Renal protective effect of enalapril in diabetic nephropathy

Staffan Björck, Henrik Mulec, Svend Aage Johnsen, Gunnela Nordén, Mattias Aurell

Abstract

***Objective*—To determine whether inhibition of angiotensin converting enzyme can reduce the rate of decline in kidney function more than reducing blood pressure with other antihypertensive treatment.**

***Design*—Prospective, open randomised study lasting a mean of 2·2 years in patients with diabetic nephropathy.**

***Setting*—Three outpatient nephrology clinics.**

***Patients*—40 patients with insulin dependent diabetes and diabetic nephropathy with reduced renal function.**

***Intervention*—Antihypertensive treatment with enalapril or metoprolol, usually combined with frusemide.**

***Main outcome measure*—Rate of decline in glomerular filtration rate measured as chromium-51 edetic acid clearance.**

***Results*—Glomerular filtration rate declined a mean of 2·0 (SD 3·2) ml/min/year in the group given enalapril and 5·6 (5·9) ml/min/year in the control group. The mean arterial blood pressure during the study was 102 (5) mm Hg in the patients given enalapril and 103 (5) mm Hg in the patients given metoprolol. Urinary albumin excretion during treatment with enalapril was 60% lower than during treatment with metoprolol.**

***Conclusions*—Enalapril has an antiproteinuric effect independent of the effect on systemic blood pressure. Treatment with enalapril can reduce the rate of decline in kidney function in patients with diabetic nephropathy more than equally effective antihypertensive treatment with metoprolol. This points to a specific renal protective effect of angiotensin converting enzyme inhibitors in diabetic nephropathy.**

Department of Nephrology, Sahlgrenska Hospital, University of Göteborg, S-413 45 Göteborg, Sweden
Staffan Björck, PHD, *registrar*
Gunnela Nordén, PHD, *registrar*
Mattias Aurell, PHD, *head*

Department of Nephrology, Northern Älvsborg Hospital, Trollhättan, Sweden
Henrik Mulec, MD, *senior registrar*

Department of Nephrology, Borås Hospital, Sweden
Svend Aage Johnsen, PHD, *senior registrar*

Correspondence to:
Dr Björk.

BMJ 1992;304:339-43

Introduction

Clinical studies of treatment with angiotensin converting enzyme inhibitors in patients with diabetes mellitus have shown the clinical efficacy of these agents. Preliminary studies show that they have no adverse effects on metabolic control of diabetes or lipids.[1] They may also offer superior protection of renal function compared with other antihypertensive drugs.[2] This would be an additional advantage in patients with insulin dependent diabetes, because a third of these patients develop diabetic nephropathy.[3] In an earlier uncontrolled study we found a reduction in the rate of decline of kidney function after treating patients with diabetic nephropathy with angiotensin converting enzyme inhibitors.[2] The present randomised prospective study aimed to study the effect of the angiotensin converting enzyme inhibitor enalapril on the rate of decline of kidney function in diabetic patients with nephropathy and to compare the rate of change with that in a control group treated with metoprolol—so far the most effective treatment in this respect.[4] An interim report that showed an antiproteinuric effect of enalapril independent of blood pressure was published in 1990.[5] We now report on the long term effect of enalapril on kidney function and proteinuria.

Patients and methods

Forty patients with insulin dependent diabetes and nephropathy were studied. The entry requirements were insulin dependent diabetes, diabetic nephropathy, reduced renal function, and other diabetic complications such as retinopathy. The patients had a mean age of 42 (range 21-58) years and mean onset of diabetes at 17 (3-39) years of age. The mean duration of diabetes was 25 (13-45) years. All patients had retinopathy and three patients were blind. The onset and development of the kidney disease had to be typical of diabetic nephropathy. If there was any suspicion of other renal disease a kidney biopsy was performed. This was done in four patients showing diabetic nephropathy only. Presence of hypertension was not an inclusion criterion, but only two patients were not receiving antihypertensive treatment before the study. At screening the glomerular filtration rate was lower than our age adjusted normal value[6] but higher than 24 ml/min/1·73m^2. Reasons for exclusion from the study included pregnancy, uraemia, other conditions affecting renal function, and other factors impairing the patient's ability to participate in the study.

Twenty two patients were randomised to enalapril and 18 to metoprolol. The initial goal was to include 60 patients but because previous treatment with angiotensin converting enzyme inhibitors was a criterion for exclusion there was a diminishing number of eligible patients in the participating centres owing to the increasing popularity of these drugs. The inclusion of new patients was therefore stopped after two years and 40 patients. The study was performed after obtaining the patients' informed consent and approval by the local ethics committee.

