[26] Wilson JT, Brown RD. Reye's syndrome and aspirin use: the role of prodromal illness severity and the assessment of relative risk. *Pediatrics* 1982;**69**:822-5.
[27] Reye's Syndrome Working Group. (Aspirin Foundation of America Inc.) Reye syndrome and salicylates: a spurious association. *Pediatrics* 1982; **70**:158-60.
[28] Partin JS, Partin JC, Schubert WK, Hammond JG. Serum salicylate concentrations in Reye's disease. A study of 130 biopsy-proven cases. *Lancet* 1982;i:191-3,4.
[29] Andreson BD, Alexander MS, Ng KJ, Bianchine JR. Aspirin and Reye's disease: a re-interpretation. *Lancet* 1982;i:903.
[30] Starko KM, Mullick FG. Hepatic and cerebral pathology findings in children with fatal salicylate intoxication: further evidence for a causal relation between salicylate and Reye's syndrome. *Lancet* 1983;i:326-9.
[31] Ulshen MH, Grand RJ, Crain JD, Gelfand EW. Hepatotoxicity with encephalopathy associated with aspirin therapy in rheumatoid arthritis. *J Pediatr* 1978;**93**:1034-7.
[32] Fitzgerald JF, Clark JH, Angelides AG, Wyllie R. The prognostic significance of peak ammonia levels in Reye syndrome. *Pediatrics* 1982; **70**:997-1000.

Treating the menopause

The guidelines for community menopausal clinics presented by the Family Planning Association (p 2033) show another facet of the association's activities that has been developed since the National Health Service took over its family planning clinics. These are sensible administrative recommendations, but the long term aims of the treatment are still not clear. The crucial question is whether treatment should be confined to symptoms related to the perimenopause just as long as they last or whether it should attempt the long term prophylaxis against osteoporosis.

Medication may be difficult to maintain because of poor long term compliance if prophylaxis is the main objective. The regular withdrawal bleeds induced by the oestrogen-progestogen combination may upset patients and general practitioners, and gynaecologists may be unwilling to provide their supervision. A further disincentive for the patient is the need to have an endometrial aspiration before treatment and at intervals later. A long term prophylactic regimen might be more acceptable if it were possible to predict those who may ultimately develop osteoporosis, as each patient would then have much more to gain. Clinical judgment may suggest the asthenic, fair, coffee drinker as the most likely victim, but no laboratory test is readily available—though screening with labelled diphosphonate has been suggested as a predictive test of spinal osteoporosis.[1]

Our present approach attempts to treat all perimenopausal women, recognising that only half those aged 50-55 have symptoms[2] (indeed, only half have symptoms even after oophorectomy)[3] and in only 10% are they severe enough to interfere with life style.[4] No correlation has been attempted between symptoms and the ultimate development of osteoporosis, though symptoms are associated with lower circulating concentrations of oestrone and oestradiol than are found in asymptomatic women.[5]

Yet osteoporosis is clinically very important: its long term ravages are striking. One quarter of all women over the age of 60 will develop spinal compression and one fifth will suffer a fractured hip by the age of 90. Put another way, four out of five elderly women with hip fractures have osteoporosis and one in seven will die within three months.[6] The data of Lindsay *et al* on women who had had a hysterectomy and bilateral oophorectomy and were being treated with ethinyloestradiol alone showed that if treatment was begun within two years of this precisely defined artificial menopause (the naturally occurring state is more difficult to define) the loss of bone was arrested and that by eight years later the treated and non-treated groups differed substantially.[7] If the treatment was stopped, however, there was a rapid loss of bone to the level of the untreated women at the same stage after the menopause. This is an important finding—implying that there is little long term benefit unless the treatment is maintained for a time sufficient to delay osteoporosis. The patients of Lindsay and colleagues did not have their uteruses and so had no worries about endometrial carcinoma, and they did not have the aesthetic problems of the long term maintenance of regular withdrawal bleeding. Indeed, implants of oestrogen would have been an effective alternative treatment.[8] They were also younger than the mean age of menopause in Britain (50·8).[9]

If, then, as seems possible, 10 to 15 years' treatment is required to defer the impact of osteoporosis women will need to be encouraged to take treatment until perhaps the age of 65. Treatment has proved acceptable in the short term in highly motivated younger women supported by convinced doctors, but there is little evidence for its long term acceptability in the older woman who still has her uterus. Anxiety about endometrial carcinoma has been reduced recently with the addition to the oestrogen of a sequential progestogen, which appears to prevent adverse endometrial change if given for 10 days.[10] All carcinomas found by Thom *et al* in 850 patients were in the pretreatment biopsy specimens,[11] and with the acquisition of more data it may be possible ultimately to dispense with follow up biopsies.

