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Hypertension in the Young and the Old

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Antihypertensive Therapy in Patients Above Age Sixty*

High blood pressure is a major risk factor for stroke[1] and coronary heart disease both for middle age subjects and persons over the age of 60-yr.[2] However, the presence of a relationship between increased pressure and increased morbidity and mortality does not necessarily imply that the latter will be diminished by decreasing the arterial pressure using hypotensive agents. Attempts have been made to study the outcome of elderly hypertensive patients treated with or without hypotensive agents. Controlled trials with hypotensive agents in these patients failed to reveal an increased mortality or morbidity with active treatment and suggested either no difference[3,4] or some possible, but not statistically significant, benefit.[5-7]

A recently published paper of the Hypertension Detection and Follow-up Program (HDFP)[8] of the United States reported on the mortality in a randomized study comprising a group of hypertensive patients with referred care available to them and a group of patients treated with stepped care. For the total study (n = 10,940) a 17 percent reduction ($p < 0.01$) in 5 yr total mortality (from 7.7 to 6.4 percent) was observed in the special-care group. Also, in the subgroup between age 60 and 69 (n = 2376), a 16.4 percent reduction in mortality was observed, although the difference in diastolic blood pressure at the end of the 5-yr observation was only 5.1 mm Hg in the stepped-care compared to the regular-care group.[8a]

In interpreting these results one wonders whether this 17 percent decrease in mortality is caused by the 5 mm Hg diastolic blood pressure reduction or if other components of care contributed to the success, especially since the noncardiovascular deaths also were reduced by 14 percent. The latter finding suggests that the mortality reduction could be related to a great extent to better general care. Furthermore, 77 percent of the difference in deaths occurred in the black participants, although blacks made up only 44 percent of the study population. Thus, in white women the reduction in mortality was − 2.1 percent, a nonsignificant change. Also, it is not clear from the published data if there was a significant benefit in the white males above age 60.

In 1973, the European Working Party on High Blood Pressure in Elderly (EWPHE) started to study

*Sixth interim report of the EWPHE.

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the influence of antihypertensive drug therapy in the elderly using a protocol[9] for a double-blind multicenter trial. Previous interim reports dealing with the pilot trial,[10] the 2-yr follow-up,[11] the 4-yr follow-up,[12] glucose intolerance,[13] serum uric acid,[14] and the changes in renal and cardiac function[15] have been published.

The present paper reports changes in blood pressure and biochemical measurements observed up to January 1980 for a 5-yr follow-up. This paper deals only with treatment effects that are not end-points for the study. Mortality and morbidity are deliberately omitted since the trial is continuing in all the centers and interim results are known only to the coordinating office.

METHODS

Study Protocol

Elderly patients with high blood pressure are admitted to the study if they fulfill certain criteria. Before final admission of a patient, his or her initial record form is sent to the coordinating office after the patient has been followed for a run-in period on placebo capsules.

The positive (selection) criteria are as follows: (1) age of 60 yr or more on admission into the study; (2) sitting blood pressure (average of readings on three separate visits) on placebo during the run-in period within certain limits: 160 to 239 mm Hg for systolic and 90 to 119 mm Hg (90 to 114 mm Hg diastolic in one center) for diastolic blood pressure; and (3) the patients' willingness to cooperate and to be followed-up regularly (informed consent).

The negative (exclusion) criteria are as follows: (1) certain specific causes of blood pressure elevation: all patients with hyperthyroidism or phaeochromocytoma, coarctation of the aorta, Cushing's or Conn's syndrome, or renovascular hypertension who may be treated by surgery; (2) certain complications of hypertension: hypertensive retinopathy grade III or IV, congestive heart failure, enlarging aortic aneurysm, severe renal failure, past history of cerebral or subarachnoid haemorrhage; and (3) certain other diseases: active hepatitis or active cirrhosis, life-threatening diseases, gout, and so on.

The patients are stratified for each collaborating center into one of eight categories according to age, sex, and the presence or absence of cardiovascular complications of their high blood pressure.

After stratification, the patients are randomly allocated to an actively or placebo-treated group for the duration of the study. The corresponding drugs are sent to the different centers where the patient can be admitted into the study if he or she continues to fulfill the admission criteria.

