to show was that there were true social judgments that were not open to challenge by majority opinion, and to illustrate this he turned to medicine because of the newly emerging confidence being expressed in the absolute truth of the germ theory of disease. The contemporary belief in the power of this theory was perhaps most clearly shown in the acclaim given to Robert Koch's work on the role of the bacillus in tuberculosis, which was published in the same year as *An Enemy of the People*. It is unlikely that a playwright would look to medicine for such inspiration today; our confidence in the ability of medical science to solve all ills has declined.

Ibsen raised two important questions that remain with us: firstly how to distinguish medical areas from social and political areas and define the relation between them, and, secondly, if we cannot rely on absolute truths in either of these domains, how to assess the claims of the individual as opposed to the majority.

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I Kohler HG. Henrik Ibsen's "An Enemy of the People" and Eduard Meissner's expulsion from Teplitz. *Br Med J* 1990; 300:1123-6.

Antihypertensive and adverse biochemical effects of bendrofluazide

SIR,—In their article Dr Jan E Carlsen and colleagues report that 1.25 mg bendrofluazide possesses similar antihypertensive activity to that of a conventional dose and has few adverse biochemical effects.¹ Observations that thiazide diuretics reduce blood pressure without upsetting the biochemical profile are not new. We have shown that 125 µg cyclopentiazide possesses similar antihypertensive activity to 500 µg and produces no adverse biochemical effects.² Our original observations should have been referred to by Dr Carlsen and colleagues because their study was remarkably similar to our own in design, presentation, and conclusions.

It is not clear how much potassium chloride each patient received during Dr Carlsen and colleagues' study. Identical placebo tablets were prescribed with active medications containing 1.25 mg or 2.5 mg bendrofluazide and 573 mg potassium chloride. All patients received four tablets daily, two in the morning and two with lunch, and if fewer than four active tablets were prescribed the active preparations were taken in the morning. If a patient took 1.25 mg bendrofluazide he or she would have also received 573 mg potassium chloride and three placebo tablets. If, however, 2.5 mg bendrofluazide was prescribed the patient could have received a 2.5 mg tablet of bendrofluazide and 573 mg potassium chloride or two 1.25 mg tablets and 1176 mg potassium chloride. This point requires clarification: the potassium chloride prescribed with low and conventional doses of bendrofluazide introduces a confounding variable that could have influenced the degree of potassium loss and the validity of the potassium dose response relation.

The conclusion that the relevant range of doses of bendrofluazide to treat mild to moderate hypertension is 1.25 mg to 2.5 mg a day cannot be supported for two reasons. Firstly, a dose of bendrofluazide lower than that studied could possess considerable antihypertensive activity, and, secondly, a subset of hypertensive patients might not respond to treatment with a low dose and might have a clinically relevant drop in blood pressure with higher doses.

Thiazide diuretics used for the treatment of arterial hypertension have received a bad press in recent years. We strongly support the conclusions

that when thiazide diuretics are prescribed in low doses they are cheap, effective, and well tolerated and that they should remain the first line treatment for mild to moderate hypertension.

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- 1 Carlsen JE, Kober L, Torp-Pedersen C, Johansen P. Relation between dose of bendrofluazide, antihypertensive effect, and adverse biochemical effects. *Br Med J* 1990;300:975-8. (14 April.)
- 2 McVeigh G, Galloway D, Johnston D. The case for low dose diuretics in hypertension: comparison of low and conventional doses of cyclopentiazide. *Br Med J* 1988;297:95-8.

SIR,—We are concerned at the possibility of bias in the interpretation of data presented by Dr J E Carlsen and colleagues in their recent report.¹ The active tablets used in the study all contained potassium chloride, and thus the results relate to the effect of increasing doses of bendrofluazide and potassium chloride. If giving potassium with the bendrofluazide was not important, either in its effect on blood pressure or in its effect on the serum concentration of potassium, why was that preparation studied?

The authors state that hypokalaemia induced by thiazides seems not to cause arrhythmias. This remains controversial,² but what is not controversial is that hypokalaemia does affect considerably the incidence of ventricular fibrillation and of death after myocardial infarction.³ Furthermore, while it seems that the hypokalaemia induced by diuretics is dose responsive, the hypokalaemia occurs even after 1.25 mg of bendrofluazide with potassium.

Dr Carlsen and colleagues claim that blood pressure was not significantly affected by the dose of drug used. But reductions in systolic blood pressure among patients receiving 1.25 mg and 10.0 mg of bendrofluazide with potassium were 12.7 and 17.0 mm Hg respectively. This difference in response is biologically important, given that systolic blood pressure is a better predictor of cardiovascular disease than diastolic blood pressure, and the lack of statistical significance may merely reflect sample size. This would be a type II error.

Similarly, the adverse metabolic effects of diuretics on lipids and carbohydrates are described as irrelevant (surely the authors mean non-significant) and avoidable (surely the authors mean reduced) when the lower doses of bendrofluazide were used, yet the adverse effects occurred at the lowest doses of the combined treatment. The lack of statistical significance at the lowest doses for all biochemical variables except the serum concentration of urate may well be further examples of type II errors.

