of joint destruction arising from the detailed analysis and investigation of their four patients. Further investigation of the role of crystals in the pathogenesis of chronic destructive joint disease and the mechanisms of damage may shed new light on osteoarthritis and open up new therapeutic avenues in chronic arthritis.

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Social drinking and drugs

The interaction between alcohol and other drugs has been a subject of continued study, particularly the effect of alcohol on the hepatic metabolism of drugs.¹ A single episode of heavy drinking prolongs the elimination of many drugs from the body,^{2 3} though the clearance of antipyrine is apparently not prolonged by solitary large doses of alcohol.⁴ This response is thought to be due to inhibition of drug metabolism as well as perhaps competition for enzyme binding sites. In contrast, long-continued drinking of large quantities of alcohol causes induction of hepatic microsomal enzymes, so increasing the clearance of drugs such as phenytoin, tolbutamide, and warfarin.⁵⁻⁷ In due course chronic alcohol abuse will sometimes lead to cirrhosis of the liver, at which time the metabolic clearance of many drugs will again become slowed.^{8 9}

These observations do not tell us what may happen to drug metabolic processes in patients who engage only in so called “social drinking.” This might be a problem in patients having treatment for cardiovascular disease, since alcohol may worsen their symptoms.^{10 11} A recent study from Finland looked at the effects of propranolol and sotalol taken by 14 medical students before and 12 hours after a drinking party.¹² Alcohol increased the plasma clearance of propranolol—a beta-adrenoceptor antagonist that is cleared largely by metabolism in the liver. In contrast, the clearance of sotalol, which is mainly excreted unchanged in the urine, was unaffected by alcohol. In parallel

with these kinetic observations, Sotaniemi and his colleagues¹² found that the effect of propranolol in reducing the blood pressure was diminished after alcohol while the effects of sotalol were enhanced.

Should we now advise our patients to take an extra dose of propranolol if they go out to a party? The answer at the moment is probably "No." Blood alcohol concentrations 12 hours after drinking were still on average 68 mg/100 ml (14.76 mmol/l), indicating a substantial initial intake of alcohol. The reduction in the effect of propranolol after alcohol was small and not seen consistently. Nor need any reduced effect of propranolol necessarily be associated with its reduced blood concentrations, since correlation between the plasma concentrations of propranolol and its hypotensive effect is poor.^{13 14} Furthermore, other social activities affect the pharmacokinetics of propranolol—as well as other drugs; thus the bioavailability of propranolol is increased by food^{15 16} but decreased by cigarette smoking,¹⁷ with a resultant reduced antianginal effect.¹⁸ Clearly patients cannot be advised to take more or less propranolol depending on their various social activities. If patients develop angina or tachycardia after drinking (or smoking) then we should advise them to reduce their consumption of alcohol or tobacco. Nevertheless, clinicians need to remember that the effects of beta-adrenoceptor blocking drugs such as atenolol or sotalol, which are not extensively metabolised by the liver, will be less influenced by consumption of food and alcohol and by cigarette smoking.

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M L'E ORME

Patent ductus arteriosus in premature babies

A systolic or continuous heart murmur and bounding peripheral pulses in a premature baby suggest persisting patency of the ductus arteriosus. These signs may be observed during the first few weeks of life in 20–30% of babies under 35 weeks' gestation. Normally the ductus closes spontaneously during the ensuing weeks, and the matter could rest there were it not that some infants develop troublesome, even life-threatening, pulmonary congestion and cardiac failure because of large left-to-right shunts. Symptomatic patent ductus arteriosus is more common in premature babies with respiratory distress syndrome, and may result in the lung disease becoming protracted and complicated by recurrent bradycardia and episodes of apnoea. Babies receiving respiratory support may be resistant to weaning from their ventilators.

Early experience with surgical ligation of the ductus showed that while it quickly controlled the overt signs of cardiac failure the operation's success was limited both by mortality (ranging from a quarter to a half of all cases¹) and by morbidity from bronchopulmonary dysplasia and various complications of prematurity, including the sequelae of intraventricular haemorrhage.^{2–5} Many investigators argued that results could be improved by early operation before persistent pulmonary congestion and prolonged mechanical ventilation lead to chronic lung disease.^{3–5} The question was, how early is early? Clinically silent left-to-right ductal shunts occur in most babies with respiratory distress syndrome after 12 hours and are accepted as part and parcel of the disease.⁶ In extremely premature babies very large shunts may occur during the first few days, and the resulting cardiorespiratory deterioration may be masked by or attributed to the underlying surfactant-deficiency lung disease, particularly if a heart murmur is inapparent, as sometimes is the case.^{7 8} Clearly the sharpness of diagnostic aids will influence the timing of surgery. Radiological appearances of pulmonary congestion and cardiomegaly may be obscured by those of underlying respiratory distress syndrome, and the electrocardiogram contributes little. Echocardiographic measurement of left atrial size compared with the dimension of the aortic root reflects the size of the ductal shunt⁹ and has become standard practice in many units, though interpretation of the results has its pitfalls.^{10 11} Retrograde aortography through the umbilical arterial catheter also has its proponents.⁷

Once evidence accumulated that prostaglandins of the E type were responsible for maintaining ductal patency in fetal life^{12 13} treatment with the prostaglandin synthetase inhibitor indomethacin was soon shown to be effective in closing the ductus in premature babies with respiratory distress syndrome.^{14 15} The promise of indomethacin was that, if it proved effective and safe, very early closure of the ductus could be carried out pharmacologically, well before progressive pulmonary changes developed. Uncontrolled studies using different treatment regimens in groups of babies of various postnatal ages indicated that some responded to a single dose of indomethacin with disappearance of the murmur and clinical improvement within 24 hours but some showed no response, and in others the signs returned after an initial response. Reported rates of closure with indomethacin ranged from 18%¹⁶ to 89%.¹⁷ Permanent first-time closure appears less likely in babies who are very premature,¹⁶ of very low birth weight,^{18 19} and of advanced conceptional²⁰ and postnatal ages.²¹ According to a recent report²² from Vanderbilt

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