CONVERTING-ENZYME INHIBITION EXPERIENCES WITH CAPTOPRIL IN HYPERTENSIVE PATIENTS

E. J. L. PRINS

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STELLINGEN

I. Polyuria in lithium-treated patients can not be explained by a disturbed renal concentrating ability and is probably due to an excessive fluid intake. The latter may be caused by angiotensin II.

II. Given proper dosage and surveillance, long-term treatment with lithium is not likely to cause disturbances in renal function, including maximal renal concentrating ability.

Clin Nephrol, in press

III. Evidence of effectiveness of a newly developed drug is obtained from an organized search for an expected result in a selected population. In contrast, the search for risks is open-ended and must be conducted without advance specification of the end-point, with no guarantee that the correct population has been chosen, and with no secure knowledge that the correct laboratory or clinical observations have been applied.

N Engl J Med (1979) *300*: 1046

IV. Reports from alert physicians are still the most important source of information on the adverse effects of a drug during the first few years of its marketing.

N Engl J Med (1979) *300*: 1046
Lancet (1979) *II*: 306

V. In the absence of encephalopathy no attempt should be made to restore blood pressure acutely to normal in patients with longstanding hypertension, although this should be the aim of long-term treatment.

Lancet (1979) II: 510

VI. Chronic clonidine treatment may desensitize α-adrenoreceptors in the nucleus tractus solitarii to the effect of endogenous noradrenaline, such that abrupt removal of the exogenous transmitter (clonidine) leaves the patient with a reduced capacity to modulate baroreceptor reflexes.

Clin Sci (1979) *57*: 195

VII. There exists an antagonistic effect between clonidine and β-adrenergic receptor blocking agents. Therefore combined treatment with these drugs should be avoided.

VIII. Criteria must be sought to establish the real need for long-term immunosuppressive treatment after kidney transplantations.

B M J (1979) *11*: 421

IX. Activation of platelets on the surface of dialyser membranes and subsequent microembolization can be prevented by infusion of prostacyclin.

X. Inhibition of prostaglandin synthesis in patients with congestive heart failure and prerenal azotaemia can be dangerous.

XI. Verapamil, a calcium inhibitor, is superior to β-blocker therapy in the treatment of hypertrophic obstructive cardiomyopathy.

Brit Heart (1979) *42*: 35

XII. Voor het vroegtijdig herkennen van een zich ontwikkelende pneumothorax bij een reeds gediagnostiseerde traumatische haematothorax is een goede bekendheid met physisch-diagnostisch onderzoek noodzakelijk.

G. Wichers, co-assistent

XIII. Grafische weergave van relevante biochemische uitslagen in relatie tot diagnostiek en therapie verhoogt in aanzienlijke mate het inzicht in (patho)physiologische processen. Derhalve dient een universitaire kliniek over ruime professionele tekenfaciliteiten te beschikken.

XIV. Het lesgeven aan leerling-verpleegkundigen door arts-assistenten is van positieve invloed op beider vorming.

XV. De uitvoering van ruilverkavelingsplannen lijkt aanzienlijk in waarde te winnen wanneer reeds bij het opstellen ervan rekening wordt gehouden met toekomstige landschappelijke renovatie, zoals van houtwallen.

Gemeente Vries (Dr)

XVI. De accijns op rookwaren dient te worden beschouwd als een aanvullende ziektekostenverzekering.

Stellingen behorende bij E. J. L. Prins, Coverting-enzyme inhibition, experiences with captopril in hypertensive patients. Groningen 1979.

