attacks. Oestrogens may increase the plasma concentrations of some of the coagulation factors with shortening of the prothrombin time. Toy *et al*[2] found this effect with synthetic oestrogens but not with "natural" oestrogen (oestriol succinate). Thus it is improbable that this mechanism was responsible for thromboembolic episodes in our patient. The oestrogen preparation she was taking was a naturally occurring one (conjugated equine oestrogen), and the patient's prothrombin times remained within the therapeutic range, at levels similar to those maintained in the past without embolic symptoms.

An increase in platelet adhesiveness, which can be shown during oestrogen therapy,[3] was probably responsible for the appearance of embolic phenomena in our patient. The importance of platelets in the genesis of emboli from prosthetic heart valves is further illustrated by reports that patients being treated with dipyridamole in addition to oral anticoagulants derive greater protection from non-fatal thromboembolism than those taking anticoagulants alone.[4]

In an extensive review of reports on oestrogen treatment in post-menopausal women, Shoemaker *et al*[5] concluded that there was no proved risk of thromboembolic disease on such treatment. While this may be true for most women, it does not necessarily apply in those with an additional predisposing factor, such as a prosthetic heart valve. Our case illustrates the potential risks of oestrogen therapy in patients with valve prostheses. Anticoagulation with warfarin or phenindione alone should not be considered to protect these patients adequately against thromboembolic complications of oestrogen treatment. Non-essential oestrogen administration should be avoided in all patients with prosthetic heart valves.

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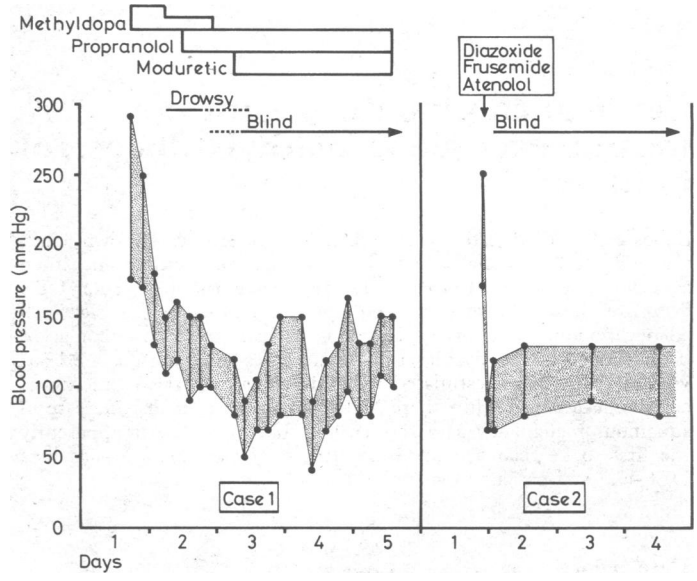
Blindness after treatment for malignant hypertension

Patients with untreated malignant hypertension are at risk of developing encephalopathy, renal failure, and cardiac failure and require urgent correction of blood pressure. Rapid reduction of hypertension, however, has been associated with cerebral and myocardial infarction.[1 2] We report on two patients who became blind after treatment for malignant hypertension.

Case reports

Case 1—A 30-year-old Caucasian housewife presented with a three-week history of blurring of vision of the left eye, two weeks' morning nausea and vomiting, and three days' haematuria. She had no history of hypertension and was taking no medication. She smoked five cigarettes daily. She had a sinus tachycardia of 124/min, blood pressure of 270/175 mm Hg, and clinical and electrocardiographic features of left ventricular hypertrophy. Fundoscopy showed grade IV hypertensive retinopathy, and visual acuity was decreased in the left eye. After admission to hospital she received methyldopa 500 mg by mouth six-hourly (figure). The next day she was confused and drowsy but there were no new focal neurological signs. Methyldopa was withdrawn and propranolol 80 mg eight-hourly and Moduretic two tablets daily given. Thirty-six hours after admission her conscious level was normal but she complained of total loss of vision and hallucinations. The pupils were bilaterally dilated and unresponsive to light. Fundal appearances were unchanged. Dexamethasone 4 mg six-hourly was given from the fourth day without measurable benefit. The only other neurological abnormality was transient urinary retention 40 hours after admission. The patient has remained blind despite good blood-pressure control, and bilateral optic atrophy has developed.

