Regular Review

Postmenopausal hormone replacement therapy

H S Jacobs, F E Loeffer

Several comprehensive accounts of postmenopausal hormone replacement treatment have been published in the United Kingdom in the past year so in this review we concentrate on areas which, while often controversial, are of concern to the practising physician. We discuss the effects of postmenopausal hormone replacement therapy on the risks of developing coronary heart disease, osteoporosis, and cancer and comment on the concepts of oestrogen tachyphylaxis and dependence. We conclude with our present recommendations for hormone treatment of the menopause.

Certain general concepts must be kept in mind in evaluating the burgeoning literature on postmenopausal hormone replacement therapy. The first is that nearly all the reports in this field are observational rather than experimental and many are retrospective rather than prospective. Groups of women who have chosen to take hormone treatment have been followed for varying periods and their state of health has been compared with that of a control group. Matching the control to the treatment group is an obvious problem in any such study. Quite apart from questions of whether the control group is obtained from a hospital based population or from the community, is appropriately matched for age, social class, compliance with advice related to the promotion of health, etc, women who decide to take postmenopausal hormone replacement therapy may have attitudes and behaviour with respect to healthy living and the use of medical resources that are quite different from those who decide against it. For example, Barrett-Connor recently reported that as a group such women eat healthier diets, take more exercise, and have more contacts with their practitioners than women who elect not to go on to treatment.

Although considerable consistency is developing in the reports of the benefits of oestrogen treatment, the effects of these and other biases, known and unknown, erode confidence in the magnitude of the benefits claimed. Accurate answers will only come when the evaluations are made after such biases have been allocated randomly to control and treatment groups alike. We find the arguments for substantial prospectively conducted randomised controlled trials of postmenopausal hormone replacement therapy most compelling. Moreover the evidence is that general practitioners in the United Kingdom are keen to collaborate.

The second general concept to be borne in mind concerning the evaluation of postmenopausal hormone replacement therapy is the reliance presently placed on surrogate markers of risks and benefits. Because very large trials over prolonged periods are needed to detect changes in the incidence of clinical events, attention has been focused on surrogate markers of risk such as measurements of bone density or serum concentrations of cholesterol and its subfractions. We discuss the value of this approach in more detail later; here it is necessary to recall that a distinction should be drawn between markers and mediators of risk. For example, there is agreement that a subnormal bone mineral density is both a marker and a mediator of the risk of fracture. While a low serum high density lipoprotein concentration is certainly a marker of the risk of coronary heart disease in women, there is less certainty about the extent to which it should be regarded as a mediator. Moreover, as we shall see, as new surrogates are developed conflicting results can arise.

These uncertainties may prove important in the debate concerning the possible negative impact of progestogens on the cardiovascular benefits of treatment with oestrogen (see below). Whether cotreatment with progestogens does indeed reduce the cardiovascular benefits of treatment with oestrogen will therefore only be decided by a randomised controlled trial which measures clinical end points. Meanwhile the practising clinician can but keep a close eye on the shifting interpretation of surrogate measurements of risks and benefits.

Postmenopausal hormone replacement therapy and cardiovascular disease

The commonest cause of death in postmenopausal women is a heart attack; after the age of 65 years, for every five American women who die, three will have died from cardiovascular disease and fewer than one each from cancer and from the sum of all other causes. For this reason the possibility that postmenopausal hormone replacement therapy alters a woman's risk of developing coronary disease has become a major issue. Many doctors have, however, been surprised to discover that a hormonal treatment they had learnt to avoid in women at high risk of cardiovascular disease is now being specifically advised in this situation. The paradox is partly attributable to the experience gained with the birth control pill and partly to the known relation of the incidence of coronary disease to age in men and women.

To take the latter situation first, it may seem a
paradox that while the crude death rate from coronary disease in women continues to rise at the same rate after the age of 50 as before it, the rate of increase falls off in men—that is, any change in the rate of increase of heart attacks at the time of the menopause seems to occur in men rather than women. Tunstall-Pedoe recently published a graph of mortality from coronary heart disease by sex in England and Wales which illustrates this point (figure).

It can be seen that the graph bends over much more in men than in women, the inflexion in men occurring at the 50-54 year point. The impact of these figures is increased by there being more women than men alive in the older age groups; moreover after the age of 65 years cardiovascular disease is responsible for 55-7% of deaths of American women compared with 49.9% of men.