RIJKSUNIVERSITEIT TE GRONINGEN

CONVERTING-ENZYME INHIBITION EXPERIENCES WITH CAPTOPRIL IN HYPERTENSIVE PATIENTS

PROEFSCHRIFT

TER VERKRIJGING VAN HET DOCTORAAT IN DE GENEESKUNDE
AAN DE RIJKSUNIVERSITEIT TE GRONINGEN
OP GEZAG VAN DE RECTOR MAGNIFICUS DR. J. BORGMAN
IN HET OPENBAAR TE VERDEDIGEN OP MAANDAG 3 DECEMBER 1979
DES NAMIDDAGS TE 4.00 UUR
DOOR

ERIK JAN LEONARD PRINS

GEBOREN TE ASSEN

VAN GORCUM ASSEN 1979

PROMOTOR: DR. G. K. VAN DER HEM
CO-PROMOTOR: PROF. DR. E. MANDEMA
REFERENT: DR. A. J. M. DONKER

to my parents
to Marianne, Eelco and Jeroen

Je kunt niet
zonder de anderen

Zjef Vanuytsel

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ABBREVIATIONS

A_I	angiotensin I
A_{II}	angiotensin II
ANA (ANF)	anti-nuclear antibodies (factors)
BK	bradykinin
C	captopril
D	diuretic(s)
ERBF	effective renal blood flow
ERPF	effective renal plasma flow
FF	filration fraction
GFR	glomerular filtration rate
HCT	hydrochlorothiazide
MAP	mean arterial pressure
$\overline{MAP}$	average mean arterial pressure
PAC	plasma aldosterone concentration
PRA	plasma renin activity
SDBP	supine diastolic blood pressure

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CHAPTER I

INTRODUCTION

Hypertension, defined as a blood pressure level above 160 mmHg systolic and/or above 95 mmHg diastolic[1], has a morbidity of approximately 20 per cent in the adult population of The Netherlands[2,3], a figure comparable to that in other western countries[4,5,6]. In The Netherlands 50 per cent of the overall mortality is due to vascular disease[7], a percentage predominated by the occurrence of hypertension (besides cigarette smoking, hyperlipidaemia, physical inactivity and other factors).

The well-known Veterans Administration Cooperative Study conducted by Freis and his colleagues, has clearly demonstrated the efficacy of anti-hypertensive drug treatment in reducing the mortality and morbidity rates of hypertensive disease[8,9]. However, since in most patients the aetiology of hypertension can not be established, a multifactorial disorder often exists for which there may be no specific treatment.

In an attempt to clarify the mechanisms involved in essential hypertension and to identify causal factors responsible for the elevation of blood pressure (leading to a more simple therapy), a subdivision has been made according to renin levels[10,11]. However, treatment with propranolol – a renin lowering agent in high renin hypertensives – proved to be successful both in hypertensive patients with high *and* with normal renin levels[12,13,14,15]. In hypertensive patients with low plasma renin activity, propranolol was sometimes shown to increase the blood pressure[16]. Currently it is generally accepted that the hypotensive effect of β-adrenergic blockade therapy can not be explained by one particular effect alone, such as the suppression of renin release, since other factors including a reduction of cardiac output[17] and interference with central noradrenergic neurons and presynaptic adrenergic receptors have also been shown to play a role[18,19,20].

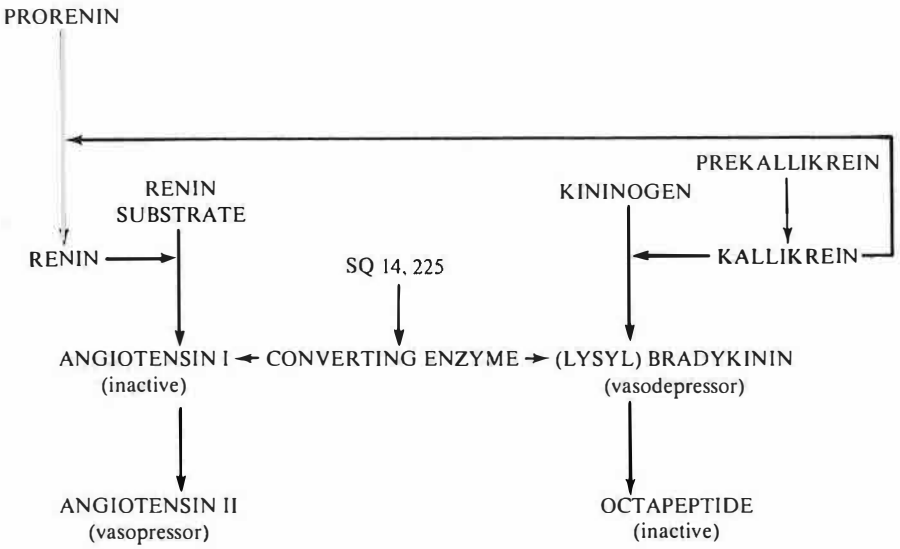
A step forward in the investigation of the role of the renin-angiotensin-aldosterone system in hypertension, was made by the development of specific angiotensin II analogues such as 1-sar-8-ala-angiotensin II (saralasin)[21]. In animals and in humans with high renin activity the latter agent lowers blood pressure[22,23,24] but it has agonistic effects when endogenous angiotensin II synthesis is suppressed[25,26,27,28,29]. This is not surprising since saralasin is an analogue of the angiotensin II molecule and can thus exhibit inherent intrinsic activity at the angiotensin II receptors[30].