Treatment randomization is restricted so that in each of the categories for a participating center, approximatively the same number of patients will receive active or placebo treatment (restricted randomization per center and per category).

At first all patients receive one capsule containing either 25 mg of hydrochlorothiazide and 50 mg of triameterene, or a matching placebo. The dosage may be increased, after not less than 2 wk, to two capsules per day.

If the blood pressure remains high after 1 mo, alphamethyldopa or matching placebo can be added; first half a tablet of 500 mg and later one tablet, increasing eventually to four 500-mg tablets daily. Both capsules and tablets are identical in shape, taste, and color to their matching placebo.

All patients may end the study for one of the following reasons: (1) by completion of 7 yr of observation; (2) by being lost to follow-up; (3) by interruption of all study treatment for more than 3 mo; or (4) by the following study terminating events: death; cerebral or subarachnoid hemorrhage; papilledema, retinal haemorrhage, or retinal exudates; enlarging or dissecting aortic aneurysm; congestive heart failure requiring diuretics or antihypertensive drugs; hypertensive encephalopathy; increase in left ventricular hypertrophy (certain radiographic and electrocardiographic definitions); rise in blood pressure exceeding certain defined limits; and angina requiring long-term adrenergic β-blocking drugs.

Specific nonterminating events such as myocardial infarction are also recorded, and at certain centers measurements are made of symptomatic well-being (quality of life), plasma catecholamines, and renin levels.

The study lasts up to 7 yr per patient; the data are recorded and sent to the coordinating office every 3 mo by using a short quarterly record form, yearly by using a more detailed annual record form.

Statistical Methods

A paired t test was used for within-group changes and a standard unpaired t test for comparison between the active and placebo groups.

RESULTS

Characteristics on Admission

As of January 1, 1980, 650 patients have been admitted into the trial. Their characteristics are given in Tables 1 and 2. No significant differences between the two groups were found on admission and therefore both groups are comparable at the start of the trial.

The average age was 71.6 (Table 1) and patients up to 97-yr-old were admitted into the trial. Only 30 percent of the patients were males. Obesity was not a major problem in these patients, since their mean body weight was 67 kg for an average height of 1.59 meters. The cardiothoracic ratio averaged 52 percent, which could be considered as high in a middle-aged population, but normal in a population over age 60.[14]

The cause of the hypertension was not determined in the majority of cases, since in most patients investigations such as a renal arteriogram were not performed (Table 2). Renal parenchymal disease was considered as the cause in about 8 percent. Renovascular hypertension was suspected in 12 patients. In some cases, a probable diagnosis was made and an additional possible diagnosis suggested. The total number of etiologic diagnoses therefore exceeds the number of patients entered.

Drug Intake

The drug intake in the actively treated patients is given in Table 3. The intake of the diuretic was relatively constant over the total trial period; only a few patients were taking methyldopa after 3 mo, while from 1 yr on, the methyldopa intake averaged around 320 mg daily.

Blood Pressure

The changes in sitting systolic and diastolic (phase 5) blood pressure are given in Table 4 and Figure 1.

Table 1
Some Characteristics on Admission*

	Placebo	Active
Total number	326	324
Age (in years)	71.7 ± 0.44	71.6 ± 0.45
Sex: Male (n)	104	101
Female (n)	222	223
Body weight (kg)	67.3 ± 0.70	66.6 ± 0.72
	(319)†	(318)
Height (cm)	159.1 ± 0.53	158.6 ± 0.55
	(312)	(310)
Recumbent blood pressure (mm Hg)		
Systolic	184.4 ± 1.03	183.6 ± 1.04
	(321)	(318)
Diastolic (phase 5)	99.9 ± 0.48	99.5 ± 0.50
	(321)	(318)
Recumbent pulse rate (beats/min)	77.6 ± 0.60	78.5 ± 0.55
	(311)	(313)
Eye fundus		
Grade I (n)	103	112
Grade II (n)	132	126
Lens opacity (n)	22	14
Normal (n)	51	57
Unknown (n)	18	15
Central nervous system disturbances present (n)	57	55

*$p > 0.1$ for all items.
†Number of patients is shown in parentheses.