Case 2—A 32-year-old Caucasian woman presented with two weeks' blurring of vision. For four days before admission she had received tetracycline 250 mg six-hourly for a probable urinary tract infection. Four years previously she had failed to attend for treatment for mild hypertension (160/105 mm Hg). She was not taking an oral contraceptive. She smoked 15 cigarettes daily. She had a sinus tachycardia of 120/min, blood pressure of 250/170 mm Hg, and clinical and electrocardiographic signs of left ventricular hypertrophy. A chest *x*-ray film showed cardiac enlargement. Grade IV hypertensive retinopathy was present, and visual acuity was slightly decreased bilaterally. She was treated with diazoxide 300 mg given as an intravenous bolus, frusemide 80 mg intravenously, and atenolol 100 mg by mouth. Her blood pressure fell to 90/70 mm Hg within 10 minutes but rose to 120/70 mm Hg after immediate administration of intravenous saline (figure). She



Changes in blood pressure with treatment in both patients, showing when blindness first developed.

complained of blindness in both eyes and developed dilated pupils unresponsive to light. The fundal appearances did not change. The only other neurological defect was urinary retention, which developed on the day of admission and required catheterisation for two weeks. Blindness has persisted despite satisfactory blood pressure control, and bilateral optic atrophy has developed.

Further disease—In both patients renal function improved after correction of hypertension (case 1: creatinine clearance 13 ml/min rising to 33 ml/min by six weeks; case 2: serum creatinine concentration 275 μmol/l (3·1 mg/100 ml) falling to 160 μmol/l (1·8 mg/100 ml) after two weeks). The patient in case 2 had a partially treated urinary tract infection but there was no other evidence of primary renal, endocrine, or collagen disease in either patient. A cerebral computerised tomographic (CAT) scan was normal in case 1, and an isotope brain scan was normal in case 2.

Comment

We have found no published reports of blindness after treatment for malignant hypertension. Both our patients were young, active women who presented with visual impairment but none of the usual features of hypertensive encephalopathy. The predominant neurological damage was confined to the visual pathways and probably localised to the optic nerves. This site is suggested by the pupillary changes, fundal appearances, and normal CAT scan (case 1) and brain scan (case 2). The optic nerves are susceptible to ischaemic damage in temporal arteritis and arteriosclerosis.[3 4] In our patients ischaemia presumably resulted from a fall in perfusion pressure in tissue with a high interstitial pressure due to oedema. The complications of treating malignant hypertension[1 2] are usually attributed to a precipitate fall in blood pressure. Blindness occurred in case 1 despite the correction of hypertension being carried out over 24 hours, suggesting that blood pressure should be reduced even more slowly or that additional measures, such as the early use of dexamethasone, are required to prevent this devastating complication.

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Cervical carcinoma-in-situ in woman exposed to diethylstilboestrol in utero

Exposure to diethylstilboestrol (DES) in utero was shown eight years ago to be associated with vaginal adenocarcinoma[1]; since then over 300 cases have been reported. The major risk from such DES exposure, however, may not be the development of a clear-cell adenocarcinoma but of vaginal and cervical squamous neoplasia.[2] The prevalence of dysplasia in such cases is reportedly 2·1%,[3] whereas there is an estimated fivefold increase in the incidence of carcinoma-in-situ.[4] Thus there is the possibility of a vast increase in squamous malignancy as a result. The following case is apparently the first to be recorded in Great Britain of carcinoma-in-situ in a DES-exposed patient.

Case report

The patient, an unmarried woman, had been exposed to increasing doses of DES from six to 36 weeks of gestation because of a maternal history of recurrent abortion. The total dose was unknown. When she was aged 23 colposcopy showed extensive adenosis of the cervix extending on to the vaginal vault. Four years later she presented for further investigation at the Chelsea Hospital. She was nulliparous and taking oral contraceptives.