The evaluation was done when all the patients remaining in the study had been observed for a minimum of two years. The maximum follow up time was three years.

TREATMENT

Two weeks before the start of the study all previous antihypertensive treatment except frusemide was stopped. If this was considered unsafe, treatment could be continued until two days before randomisation. Randomisation into two treatment groups was done separately in our three centres and was stratified in three strata depending on renal function to ensure balance in this respect. The blood pressure goal was a mean arterial blood pressure between 90 and 110 mm Hg in the supine position. We aimed at a final enalapril dose of 20, 10, or 5 mg if the glomerular filtration rate was >50, 30-50, or <30 ml/min/1·73 m^2 respectively. The dose of metoprolol was doubled

every week to a maximum of 200 mg if the blood pressure was not satisfactory. If the blood pressure was not within the limits of the goal set the patient was seen weekly for adjustment of antihypertensive drugs. The dose of frusemide was increased or decreased. If necessary, hydralazine or nifedipine was added. A higher supine blood pressure was accepted if the patient had symptomatic orthostatic hypotension after dose adjustment.

We measured blood pressure, urinary excretion of protein and albumin, serum electrolytes, concentrations of haemoglobin and haemoglobin A_{1c} at baseline and at two month intervals, and serum concentrations of cholesterol and urinary nitrogen, glomerular filtration rate, plasma renin activity, and concentrations of angiotensin converting enzyme and angiotensin II at six month intervals. Residual urinary volumes were measured once a year.

Blood pressure was measured with a mercury sphygmomanometer by a nurse after the patient had rested for five minutes in the supine position and after one minute of standing; the mean of two supine and two standing readings was used. Mean arterial pressure was calculated as diastolic blood pressure plus one third of the difference between systolic and diastolic blood pressure and is shown as the mean of standing and supine values.

The glomerular filtration rate was measured as the rate of disappearance from plasma of chromium-51 edetic acid after a single injection. Urinary protein excretion was measured in 24 hour collections of urine with the biuret method. Albumin excretion was measured by immunochemical turbidometric assay, electrophoresis, or immunoprecipitation assay, depending on the hospital. Plasma renin activity and angiotensin II concentration were measured by radioimmunoassay and angiotensin converting enzyme activity with a radioenzymatic assay 20-24 hours after the last dose of enalapril.[7-9] Residual urinary volumes were measured once a year with a radioisotope technique.[10]

TABLE I—*Patients with diabetic nephropathy withdrawn from enalapril or metoprolol treatment during the study*

Case No	Duration of treatment (months)	Glomerular filtration rate (ml/min/1·73m²) Initial	Last	Reason for withdrawal
		Enalapril treatment		
1	6	19	21	Myocardial infarction
2	12	33	24	Kidney transplantation
3	22	28	22	Acute renal failure induced by radiocontrast medium
12	30	45	37	Myocardial infarction
13	30	33	10	Uraemia
21*	4	52		Increase in creatinine
22*	6	66		Pregnancy
		Metoprolol treatment		
23	10	75	63	Arterial insufficiency
24	6	56	53	Lost to follow up
25	14	26	23	Kidney and pancreas transplantation
26	22	37	30	Surgery and acute renal failure
32	30	27	22	Uraemia
39*	<1	74		Dizziness
40*	0	32		First dose hypotension

*Not included in evaluation of rate of decline of kidney function.

TABLE II—*Rates of change in glomerular filtration rate (GFR) in patients with diabetic nephropathy treated with enalapril or metoprolol*

Enalapril			Metoprolol		
Case No	Rate of change in GFR (ml/min/year)	Follow up (years)	Case No	Rate of change in GFR (ml/min/year)	Follow up (years)
1	4·0	0·5	23	−24·0	0·5
2	−9·0	1·0	24	−6·0	0·5
3	−2·6	1·5	25	−3·0	1·0
4	−1·0	2·0	26	−3·8	1·5
5	−4·4	2·0	27	1·4	2·0
6	−0·4	2·0	28	−1·6	2·0
7	−1·2	2·0	29	−4·8	2·0
8	−3·3	2·0	30	−4·4	2·0
9	−1·2	2·0	31	−8·2	2·5
10	−2·0	2·0	32	−4·2	2·5
11	1·5	2·5	33	−1·9	3·0
12	−1·7	2·5	34	−3·1	3·0
13	−8·5	2·5	35	−7·0	3·0
14	−0·5	2·5	36	−10·6	3·0
15	−2·0	3·0	37	0·4	3·0
16	3·3	3·0	38	−8·6	3·0
17	−2·4	3·0			
18	−5·0	3·0			
19	−2·2	3·0			
20	−1·7	3·0			
Mean (SD)	−2·0 (3·2)	2·3 (0·7)		−5·6 (5·9)	2·2 (0·9)

