one other is in progress.¹⁵ All the studies have examined unopposed conjugated equine oestrogens rather than oestrogens cycled with progestogens, the regimen recommended to reduce the risks of endometrial cancer caused by unopposed oestrogens.¹⁶ The beneficial cardiovascular effects shown for unopposed oestrogens do not necessarily apply to women using modern combination treatment, which may not have such favourable effects on the lipid profile.¹⁷

It remains possible that oestrogen use reflects some other, unidentified factor that is the true cause of the low cardiovascular risk in users. Although this explanation seems unlikely,^{9,11} it may be conclusively ruled out only by randomised controlled trials.

If oestrogens do have a beneficial effect on cardiovascular disease this effect together with the beneficial effects on osteoporosis and menopausal symptoms will outweigh any remaining risk of endometrial cancer.¹⁸ But until the results of prospective studies, including randomised controlled trials, of modern combination treatment are available I think that it is premature to recommend using postmenopausal hormones to prevent cardiovascular disease.

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Complications of central venous cannulation

Trauma, infection, and thrombosis

Central venous cannulation is widely used in treating seriously ill patients and may give rise to serious complications. It is used to measure right atrial pressure when monitoring treatment and to give intravenous fluids, drugs, and long term parenteral nutrition.^{1,2} Most central venous catheters are inserted into the subclavian vein by the infraclavicular approach.^{3,5} Insertion into the internal jugular vein is less common but is sometimes used after an operation. The commonest early complications are related to local trauma and include pneumothorax, haemothorax, subcutaneous emphysema, subclavian haematoma and arterial damage, pleural effusion and hydromediastinum, brachial plexus injury, air embolism, and cardiac perforation.⁶⁻⁸

Infection usually occurs later in 7-16% of patients^{3,9,10} and in up to a third of those receiving hyperalimentation.⁹ The commonest pathogens are skin commensals, particularly staphylococci.¹⁰ Fungal infections also occur and may be associated with the cannula rather than with the intravenous fluid.¹¹⁻¹³ Repeated flushing of the catheter with low dose amphotericin reduces the frequency of candida septicaemia.¹² Sepsis of the catheter is usually primary, and the overall incidence of sepsis is not reduced by subcutaneous tunneling.^{14,15} The relation between the incidence of infection and how long the catheter remains inserted is unclear. Ryan *et al* noted no increase in the incidence of sepsis in catheters inserted for 30 days or more,⁹ but this has not been substantiated by others.¹⁶

Endocardial damage from indwelling catheters is well recognised at necropsy and includes aseptic valvular vegetations, subendocardial haemorrhage, sterile thrombus, and ulceration of valve leaflets.^{16,17} Infective endocarditis has been reported in 7% of cases at necropsy¹⁸ and most commonly affects the right heart, particularly the tricuspid valve.¹⁹ It seems to be more common with catheters in the pulmonary

artery than with those in the right atrium. Left heart endocarditis is rare in patients without valvular disease,²⁰ and giving antibiotics through a central vein to treat infective endocarditis is now common.

Central vein thrombosis is a serious complication and occurs in between 4% and 35% of patients.^{21,22} Thrombosis increases with the duration of catheterisation and is not related to the cardiac index.²³ Other contributing factors include the nature of the line and its position, venous endothelial damage during insertion of the catheter, and concomitant infection. The most thrombogenic catheters are made from polyurethane and the least thrombogenic are from polyurethane coated with hydromer. Silicone catheters are only slightly less thrombogenic than those made of polyurethane.²⁴ Hoshal *et al* described a "fibrin sleeve" forming on polyethylene catheters and suggested that this was the initial step in the formation of a thrombus.²⁵ Clots form mainly in the innominate veins, the superior vena cava, and the right atrium and are rare in the right ventricle^{19,20}; clots in the right atrium are particularly common in neonates receiving parenteral nutrition.²⁶ Thrombosis occurs more commonly with catheters in the pulmonary artery (33%) than with those in the right atrium (29%) and is more common during hyperalimentation.¹⁶ Connors *et al* noted that three fifths of patients with catheters had evidence at necropsy of either microscopic emboli (65%) or emboli in a major pulmonary artery (15%).²³ Small mural thrombi commonly form in the great veins but are often adherent to the endothelium and so rarely produce important emboli.¹⁸ These thrombi develop within 48 hours after cannulation.²⁴

