maternal renal disease, essential hypertension, diabetes, and collagen vascular disease are all causes of fetal growth retardation,¹ and Dawes attributed 35% of growth-retarded pregnancies to maternal vascular disease.¹³ There is increasing agreement that abnormal maternal vasculature is the most important common denominator in intrauterine growth retardation. There is less agreement, however, about the role of vascular disease in growth-retarded pregnancies which occur in the absence of maternal hypertension. Sheppard and Bonnar¹² reported uteroplacental vascular lesions in idiopathic growth retardation similar to those found in pre-eclampsia, but this association was not confirmed by Brosens and his colleagues.¹⁴ Improvements in ultrasound hold out the promise of non-invasive methods of measuring uterine blood flow during pregnancy, and these could greatly add to our understanding of how vascular factors influence birth weight.

Scott *et al*¹⁵ have attempted to measure the relative contributions of different maternal factors to small-for-gestational-age pregnancies and found smoking to be the second most important after hypertension. In their population of Oxford mothers they calculated that if smoking was stopped completely, the number of affected pregnancies would fall by 39%. Those mothers who give up smoking during pregnancy in order to improve their babies' health must receive every encouragement. Cigarette smoke may not be the only noxious factor to influence birth weight; probably both alcohol and drug abuse are also causes of growth-retarded pregnancies.¹

Progress has been slow in the obstetric management of these pregnancies. The diagnosis is difficult,¹⁶ and few therapeutic options are open to the obstetrician. We do not know whether a growth-retarded baby is better remaining in utero for as long as possible or being delivered prematurely for better nourishment in the neonatal unit. An ideal method of treatment would be one which improved intrauterine growth, allowing the pregnancy to continue to term without detriment to the fetus. Progress towards this objective will not be achieved unless methods are developed which will allow the obstetrician to diagnose intrauterine growth retardation at an early stage. Once the underlying pathological processes are well established therapeutic interventions are doomed to failure.

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Osteomalacia in chronic liver disease

For 50 years now, patients with chronic liver disease have been recognised to have bone disorders.¹ Crush fractures of the vertebrae, presenting with pain in the back, are usually due to osteoporosis²⁻⁴ (pathological decrease in the amount of histologically normal bone). Our understanding of this important—and still unsolved—problem may hardly be said to have advanced since the earliest reports. On the other hand, osteomalacia (defective calcification of bone matrix, recognised by diminished calcification fronts histologically) often has more subtle presentations such as diffuse pains and myopathy, and here real advances have been made in recent years.

Osteomalacia was shown to occur in prolonged cholestatic liver disease a quarter of a century ago,⁵ and primary biliary cirrhosis has been the classic example. Osteomalacia may also be seen, however, in patients with other forms of chronic liver disease having prolonged cholestatic features—for example, some patients with chronic active hepatitis,^{6,7} cryptogenic cirrhosis, or alcoholic liver disease.^{6,8}

Advances in our understanding of vitamin D metabolism have brought renewed interest in the osteomalacia associated with chronic liver disease, but at the same time the picture has been confused by the results of research on three aspects. Firstly, one study showed no relation between low plasma concentrations of 25-hydroxy vitamin D (the storage form of the vitamin) and osteomalacia⁸; secondly, osteomalacia was reported in patients taking prophylactic vitamin D supplements⁸⁻¹¹; and, thirdly, vitamin D₂ was reportedly ineffective in patients with liver disease.^{12,13} These findings have been interpreted as showing resistance to vitamin D, and more particularly to vitamin D₂ compounds,^{8,9} either by defective metabolism or by defective responses in the gut or in the bones. One other possibility is that the osteomalacia may have been unrelated to vitamin D.

Vitamin D has to be hydroxylated for its action, and since one of the hydroxylation steps is performed by the liver, an explanation for the osteomalacia of liver disease might be a defect in this step.^{12,13} This attractive possibility has now been effectively disproved.¹⁴ Recent work^{6,15} suggests that the osteomalacia is clearly related to low plasma concentrations of 25-hydroxy vitamin D, and thus defective intake, impaired absorption, or excessive loss must be implicated. Malabsorption of fat and fat-soluble vitamins occurs in liver disease owing to low

concentrations of bile salts in the small intestine, and malabsorption of vitamin D has been proved to occur.^{14 16} Adults, however, derive most of their vitamin D from photoconversion in the skin,¹⁷ and their dietary intake is usually well below the recommended minimum for people with little exposure to ultraviolet light,¹⁸ suggesting that in liver disease malabsorption of dietary vitamin D cannot be the major source of deficiency. There is evidence that these patients have normal photoconversion,¹⁹ thus pointing to reduced exposure to sunlight as an important factor.⁶ From present evidence, interruption of any enterohepatic circulation of vitamin D seems unlikely to make an important contribution. In our opinion reduced exposure to ultraviolet light will prove to be the major factor that, when added to malabsorption, leads to the vitamin D deficiency.⁶

Since osteomalacia is defined histologically a bone biopsy is necessary for a definitive diagnosis. In most cases, however, this is impracticable, but unfortunately the more usual indices prove of little help. The conventional radiological features occur only with gross disease. For different reasons^{6 15} there are no clear relations between the histological appearances and the serum values of calcium, phosphorus, and alkaline phosphatase, except in severe cases. In particular, the serum concentration of calcium is probably maintained by secondary hyperparathyroidism,¹⁵ despite earlier denials of this.⁸ Increased urinary hydroxyproline is a sensitive but not specific finding.⁶ Low serum concentrations of 25-hydroxy vitamin D, however (though the measurements are not widely available), seem to be closely related to the histological features of osteomalacia.^{6 15 20} and the measurement of serum 25-hydroxy vitamin D may thus be the important test in selecting patients for bone biopsy.

The treatment of the osteomalacia of chronic liver disease has now become simpler. At one time native vitamin D was said to be ineffective in curing the osteomalacia⁸⁻¹³ and hydroxylated forms of vitamin D were said to be needed.^{9 10} This has not been borne out in subsequent studies.²¹⁻²³ Histological resolution has been shown after giving parenteral vitamin D₂ in doses which produced serum concentrations no higher than those seen in normal subjects.²¹ While doses used have been several times more than the recommended dietary intake,²³ the vitamin D was given parenterally, which is known to be inefficient.^{24 25}

Our present state of knowledge suggests, therefore, that osteomalacia is preventable in patients with liver disease. Until serum assays of 25-hydroxy vitamin D are freely available for monitoring, their value must remain uncertain; treatment needs to be empirical. At present (as we described at the autumn meeting of the British Society of Gastroenterology, 1981, Exeter) it is our view that 100 000 international units intramuscularly monthly is often adequate, and it may well be that oral doses of the order of 2000 international units a day will also prove satisfactory even in those with severe malabsorption of fat.²² These doses are unlikely to lead to toxicity. We recommend 100 000 international units intramuscularly monthly for prophylaxis in all patients with jaundice of longer than one year's duration⁶ if serum assays of 25-hydroxy vitamin D are not available.

So after much work on the definition and diagnosis of osteomalacia in patients with liver disease and with our much deeper understanding of the physiology and biochemistry of vitamin D we pursue a strategy suggested empirically a quarter

of a century ago⁵—and one whose value in terms of morbidity and mortality has yet to be established by rigorous studies.

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