report is equivocal or malignant the patient is told that the nature of her lump is uncertain, the frozen-section procedure is explained, and consent for mastectomy obtained.

Those aged 60 years or more—Mammography is performed, and if the lump is reported to be benign consent for only excision is obtained. If the report is equivocal or malignant the patient is warned that her lump is probably malignant and mastectomy is likely.

Frozen-section examination is carried out regardless of grouping. If these age-based groups had been used only 19 of our 61 patients would have been asked to consent to mastectomy. Only five of the 47 patients with benign lumps would have had to consent to mastectomy, and no patient would have required mastectomy as a second procedure (table III).

TABLE III—*Suggested grouping of patients and subsequent treatment according to age and results of mammography*

Age (years)	No of patients	Mammography		Procedure	Histology: Benign	Histology: Malignant
30	14			Excision of lump	14	
31-59	37	Benign	26	Excision of lump	26	
		Equivocal or malignant	11	Frozen-section procedure	5	6
59	10	Benign	2	Excision of lump	2	
		Equivocal or malignant	8	Probable mastectomy		8
Total	61				47	14

Discussion

In this series ultrasound examination at any age did not contribute to the overall accuracy. Mammography was unnecessary in patients younger than 31 years. The aim of this study was to avoid as far as possible obtaining consent for mastectomy from women with breast lumps that subsequently proved histologically to be benign. By using a combination of clinical, mammographic, and ultrasound examinations to predict the diagnosis only 15 of the 47 patients with benign lumps were asked to consent to mastectomy. The retrospective analysis showed, by careful consideration of the age of the patients and by using mammography in selected cases together with clinical examination, that this could have been further reduced to five of the 47. Every patient with a carcinoma was asked to consent to mastectomy, and this would still have been so using the proposed scheme based on age, mammography, and clinical examination. Clearly this strategy requires to be tested on a much larger series of patients; a preliminary test on 51 patients yielded encouraging results.

We conclude that by taking a critical approach most women with benign breast lumps may be saved the anguish of consenting unnecessarily to mastectomy, while at the same time consent may be obtained from all those with carcinomas.

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Randomised trial of high doses of stilboestrol and ethisterone in pregnancy: long-term follow-up of mothers

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Summary and conclusions

In 1950 a trial was set up to evaluate the effects of large doses of stilboestrol and ethisterone on rates of fetal loss in pregnant diabetic women. Eighty women were allocated at random to receive the hormonal treatment and 76 to receive inactive tablets of identical appearance. At follow-up 27 years later, information was obtained about 97% of the women, all but four being traced. All respondents were unaware of who had received hormones. The overall mortality was 4·5 times that of women of comparable age in England and Wales, most deaths being from complications of diabetes. More tumours, mainly benign, of the reproductive tract were reported in the hormone-exposed than the non-exposed group (14 (18%) and two (3%) respectively). Four cases of malignant breast disease were reported in the hormone-exposed women and none in the non-exposed.

These findings support other evidence linking oestrogen treatment and breast cancer and suggesting that the latent period before the tumour becomes clinically apparent may be 15 years or longer.

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Introduction

During the 1940s there was optimism that substantial reductions in rates of fetal loss could be achieved by administering high doses of oestrogens, with or without progestogens, during pregnancy. This form of treatment was advocated particularly for diabetic women, in whom rates of fetal loss were exceptionally high. In 1943 White and Hunt reported that regular administration of stilboestrol and progestogen during pregnancy reduced the rate of fetal loss in diabetic women from 40% to 8%.[1] In the light of these results the Medical Research Council appointed a committee to conduct a controlled trial to assess the effects of this type of hormonal treatment on the outcome of

pregnancy in diabetic women. The study was carried out in nine centres in the United Kingdom between 1950 and 1953 and was co-ordinated at the London School of Hygiene and Tropical Medicine by the late Professor D D Reid. At that time one of us (LC) assisted with the data collection and analysis. Identical rates of spontaneous abortion (8%) and perinatal mortality (23%) were noted in the hormone-treated and non-hormone-treated groups.[2] Similar results were obtained for non-diabetic women in a randomised trial of stilboestrol treatment conducted in Chicago.[3] That both studies failed to show a beneficial effect of hormonal treatment during pregnancy did much to curb the administration of sex hormones to pregnant women, although the practice continued during the 1960s.[4]