Is there an alternative? The case for non-hormonal treatment of osteoporosis has recently been made in the *BMJ*.[12] Possibly a predisposing cause of osteoporosis may be a suboptimal dietary intake of calcium exacerbated by a high fibre diet. If this is true calcium supplements might become routine in prophylaxis, with treatment with a microcrystalline hydroxyapatite compound reserved for patients with established osteoporosis. Regimens using sex hormones and calcium and 1α-hydroxyvitamin D_3 are comparable in maintaining calcium balance in patients with spinal osteoporosis.[13] In the light of medical and consumer doubts about the widespread use of prophylactic sex steroids to prevent osteoporosis what is needed is a prospective controlled trial of sequential oestrogen-progestogen versus calcium and 1α-hydroxyvitamin D_3 in women with a spontaneous menopause. An assessment of long term acceptability would be important for both the bleeding component and the "mental tonic" effect[14] induced by the steroids. These aspects may prove critical in determining the response of women at large.

While these symptomatic effects may determine acceptability the objective of treatment would remain the prevention of osteoporosis and ultimately fractures. If the regimen using calcium and 1α-hydroxyvitamin D_3 were effective then shorter term treatment with sex hormones might be selected as the optimum control of symptoms with non-sex hormone treatment used as long term prophylaxis. Each may then be seen to be complementary, and the regimens could be implemented in community menopausal clinics.

I D COOKE

Professor of Obstetrics and Gynaecology,
University of Sheffield,
Jessop Hospital for Women,
Sheffield S3 7RE

[1] Fogelman I, Bessent RG, Cohen HN, Hart DM, Lindsay R. Skeletal uptake of diphosphonate: a method for prediction of post-menopausal osteoporosis. *Lancet* 1980;ii:667-70.
[2] Bungay GT, Vessey MP, McPherson CK. Study of symptoms in middle life with special reference to the menopause. *Br Med J* 1980;**281**:181-3.
[3] Utian WH. The true clinical features of postmenopause and oophorectomy and their response to oestrogen therapy. *S Afr Med J* 1972;**46**:732-7.

[4] Rybo G, Westerberg H. Symptoms in the postmenopause—a population study. A preliminary report. *Acta Obstet Gynecol Scand* 1971;suppl 9: 25.
[5] Campbell S. Intensive steroid and protein hormone profiles in postmenopausal women experiencing hot flushes and a group of controls. In: Campbell S, ed. *The management of the menopause and postmenopausal years*. Lancaster: MTP Press Limited, 1976:63-77.
[6] Schiff I, Ryan KJ. Benefits of estrogen replacement. *Obstet Gynecol Surv* 1980;**35**:400-11.
[7] Lindsay R, Hart DM, Aitken JM, MacDonald EB, Anderson JB, Clarke AC. Long-term prevention of postmenopausal osteoporosis by oestrogen. Evidence for an increased bone mass after delayed onset of oestrogen treatment. *Lancet* 1976;i:1038-40, 1.
[8] Hunter DJS, Akande EO, Carr P, Stallworthy J. The clinical and endocrinological effect of oestradiol implants at the time of hysterectomy and bilateral salpingo-oophorectomy. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1973;**80**:827-33.
[9] Thompson B, Hart SA, Durno D. Menopausal age and symptomatology in a general practice. *J Biosoc Sci* 1973;**5**:71-82.
[10] Whitehead MI, Townsend PT, Pryse-Davies J, *et al.* Effects of various types and dosages of progestogens on the postmenopausal endometrium. *J Reprod Med* 1982;**27**:539-48.
[11] Thom MH, White PJ, Williams RM, *et al.* Prevention and treatment of endometrial disease in climacteric women receiving oestrogen therapy. *Lancet* 1979;ii:455-7.
[12] Dixon A StJ. Non-hormonal treatment of osteoporosis. *Br Med J* 1983; **286**:999-1000.
[13] Nordin BEC, Horsman A, Crilly RG, Marshall DH, Simpson M. Treatment of spinal osteoporosis in postmenopausal women. *Br Med J* 1980; **280**:451-4.
[14] Utian WH. The mental tonic effect of oestrogens administered to oophorectomized females. *S Afr Med J* 1972;**46**:1079-82.