The discovery of the angiotensin I converting-enzyme[31,32] (and the in-

hibition of its effects), provided another diagnostic and therapeutic tool for evaluating the renin-angiotensin-aldosterone cascade. Skeggs[31,33] differentiated two compounds as the product of action of porcine renin on crude equine angiotensinogen, i.e. angiotensin I and angiotensin II. The biologically active component of the renin-angiotensin system proved to be angiotensin II[34,35], the vasopressor action of angiotensin I being due to its conversion to angiotensin II by the (contaminating) converting-enzyme (which cleaves a dipeptide from the decapeptide to release an octapeptide = angiotensin II). The major site of action of this angiotensin I converting-enzyme, which appears to be a vascular endothelial component of many tissues[36,37,38,39], is the lung. Thus, Ng and Vane demonstrated that intravenously administered angiotensin I was much more potent (i.e. vasoactive) than the same dose given intra-arterially and secondly, that substantial conversion of angiotensin I to angiotensin II occurred during one single passage through the pulmonary circulation[40,41]. The enzymatically generated angiotensin II is not further metabolized within the pulmonary vascular bed but delivered intact into the systemic circulation[41,42].

In 1965 Ferreira demonstrated that a mixture of peptides from the venom of *Bothrops jararaca* potentiated the action of bradykinin in smooth muscles by inhibiting its degradation[43]. In collaboration with Vane[44] he found that the biological activity of bradykinin disappeared during transit through the pulmonary circulation. Bakhle[32] discovered that the mixture of peptides from the venom of *Bothrops jararaca* (i.e. 'bradykinin potentiating factor') also inhibited the conversion of angiotensin I to angiotension II when catalyzed by canine pulmonary particles. Finally, Ferreira[45] et al showed that pure peptides isolated from the *Bothrops* venom inhibited both angiotensin I converting- and bradykininase-activities in pulmonary extracts. It may now be considered generally accepted that the enzyme, peptidyl dipeptidase, responsible for angiotensin I conversion, also degradates bradykinin[46]. This enzyme (angiotensin I converting-enzyme or kininase II) may thus induce pressor effects through its potency in producing angiotensin II (a potent pressor molecule) and cleaving bradykinin (a powerful vasodepressor agent).

The angiotensin-I converting-enzyme also hydrolyzes other biologically active peptides such as enkephalins[47,48]. It is present in the plasma although, as mentioned above, its more important location is on the surface of endothelial cells[48,49]. Recently, it has been shown that albumin and its fragments inhibit antiotensin I converting-enzyme noncompetively, without acting as substrates of the enzyme[51]. This inhibition may be enhanced by the presence of acetyltryptophan, an additive in commercial plasma preparations[52]. By inhibiting angiotensin I converting-enzyme in plasma and on the vascular endothelial cells, albumin, its fragments, and other plasma proteins may potentiate the hypotensive effects of bradykinin, which is either present within or liberated by the infused plasma protein preparations[53,54]. The presence of kinins, prekallikrein activator and kininase II inhibitors may explain the fever, the rash and the severe hypotension encountered sometimes



Schedule I. A simplification of the interrelationship between the renin and kinin systems and the place of action of captopril (SQ 14, 225).

after infusion of such preparations, especially when the lung has been excluded from the circulation (for instance in patients with cardiopulmonary bypass) since the pulmonary vascular bed is especially active in cleaving kinins[49]. The hypotension induced by stable plasma protein solutions can be prevented by C_1-esterase-inhibitor concentrate[52].