Long term treatment with the birth control pill has been associated with an increased incidence of cardiovascular disease, particularly in women who smoke. Is it likely therefore that long term hormone replacement therapy would be associated with a reduction of cardiovascular disease? In answering this important question of plausibility, two factors should be considered. The first is the difference in hormone preparations used in the two groups, the second a possible difference in the impact of these hormones on mechanisms of thrombosis. The oral contraceptive contains a synthetic oestrogen and one of several synthetic progestogens; the oestrogens used in post-menopausal hormone replacement therapy are usually not synthetic and they and the progestogens used in combined therapy are given in lower doses than in the contraceptive pill. Moreover the majority of epidemiological studies reporting cardiovascular protection have been performed with (natural) oestrogen alone rather than with oestrogen plus progestogen. The effect of these hormones on blood pressure and surrogate risk markers is related to the dose and preparations used, so differences in their effect are to be expected. Meade and Berra have made the intriguing suggestion that the impact of these hormones on the risk of thrombosis may also be related to the level of endogenous antithrombotic factors—for example antithrombin III, levels of which are naturally high in circumstances when oestrogen treatment has proved beneficial and lower when epidemiological studies have shown it to be hazardous.

Clinical studies

In their recent review, Meade and Berra summarised the presently available data as follows: based on 12 retrospective case-control studies which described the outcome in 1874 cases of coronary disease (nearly all myocardial infarction) the results as a whole suggested a reduction in the risk of coronary disease attributable to postmenopausal oestrogen therapy of about 25%; little or no effect was detected on stroke. Based on 10 (prospective) cohort studies which recorded 1057 deaths from coronary disease and 389 from stroke in a total cohort size of more than 80,000 women, the results as a whole suggested a reduction of about 20% for coronary disease and 15% for stroke. It is to be emphasised that these are summary figures which conceal considerable variation in the results of individual studies; an American analysis which allowed, as far as possible, for the statistical power of the different studies estimated an overall reduction in the risk of coronary disease of 45%.

A point that is crucial to the evaluation of these results is the observation that nearly all the data were acquired from studies of women who were taking oestrogen alone rather than oestrogen with progestogen ("opposed" therapy)—that is, the form of treatment presently prescribed for most postmenopausal women. It is also important to note that these trials were universally conducted with oral oestrogens, for the most part using conjugated oestrogen (Premarin). There are, as yet, no comparable clinical data for the results of treatment with patches or implants.

Surrogate measures of coronary heart disease

CORONARY ANGIOGRAPHY

Three cross sectional studies comprising radiological data on 3526 women undergoing angiography recorded substantially lower relative risks (0.4 to 0.6) of coronary occlusion among users of postmenopausal oestrogen replacement therapy than among non-users. These studies did not address the issue of treatment with progestogens. Their results are considered particularly vulnerable to selection bias.

LIPIDS AND HORMONE REPLACEMENT THERAPY

Within six months of the cessation of menstrual bleeding there are increases of serum concentrations of total cholesterol (by about 6%), low density lipoprotein cholesterol (by about 11%), and triglycerides (by about 9%), together with a gradual fall in the high density lipoprotein cholesterol concentration. With the exception of triglycerides, this atherogenic profile is reversed by treatment with oestrogen. While natural oestrogens produce a more favourable response than ethinyl oestradiol, little difference was detected in the serum low density and high density lipoprotein cholesterol concentrations of women treated with Premarin in doses of 0.625 and 1.25 mg per day and oral micronised oestradiol in a dose of 2 mg per day.

The fall in low density lipoprotein concentrations results from an increased rate of low density lipoprotein breakdown; the further rise of serum triglyceride concentrations, which is related to the dose of oestrogen, is caused by increased production of triglycerides and apolipoprotein B.

