rise in blood pressure with oral contraceptives have been disappointing. While profound biochemical changes are induced by oestrogens, including rises in plasma concentrations of renin-substrate, cortisol-binding protein, and transferrin, none of these can directly cause a rise in blood pressure. The effects on the renin-angiotensin system have received most attention. Concurrent with the increase in plasma renin-substrate there is a fall in the plasma renin concentration.[8] The change has been attributed to suppression by volume expansion,[9] but this seems unlikely, since plasma concentrations of angiotensin II, which normally parallel those of renin, are not suppressed. The inverse correlation between the plasma concentrations of renin-substrate and renin suggests that the fall in renin is due to consumption during the production of angiotensin II from the increased circulating renin-substrate.[8] Angiotensin II is a potent pressor agent, but plasma concentrations do not reflect changes in blood pressure.[10] Usually changes in the renin angiotensin system are less pronounced in patients who develop hypertension than in those who do not.

Since weight gain and fluid retention are common in women taking oestrogens[11] it is tempting to attribute the rise in blood pressure to fluid retention or mineralocorticocoid activity.[9] But again the rise in blood pressure is not related to plasma concentrations of aldosterone, deoxycorticosterone, or free cortisol[10]; and in addition no relation has been found with total exchangeable sodium or potassium, total body water, stroke volume, plasma volume, cardiac output, or body weight.[10 12]

The results of attempts to predict which women are likely to develop hypertension have also been disappointing. At first women who had previously had pre-eclampsia were thought to be particularly prone to develop hypertension from oral contraceptives,[9 13 14] but recent prospective studies have not confirmed this association.[3 16] Pritchard and Pritchard[15] found diastolic pressures of 90 mm Hg or more in only nine of 180 women who had had hypertension during pregnancy. Nor is there any link with a family history of hypertension or excessive weight gain while taking the oral contraceptive.

When women discontinue oral contraceptives their blood pressures usually fall to near baseline levels, though an excess death rate in "ex-takers" has been found in mortality studies. While newer low-dose oestrogen-progestogen contraceptives may be less harmful, there has been one report of higher blood pressures in women on these oral contraceptives than in non-users.[17]

Contraceptive-induced hypertension is, then, relatively common and it cannot be predicted. All women taking the pill should have routine blood pressure checks before and a few months after starting it and thereafter at least annually. It follows that the pill should be available only from people who are qualified and competent to measure blood pressure and should not be obtainable over the counter.

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Clinical use of 1-α-hydroxyvitamin D_3

The biological activity of vitamin D_3 (cholecalciferol) is thought to be dependent on its conversion firstly to 25-hydroxyvitamin D_3 (25-OHD_3) in the liver and thereafter to more polar metabolites. The most important of these appears to be 1,25-dihydroxyvitamin D_3 (1,25$(OH)_2D_3$), which is produced exclusively in the kidney and is highly active in stimulating both intestinal absorption of calcium and phosphate, and resorption of bone.

These actions of 1,25$(OH)_2D_3$ account for most of the known physiological effects of vitamin D.[1 2] Though lack of vitamin D is associated with defective mineralisation of bone, we have no evidence that 1,25$(OH)_2D_3$ can increase skeletal mineralisation directly: it may simply allow this process to occur by increasing the availability of calcium and phosphate. Indeed, 1,25$(OH)_2D_3$ is now considered to be a hormone that regulates mineral metabolism. Among the factors that regulate its production by the kidney are vitamin D status, plasma calcium and phosphate concentrations, and a variety of hormones including parathyroid hormone.[1–3]

Production of 1,25$(OH)_2D_3$ may be defective when there is a shortage of 25-OHD_3 due to inadequate sunlight or diet; malabsorption; or disturbances in its metabolism from liver disease, anticonvulsant osteomalacia, or the nephrotic syndrome. Renal production of 1,25$(OH)_2D_3$ may be impaired by a deficiency of renal 1-α-hydroxylase (chronic renal failure and the rarely seen vitamin-D-dependent rickets) or it may be inhibited by high plasma phosphate concentrations (chronic renal failure, hypoparathyroidism, pseudohypoparathyroidism) or by lack of parathyroid hormone (hypoparathyroidism). Whatever its cause, such a deficiency of 1,25$(OH)_2D_3$ will disturb mineral metabolism in a way refractory to treatment with physiological amounts of vitamin D (vitamin D resistance).[1 3]

The synthetic analogue of 1,25$(OH)_2D_3$ is 1-α-hydroxycholecalciferol (1-α-OHD_3), which is converted into the hormone in the liver.[4] This analogue is now available for clinical use, and, apart from small differences in its biological half life and dose responses, its effects appear[5 6] equivalent to those of 1,25$(OH)_2D_3$. Great interest has been shown in the use of 1-α-OHD_3 in the management of those disorders in which a metabolic block may be circumvented.[7] So far most experience has been in renal bone disease,[8–10] where long-term treatment with 1-α-OHD_3 in microgram doses may increase calcium absorption and raise plasma calcium concentrations, thereby healing osteomalacia and preventing progressive skeletal deformity. The rise in the plasma calcium concentration may suppress secondary secretion of parathyroid hormone, so improving hyperparathyroid bone disease, but we do not

know whether long-term administration of 1-α-OHD_3 in chronic renal failure will cause involution of the parathyroid glands ("medical parathyroidectomy"). Unfortunately the healing of bone in renal osteodystrophy is frequently incomplete, particularly in patients maintained on haemodialysis, where other factors may also contribute to bone disease.[9 11] Whether 1-α-OHD_3 can prevent the development of renal bone disease is not yet known. Small doses of 1-α-OHD_3 by mouth are also effective in treating dietary deficiency of vitamin D, hypoparathyroidism, pseudohypoparathyroidism, and vitamin-D-dependent rickets.[12–14]