We suggest an alternative conclusion to the study: the adverse metabolic effects of diuretics on important risk factors for coronary heart disease including the plasma concentration of glucose and serum concentrations of urate, lipids, and potassium seemed to be dose related in this study. Although these effects were not always statistically significant at the lowest dosage used, this could reflect a type II error. Given the multiple adverse metabolic effects (however small) of diuretics on these risk factors, the use of diuretics as first line treatment in patients with hypertension remains illogical. But no trials have evaluated the long term ability of low dose thiazides (with or without potassium) or newer drugs with more favourable metabolic profiles to prevent coronary heart disease. Such data are required urgently.

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- 1 Carlsen JE, Kober L, Torp-Pedersen C, Johansen P. Relation between dose of bendrofluazide, antihypertensive effect, and adverse biochemical effects. *Br Med J* 1990;300:975-8. (14 April.)
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AUTHORS' REPLY,—Drs McVeigh and Johnston point out that our observations¹ are not new. In some respects this is true. In contrast to previous work, however, including the study by McVeigh *et al.*,² we considered all the well known biochemical adverse effects including those on lipids in the largest study so far reported on doses of thiazide diuretics. Our observations on the influence of dose on lipids are new, and two recent review articles support this.^{3,4}

Drs McVeigh and Johnston are disappointed that we did not refer to their study, which was much smaller than ours, comprising only 53 patients (a figure which corresponds to one dosage group in our study), and described only the effects on potassium and urate. We were aware of their report and of several others about thiazides and thiazide-like drugs that we also chose not to use as references.

Drs McVeigh and Johnston ask about the amount of potassium chloride given. None was given to patients in the placebo group; to the patients given 1.25 mg and 2.5 mg bendrofluazide 573 mg potassium chloride was given. The patients given 5 mg and 10 mg bendrofluazide received 1146 mg and 2292 mg potassium chloride.

We agree that a lower daily dose than 1.25 mg bendrofluazide may have a clinically relevant antihypertensive effect. It is very easy to use hindsight, but we regret not having used an even lower dose. Whether a subgroup of patients may have a further drop in blood pressure on higher doses is extremely difficult to evaluate from a study using parallel groups. Our data, however, do not support such a hypothesis.

Dr Poulter and colleagues want to know why tablets containing potassium chloride were used. The reason is simply that this is a tradition in Denmark. We are criticised for stating that thiazide diuretics seem not to cause arrhythmia. This is not our opinion, however, but the conclusion reached in two recent large clinical trials.^{5,6} We are, of course, aware of the observation quoted but do not feel convinced that hypokalaemia itself is the cause of arrhythmia.⁷ Perhaps both the degree of hypokalaemia and the presence of arrhythmia could be related to the degree of ventricular dysfunction.

We do not agree that we made a type II error and overlooked an increased effect on the systolic blood pressure when increasing the dose of bendrofluazide. There was no relation between the reduction in systolic blood pressure and the dose of bendrofluazide. Furthermore, the substudy of the Medical Research Council's trial did not show any difference in the reduction of systolic blood pressure produced by 5 mg and 10 mg bendrofluazide.⁸ Also, this study showed no effect of potassium chloride on blood pressure and only a small non-significant difference between serum potassium concentrations in the group receiving potassium chloride and the group not receiving it.

Whether the adverse metabolic effects of appropriate doses of thiazide diuretics should be described as irrelevant and avoidable or non-significant and reduced is a question of semantics. We acknowledge that increasing the sample size might have led to the conclusion that even the smaller doses induced significant biochemical adverse effects. But would these effects be clinically relevant? Long term trials often find smaller adverse biochemical effects than shorter term trials, or none at all.⁹

Thiazide diuretics are often used as the standard treatment with which new drugs for arterial

hypertension may be compared. It is still common to use a too high a dose, making the new treatment look superior. We agree that some new drugs do not have any adverse metabolic effects, even in high doses. It should be remembered, however, that there are no clinical data showing that such new drugs reduce the mortality and morbidity of hypertension. Thiazides in doses that we consider high affect the risk of stroke in hypertensive patients—we now need to know whether lower doses of thiazides also prevent myocardial infarction and decrease related mortality.

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Splints

SIR,—In her article on splints Ms Patricia M Riley states that orthotists are usually apprentice trained by commercial companies. This statement is not correct: the professional training and education of orthotists and prosthetists in Britain are carried out by two establishments, the National Centre for Training and Education in Prosthetics and Orthotics, Strathclyde University, Glasgow (BSc honours), and the City of Westminster College, London (Higher National Diploma in orthotics and prosthetics).

The course provided in Strathclyde University is of four years' duration. The first three years of the course are devoted to academic study, interlinked with practical training in the fitting and fabrication of prosthetic and orthotic devices, including arm orthoses. The final year is devoted to clinical practice within the hospital environment under appropriate supervision.

The course provided by the City of Westminster College is of three years' duration. After obtaining the Higher National Diploma in orthotics and prosthetics the student is required to complete a further intern year and, on completion, is awarded a diploma in orthotics or prosthetics, depending on the chosen discipline.