In 1978 Bibbo *et al* reported the results of 25-year follow-up of the mothers who had participated in the Chicago-based trial.[5] They found an excess of breast cancer in the group treated with stilboestrol, although the difference was not statistically significant. We report the follow-up of the diabetic mothers in the United Kingdom trial.

Methods

Details of the study design have been reported.[2] Briefly, between July 1950 and January 1953, 161 pregnancies in diabetic women were considered to be eligible and enrolled in the trial. Each pregnancy was randomly allocated to a hormone-treated or non-hormone-treated group, after classification by the woman's age and parity and the participating centre. Both groups were given tablets that looked identical. Although 161 pregnancies were included, the pregnancies were distributed among 156 women, as five women had two pregnancies included in the trial. For each of these the second pregnancy was allocated to the opposite group to that of the first pregnancy. Since all five women received hormones at some stage they are included here in the hormone-treated group. We therefore followed up 80 hormone-treated and 76 non-hormone-treated women.

Table I shows the daily hormone dosage schedule for the treated group. The original record forms, on which progress during pregnancy

TABLE I—*Dosages of hormones given to treated women*

Stage of pregnancy	Stilboestrol (mg/day)	Ethisterone (mg/day)
Up to end of 19th week	50	25
20-23rd week inclusive	100	50
24-27th week inclusive	100	75
28-31st week inclusive	150	125
32nd week until delivery	200	250

was recorded in a standard manner, were stored at the London School of Hygiene and Tropical Medicine. These records were used to calculate the total doses of stilboestrol and ethisterone to which each woman had been exposed. Details of failure to comply with the regimen were recorded in some cases, and this was taken into account. When no additional information was recorded we assumed that tablets were taken beginning on the third day after they were dispatched and continued until the day of abortion or delivery. Since some women may not have taken all their tablets, our estimates of total hormone dose represent the highest stilboestrol and ethisterone doses to which they were likely to have been exposed.

Several methods were used to trace the women, who were never contacted direct. Instead, information was sought from their general practitioners, from hospitals and diabetic clinics, and from the Office of Population Censuses and Surveys. None of the respondents to our inquiries knew which women had received hormones. With the collaboration of the Office of Population Censuses and Surveys we were notified of all deaths, registrations of cancer, and emigrations identified by them. Copies of relevant death certificates and cancer registration forms were obtained. For those who, according to the Office of Population Censuses and Surveys, were alive and registered with a general practitioner we asked the general practitioner to complete a short questionnaire about the patient. This included demographic questions and questions about the occurrence of malignant and benign neoplasms. For women who could not be located by the Office of Population Censuses and Surveys we inquired further at the hospitals and diabetic clinics that they had attended during 1950-3. Finally, since we are also following up their children, we wrote to the children's general practitioners, asking if they knew the whereabouts of the mother and, if so, would provide us with the name and address of her general practitioner or other information by which her general practitioner could be identified.

Results

Follow-up was remarkably successful in both treatment groups (table II), information being obtained for 152 women (97%). One woman had emigrated and 50 had died during the average 27·3 years of follow-up, leaving 101 women who in January 1979 were still alive and resident in the United Kingdom. A completed questionnaire was obtained from the general practitioners of 98 of these 101 women. The medical records of two of the remaining three women could not be located by the general practitioner, and the third woman's general practitioner was reluctant to complete our questionnaire.