Table 2
Diagnosis on Admission, Number of Patients in each Diagnostic Category*

	Number of Patients	
	Placebo Group	*Active Group*
Functional diagnosis of hypertension		
Hypertension without organ involvement	204	211
Hypertension with only left ventricular hypertrophy	58	53
Hypertension with myocardial infarction or angina pectoris	21	16
Hypertension with only central nervous system involvement	11	15
Hypertension with only renal involvement	6	7
Hypertension with eye fundus grade III only	0	0
Hypertension with multiple organ involvement	26	22
Etiologic diagnosis of hypertension		
Essential	312	314
Renal parenchymal hypertension	29	21
Possible renovascular hypertension	5	7
Other secondary causes	8	6

*$p > 0.1$ for all items.

In the placebo group, both the systolic and diastolic blood pressure fell significantly ($p < 0.001$) between the initial pressure and the blood pressure after 3 mo; subsequent changes in pressure were small. In the actively treated group, the fall in blood pressure during the first 3 mo was 24/10 mm Hg, and at 3 mo the fall in blood pressure was significantly larger in the actively treated group; this difference was mainly due to the administration of the diuretic. After 3 mo, the systolic and diastolic blood pressures continue to decrease in the actively treated group, probably as a consequence of the administration of methyldopa. At 5 yr, the average sitting blood pressure was 27/18 mm Hg higher in the placebo-treated group than in the actively treated group.

A minority of patients have been followed for 5 yr. Not all patients have been followed for 3 mo.

Body Weight

On admission, the body weight was similar in both groups (Table 1); and at no time during the first 5 yr was there a significant difference in body weight between the two groups.

Serum Creatinine

The serum creatinine levels (Table 5) were similar in both groups on admission. In the placebo group, the serum creatinine rose slightly but significantly ($p = 0.04$) during the first 3 mo but later changes were not significant. In the active-treatment group, the increase in serum creatinine was more pronounced during these first 3 mo ($p < 0.001$); during the trial, serum creatinine was significantly higher in the actively treated group than in the placebo group (Fig. 2).

The increase in serum creatinine was related to the hypotensive effect in the actively treated group (Fig. 3). The decrease of sitting blood pressure in the first 3 mo was significantly correlated with the increase in serum creatinine in this period. In the placebo group, there was no such correlation ($r = -0.06; p > 0.1$).

Serum Uric Acid

The serum uric acid level (Table 6) was slightly different in both groups on admission ($p = 0.04$). In the placebo group, a small but unsignificant increase

Table 3
Average Drug Intake in the Active-Treatment Group

	Hydrochlorothiazide (mg)	Triamterene (mg)	Methyldopa (mg)
After 3 mo	34 ± 0.8	68 ± 1.7	46 ± 13
After 1 yr	38 ± 1.0	76 ± 2.0	273 ± 35
After 2 yr	38 ± 1.2	77 ± 2.3	311 ± 50
After 3 yr	38 ± 1.7	76 ± 3.4	340 ± 81
After 4 yr	40 ± 2.4	80 ± 4.8	343 ± 104
After 5 yr	40 ± 4.1	80 ± 8.2	375 ± 221

was observed (Fig. 4). In the active treatment group, serum uric acid increased by 25 percent during the first year and remained high during the subsequent years. The changes in serum uric acid *(y)* within the first year were significantly correlated with the changes in serum creatinine *(x)* according to the following formula:

in the placebo treatment group:

$$y = 0.001 + 1.39x$$
$$n = 155$$
$$r = 0.252$$
$$p < 0.001$$

Table 4
Sitting Blood Pressure

	Blood Pressure (mm Hg)		Probability of Between-Group Differences
	Placebo Group	*Active Group*	
During run-in period	182.7 ± 0.89	183.2 ± 0.95	> 0.1
	101.0 ± 0.43 (326)*	101.2 ± 0.45 (324)	> 0.1
After 3 mo	175.0 ± 1.35	159.6 ± 1.19	< 0.001
	97.3 ± 0.70 (257)	91.7 ± 0.68 (264)	< 0.001
After 1 yr	171.0 ± 1.76	150.2 ± 1.19	< 0.001
	95.0 ± 0.89 (168)	87.5 ± 0.74 (175)	< 0.001
After 2 yr	172.0 ± 2.17	149.3 ± 1.31	< 0.001
	95.1 ± 1.16 (102)	84.8 ± 1.08 (114)	< 0.001
After 3 yr	164.6 ± 3.23	145.8 ± 2.27	< 0.001
	90.4 ± 1.85 (51)	85.0 ± 1.38 (53)	= 0.022
After 4 yr	169.6 ± 5.61	146.2 ± 3.92	< 0.001
	94.2 ± 2.57 (24)	81.5 ± 2.30 (27)	< 0.001
After 5 yr	172.9 ± 11.40	146.0 ± 5.03	= 0.056
	99.6 ± 6.51 (8)	81.6 ± 2.90 (10)	= 0.030

*Numbers of patients are given in parentheses.

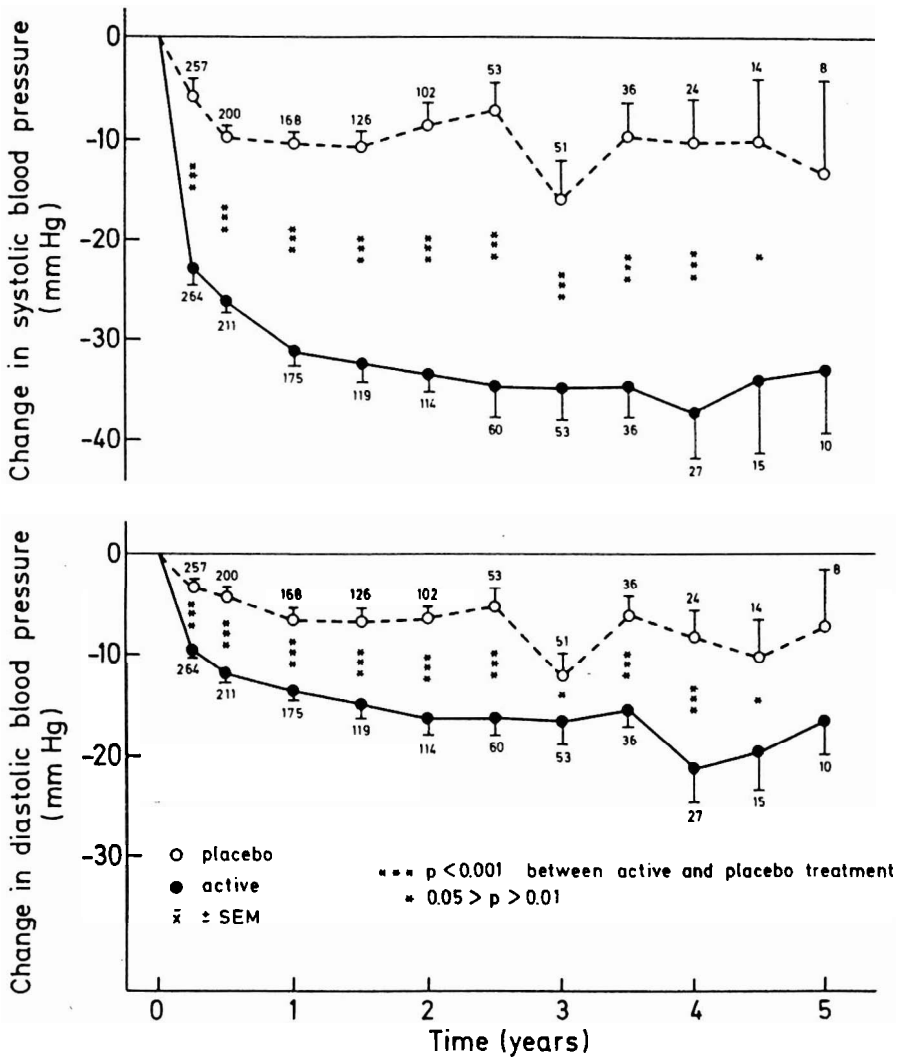

Fig. 1. Change in sitting blood pressure. In this and the other figures, the mean of the individual changes between base line (time 0) and a given year are given together with the standard error and the number of patients contributing to the mean change. The *p* value was calculated between the active- and the placebo-treatment group using an unpaired t test.