Reflux nephropathy

One of the many contributions which Hodson has made in reflux nephropathy has been the organisation of two small multidisciplinary international workshops, the first held in Bermuda in 1978[1] and the second sponsored by the Kroc Foundation in the Santa Ynez Valley in California in October 1982. This four year period has seen some important advances in our knowledge of this renal disease, which ranks second only to glomerulonephritis as a cause of end stage renal failure[2 3] and is the most common cause of severe hypertension in childhood.[4]

Radionuclide methods are now widely used in the assessment of reflux nephropathy, and at the workshop M J Dillon showed how parenchymal scars could be located accurately with ^{99m}Tc labelled dimercaptosuccinic acid (DMSA); he had found high renin concentrations in segmental renal veins draining scarred areas detected on these scans. The concept that scars in kidneys affected by chronic atrophic pyelonephritis or reflux nephropathy are ischaemic and might produce renin is not new,[5] but Dillon's recent data are by far the most convincing evidence that scarred areas of this origin produce renin. He also reported that eight of 10 children with high concentrations of renin in the renal vein from a unilateral scarred kidney and three of six children with bilateral segmental scars were cured of their hypertension by surgical removal of the scarred areas. In general improved drug treatment reduced the need for such surgical excision. The young child with severe refractory hypertension, however, presents a special problem and surgery may achieve remarkable results.

One of the most reassuring papers was given by Kate Verrier-Jones, of Cardiff, who reported on long term follow up of renal function in children with vesicoureteric reflux detected during the Oxford-Cardiff bacteriuria study, based on screening 14 000 asymptomatic schoolgirls.[6] The function of individual kidneys was measured by ^{99m}Tc labelled diethylenetriaminepenta-acetic acid (DTPA); the scarred kidneys had a mean glomerular filtration rate of 30 ml/minute compared with 62 ml/minute for unscarred kidneys. There was, however, no difference between kidneys with and without reflux whether they were scarred or not. The girls attended at three monthly intervals for urine culture, but they showed poor compliance with treatment, which was prescribed only in short courses for those with infection. The actual rate of infected urine specimens was quite high; no decline in the glomerular filtration rate of individual kidneys could be found as the result of urinary tract infection in either scarred or non-scarred kidneys. The total glomerular filtration rate was the same in 21 patients in the original control group and 27 in the original treated group.

The results of this study have done much to alleviate the concern which we all may have about the impact of vesicoureteric reflux on the renal parenchyma when it continues through childhood and persists in the adolescent and adult. Some previous radiological studies have painted a much more worrying picture of increasing scar formation with age,[7 8] but Verrier-Jones's results lend some support to Jean Smellie's view of the benign course of reflux nephropathy in girls over 5 years old who are under medical supervision. Normand and Smellie advocate continuous chemotherapy and close follow up,[9] but in the Cardiff study function did not decline despite short courses of treatment and poor compliance. N Goldraich from Brazil reported on reflux nephropathy in a large paediatric service and, like Verrier-Jones, could not find progressive impairment of function after the age of 5 in children whose acute incidents were treated with antibiotics.

Though these results are reassuring to those who advocate conservative management of reflux nephropathy in childhood, we must not lose sight of the need to identify the group who end up having dialysis. The proportion of patients with reflux nephropathy who develop end stage renal failure cannot easily be calculated because in general only patients with symptoms are studied. Follow up of these detected by screening for bacteriuria (without symptoms) has produced little evidence of progression. Screening studies suggest that 0·5-1·0% of women have reflux nephropathy.[10 11] The highest estimates suggest that no more than 5-10 women per million of the population present yearly with end stage renal failure from this cause, so that probably only one woman in every 1000 with reflux nephropathy is at risk of progressing to end stage renal failure. Men who develop end stage renal failure do so at an early age (mean 22), whereas women require dialysis a decade later (mean age 33). The rate of progression may be accelerated by pregnancy. Four patients with impaired renal function in early pregnancy deteriorated rapidly requiring dialysis within a few months of delivery, in contrast to the usual slowly progressive course over 7-10 years.

Proteinuria, which reflects an underlying glomerular lesion, is the most important prognostic feature. All those whose disease progresses have proteinuria, and those with proteinuria exceeding 1 gram in 24 hours show a progressive decline in renal function. The suggestion first made 10 years ago that the development of a glomerular lesion in non-scarred parenchyma might cause progression in reflux nephropathy[2 12] arose from finding a progressive course in adults with unilateral scarring. Three more examples of progressive decline in function in women with unilateral scarred kidneys were presented at Santa Ynez. In one, the hypertrophied contralateral kidney measured 16 cm in length. The importance of a progressive glomerular lesion has been well documented by others[13 14] but the reason that it develops is uncertain. Some strongly favour the view that it is due to hyperperfusion.[15] If hyperperfusion of glomeruli in a normal sized or hypertrophied kidney in