STATISTICS

Results are presented as means (SD or range) except urinary albumin and protein excretion, plasma renin activity, and serum concentrations of angiotensin converting enzyme and plasma angiotensin II, which are expressed as geometric means (antilog 95% confidence interval of the logarithms) owing to their skewed distribution. Variables measured during treatment for each patient are summarised by one mean value of all measurements during treatment. These values were used to calculate means (SD) and geometric means (confidence intervals). Frusemide doses and residual volumes of urine are given as medians (ranges).

The rate of deterioration of renal function was analysed by regression lines for Cr-51 edetic acid clearance over time determined for each patient over the whole period for that patient. Wilcoxon's signed rank or rank sum test was used for comparisons and $p<0·05$ was considered as significant. Spearman's rank correlation test was used for correlations. A sliding geometric mean value method was used to illustrate the relation between albuminuria and blood pressure as previously described.[5]

Results

Fourteen patients were withdrawn during the study (table I). Four patients were studied for less than six months; the remaining 36 patients were included in the determination of the rate of decline of kidney function. The mean follow up time was 2·3 (0·7) years in patients treated with enalapril and 2·2 (0·9) years in patients treated with metoprolol (table II).

On the day before randomisation the enalapril patients were being treated with median daily dose of 50 (0-160) mg of frusemide and the metoprolol group with 120 (0-375) mg. During the follow up period the median of the individual mean frusemide doses was 80 (0-559) mg in the enalapril group and 140 (40-836) mg in the metoprolol group. Four of the patients treated with enalapril and none treated with metoprolol were not given diuretics. The mean enalapril dose was 11 (5) mg/day and the mean metoprolol dose was 144 (57) mg/day. One of the patients treated with enalapril and two treated with metoprolol were given other drugs (nifedipine or hydralazine). There was no difference in the frequency of visits to the outpatient department between the two groups. The median residual volumes of urine were 16 (0-201) ml in the patients treated with enalapril and 11 (0-130) ml in the patients treated with metoprolol.

GLOMERULAR FILTRATION RATE

The glomerular filtration rate before randomisation was 46 (14) ml/min/1·73m² in the patients given enalapril and 48 (15) ml/min/1·73m² in those given metoprolol. The rate of decline of the glomerular filtration rate was significantly lower in the patients treated with enalapril (2·0 (3·2) *v* 5·6 (5·9) ml/min/year; $p=0·021$) (table III). Figure 1 shows the accumulated decline in glomerular filtration rate from the initial determination. After an early fall in glomerular filtration rate in the patients treated with enalapril there was no further significant decline in

TABLE III—*Effect of long term treatment with enalapril or metoprolol in 40 patients with diabetic nephropathy. Variables during treatment are summarised by one value. Values are the means (SD) except for urinary albumin and protein excretion, which are geometric means (antilog 95% confidence intervals of the logarithms)*

	Enalapril treatment	Metoprolol treatment	p Value (between groups)
Change in glomerular filtration rate (ml/min/year):			
From baseline	−2·0 (3·2)	−5·6 (5·9)	0·021
From month 6	−0·4 (6·9)	−2·8 (4·5)	0·09
Supine blood pressure (mm Hg):			
Before treatment	163/96 (17/9)	161/91 (25/9)	0·83/0·14
During treatment	146/84 (14/5)	150/90 (15/6)	0·59/0·005
p Value*	0·0001/0·0001	0·03/0·39	
Standing blood pressure (mm Hg):			
Before treatment	147/91 (18/9)	140/87 (20/9)	0·29/0·12
During treatment	132/81 (13/5)	127/82 (13/8)	0·20/0·30
p Value*	0·0005/0·0001	0·02/0·047	
Mean arterial blood pressure (mm Hg):†			
Before treatment	114 (8)	109 (10)	0·18
During treatment	102 (5)	103 (5)	0·41
p Value*	0·0001	0·01	
Proteinuria (g/24 h):			
Before treatment	2·0 (1·3-3·1)	2·0 (1·4-2·8)	0·68
During treatment	0·9 (0·6-1·4)	2·1 (1·4-3·0)	0·007
p Value*	0·0009	0·53	
Albuminuria (g/24 h):			
Before treatment	1·6 (1·1-2·5)	1·4 (0·9-2·0)	0·41
During treatment	0·6 (0·4-0·9)	1·5 (1·0-2·2)	0·002
p Value*	0·0004	0·73	

*Before *v* during treatment.
†Based on mean of supine and standing blood pressure.