With the finding of the snake venom peptide inhibitors of angiotensin I converting-enzyme, an important tool for studying the contribution of the renin-angiotensin system in the maintenance of blood pressure was provided. A number of venom inhibitors were pharmacologically characterized, for instance the nonapeptide SQ 20,881 (teprotide) and several related peptides[55,56,57,58,59,60]. Engel and coworkers demonstrated that teprotide decreased the pressor effect of angiotensin I, increased the vasodepressor activity of bradykinin, and lowered blood pressure in some animal models with renovascular hypertension[59]. The potential therapeutic usefulness of these inhibitors of angiotensin I converting-enzyme in man has also been demonstrated in several clinical studies[61,62]. The antihypertensive effect was significantly shown in patients with high and normal renin levels, whereas low renin hypertensives were unresponsive[61]. During sodium depletion an even more pronounced decrease of the blood pressure was observed in both renin subclasses, whereas the low renin patients still did not show a fall in blood pressure[61]. (However, Gavras et al reported a blood pressure lowering effect

in all three subclasses when using SQ 14,225, an orally active converting-enzyme inhibitor)[63].

Since angiotensin I converting-enzyme is also a bradykininase, studies with agents inhibiting this enzyme can not distinguish between the decrease of vasopressor effects due to an impaired generation of angiotensin II, and between the increase of endogenous kinin activity which will cause an enhanced vasodepressor effect. That bradykinin is a major mediator of the blood pressure change when teprotide is administered, seems unlikely since SQ 20,881 does not lower the blood pressure in anephric patients[64], in primary hyperaldosteronism[61], or in low renin essential hypertensives[61]. In animals converting-enzyme inhibition did not affect the development of desoxycorticosterone acetate-sodium chloride hypertension[65]. Mersey and colleagues demonstrated only a transient elevation in bradykinin concentration after a threshold dose of teprotide[66], although the plasma renin activity remained elevated and the angiotensin II concentration depressed subsequently. These findings indicated that the haemodynamic effects, including the decrease in blood pressure, could not be attributed to bradykinin alone. Williams and Hollenberg failed to demonstrate an increased venous bradykinin concentration in normal subjects given SQ 20,881[67], whereas hypertensive subjects did show an increase in bradykinin levels[67]. Other investigators however, have failed to confirm these results in hypertensive patients treated with SQ 20, 881 measuring bradykinin arterially[68].

The interpretation of the hypotensive effect of converting-enzyme inhibitor is further hampered, since the affinity of pulmonary converting-enzyme (kininase II) appears to be higher for bradykinin than for angiotensin I[69,70]. Furthermore, extrapulmonary generation of angiotensin II has recently been demonstrated by Oparil et al[71]. Their results suggest generation of angiotensin II in the systemic vascular bed without releasing the peptide into the circulation. Plasma moreover contains large amounts of a second bradykininase, carboxypeptidase N (= kininase I), which is more resistant to converting-enzyme inhibition than pulmonary kininase II[72].

The antihypertensive effect of converting-enzyme inhibition will also be mediated through a decrease in aldosterone secretion, induced by a sustained decrease in biologically effective plasma angiotensin II[73]. In addition, an increase in renal blood flow during converting-enzyme inhibition – by reduced intrarenal angiotensin II formation and possibly by an increase in renal kinin levels – may lead to an increase in sodium and water excretion[74].

