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.

Patients and methods

In the Sheffield hypertension clinic patients whose blood pressure is not controlled on three or more drugs including a thiazide (usually bendrofluazide 5 mg or cyclopenthiazide 0·5 mg) and who are thought to be compliant have their treatment changed either by substituting frusemide for the thiazide or by adding spironolactone. In the 15 months from October 1978 to December 1979 31 patients were treated in this way. Four patients were excluded from this analysis: two had newly entered the clinic, one had the dose of another drug increased simultaneously, and one died shortly after starting spironolactone (cause unknown). The results for the remaining 27 patients were examined retrospectively.

Patients with normal renal function (serum creatinine < 130 μmol/l (1·5 mg/100 ml)) were treated either by adding spironolactone or by substituting frusemide, while those with creatinine values of over 130 μmol/l all received frusemide instead of the thiazide. The dose of spironolactone was 100 mg (in 10 patients) or 200 mg (in 1) and that of frusemide 80 mg (in 11) or 40 mg (in 5) as a single morning dose. Blood pressure was measured with a standard mercury sphygmomanometer taking phase 5 (disappearance) as the diastolic value. Mean arterial pressure was calculated as diastolic plus one-third pulse pressure. The results were analysed by the Wilcoxon rank sum test for paired or non-paired observations.

Results

Patients—The 27 patients (17 men) had a mean age of 54 years (range 34-70); three had renal hypertension. Sixteen patients suffered complications of hypertension, and seven had renal impairment (serum creatinine 135-361 μmol/l (1·5-4·1 mg/100 ml)). Immediately before diuretic treatment was changed the mean blood pressure was 190/110 mm Hg lying, with a mean arterial pressure of 120 mm Hg or more in all (range 120-157 mm Hg) while they were taking three (16) or four (11) antihypertensive drugs including the thiazide diuretic. The other drugs (and mean daily doses) were as follows: 26 patients were taking beta-blockers, 15 hydrallazine (200 mg), 11 methyldopa (1700 mg), 7 prazosin (10 mg), 3 debrisoquine (80 mg), 2 bethanidine (75 mg), and 1 guanethidine (100 mg). These drugs were not changed. Two patients had ankle swelling and none had cardiac failure.

Evidence for resistant hypertension—At the three visits before the change of diuretic treatment, spanning an average of 12 weeks, blood pressure and body weight remained constant (table I). During this time antihypertensive treatment was increased 28 times in 20 patients, which produced a mean reduction at the next visit of 4·8/1·8 mm Hg recumbent, which was not significant. In five patients a new drug had been introduced and produced a mean increase of 2·2/1·0 mm Hg.

Response to frusemide and spironolactone—Frusemide was substituted for the thiazide in 16 patients and spironolactone was added to the thiazide in 11. At the next visit, on average four weeks later, there was a significant fall in blood pressure (22/9 mm Hg lying, 21/11 mm Hg standing) and body weight (0·8 kg; table I). The lying mean arterial pressure was reduced below 120 mm Hg (equivalent to 160/100 mm Hg) in 11 patients, with individual falls of 9·7-35·3 mm Hg, although it was strictly normal (< 110 mm Hg) in only three (11%) patients. In nine patients treatment was held constant for three visits, covering on average 18 weeks. The fall in blood pressure (22/13 mm Hg lying) and weight (1·6 kg) was maintained over this period. The responses to frusemide and spironolactone are shown separately in table II. Falls in blood pressure were significant for each drug. Spironolactone lowered blood pressure (30/12 mm Hg lying) and body weight (1·2 kg) more than frusemide (18/7 mm Hg lying; 0·5 kg), but not significantly so. Women showed larger responses in both blood pressure (lying 33/16 mm Hg *v* 16/6 mm Hg) and body weight (1·03 kg *v* 0·66 kg) than men, though only the difference in blood pressure was significant ($p < 0·05$). These responses were not related to initial blood pressure, age, weight, serum creatinine concentration, or type of antihypertensive drug used. One patient stopped frusemide because of vague side effects, and one stopped spironolactone because of menstrual disturbance.

TABLE I—*Response (mean and range) of blood pressure and body weight to altered diuretic treatment (addition of spironolactone or substitution of frusemide) in 27 patients with resistant hypertension. Diuretic treatment was altered at time 0*

Time (weeks)	−12	−6	0	+4
Blood pressure (mm Hg):				
Lying systolic	192 (146-235)	193 (140-248)	190 (150-230)	168* (130-234)
Lying diastolic	112 (92-140)	112 (95-130)	110 (84-124)	101* (80-118)
Standing systolic† ..			170 (108-214)	149* (100-210)
Standing diastolic† ..			106 (82-124)	95* (70-120)
Body weight (kg)	74·5 (54·8-93·7)	74·3 (58·1-90·5)	74·7 (59·0-90·3)	73·9* (58·1-90·7)

*$p < 0·01$ versus day 0 values.
†n = 25; 2 patients had missing values.

TABLE II—*Changes in blood pressure and body weight four weeks after frusemide was substituted for, or spironolactone added to, the thiazide diuretic at time 0*

	Frusemide (n = 16)		Spironolactone (n = 11)	
	Week 0	Week 4	Week 0	Week 4
Blood pressure (mm Hg):				
Lying systolic	185	167**	199	169**
Lying diastolic	109	102**	111	99**
Lying MAP	134·1	123·5**	140·4	121·3**
Standing systolic	167	152**	176	146**
Standing diastolic	104	96*	109	94*
Body weight (kg)	76·9	76·4	71·6	70·4*

*$p < 0·05$; **$p < 0·01$ versus week 0.