Except for the effect on triglycerides, these changes are consistent with the beneficial impact of oestrogen treatment on cardiovascular disease described above and have been interpreted as being consistent with these markers of risk being mediators of disease. Certainly the particular substitution of high density lipoprotein that is most increased during treatment with oestrogen is the one shown some years ago to stimulate removal of cholesterol from cultured adipocytes that had been loaded with low density lipoprotein. The problem comes, however, when we consider the effects of the addition of progestogens to the treatment with oestrogen—a regimen that is almost axiomatic nowadays in women who have not had
hysterectomy (including those who have had an endometrial ablation) in order to avoid endometrial neoplasia. In general, treatment with 19 nortestosterone derivatives (for example, norethisterone acetate, norgestrel) blocks the oestrogen induced increase of the cardioprotective high density lipoprotein in a dose and duration related fashion. The same is true for the 17-hydroxyprogesterone derivatives such as medroxyprogesterone acetate, cyproterone acetate, and megestrol acetate, with the important proviso that although the modification of high density lipoprotein is smaller than that seen with the 19-nortestosterone derivatives, less is known about the dose and duration of treatment required for endometrial protection with these compounds. With combined therapy it seems that the final high density lipoprotein concentration, like the histological status of the endometrium, reflects the balance between oestrogenic and progesterogenic stimulation.42

Another surrogate of coronary risk that is receiving much attention at present is lipoprotein(a).43 Quite apart from its considerable strength as a marker of coronary disease, this lipoprotein is of interest because in vitro it competes with plasminogen for endothelial binding sites and so may alter the balance in blood vessels between fibrinolytic and antifibrinolytic processes.44 In addition, it may accumulate in the vessel wall of atherosclerotic arteries. It is therefore of great interest that treatment with norethisterone has been shown in one study to cause a striking fall in serum lipoprotein(a) concentrations45 and in another, treatment with medroxyprogesterone acetate (10 mg per day for 10 days per month) together with conjugated oestrogen (1-25 mg per day continuously) resulted in a halving of the plasma lipoprotein(a) concentration throughout the year of study.46 These results indicate the uncertainty implicit in basing major decisions about the safety and efficacy of postmenopausal hormone replacement therapy on surrogate measures of risk rather than on controlled trials with measurements of clinical events.

Treatment with oestrogens, which may increase fibrinogen and the activity of factors VII and X and reduce antithrombin III (see above), reduces vascular impedance in large arteries, as shown by Doppler ultrasonography.12 In the uterine arteries the effect is attenuated by treatment with progestogen.47 Parenteral administration of oestrogens may elicit similar changes in lipids and lipoproteins but the results are inconsistent.48 Avoidance of the “first pass” effect on the liver may reduce these putative beneficial actions—for example, in one study,11 while the doses of transdermal and oral conjugated oestrogens that were used produced comparable suppression of serum follicle stimulating hormone, the changes in lipoprotein concentrations and metabolism observed with the oral route were not observed with the transdermal route. It may be that higher serum oestrogen levels are needed with parenteral than with oral therapy to achieve the same intrahepatic concentrations and therefore the same effect on cholesterol metabolism. This would imply that for parenteral treatment to achieve as beneficial a lipoprotein profile as oral treatment extraplanchnic serum oestrogen concent-

Cardiovascular disease

- There is evidence that unopposed oestrogen therapy can (a) reduce the risk of coronary disease by as much as 45% and (b) reverse the postmenopausal "atherogenic" lipid profile
- It is not known whether or not opposed oestrogen therapy (that is, the addition of progestogens to protect the endometrium) diminishes these beneficial effects

Postmenopausal hormone replacement therapy and osteoporosis

Osteoporosis, which is essentially a condition of the postmenopausal years, is characterised by low bone density with microarchitectural deterioration and a consequent increased risk of fracture.13 It is the occurrence of fracture that makes the condition so serious: it has been estimated that the lifetime risk of a hip fracture is 15% in white American women and 5% in men, figures that are equivalent to the combined lifetime risk of developing breast, uterine, and ovarian cancer in women and prostatic cancer in men.14 The lifetime risk of a fracture of the radius after the age of 50 years is also 15% in women; vertebral fractures have been detected in 21% of 70 year old Danish women.15 The morbidity, mortality, and cost of this one condition are prodigious; since the population is aging and the incidence and consequence of fracture rises with age, the prospect of osteoporosis dominating our health care resources seems frightening but realistic.