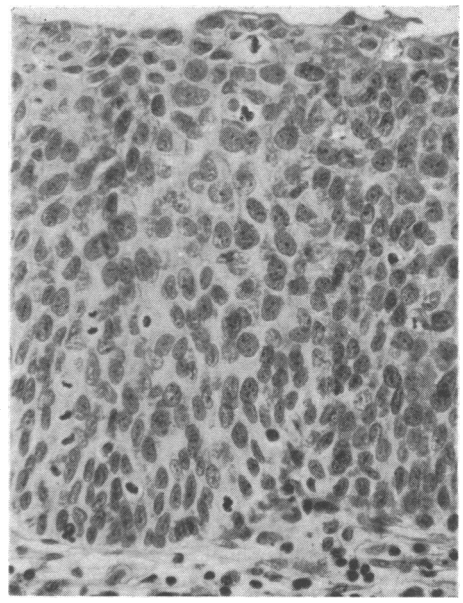
Colposcopy showed a cockscomb on the anterior lip of the cervix with pronounced punctation and aceto-white epithelium (cervical intraepithelial neoplasia grade III) in a wide transformation zone. Metaplastic changes extended on to both fornices in areas of adenosis: cytology showed dyskaryotic and malignant squames, class IV. A cone biopsy specimen was taken from the cervix, pathological examination of which showed a small os and rough nodular surface epithelium. Microscopy disclosed a squamo-columnar junction and distal immature squamous epithelium overlying endocervical glands corresponding to the area of colposcopic adenosis. Varying lengths of this squamous epithelium were severely dysplastic with changes of carcinoma-in-situ in some glands. There was no evidence of invasive carcinoma, but in two blocks the abnormal epithelium extended to the outer, resected margin.

Subsequent management included admission for cervical dilatation because of stenosis. The remaining areas of moderate dysplasia on the cervix and vaginal fornices were locally destroyed with a carbon dioxide laser. Continuing colposcopic and cytological surveillance showed no abnormality.

Comment

This case illustrates the risk of cervical intraepithelial neoplasia developing in association with adenosis, itself the result of exposure to DES in utero. We recommend that clear-cell adenocarcinoma of the vagina should be sought by careful clinical, cytological, or colposcopic observation from the menarche or age 14 onwards, whichever is the earlier. Yearly examinations or occasionally more frequent ones have been recommended. It is clearly also necessary to look for areas of abnormal metaplasia in the much-enlarged transformation zone found in these cases. Abnormal areas should be biopsied and subjected to careful histological examination. Should carcinoma-in-situ be detected precise local eradication is needed.

Ultimately invasive carcinoma may develop in some—perhaps many—of these patients, and the greatest care in follow-up will be required.



High-power photomicrograph of cone biopsy specimen from cervix showing carcinoma-in-situ. ×25 objective (original magnification).

Although satisfactory healing of the areas of adenosis may occur by squamous metaplasia within a year of onset, colposcopic changes may persist for longer.[5] Despite this degree of reassurance clearly great vigilance will be needed for some years before the risks can properly be evaluated.

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ONE HUNDRED YEARS AGO A trial for homicide has recently taken place at Avallon in France, in consequence of the poisoning of a patient by mistake. M R, a *pharmacien* at Avallon, sold to Dr L, a medical practitioner in the same town, a quantity of false angustura bark instead of pomegranate root. Dr L, misled by a certain degree of resemblance between the two substances, and believing that he was using pomegranate root, made an infusion of the substance and gave it to a patient, who died in consequence of taking it. An action for homicide by imprudence was brought against the *pharmacien* and the doctor. The tribunal at Avallon and the Court of Appeal in Paris decided that both were guilty. They refused to admit the plea that Dr L might have been misled by the similarity of the two substances, alleging that he ought to have noticed that the infusion which he prepared had not the ordinary appearance of infusion of pomegranate bark, and emitted an unusual odour; and that his suspicion ought to have been excited by the symptoms produced in another patient to whom he had given the same medicine a few days previously. The local tribunal fined M R two hundred *francs*, and Dr L twenty-five *francs*. The Court of Appeal added to the fine on the *pharmacien* a sentence of imprisonment for fifteen days, and increased Dr L's punishment to a fine of two hundred *francs*. (*British Medical Journal*, 1879.)