The use of 1-α-OHD_3 is not confined to disorders where production of $1,25(OH)_2D_3$ is impaired. In vitamin-D-resistant rickets due to defective renal tubular reabsorption of phosphate (for example, in X-linked or type I hypophosphataemia) small doses of 1-α-OHD_3 may increase plasma phosphate and improve bone lesions.[13] The use of 1-α-OHD_3 in primary, secondary, or tertiary hyperparathyroidism before parathyroid surgery will diminish postoperative hypocalcaemia in patients with bone disease.[15] Since osteoporosis has been thought to be associated with a form of vitamin-D resistance[16] and low plasma concentrations[17] of $1,25(OH)_2D_3$, treatment with 1-α-OHD_3 has been tried in this condition too. While it may improve the calcium balance in such patients, particularly when given in combination with oestrogens,[18] the longer-term effects on bone loss and fracture require further study. Furthermore, some elderly patients with clinical osteoporosis may have histological evidence of osteomalacia, so that apparent increases in mineral mass in osteoporosis[19] may reflect mineralisation of osteoid rather than increases in bone matrix.

We have little clinical evidence that 1-α-OHD_3 or $1,25(OH)_2D_3$ have any biological actions which are not also possessed by vitamin D_3 or its derivatives, vitamin D_2, dihydrotachysterol, and 25-OHD_3. In renal bone disease, for example, comparatively large doses of 25-OHD_3 seem effective—even in anephric patients, in whom its conversion to $1,25(OH)_2D_3$ is presumably totally blocked.[20] Has, then, the availability of 1-α-OHD_3 improved the medical management of any of these conditions—apart from allowing low doses to be used? Clinical difficulties often do arise in finding the appropriate dose for the treatment of vitamin-D-resistant states with vitamin D_2, D_3, 25-OHD_3, or dihydrotachysterol, since requirements in individual patients differ and may change abruptly. Some of these problems are chemical rather than physiological owing to the instability of the older preparations during storage. But dose requirements also change with 1-α-OHD_3 independently of storage conditions.[9 14] In treating bone disease associated with uraemia, more 1-α-OHD_3 is required in the presence of overt bone disease, and both requirements and tolerance decrease as the plasma alkaline phosphatase concentration becomes normal and bone is repaired. The reasons for this change are not clear, but in consequence plasma calcium concentrations should be monitored frequently if prolonged hypercalcaemia is to be avoided. Because there is a narrow dose range between requirement (the amount needed to elicit a satisfactory response) and tolerance (the dose which just fails to give unacceptable side effects), both of which decrease with time, treatment is best started at a dose of 2-3 μg daily in adults with bone disease, decreased later to avoid hypercalcaemia. In infancy and in patients with overt bone disease a starting dose of 1-2 μg is preferable. Requirements for 1-α-OHD_3 may be greater in patients taking anticonvulsants.

Any of the vitamin D preparations may induce hypercalcaemia, but its rate of onset and reversal are more rapid with 1-α-OHD_3 than with other available forms of vitamin D, which have a much longer biological half life.[3 6] These rapid effects confer definite advantages, but whether they are the only clinical merits that distinguish 1-α-OHD_3 from other vitamin D preparations remains to be seen.

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Surgical approaches and drug treatment in the carcinoid syndrome

The carcinoid syndrome, characterised by flushing, diarrhoea, wheezing, and valvular lesions of the right heart, is due to the release of pharmacological mediators from carcinoid tumour tissue. Substances so far identified include 5-hydroxytryptamine (5HT), histamine, kallikrein, and prostaglandins. These are normally metabolised by the liver, and with tumours of intestinal origin (the most common primary site) metastases have to be present in the liver for the systemic syndrome to develop. Only about a half of the patients with hepatic deposits do in fact develop the syndrome.[1] Even when metastases are found the prognosis is relatively good: in one series of 60 patients[2] the median survival was 38 months, with 15 still alive at six years.

Carcinoid tumours arising in other sites, including the stomach, pancreas, bronchus, and thyroid teratomas of the testis or ovary, often differ from those of intestinal origin. The classic carcinoid syndrome is relatively uncommon, but since the venous drainage from these tumours is directly into the systemic circulation symptoms may occur without liver metastases.[3] Metastases in bone and skin are much more common, and the prognosis is less favourable.

The first aim in treatment should be to reduce the tumour mass—which determines, at least in part, the amount of pharmacologically active substances synthesised.[4] Even though removing all the metastases may not be feasible partial hepatectomy[5] or simple enucleation of the tumour deposits