Oestrogen deficiency at any age causes bone rarefaction and eventually fractures occur. For example, in a series of 200 women with amenorrhoea, of mean age 28 years, Davies and her colleagues16 found on average a 15% reduction in vertebral bone mineral density; this impairment was independent of the cause of the amenorrhoea, being of the same severity in women with primary amenorrhoea caused by premature ovarian failure as in those with secondary amenorrhoea due to weight loss. The mean bone density was lower in the 57 women who gave a history of fracture than in those who did not. We have observed that experimental oestrogen deficiency, as seen in young women treated with gonadotrophin releasing hormone analogues, may be associated with (reversible) vertebral demineralisation of as much as 10% after treatment for as little as six months. In the menopausal situation, the skeletal demineralisation caused by oestrogen deficiency may be compounded by the effects of age, by the woman having achieved a subnormal peak bone mass because of a calcium deficient diet during childhood and adolescence, by the effects of smoking and of little exercise being taken, and of course by a familial predisposition to osteoporosis. In addition there are certain specific conditions that may worsen bones, such as high dose steroid therapy and alcohol excess; inactivity caused by disease (fracture, arthritis, or stroke) also needs to be considered.

Oestrogen has a direct receptor mediated action on bone cells17 and after the menopause there is an increase in bone turnover, but with a greater increase in resorption than formation.18 Osteoclasts penetrate the trabecular units of cancellous bone and eventually destroy its microarchitecture, removing some of the template on which new bone can be formed and so contributing an irreversible element to osteoporosis.19 Up to a half of all the bone loss that occurs in women may be attributable to the menopause.20 Treatment with oestrogen increases calcium absorption and reduces its excretion, suppresses bone turnover, and so restores calcium balance to premenopausal levels.20 Both oral and parenteral oestrogen therapy restore bone mineral density measurements towards normal: potency estimates suggest minimum daily doses to prevent bone loss of 15 μg of ethinyl oestradiol, 2 mg of 17-oestradiol, 0-625 mg of conjugated oestrogens,20 and 50 μg of transdermal oestradiol.21
The risk of fracture of the hip has been shown in several trials to be reduced by between 50% and 75% after about five years of treatment with both unopposed and opposed estrogens. Kanis et al recently reported the result of a retrospective, population based case-control questionnaire study in 14 centres in six countries in southern Europe; the study aimed at examining the effects of drugs affecting bone metabolism on the risk of hip fracture in women over 50 years old. They concluded that oestrogen, high calcium intake, and calcitonin significantly decreased the risk of hip fracture. Their study did not, however, examine socioeconomic factors. Furthermore, 18% of their 2068 index cases as against only 6% of their 3532 controls had senile dementia, and women taking the drugs had a significantly better mental score than those not taking them. The authors claim that their results were not affected by excluding the dementias and adjusting for mental scores.

Apparently as soon as treatment with oestrogens is stopped preservation of bone ceases and bone density declines at its pretreatment rate. Since the incidence of hip fractures peaks after the age of 75 years and life expectancy for women is about 80 years, the hope is that, at least on a population basis, the main increase in the rate of hip fracture can be deferred until it no longer matters. Vertebral bone is also preserved by treatment with oestrogen, and radiological studies suggest that 75-85% of vertebral fractures can be prevented by long term treatment. Similar benefits have been claimed for a reduction in radial fractures.

Adverse effects of postmenopausal hormone replacement therapy

**BREAST CANCER**

Before attempting to summarise the results of the numerous epidemiological studies published in this area, it is helpful to consider the likely nature of the link that exists between oestrogens and breast cancer. We find the evidence from animal and in vitro studies, from the natural history of breast cancer (for example, its relation to the ages of menarche and menopause, to parity and body weight, the increasing incidence of breast cancer after puberty and its fall off after the menopause), and from the beneficial effects of oophorectomy and antioestrogen treatment on established disease, to constitute a persuasive argument in favour of the hypothesis that oestrogens are involved in the cause of breast cancer. If this notion is accepted, it follows that the aim of a scientific evaluation of the link is to try to fault the hypothesis rather than to attempt to prove that oestrogens cause cancer of the breast.

The relationship of postmenopausal hormone replacement therapy and breast cancer was the subject of a recent conference at the Royal Society of Medicine. To the 21 published case-control studies the participants added an additional nine, and to the 10 published cohort studies an additional four were added. Overall the results were consistent with the five published meta-analyses in showing that the relative risk of developing breast cancer is about 1:1 after 10 years of treatment and is unlikely to exceed 1:3. Little evidence could be adduced of an effect of dose or of the particular type of oestrogen used, although there was evidence that the risk increases with the duration of treatment. The data available therefore provide no reason to doubt the hypothesis of a causal role for long term treatment with oestrogens. There is too little information available to assess the role of cotreatment with progestogens.