Table 5
Serum Creatinine

	Serum Creatinine (mg/dl)		Probability of Between-Group Differences
	Placebo Group	*Active Group*	
During run-in period	1.03 ± 0.02 (325)*	1.00 ± 0.01 (321)	> 0.1
After 3 mo	1.04 ± 0.02 (247)	1.16 ± 0.02 (256)	< 0.001
After 1 yr	1.03 ± 0.03 (163)	1.19 ± 0.03 (165)	< 0.001
After 2 yr	0.99 ± 0.03 (100)	1.17 ± 0.04 (109)	< 0.001
After 3 yr	1.06 ± 0.06 (50)	1.27 ± 0.07 (52)	= 0.028
After 4 yr	1.01 ± 0.06 (24)	1.32 ± 0.13 (25)	= 0.031
After 5 yr	1.06 ± 0.12 (8)	1.32 ± 0.14 (10)	> 0.1

*Numbers of patients are given in parentheses.

in the active treatment group:

$$y = 0.84 + 1.80x$$
$$n = 158$$
$$r = 0.319$$
$$p < 0.001$$

Serum Potassium and Sodium

The combination of a thiazide diuretic and a potassium-sparing agent provoked only small changes in serum potassium (Table 7). However, since the

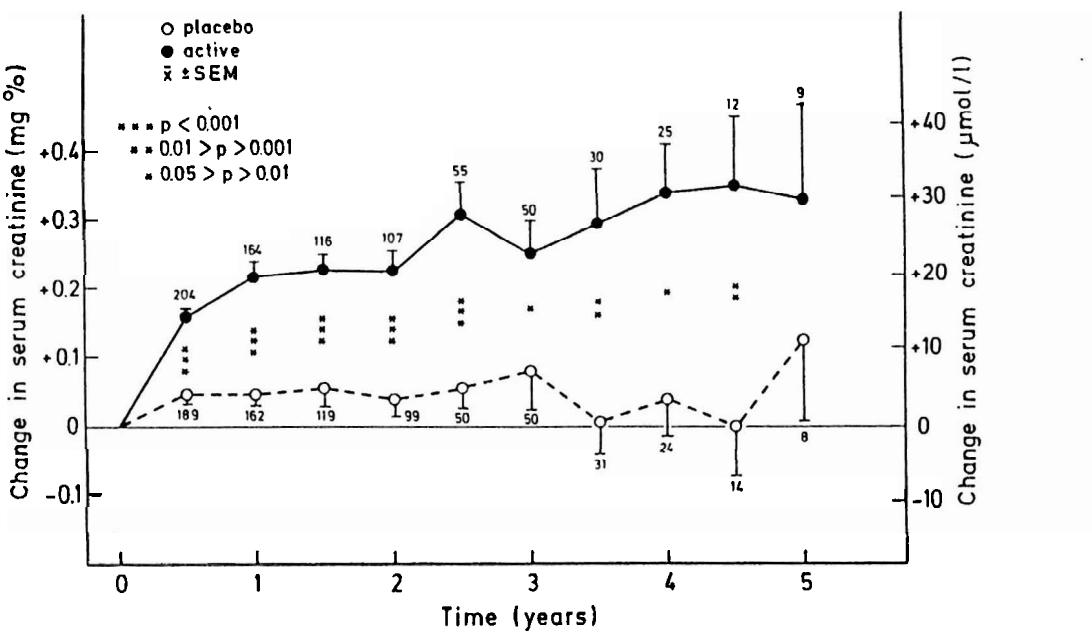

Fig. 2. Change in serum creatinine.