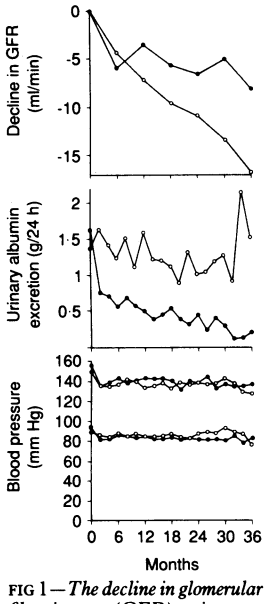

FIG 1—*The decline in glomerular filtration rate (GFR), urinary albumin excretion, and blood pressure before and during treatment with enalapril (●) or metoprolol (○) in 40 patients with diabetic nephropathy*

glomerular filtration rate from six months, in contrast, to the patients treated with metoprolol. One patient in the enalapril group with an initial glomerular filtration rate of 52 ml/min/1·73 m² was withdrawn before obtaining the first clearance after the randomisation because of a rise in serum creatinine concentration from 126 to 210 μmol/l. Renal scintigraphy did not confirm the presence of renal artery stenosis. Including this patient in the analysis, assuming the worst possible outcome (that the glomerular function would have been lost completely during the first year) does not change the significance of the difference between the groups regarding rate of decline of glomerular filtration rate (p=0·048). There was a tendency, although not significant, irrespective of treatment for those with the best renal function to remain more stable as regards glomerular filtration rate. There was no correlation between rate of decline of glomerular filtration and frusemide dose, serum sodium concentration, plasma renin activity, or angiotensin II concentrations measured during the study. The means of mean arterial blood pressure and proteinuria during the study were correlated with the rate of decline of kidney function (p<0·05).

BLOOD PRESSURE

In both groups the mean arterial blood pressure was reduced during treatment compared with at baseline. In the supine position the diastolic blood pressure was lower in the enalapril group. The orthostatic fall in mean arterial blood pressure throughout the study was considerably smaller in the enalapril group (−6·3 (4·6) mm Hg *v* −12·2 (10·5) mm Hg; p=0·06). This resulted in blood pressure (expressed as mean of supine and standing blood pressure) being almost the same throughout the study (fig 1).

PROTEIN EXCRETION

Urinary excretion of albumin and protein was reduced in patients treated with enalapril but not in patients treated with metoprolol (table III). The reduced albumin excretion persisted during the observation time and there was a continuing decrease with time (fig 1). Six of the 17 patients treated with enalapril had an albumin excretion rate within the microalbuminuric range after two years (<300 mg/24 h). Figure 2 shows the relation between blood pressure and albuminuria. Below a mean arterial blood pressure of 101 mm Hg there was no correlation between blood pressure and albuminuria in the patients treated with enalapril.

LABORATORY VALUES

Serum potassium concentrations rose from 4·4 (0·5) mmol/l to 4·7 (0·4) mmol/l during treatment with enalapril, but this did not lead to change of treatment in any patient. During enalapril treatment the mean concentration of haemoglobin was 119 (15) g/l, as compared with 131 (13) g/l in patients treated with metoprolol (p<0·02). There was no difference in concentrations of haemoglobin A_{1c} between the groups (9·1 (1·5)% *v* 9·1 (2·3)%). The plasma renin activity before randomisation, 1·7 (1·3-2·1) nmol/l/h, was significantly higher in treated patients than in healthy controls (p<0·01). It increased in the enalapril group to 5·9 (4·3-8·1) nmol/l/h (p<0·01). The serum angiotensin converting enzyme concentrations during treatment were 3 (2-5) units in patients treated with enalapril and 47 (41-53) units in patients treated with metoprolol. The plasma angiotensin II concentrations were 5·9 (4·5-7·8) pmol/l and 8·6 (6·4-11·4) pmol/l respectively (p>0·05). Serum cholesterol was 6·5 (1·3) mmol/l and 7·1 (2·0) mmol/l respectively (p>0·05). The rate of decline of glomerular filtration rate was related to serum cholesterol concentrations during the study (*r*=0·41, p=0·01). The dietary protein intake, assessed from urinary nitrogen excretion,[11] was 1·1 (0·4) g/kg body weight/24 h in patients treated with enalapril and 0·9 (0·3) g/kg body weight/24 h in patients treated with metoprolol.