What is the practising clinician to make of all these reports? While retaining a degree of scepticism about the power of the studies available to verify relative risks below 2, we may conclude that for a woman of about 50 years of age, a 10% increase in relative risk translates into an increase in the absolute risk of developing breast cancer of 9% to 10% during the remainder of her life. The situation is clearly more serious in women with a first degree relative with the disease. The presence of benign breast disease indicates the need for very careful surveillance.

**ENDOMETRIAL AND OVARIAN CANCER**

There is widespread agreement that treatment with unopposed oestrogen increases the risk of developing endometrial carcinoma in direct relation to the dose and duration of therapy. As reviewed by Barrett-Connor, the increase in risk, which because of the proliferative action of oestrogen on the endometrium seems biologically perfectly plausible, is threefold to sixfold after five years of use and more than 10-fold after 10 years—that is, an increase in absolute risk from about 1:1000 to 1:100 per year. The increased risk can be detected after as little as three years of use and persists for several years after the oestrogen is stopped. The addition of cyclical treatment with progestogen for 12 days per month virtually eliminates the risk of endometrial cancer. Addition of continuous progestogen, in an attempt to avoid withdrawal bleeding, seems attractive but minor unscheduled bleeding is common and the risk of endometrial carcinoma cannot be considered to have been eliminated.

A reduction in the incidence of ovarian cancer is regarded as one of the non-contraceptive benefits of the birth control pill but a similar effect of postmenopausal hormone replacement therapy has not been shown. Indeed the published reports are so conflicting that at the present time one cannot exclude an adverse effect of long term treatment on the risk of ovarian cancer.
OSTEOPOROSIS: TACHYPHYLAXIS AND ADDICTION?

There have been reports from two groups in the United Kingdom that a small proportion of women (3-15%) being treated with subcutaneous implants of oestrogen return to the clinic requesting reimplantation after decreasing intervals of time.‘ 5 7 It seems that their symptoms recur despite their having plasma oestradiol values that are still supraphysiological. A further implant at this time leads to yet higher plasma oestrogen concentrations. At least two interpretations are possible. The first is that they have developed true tachyphylaxis, the oestrogen sensitive cells in their bodies having lost the ability to respond. The second is that the symptoms leading to the request for reimplantation are not specific to oestrogen deficiency and, though sometimes including those of vasomotor instability, are more closely related to depression and a general loss of well-being. If the latter proves to be the case—and this suggestion is supported by the finding in one of the studies‘ that about half of the patients had a psychiatric history sufficiently severe to warrant referral to a psychiatrist before or during therapy—the implication will be that review of the objectives of treatment with oestrogen rather than reimplantation is the clinically appropriate response. In our opinion this approach will be more helpful than drawing the conclusion that oestrogen has become a drug of dependence.

Postmenopausal hormone replacement therapy: recommendations

There are essentially two indications for postmenopausal hormone replacement therapy: treatment of symptoms of oestrogen deficiency, and prevention of long term complications such as osteoporosis and cardiovascular disease. So far as the first is concerned, flushing and sweating attacks and symptoms of lower genital tract atrophy respond readily to oral and parenteral oestrogen. Natural oestrogens are preferred to synthetic compounds; they should be given continuously rather than in 21 day cycles; in the presence of a uterus (and that includes women who have had an endometrial ablation), co-treatment with cyclical progestogen is required (unless the patient is prepared to undergo endometrial surveillance by biopsy); and the duration of treatment is determined by the duration of symptoms. Many women being treated with oestrogens for severe symptoms report an improvement in sleep, concentration, and sense of wellbeing. The progestogens (which are not required in women who have had a hysterectomy) are taken for 12 days per cycle in the following daily doses: medroxyprogesterone acetate 10 mg, norethisterone acetate 0-7-2.5 mg, norgestrel 0-15 mg, or dydrogesterone 10-20 mg. We generally advise starting with oral combined preparations and recommend skin patches to women who have had specific problems with tablets. Available preparations are listed in the table. Subcutaneous implants of pellets of oestrogen at six monthly intervals are of particular value for women who do not wish to be bothered with tablets, but, of course, this treatment does commit them to monthly courses of oral progestogens for contraception and protection. When reimplantation is discontinued these courses of progestogen need to be continued until bleeding no longer occurs, which may take up to two years after the last implant.