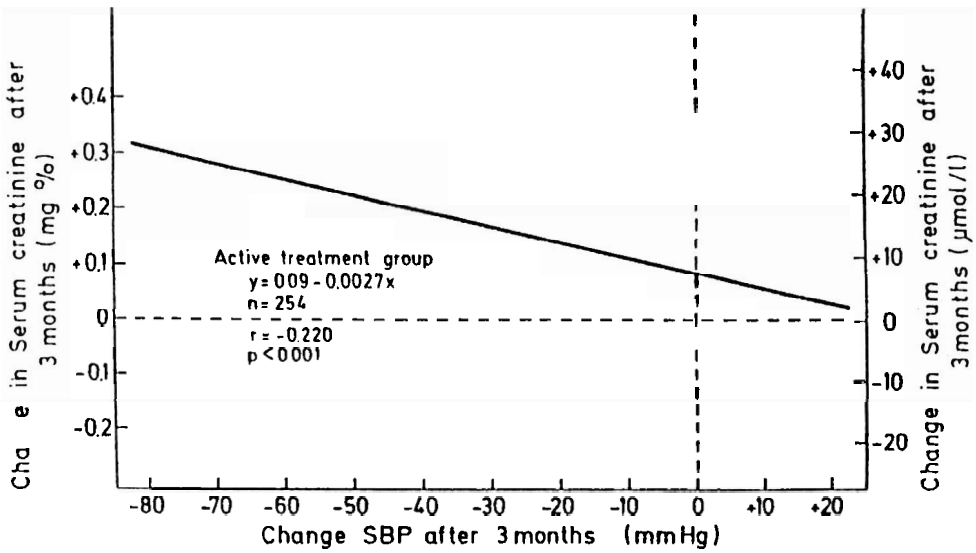

Fig. 3. Change in systolic blood pressure and serum creatinine.

potassium level tended to increase in the placebo group and to decrease in the actively treated group this small difference in serum potassium level could reach statistical significance (Fig. 5).

The serum sodium concentrations were similar in both groups on admission and subsequent changes were small and mostly statistically insignificant.

Blood Glucose

As reported elsewhere,[13] the fasting blood glucose level did not change significantly in the placebo-treated group during the first years (Fig. 6), but rose significantly in the actively treated group.

DISCUSSION

The ultimate aim of antihypertensive therapy is to reduce mortality and morbidity while maintaining the quality of life. The purpose of the present multicenter trial is to evaluate this aim with diuretic ± methyldopa treatment. A definite answer cannot yet be given since it was decided in the study protocol that (1) these data should not be communicated during the course of the trial, and (2) the trial should be terminated when significant results are found. The rules for stopping the trial have been agreed on. The pilot trial[10] has already shown, however, that initiation of hypotensive therapy can produce a slow progressive fall in pressure without an excess of terminating events in the actively treated group as compared with the placebo group.

A blood pressure difference of about 25/10 mm Hg between the two groups was maintained during the 5 yr of observation (Table 4); in the actively treated group the diastolic blood pressure was maintained in the normal range of around 85 mm Hg against 95 mm Hg in the placebo group. According to Kannel et al.,[1] for each 10-mm increase in systolic blood pressure the risk of an atherothrombotic brain infarction increases about 30 percent. Therefore the present trial may be expected to detect a difference in stroke incidence. However, it is not clearly established how long such a difference in blood pressure has to be maintained or whether a reduction of pressure from a previously high level has the same beneficial effect as that calculated from observed casual blood pressure differences in epidemiologic studies not involving intervention.

The serum creatinine rose during the first 3 mo of active treatment (Fig. 2 and Table 5), and thereafter the creatinine concentration in the active treatment group exceeded that of the placebo group. This increase in serum creatinine was associated with the hypotensive effect (Fig. 3), due either to a nonspecific effect of blood pressure reduction leading to a decrease in glomerular filtration rate or to a direct effect of diuretics on renal secretory function.

In the placebo group there was only a slight

Table 6
Serum Uric Acid

	Serum Uric Acid (mg/dl)		Probability of Between-Group Differences
	Placebo Group	*Active Group*	
During diagnosis period	5.54 ± 0.08 (315)*	5.32 ± 0.07 (319)	= 0.039
After 1 yr	5.60 ± 0.12 (166)	6.64 ± 0.13 (169)	< 0.001
After 2 yr	5.53 ± 0.15 (96)	6.69 ± 0.17 (106)	<0.001
After 3 yr	5.68 ± 0.20 (49)	6.76 ± 0.25 (49)	< 0.001
After 4 yr	5.66 ± 0.32 (24)	7.07 ± 0.31 (24)	= 0.003
After 5 yr	5.55 ± 0.62 (8)	7.55 ± 0.43 (9)	= 0.020