Also mentioned in the article is the subject of suitable materials for wrist-hand orthoses. The orthotist should have the facilities to use both high and low temperature thermoplastic materials. The type of material used will depend on a number of factors including strength requirements, whether serial adjustment is required, and durability. I would agree that low temperature thermoplastics are suitable materials for many wrist-hand

orthoses, but in many instances it is essential to use high temperature materials. Many occupational therapy departments do not have the facilities, or the expert knowledge, to provide orthoses made with high temperature thermoplastics; thus the orthotist is usually called on to provide these orthoses.

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Enalapril and metoprolol in diabetic nephropathy

SIR,—Dr S Björck and colleagues report significantly lower rates of proteinuria in patients with diabetic nephropathy treated with enalapril compared with those treated with metoprolol.¹ The study, however, looked only at effects in the short term, and no randomised controlled long term studies of such adverse effects of angiotensin converting enzyme inhibitors have been reported.

We performed a meta-analysis of studies of long term antihypertensive treatment in patients with overt diabetic nephropathy. Six studies met our criteria for analysis: specific antihypertensive treatment for more than 12 months, sequential measurements of glomerular filtration rate, and no duplication of patients in repeated publications.²⁻⁷ Of 38 patients given angiotensin converting enzyme inhibitors, some also received diuretics and vasodilators. We compared these data with those on 39 patients who received cardioselective β blockers, diuretics, and vasodilators but no angiotensin converting enzyme inhibitors. Age and duration of diabetes did not differ between the groups.

Blood pressure was lowered to $146 \pm 16/90 \pm 7$ mm Hg in the group given angiotensin converting enzyme inhibitors compared with $138 \pm 15/85 \pm 7$ mm Hg in the group given other antihypertensive treatment ($p < 0.01$). Albuminuria and proteinuria decreased less in the group given angiotensin converting enzyme inhibitors to a median of 67% (range 5 to 363%) of the initial values compared with a median of 42% (range 2 to 129%) in the group given other antihypertensive treatment ($p < 0.04$).²⁻⁷

The fall in glomerular filtration rate was not significantly different between the groups—it fell by a median of $4.4 \text{ ml/min/1.73 m}^2$ (range 0 to 15) in the group given angiotensin converting enzyme inhibitors compared with $4.4 \text{ ml/min/1.73 m}^2$ (range -7 to 29) in the group given no angiotensin converting enzyme inhibitors.

The results of this meta-analysis confirm the conclusions of Dr Björck and colleagues that the decrease in proteinuria observed in patients taking enalapril depends primarily on the degree of blood pressure reduction. In the long run angiotensin converting enzyme inhibitors do not seem to have a specific adverse or beneficial effect on diabetic nephropathy. The quality of care for patients with hypertension and diabetic nephropathy depends primarily on early diagnosis and effective lowering and maintenance of blood pressure rather than on introducing new pharmaceutical principles.⁸

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Autonomic neuropathy after cisplatin based chemotherapy

SIR,—Dr Steen Werner Hansen recently showed some evidence of autonomic neuropathy in 10 out of 28 patients who had received six courses of cisplatin, vinblastine, and bleomycin for metastatic germ cell cancer.¹ No patient had postural hypotension. We observed postural hypotension in five (7%) out of 71 patients treated with cisplatin based combination chemotherapy for metastatic germ cell cancer.

Thirty two patients had cisplatin, etoposide, and bleomycin; 10 had cisplatin and etoposide only; and the remaining 29 had other cytotoxic drugs, including either vinblastine or vincristine, in addition to cisplatin, etoposide, and bleomycin. One heavily treated patient had severe postural hypotension, causing collapse, and required treatment with mineralocorticoids. In addition to postural hypotension, another patient had intermittent palpitations and dyspnoea on exertion. He was mildly anaemic (haemoglobin 109 g/l), and an electrocardiogram showed type 1, second degree atrioventricular block with a prolonged PR interval and premature beats. Two weeks later a 24 hour electrocardiogram was normal. After a blood transfusion his symptoms completely resolved. Another patient who complained of dyspnoea and dizziness on postural change did not show a postural change in blood pressure recordings, and subsequent investigations led to a diagnosis of pulmonary infarction.²

Our cases tend to support Dr Hansen's observation that some patients with metastatic germ cell cancer have autonomic neuropathy, presumably related to cytotoxic chemotherapy based on cisplatin. The origins of autonomic neuropathy in patients with cancer, however, are probably multifactorial, and cytotoxic drugs may be only one factor.³ We are less convinced of Dr Hansen's view that sudden deaths in these patients have been wrongly ascribed to vascular toxicity and may in fact have been due to autonomic dysfunction. In the paper quoted by Hansen necropsies showed vital organ infarction and evidence of severe vascular disease in two out of five patients, and in two others there was strong evidence of severe vascular disease before death.⁴ Detailed clinical investigations showing vascular toxicity during life have been reported,^{5,6} and it has been suggested that vital organ vascular toxicity might be enhanced by cisplatin induced hypomagnesaemia provoking coronary artery spasm.⁶

It is thus important to differentiate the dominant toxicity, vascular or neuropathic, in individual patients, recognising that they may coexist. Management might differ, depending on this differentiation.

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