Discussion

In this type of survey it is often difficult to be sure that apparent responses to treatment are not due to phenomena such as regression to the mean, placebo effect, or observer bias. Our data are sufficient to exclude regression to the mean, while placebo effect and observer bias are unlikely for several reasons. These patients were long accustomed to the clinic routine, had been treated by the same doctors throughout, and had not responded to many increases of treatment. At the time frusemide and spironolactone were prescribed we had no intention of surveying the outcome of changing diuretic treatment. Finally, the highly significant fall in body weight is not readily explained by placebo effect or observer bias.

Addition of spironolactone to the thiazide, or substitution of frusemide, produced highly significant reductions in blood pressure and body weight in these patients with resistant hypertension.[1] In 40% the lying mean arterial pressure was reduced below 120 mm Hg (equivalent to 160/100 mm Hg), and this would generally be accepted as adequate control. As in other studies,[9 10] the response was sustained for at least three months. The response to frusemide (18/7 mm Hg) was modest compared with that reported by Wilson *et al*[9] (26/19 mm Hg in four patients) and Mroczek *et al*[10] (30/20 mm Hg in 22 patients). Wilson *et al* added frusemide to the thiazide, while Mroczek *et al* used much higher doses of frusemide (at least 200 mg daily). Our results might have been better had we added frusemide (rather than substituting it for the thiazide) and used higher doses when the response was inadequate. Kincaid-Smith *et al*[11] showed that high doses of spironolactone (400 mg daily) were better than placebo in controlling resistant hypertension; they showed a mean response of 30/20 mm Hg. We obtained a useful response (30/12 mm Hg) to spironolactone 100 mg daily a more acceptable dose as regards side effects.[18] The response to spironolactone was larger than that to frusemide, but not significantly so, and it should be noted that the drugs were not randomly allocated and that the dose of frusemide was probably suboptimal. Women had larger responses than men, and it is of interest that women develop fluid retention more readily than men when treated with guanethidine.[19]

The results support the contention that expansion of the plasma or extracellular fluid volume is often a factor in resistance to treatment.[7 9-11] Such expansion occurs despite the use of a thiazide, in the absence of clinical evidence of fluid retention, in patients with normal renal function, and in patients taking antihypertensive drugs of only moderate potency. Increased

diuretic treatment is worth trying before resorting to potent drugs such as postganglionic adrenergic blockers or minoxidil in resistant hypertension. If false tolerance is present a postganglionic adrenergic blocker will cause further volume expansion and is unlikely to lower the blood pressure. Minoxidil will reduce the blood pressure in the face of expanded plasma and extracellular fluid volumes,[20] but concurrent use of high doses of diuretics is almost invariably needed. It would be sensible to observe first the effect of increased diuretic treatment alone.

The optimal method of using diuretics in resistant hypertension is not established. The effect of frusemide as a single daily dose seems satisfactory,[21] but it is not clear whether it should be added[5 9] or substituted,[7] given continuously[9 10] or intermittently,[5] or whether it is more[5] or less[11] effective than spironolactone. At present we suggest that compliant patients resistant to an adequate regimen of three drugs should have frusemide 80 mg or spironolactone 100 mg added to the thiazide. Frusemide should be used when there is renal impairment (serum creatinine >130 μmol/l). If the patient does not respond the dose of frusemide or spironolactone may be increased according to tolerance until weight loss of 1 kg is attained, before abandoning the manoeuvre as ineffective. Urea and electrolyte concentrations should be monitored whichever diuretic is added.

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Secondary drowning in children

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Summary and conclusions

Secondary drowning (and near-drowning) is one of the post-immersion respiratory syndromes. It is defined as deterioration of pulmonary function that follows deficient gas exchange due to loss or inactivation of surfactant. A review of 94 consecutive cases of near-drowning in childhood showed that this syndrome occurred in five (5%) cases. Its onset was usually rapid and characterised by a latent period of one to 48 hours of relative respiratory well being. It occurred more rapidly after immersion in fresh water. The two children immersed in salt water died of secondary drowning, while the three immersed in fresh water recovered completely.

If it is anticipated, recognised, and treated vigorously prognosis of secondary drowning is good in fresh water cases but bad after salt water immersion.

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Introduction

In any series of drowned or near-drowned individuals, patients are described who initially respond well to resuscitation but whose respiratory function deteriorates over the next few hours. The phenomenon is well known from case reports,[1-4] and is thought to be due to loss of surfactant from chemical, anoxic, or osmotic damage to the pneumatocytes that line the alveoli. It may be fatal in both children[5] and adults[1] and is one of the causes of "delayed death subsequent to near-drowning."[6]

This phenomenon has been called "secondary drowning"[2 7-9] and is characterised by a latent period of several hours,[4] or even longer.[2 8 10] The syndrome may be defined as the occurrence of respiratory deterioration after successful resuscitation owing to primary alveolar membrane dysfunction. Estimates of its frequency have been unsatisfactory because of case selection, but the syndrome is thought to occur in at least 2% of sea water near-drownings.[11] The syndrome has occurred after both fresh water[1-7] and salt water immersions.[1 2]

As part of the Brisbane Drowning Study[12-14] we have encountered several examples of this phenomenon. Some children responded so well to rescue-site resuscitation that they were not initially admitted to hospital, only to be found in grave respiratory distress several hours later. This report describes five cases of