Discussion

This study shows that enalapril treatment of patients with diabetic nephropathy resulted in a lower rate of decline of kidney function than treatment with metoprolol during similar blood pressure control. In the enalapril group the main fall in glomerular filtration rate occurred during the first six months, and at two months there was already a significant rise in serum creatinine concentration.[5] During the latter part of the follow up period there was no further significant fall in glomerular filtration rate. This late decline in glomerular filtration rate is so far the best result reported in this type of patients. There are no previous long term studies in diabetic nephropathy comparing angiotensin converting enzyme inhibitors with other types of antihypertensive drugs except for our previous report. In that investigation we also found a delayed stabilisation of renal function. The same phenomenon can be observed in the studies by Parving and co-

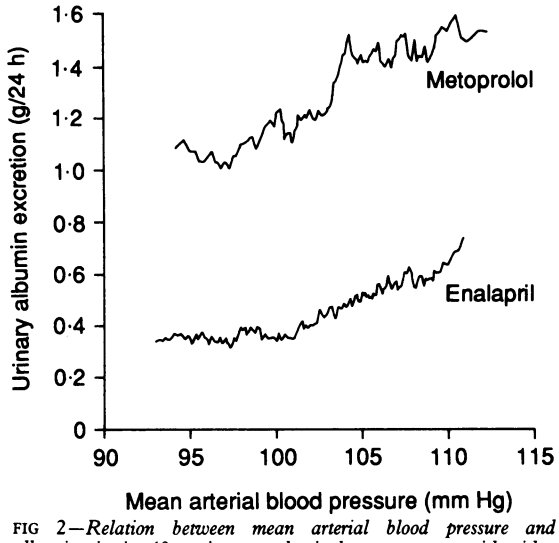

FIG 2—*Relation between mean arterial blood pressure and albuminuria in 40 patients randomised to treatment with either enalapril or metoprolol. Lines represent sliding mean values of relations between all simultaneous measurements of mean arterial blood pressure and urinary albumin excretion during treatment (n=417)*

workers.[12 13] In one patient the rise in serum creatinine after two months cautiously led to discontinuation of enalapril. Today we would probably have continued the treatment but with a reduced dosage of enalapril or frusemide. The exclusion of this patient will have biased the results but not enough to change the main results; even when we assumed that this patient would have lost all his renal function during the first year there was no change in the difference between the groups. The early fall in glomerular filtration rate is likely to be an effect on the renal haemodynamics induced by enalapril.

The decline in glomerular filtration rate early after the start of treatment with angiotensin converting enzyme inhibitor may be great enough to be of clinical importance.[14] Some patients may have to be withdrawn from treatment and investigated to exclude the possibility of renal artery stenosis. Monitoring of renal function seems warranted during the first weeks of treatment. This early reduction in glomerular filtration rate may be attenuated by a reduction in diuretic treatment.[15] There was a tendency towards a recovery of renal function after six and 12 months in the patients treated with enalapril.

The rate of fall of glomerular filtration rate in the control group was similar to what has been previously reported during this degree of blood pressure control,[4] although a substantially higher rate of decline of kidney function has been reported.[16] Metoprolol was used in the control group since this is an established treatment which so far has been associated with the best effect on the rate of decline of kidney function in diabetic nephropathy.[4] As the angiotensin converting enzyme inhibitor we used enalapril because we wanted a drug that in a single dose could inhibit angiotensin converting enzyme for 24 hours. However, the dose we chose to give seems to have been slightly too small to give complete 24 hour angiotensin converting enzyme inhibition since the angiotensin II concentrations did not differ significantly between the groups.

We believe that we succeeded in maintaining similar blood pressure in both groups. In the supine position, the blood pressure was slightly higher in the group given metoprolol, whereas the opposite occurred in the standing position. The patients treated with metoprolol were more difficult to keep within the set limits of blood pressure measured in the supine position because of symptomatic orthostatism, and we sometimes had to accept too high a supine blood pressure.