*Numbers of patients are given in parentheses.

increase in serum creatinine concentration (Fig. 2); the serum uric acid level remained unchanged (Fig. 4). On the contrary, in the active treatment group, the serum uric acid level was increased by 1 mg/dl even when the serum creatinine concentration remained constant. When the serum creatinine level increased or decreased, a parallel change in uric acid level was observed, the uric acid level being maintained at a level 1 mg/dl higher in the active-treatment than in the placebo group. As previously reported, the change in serum uric acid level with diuretic treatment does not only reflect the changes in serum creatinine level.[17]

With the drugs used in the present trial, the reduction in pressure was maintained without major disturbances in the serum potassium level. Although the serum sodium decreased during the first months,

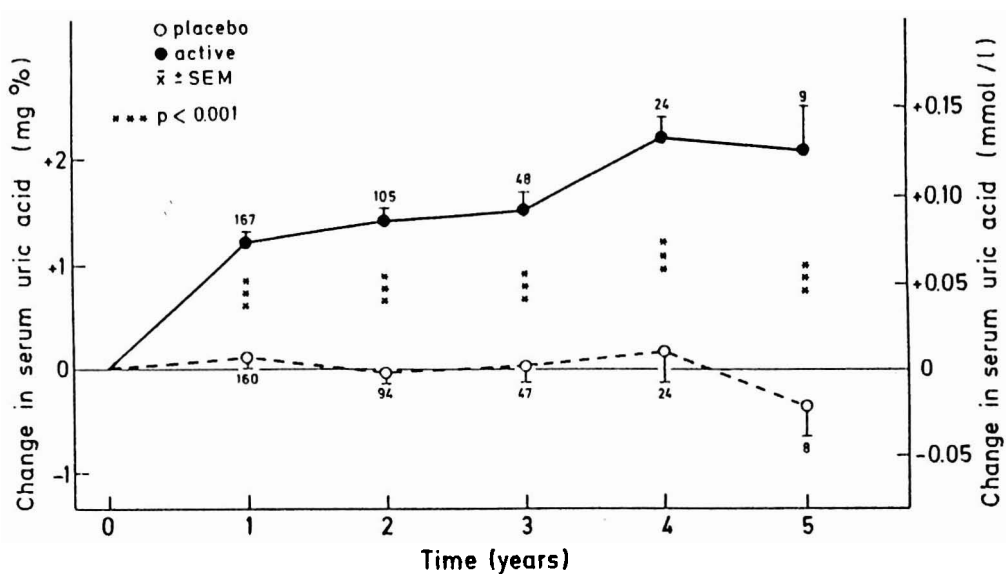

Fig. 4. Change in serum uric acid.

Table 7
Serum Potassium

	Serum Potassium (mEq/liter)		Probability of Between-Group Differences
	Placebo Group	*Active Group*	
During diagnosis period	4.21 ± 0.03 (323)	4.16 ± 0.03 (323)	>0.1
After 3 mo	4.21 ± 0.03 (244)	4.09 ± 0.03 (255)	= 0.004
After 1 yr	4.25 ± 0.04 (165)	4.09 ± 0.04 (170)	=0.002
After 2 yr	4.22 ± 0.04 (101)	4.05 ± 0.05 (108)	= 0.007
After 3 yr	4.21 ± 0.06 (51)	4.03 ± 0.07 (51)	= 0.053
After 4 yr	4.25 ± 0.06 (23)	4.02 ± 0.10 (26)	= 0.055
After 5 yr	4.36 ± 0.13 (8)	4.11 ± 0.16 (10)	> 0.1

*Number of patients are given in parenthesis.