TABLE II—*Status at follow-up on 1 January 1979 of all women studied*

	Hormone-treated	Non-hormone-treated
Alive:		
Questionnaire answered	56	42
Questionnaire not answered	1	2
Dead	22	28
Emigrated		1
Not traced	1	3
Total	80	76

Table III shows the characteristics of the 79 hormone-treated and 72 non-hormone-treated women who were traced by the Office of Population Censuses and Surveys and still resident in the United Kingdom. Their mean age, weight, parity, age at first live birth, and history of fetal loss were similar both at the time of entry and at the completion of the original study. Mean systolic and diastolic blood pressures were somewhat higher in the non-exposed than the exposed group. The proportions of surviving women who had subsequently had a hysterectomy were similar (seven women (13%) and six (14%) respectively). More women from the hormone-treated group had since taken oral contraceptives or other preparations containing sex hormones (14 (25%) and six (14%) respectively), but the differences were not statistically significant.

TABLE III—*Characteristics of women at time of recruitment into original trial, excluding those not traced or emigrated. Figures are means ± SD*

Characteristic	Hormone-treated (n = 79)	Non-hormone-treated (n = 72)
Age	29·3 ± 4·7	29·9 ± 5·4
Weight (kg)	59·7 ± 8·6	59·8 ± 8·7
Systolic blood pressure (mm Hg)	122·9 ± 11·9	126·1 ± 13·9
Diastolic blood pressure (mm Hg)	74·3 ± 8·6	76·9 ± 8·1
Age at birth of first child*	26·4 ± 4·2	26·5 ± 5·0
No of live births*	1·7 ± 1·5	1·6 ± 0·9
No of fetal losses*	0·7 ± 1·0	0·7 ± 1·1

*Including the trial pregnancy.

The mortality of the diabetic women was 4·5 times that of women of comparable age in England and Wales: 50 deaths were recorded, whereas only 11·1 would have been expected.[6 7] Table IV lists the causes of death, most being complications of diabetes. This is not surprising, since 27 years earlier 148 of the 152 women (97%) had required insulin for their diabetes. The mortality in the hormone-treated group (28%) was lower than that in the non-hormone-treated group (39%), but the difference was not significant. The difference is partly related to the initially higher average blood pressures of the non-hormone-treated women (table III). The mortality for those with a diastolic pressure below 80 mm Hg was 27% in the treated group and 29% in the untreated; for those with a blood pressure equal to or greater than 80 mm Hg the mortality was 30% and 47%, respectively.

TABLE IV—*Causes of death in the women studied*

	Hormone-treated	Non-hormone-treated
Complications of diabetes		
Heart disease	7	12
Renal disease	4	7
Diabetic ketoacidosis, infections, etc	4	5
Other causes		
Cancer	2	1
Cerebrovascular disease	2	2
Asthma	1	
Accidents and suicide	1	1
Unknown	1	
Total (%)	22 (28)	28 (39)

TABLE V—*Tumours reported in the women*

	Hormone-treated	Non-hormone-treated
Reproductive sites		
Breast:		
Malignant	4	
Benign	1	1
Uterus:		
Malignant		
Benign	8	1
Ovary:		
Malignant		
Benign	1	
Other sites		
Skin:		
Malignant	1	
Benign	1	
Oesophagus:		
Malignant		1
Brain:		
Malignant	1	
Bone:		
Benign	1	1
Total	18	4

Table V lists the tumours, both malignant and benign, reported in the two groups. Four breast cancers were reported, all in hormone-treated women ($p=0.06$, Fisher's exact test); these were diagnosed 18, 20, 22, and 22 years respectively after treatment. Three of the four tumours showed spread beyond the breast at surgery, and one later proved fatal. The lesions were described as "spheroidal cell carcinoma," "adenoid cystic cylindroma," "massive intraduct and intra-acinar carcinoma of the comedo type," and "adenocarcinoma." The incidence of breast cancer in the hormone-treated group was higher than our estimate of that expected in women of comparable age in England and Wales,[8] where 1·4 cases would have been expected; 1·2 cases would have been expected in the non-hormone-treated group. Two women, one in each group, underwent surgical treatment for benign breast disease. The pathology and severity of the lesions differed: the hormone-treated woman had extensive sclerosing adenosis of both breasts, which was sufficiently severe to warrant bilateral mastectomy, whereas the woman in the non-hormone-treated group had a breast cyst from which clear fluid was aspirated and no further surgery was performed.