The urinary albumin excretion decreased in the patients treated with enalapril as previously reported,[5] and the reduction persisted during the observation time. There was no decrease in proteinuria in the metoprolol group. This contrasts with previous reports that blood pressure reduction irrespective of treatment reduces proteinuria.[3 17-19] However, metoprolol treatment usually represented a continuation of the treatment before randomisation. The remarkable antiproteinuric effect of enalapril is shown in figure 2: independent of blood pressure level, the patients treated with enalapril had lower urinary albumin excretion than the control group. This difference between the groups is more pronounced than in our previous report because of the progressive decline in albuminuria in the patients treated with enalapril. Figure 2 also shows the relation between blood pressure and albuminuria; it gives the impression that there is a threshold of around 101 mm Hg in mean arterial blood pressure in the patients treated with enalapril, below which a further decrease in blood pressure is not followed by a further reduction in albuminuria. This might indicate that this blood pressure level is a goal for antihypertensive treatment in diabetic nephropathy. A similar threshold in the patients treated with metoprolol is not evident from the graph.

EXPLAINING THE BENEFICIAL EFFECT

One explanation for the beneficial effect of enalapril is the renal haemodynamic effect induced by inhibition of angiotensin converting enzyme.[20] The early renal abnormality of diabetes is characterised by an increase in the filtration fraction, perhaps reflecting an increase in glomerular filtration pressure.[21] Its reversal by treatment with angiotensin converting enzymne inhibitors might be beneficial if the haemodynamic alterations are of pathogenetic importance for development of diabetic nephropathy. Other proposed explanations for a beneficial renal effect of angiotensin converting enzyme inhibitors are a direct effect on mesangial cell growth,[22] an effect on the vascular permeability,[23] and an immunomodulating effect of the inhibitors.[24]

Raised serum concentrations of cholesterol have recently been found to be associated with a more rapid decline in kidney function in diabetic nephropathy[25]; this is supported by experimental evidence.[26 27] In the present study serum cholesterol was significantly correlated with the rate of decline of kidney function.

We believe that the renal haemodynamic effect is the main explanation for the beneficial renal effect of enalapril. This is supported by the finding that further activating the renin-angiotensin system augments both the renal haemodynamic effect and the antiproteinuric effect of angiotensin converting enzyme inhibition.[28] Such a phenomenon is less compatible with the other theories. The concomitant diuretic treatment may have been important for the renal effect of enalapril in our patients.

The remarkable reduction in mortality in patients with diabetic nephropathy during the past decade is probably the result of improved blood pressure control.[29] It is not known whether angiotensin converting enzyme inhibitors are equally effective in reducing mortality. However, in a larger group of patients the antiproteinuric effect of this inhibition can be anticipated to result in an antihyperlipidaemic effect that might influence cardiovascular morbidity.

Haemoglobin concentrations decreased in the enalapril patients. This is a well known effect of angiotensin converting enzyme inhibition and seems to be explained by a reduction in erythropoietin concentration induced by these drugs.[30]

The beneficial renal effect of enalapril on kidney function is likely to be the result of combined positive effects on multiple risk factors for the kidney associated with diabetic nephropathy—namely, systemic hypertension, raised serum cholesterol concentration, proteinuria, and the renal haemodynamic alterations of diabetes. Our results show that long term treatment with enalapril can protect kidney function in diabetic nephropathy more than treatment with β blockers. Enalapril should be considered for use as a renal protective drug in diabetic nephropathy.

The study was supported by grants from the Swedish Medical Research Council (project number 05230), and Merck Sharp and Dohme. We are grateful to the departments of chemistry and clinical physiology at Sahlgrenska, Vänersborg, and Borås hospitals for performing the blood and urine chemistry and the clearance estimations.

1 Pollare T, Lithell H, Berne C. A comparison of hydrochlorothiazide and captopril on glucose and lipid metabolism in patients with hypertension. *N Engl J Med* 1989;**321**:868-73.
2 Björck S, Nyberg G, Mulec H, Granerus G, Herlitz H, Aurell M. Beneficial effects of angiotensin converting enzyme inhibition on renal function in patients with diabetic nephropathy. *BMJ* 1986;**293**:467-70.
3 Andersen AR, Christiansen JS, Andersen JK, Kreiner S, Deckert T. Diabetic nephropathy in type 1 (insulin-dependent) diabetes: an epidemiological study. *Diabetologia* 1983;**25**:496-501.
4 Parving HH, Andersen AR, Smidt UM, Hommel E, Mathiesen ER, Svendsen PA. Effect of antihypertensive treatment on kidney function in diabetic nephropathy. *BMJ* 1987;**294**:1443-7.
5 Björck S, Mulec H, Johnsen SA, Nyberg G, Aurell M. Contrasting effects of enalapril and metoprolol on proteinuria in diabetic nephropathy. *BMJ* 1990;**300**:904-7.