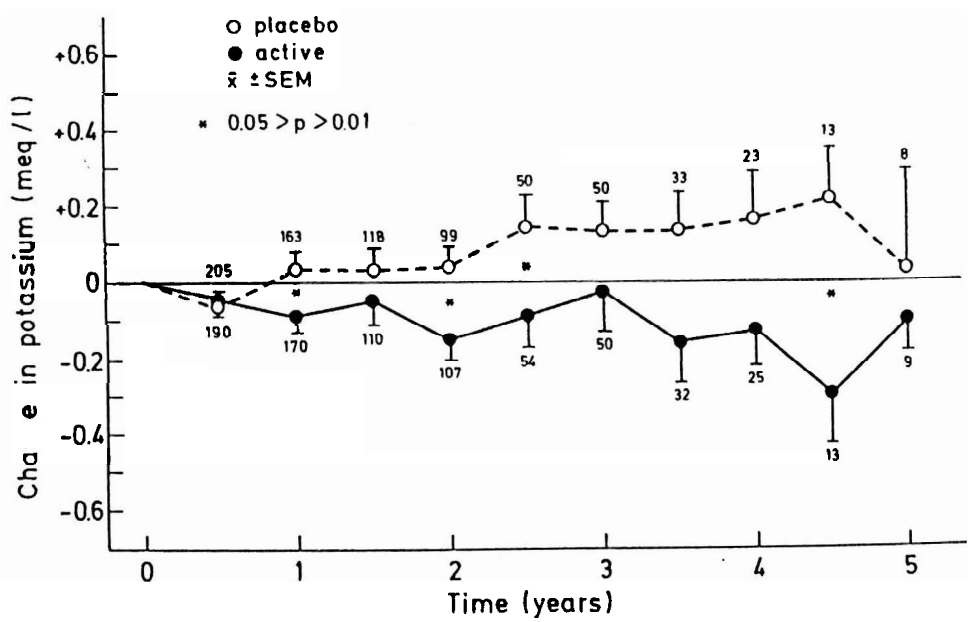

Fig. 5. Change in potassium.

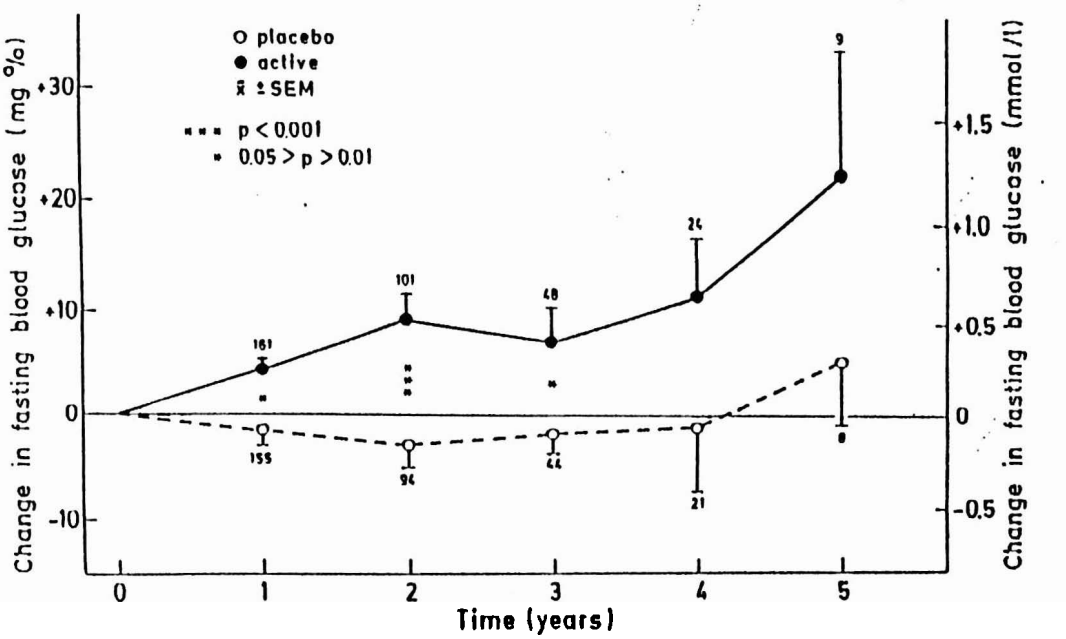

Fig. 6. Change in fasting blood glucose.

the average concentration was maintained at a normal level thereafter.

Glucose intolerance is also a major risk factor for coronary artery disease. In this study, the thiazide diuretics did enhance this risk factor. Therefore, the balance between the increased risk provoked by the rise in blood glucose and the decreased risk brought about by blood pressure reduction remains to be determined. The overall result of this trial should provide this information.

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