The position of the catheter may reduce thrombosis and endothelial damage. Right atrial catheters are best placed high in the atrium or at the lower end of the superior vena cava. Catheters placed well within the body of the atrium may

abrade the tricuspid valve or right ventricular endothelium, and if infection arises the risk of right heart endocarditis must increase.

Many of these complications may be reduced. Puncture of the subclavian vein with the patient in the head down position reduces air embolism. Strict attention to aseptic technique and the availability of a parenteral nutrition team reduce infection as does subsequent careful handling of the catheter.²⁷ Flushing antifungal agents through the catheters reduces infection. Some centres advocate low dose heparin, either subcutaneously or through the catheter, to prevent thrombosis.¹³

We have recently seen a patient with tricuspid endocarditis after central venous cannulation and a patient who died after pulmonary embolus from a sterile right ventricular thrombus. Both patients had a septicæmic illness. In the patient who died two dimensional echocardiography clearly showed the catheter prolapsing across the tricuspid valve during atrial systole. This emphasises that all right atrial catheters must be carefully positioned within the high right atrium (and confirmed by chest radiography) to avoid damage to the tricuspid valve. Furthermore, patients who develop a septicæmic illness should undergo two dimensional echocardiography even after withdrawal of the catheter to detect any potentially serious intracardiac thrombi or vegetations.

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Selenium and cancer

Whether selenium protects against cancer is still unknown

The relation of selenium with cancer has a long and tortuous history. Early in this century high doses of selenium were briefly advocated for treating haematological malignancies,¹ but in a study in 1943 high doses of selenium were shown to have induced cirrhosis and hepatocellular tumours in laboratory animals.² Better designed and more extensive studies showed, however, that selenium produced fewer rather than more tumours. Combs and Combs recently summarised 55 studies published since 1949, 49 of which found that selenium inhibited cancer.³ Yet the question of whether selenium protects against cancer is still wide open.

Selenium is an essential nutrient for man,⁴ and in central China a profoundly low intake causes cardiomyopathy in children.⁵ The plausibility of a link with cancer was increased when selenium was found to be a component of glutathione peroxidase,⁶ which helps protect macromolecules from oxidation stress.

Nearly 20 years ago Shamberger and Frost showed that mortality from cancer in the United States was inversely correlated with selenium concentrations in forage crops.⁷ This finding was refined by Shamberger *et al*⁸ and others⁹ and extended to international comparisons by Schrauzer *et al*, who found particularly strong inverse correlations for cancer of the breast and colon by either calculating selenium intake or analysing selenium concentrations in pooled blood

specimens.¹⁰ Although these geographical studies support the hypothesis that higher selenium intake reduces the risk of cancer, other dietary and non-dietary factors could account for the associations.

Studies among individuals permit a greater opportunity for controlling potential confounding factors. As selenium in foods varies with concentrations in soil the calculation of intake based on diet will generally provide a poor measure of an individual person's intake: thus most studies have used blood or tissue concentrations. In most case-control studies patients with cancer had lower concentrations of selenium. But studies based on blood concentrations are difficult to interpret; cancer may cause lower concentrations by sequestering selenium,¹¹ reducing intake, and altering absorption or secretion. Selenium concentrations decline in patients with cancer as the disease progresses,^{12,13} and patients with more advanced disease tend to have lower concentrations.^{14,15} One approach to reduce the effect of disease on selenium values is to select patients with small or early tumours. Thus Clark *et al* found reduced plasma selenium concentrations in patients with skin cancers that were not melanomas.¹⁶

In prospective studies the potential for cancer to alter selenium concentrations is minimised. An efficient design is to collect samples at the outset of the study and later analyse