6 Granerus G, Aurell M. Reference values for Cr-EDTA clearance as a measure of glomerular filtration rate. *Scand J Clin Lab Invest* 1981;**41**:611-6.
7 Ikeda I, Iinuma K, Takai M, Yanagawa Y, Kurata K, Oginara T. Measurement of plasma renin activity by a simple solid phase radioimmunoassay. *J Clin Endocrinol Metab* 1981;**54**:423-8.
8 Kappelgaard AM, Damkjær Nielsen M, Giese J. Measurement of angiotensin II in human plasma: technical modifications and practical experience. *Clin Chim Acta* 1976;**10**:299-306.
9 Neels HM, Scharpé SL, van Sande ME, Verkerk RM, van Anker KJ. Improved micromethod for assay of serum angiotensin-converting enzyme. *Clin Chem* 1982;**28**:1352-5.
10 Nordén G, Granerus G, Nyberg G. Diabetic cystopathy—a risk factor in diabetic nephropathy? *J Diabetic Complications* 1988;**2**:203-6.
11 Nyberg G, Nordén G, Attman PO, Aurell M, Uddebom G, Arvidsson R, *et al*. Diabetic nephropathy: is dietary protein harmful? *J Diabetic Complications* 1987;**1**:37-40.
12 Parving HH, Hommel E, Smidt UM. Protection of kidney function and decrease in albuminuria by captopril in insulin dependent diabetics with nephropathy. *BMJ* 1988;**297**:1086-91.
13 Parving HH, Hommel E, Damkjær Nielsen M, Giese J. Effect of captopril on blood pressure and kidney function in normotensive insulin dependent diabetics with nephropathy. *BMJ* 1989;**299**:533-6.
14 Cheng IK, Ma JT, Chan MK. Comparison of captopril and enalapril in the treatment of hypertension in patients with non-insulin dependent diabetes mellitus and nephropathy. *Int Urol Nephrol* 1990;**22**:295-303.
15 Bilo HJ, Westerman RF, Nicolaas-Merkus AM, Donker AJ. Effects of enalapril with and without hydrochlorothiazide in hypertensive patients with non-insulin dependent diabetes mellitus. *Diabetes Res* 1988;**9**:21-5.
16 Zeller K, Whittaker E, Sullivan L, Raskin P, Jacobson HR. Effect of restricting dietary protein on the progression of renal failure in patients with insulin-dependent diabetes mellitus. *N Engl J Med* 1991;324:78-84.
17 Mogensen CE. Long term antihypertensive treatment inhibiting progression of diabetic nephropathy. *BMJ* 1982;**285**:685-8.
18 Christensen CK, Mogensen CE. Effect of antihypertensive treatment on progression of incipient diabetic nephropathy. *Hypertension* 1985;7:9-13.
19 Hommel E, Mathiesen E, Edsberg B, Bahnsen M, Parving HH. Acute reduction of arterial blood pressure reduces urinary albumin excretion in type 1 (insulin dependent) diabetic patients with incipient nephropathy. *Diabetologia* 1986;**29**:211-5.
20 Björck S, Herlitz H, Nyberg G, Granerus G, Aurell M. Effect of captopril on renal hemodynamics in the treatment of resistant renal hypertension. *Hypertension* 1983;5(suppl 3):152-3.
21 Sandahl Christiansen J. On the pathogenesis of the increased glomerular filtration rate in short-term insulin-dependent diabetes. *Dan Med Bull* 1984;**31**:349-61.
22 Yoshida Y, Kawamura T, Ikoma M, Fogo A, Ichikawa I. Effect of antihypertensive drugs on glomerular morphology. *Kidney Int* 1989;**36**: 626-35.
23 Keane WF, Raij L. Relationship among altered glomerular barrier permselectivity, angiotensin II and mesangial uptake of macromolecules. *Lab Invest* 1985;**52**:599-604.
24 Herlitz H, Tarkowski A, Svalander C, Volkman R, Westberg G. Beneficial effect of captopril on systemic lupus erythematosus-like disease in lpr/lpr mice. *Int Arch Allergy Appl Immunol* 1988;**85**:272-7.
25 Mulec H, Johnsen S-A, Björck S. Relation between serum cholesterol and diabetic nephropathy. *Lancet* 1990;**335**:1537-8.
26 Keane WF, Kasiske BL, O'Donell MP. Hyperlipidemia and the progression of renal disease. *Am J Clin Nutr* 1988;**47**:157-60.
27 Kasiske BL, O'Donnell PM, Schmitz PG, Kim Y, Keane WF. Renal injury of diet-induced hypercholesterolemia in rats. *Kidney Int* 1990;**37**:880-91.
28 Heeg JE, De Jong PE, van der Hem GK, de Zeeuw D. Efficacy and variability of the antiproteinuric effect of ACE inhibition by lisinopril. *Kidney Int* 1989;**26**:272-9.
29 Parving HH, Hommel E. Prognosis in diabetic nephropathy. *BMJ* 1989;**299**: 230-3.
30 Kamper A-L, Juul-Nielsen O. Effect of enalapril on hemoglobin and serum erythropoietin in chronic nephropathy. *Scand J Clin Lab Invest* 1990;**50**: 611-8.