No malignant disease of the uterus was reported. A cervical smear in one woman (hormone-treated) was abnormal, but the atypia finally disappeared and no specific treatment was instituted. Eight benign tumours of the uterus were reported in the hormone-treated group (four fibroids and four uterine or cervical polyps), but only one fibroid was reported in the non-hormone-treated group ($p=0.04$, Fisher's exact test). Tumours of non-reproductive sites were few. Overall there were 18 tumours in the hormone-treated group and four in the untreated group ($\chi^2=7.8$, $p<0.01$).

Not all women allocated to the hormone-treated group had received equal amounts of stilboestrol or ethisterone; table VI shows the dosages of stilboestrol. Some women who, for example, had aborted before the tablets reached them had received no hormones at all. The occurrence of tumours of reproductive sites was examined in relation to the estimated dose of stilboestrol to which a woman was exposed. The incidence was 7·1% (1/14) in women who had received ≥ 20 g; 21·8% (12/55) in those who had received 10-19 g; 10·0% (1/10) in those who had received <10 g; and 2·8% (2/72) in those in the untreated group. Some evidence of a dose-response relation was obtained (χ^2 for trend $=7.0$, $p<0.01$), but the incidence was lower in those exposed to the highest doses of stilboestrol—that is, over 20 g—than in those exposed to the lower doses.

Discussion

Although the numbers reported here are small, the higher incidence of breast cancer in hormone-treated than non-hormone-treated women is consistent with the findings from the Chicago study.[5] In both studies the allocation of women to hormonal or inactive treatment was random, the groups were initially similar, and those reporting disease did not know which patients had been treated. Thus the differences in disease patterns between the groups cannot be accounted for by any process of self-selection or by reporting bias. Preliminary findings from the National Co-operative Diethylstilbestrol Adenosis Project in the United States are reported to show no excess of breast cancer in women who had been exposed to stilboestrol during pregnancy.[9] Unlike our studies, and those done in Chicago stilboestrol was not allocated at random nor were data presented on the incidence of breast cancer in a control group followed up in the same manner as in the exposed women.

The high incidence of benign uterine tumours, particularly uterine polyps, reported here in the hormone-treated group is of interest. As early as 1949 White, one of the main proponents of hormonal treatment for pregnant diabetics, noted that hyperplastic endometritis and its complications were the most common short-term sequelae of this form of treatment.[10] Five per cent of her patients treated with high doses of oestrogen and progestogen were reported to develop severe postpartum bleeding between three months and one year after delivery. Examination of curettage specimens in 50 such patients showed pronounced adenomatous hyperplasia in all cases, with frequent polypoid and cystic changes.[11] Later Meissner *et al* showed that similar endometrial hyperplasia and polyps, as well as endometrial carcinoma and uterine fibroids, could be induced by giving stilboestrol to either diabetic or non-diabetic rabbits but did not occur when placebos were used.[12] A similar increase in benign uterine tumours was not noted in the Chicago study.