We think that there are few contraindications to treatment of women with symptomatic oestrogen deficiency. Undiagnosed vaginal bleeding must always be investigated before and during treatment. A history of endometrial hyperplasia or carcinoma is usually considered a contraindication even though there is no evidence that after radical cure the prognosis is worsened by combined therapy. A history of breast cancer is again widely regarded as a contraindication; none the less, in the absence of scientific data on this point some authorities do not rule out cautious treatment of the severely symptomatic patient who has been fully informed about the risks and benefits of treatment.‘ 5 Hyperlipidaemia (with the exception of hypertriglyceridaemia) usually improves on treatment with oestrogen and we do not regard coronary disease, hypertension, diabetes, or impending elective surgery as contraindications. Moreover a case-control study of women with an average age of 65 years did not reveal an increased risk of venous thrombosis attributable to oestrogen replacement treatment.

Adverse effects of postmenopausal hormone replacement treatment are few. Oestrogen may cause breast tenderness and occasionally episodic discomfort. Both usually pass quickly but should always raise the suspicion that the dose being taken is too high. Side effects of the progestogens are more numerous and severe and are what usually limit compliance. They include breast tenderness, bloatedness, abdominal cramps, depression, anxiety, and irritability. Changing the particular progestogen, dividing the dose, or taking it last thing at night may help.‘ 6 Tibolone, a synthetic steroid related to norethynodrel which possesses weak oestrogenic, progestational, and androgenic properties, has recently been introduced in an attempt to overcome the problem of withdrawal bleeding and progestogenic side effects. Taken continuously, it certainly resolves menopausal symptoms and prevents bone demineralisation.‘ 7 Vaginal bleeding may, however, occur‘ 8 and for this reason it should not be used within a year of the last natural menstrual period.

PREVENTION OF OSTEOPOROSIS AND CORONARY DISEASE

The potential value of postmenopausal hormone replacement treatment for preventing osteoporosis and hip fracture was recently the subject of a comprehensive review in this journal.‘ 9 From their analysis of available publications, Law et al‘ 0 showed that differences in measured bone density between patients with hip fractures and controls are too small for densitometry to provide an effective screening test for the risk of hip fracture and therefore for the targeting of prophylactic hormone treatment. The same is true for vertebral fracture. The implication is that selective use of oestrogen treatment will not provide an effective strategy for reducing the community’s burden of osteoporosis. In contrast, regular exercise and stopping smoking are measures that most people can aspire to and if adopted by the whole female population may be expected to reduce the risk of hip fracture by 50% and 25% respectively.

So far as the individual woman is concerned, in
addition to advising the above measures, it seems prudent to consider long term prophyactic hormone replacement treatment for women who have had an early menopause (or an episode of premenopausal amenorrhoea), who are thin and have a slight frame, who smoke cigarettes, who have a family history of osteoporosis, or who have been on glucocorticoids. Measurements of bone density should be made before and during treatment because a significant proportion may continue to lose calcium despite oestrogen replacement in conventional doses.10

So far as the prevention of cardiovascular disease is concerned, the value to the community of targeting treatment, particularly with the combination of oestrogen and progestogen that at present seems necessary, is uncertain. For the individual woman, it seems prudent to advise those with coronary risk factors to consider long term hormone replacement treatment in addition to the above mentioned measures.

### Recommendations

- Only a minority of breast cancer or endometrial cancer would make one hesitate about treating symptomatic oestrogen deficiency with hormone replacement therapy
- Asymptomatic women with clinical risk factors for osteoporosis should be advised to consider hormone replacement therapy
- The case for bone densitometry as a basis for the selective use of hormone replacement therapy is not proved
- Asymptomatic women without risk factors for osteoporosis should make their own decisions about hormone replacement therapy after being given up to date information about risks and benefits
- Opposed oestrogen therapy is only indicated for women with a uterus (and that includes those who have had an endometrial ablation). Women who have had a hysterectomy do not need to be given progestogens


Bmj, first published as 10.1136/bmj.305.6866.1403 on 5 December 1992. Downloaded from http://www.bmj.com on 5 October 2023 by guest. Protected by copyright.