(Accepted 18 October 1991)

First day neonatal mortality since 1935: re-examination of the Cross hypothesis

R K Whyte

Abstract

***Objectives*—To describe the change in first day infant mortality during 1935-87. To examine the hypothesis that excess first day mortality in the 1950s and 1960s was attributable to restricting oxygen for sick newborn infants.**

***Design*—Time series analysis of first day infant mortality and stillbirth rates.**

***Setting*—England and Wales and the United States of America.**

***Subjects*—All first day infant deaths, all neonatal deaths, and all stillbirths.**

***Main outcome measures*—Rate of fall in mortality, dates of deviation of mortality from established fall, and correlation with stillbirths.**

***Results*—In England and Wales first day infant mortality fell by 3·1% a year, except between 1951 (95% confidence interval 1951 to 1954) and 1980 (confidence interval <1 year). During these years there were 37 000 excess deaths. In the United States an annual fall of 2·7% was interrupted in 1955 (1951 to 1954) and resumed in 1980 (1978 to 1980), resulting in 195 000 excess deaths. A similar pattern was observed in stillbirth rates.**

***Conclusions*—Restriction of oxygen in sick newborn infants cannot be the sole cause of the interruption in fall of first day neonatal mortality as stillbirth rates were also affected. The timing of onset and the course of the deviation is not consistent with the oxygen restriction hypothesis. Further investigation is needed to identify a factor affecting both fetal and newborn survival between 1950 and 1980.**

Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada
R K Whyte, FRCPC, *associate professor*

Correspondence to:
Department of Neonatal Pediatrics, Grace Maternity Hospital, Halifax, Nova Scotia, Canada B3H 1W3.

BMJ 1992;**304**:343-6

Introduction

In 1973 Cross reported first day mortality in England and Wales and the United States for 1935-71.[1] In both American and British populations first day mortality fell during 1935 to 1950. He described "an abrupt hold up" in the steady rate of fall around 1950 in England and Wales, and a "very distinct hump in the curve of mortality" from 1954 in the United States. This pattern was not seen in death rates of infants dying between 1 and 6 days of age. The interruption in the fall occurred only in low birthweight infants and was more noticeable in infants born in urban centres.[2]

Cross hypothesised that the reversal of the previous improvement in mortality was attributable to oxygen restriction. This had become normal practice in neonatal care after the discovery that excessive ambient oxygen was a cause of retrolental fibroplasia.[3,4] He calculated that for every infant saved from blindness 16 died of hypoxia. Later the oxygen restriction hypothesis was generally cited as evidence of the fatal effects of hypoxia in the newborn.[5-8]

Data on neonatal mortality are now available up to 1987. I examined the data to determine the characteristics of the disturbance in reduction of first day infant mortality, to determine its contribution to neonatal death, and to re-examine the oxygen restriction hypothesis.

Methods

I examined statistics for England and Wales[9-15] and for the United States[16-18] for the 53 years from 1935 to 1987. The definition of fetal death in England and Wales included fetuses up to 28 weeks' gestation, whereas in the United States it applied to a fetus before 20 weeks' gestation.[19] A neonatal death was defined as the death before 28 days of age of a liveborn infant born beyond these gestational age limits. Stillbirths were defined by the same lower limits of gestational age. Neonatal mortality was expressed as deaths per thousand live births and stillbirth rates as deaths per thousand total births.

The data seemed to describe a disturbance of an established exponential rate of fall in first day infant mortality. They were therefore analysed after