There are several possible reasons for this discrepancy. In our study the treated women received stilboestrol and ethisterone, whereas the women in the Chicago study received only stilboestrol, so the occurrence of benign tumours may be related to the progestational component of their treatment. Secondly, the women in our study were diabetic, whereas those in the Chicago study were not. Neither of these explanations, however, accords with evidence from animal experiments.[12] The medical histories of the women in our survey were obtained from general practitioners, hospitals, cancer registries, and other official sources, whereas the medical histories of women in the Chicago study were obtained by interviewing them over the telephone. Possibly women are less aware of or less able to describe

TABLE VI—*Distribution of maximum dose of stilboestrol to which the 79 hormone-treated women were exposed during pregnancy. (The one woman who could not be traced was recorded as having taken no tablets)*

Dosage (g)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
No of women	2	1	2	1		1	1		1	1			2	1	6	6	8	11	14	7	3	5	2	2	2

accurately benign lesions than are their general practitioners or other medical personnel. Finally, we followed up 97% of the original study population, compared with 63% in the Chicago study. Clearly more information is needed on the occurrence of benign uterine tumours in women exposed to oestrogens, with and without progestogens, particularly as these lesions may be precursors of malignant disease.

We must emphasise that the doses of hormones to which the pregnant women were exposed were massive. The average dose of stilboestrol was estimated to be 16·3 g and of ethisterone 13·8 g. In the Chicago study the women were exposed to about 11 g of stilboestrol.[5] Stilboestrol when given for menopausal symptoms is usually administered as a daily dose of 0·5 mg. Thus the average dose accumulated by the pregnant women in our study was equivalent to more than 80 years of continuous menopausal oestrogen treatment. None the less, the incidence of breast cancer was high, 5% of the treated group having already developed breast cancer although the average age of those who were still alive was only 55·8 years. Interestingly, no breast cancer occurred until 18 years after treatment; a similarly long latent period was evident in the Chicago study. Another study of breast cancer and menopausal oestrogen use found an increased risk of breast cancer after a delay of 15 years or longer.[13] Although breast cancer has been reported in association with stilboestrol treatment alone, our findings suggest that stilboestrol in combination with ethisterone may have a similar effect. It is obviously impossible to know whether the induction of breast cancer by hormonal treatment is specific for high doses given to pregnant women or whether it may also occur when lower doses are given to non-pregnant women. If it does occur in non-pregnant women, these results, the Chicago findings, and observations in menopausal women all suggest that the induction period may be 15 years or longer.

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Requests for reprints should be sent to Dr V Beral.

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Diuretic treatment of resistant hypertension

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Summary and conclusions

In patients with hypertension resistant to three or four drugs including a thiazide diuretic substitution of frusemide for the thiazide, or the addition of spironolactone, produced significant reductions in blood pressure and body weight. The response did not depend on the presence of overt fluid retention, renal impairment, or the use of antihypertensive drugs of high potency. Women had larger responses than men.

Expansion of the plasma or extracellular fluid volume is an important cause of resistance to treatment even when a thiazide diuretic is used. An increase in diuretic treatment should be tried before using the postganglionic adrenergic blockers or minoxidil in resistant hypertension.

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Introduction

Hypertension is considered resistant when it remains uncontrolled by an adequate regimen of three drugs in a compliant patient.[1] In Britain the regimen is usually a thiazide, a beta-blocker, plus full doses of either hydrallazine, methyldopa, or prazosin.[2] Although relatively uncommon[3] resistant hypertension has a bad prognosis[4] and is difficult to treat. One option is to increase the diuretic component of the regimen, on the basis that all antihypertensive drugs in common use except diuretics and beta-blockers tend to expand the plasma and extracellular fluid volumes.[5 6] This volume expansion attenuates their antihypertensive effect,[7 8] a phenomenon termed "false tolerance." In these circumstances reduction of the plasma and extracellular fluid volumes by frusemide[7 9 10] or spironolactone[11] may lower the blood pressure. False tolerance may occur despite full doses of a thiazide,[5 7-10 12 13] without clinical evidence of fluid retention,[7 9 10] and in patients with normal renal function.[9 10] It occurs with drugs of only moderate potency such as hydrallazine or methyldopa.[7-10]

While the importance of false tolerance is well recognised in the United States[1 5 6 12-17] it is scarcely mentioned in European reports, and British doctors seem largely unaware of the phenomenon. For this reason we report our experience with diuretic treatment of resistant hypertension.