The therapeutic usefulness of the inhibitor SQ 20, 881 is limited to relative acute experiments, since it may only be given intravenously and also exhibits a short duration of action. The specific site of action is questioned since it has been reported that a group of venom peptides potentiates the biologic activity of certain bradykinin analogues which are not themselves substrates for the converting-enzyme; this suggests that they may inhibit other enzymes with bradykinin activity[75,76].

The recently developed orally active, highly potent and apparently more

specific inhibitor of converting-enzyme, SQ 14,225 (D-3-mercapto-2-methylpropanoyl-L-proline; captopril)[77] can be an important agent with which one can investigate whether chronic blockade of angiotensin I converting-enzyme is a safe and useful approach in the regulation of blood pressure.

Captopril was developed from a wide range of inhibitors of angiotensin I converting-enzyme[78], all based on a hypothetical model of the active site of angiotensin I converting-enzyme was assumed to be similar to that of the pancreatic carboxypeptidase A. Data, obtained from animal studies, indicate that captopril on a weight basis may be about 10 times as potent as teprotide[79]. Furthermore, not only has captopril a rapid and marked antihypertensive action in several models of renovascular hypertension, but it has also an antihypertensive effect in several types of genetically hypertensive animals, including spontaneously hypertensive rats[80]. The drug has a relatively large margin of acute safety in the rat after oral administration. For instance, the acute oral LD_{50} dose is 5.8 g/kg, which is about 25,000 times the dose necessary to eliminate the pressor response to angiotensin I in conscious normotensive rats, and about 150 to 1,500 times the oral antihypertensive dose range of SQ 14,225 in conscious two-kidney Goldblatt type renal hypertensive rats and in Wistar-Kyoto spontaneously hypertensive rats[80,81]. More details of the drug will be provided in the first part of the discussion (chapter IX).

In the present study our own experiences with the blockade of the renin-angiotensin-aldosterone system by captopril (SQ 14,225) in human hypertensives will be described. Nineteen outpatients with mild hypertension were treated with captopril (C), with hydrochlorothiazide (D), or with a combination of the two (C + D). A further 11 patients, previously unsuccessfully treated with a combination of several antihypertensive agents and who were considered to have severe hypertension, were prescribed captopril clinically and studied over various periods of time. Twenty-nine patients were followed subsequently according to a long-term protocol.

The objectives of the investigation were:

- to investigate the short- and long-term efficacy of captopril in the treatment of human hypertension;
- to study the relationship between the magnitude of the blood pressure response to captopril and the base-line plasma renin activity and the changes in plasma aldosterone concentration, respectively:
- to study the influence of captopril on renal function;
- to study the influence of captopril on the vascular responsiveness to exogenously administered angiotensin I, angiotensin II and bradykinin, respectively;
- to examine the possible side-effects of the treatment;
- to compare our results with those of other workers reported in the medical literature.

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CHAPTER II

PROTOCOLS, PATIENTS AND METHODS

In this chapter the 30 patients will be introduced. The sponsor's protocols according to which they initially had to be treated are described. The exceptions made to these protocols with regard to the selection and the treatment of some patients will be mentioned. The methodology involved in the determinations of plasma renin activity (PRA), plasma aldosterone concentration (PAC) and renal function will be described. Finally, the statistical procedures used, will be provided.

I. PROTOCOLS, PATIENTS, MANAGEMENT

a) Comparison of captopril (SQ 14,225) with hydrochlorothiazide in the treatment of mild and moderate essential hypertension (Squibb protocol ≠ 12, 928 - 15A).

The purpose of this study is to compare the efficacy and safety of captopril with hydrochlorothiazide. A secondary purpose is to determine the need for and the value of combining a diuretic agent with captopril.

The choice of the patient population: males and non-pregnant females aged between 18 and 60 years with a primary diagnosis of mild or moderate essential hypertension. An effective method of contraception is required for women of childbearing potential. A pregnancy test obtained at the end of the placebo run-in phase has to be negative.

Criteria for entry (schedule II): hypertension classified as World Health Organization Stage I or II, i.e. without evidence of organic changes in the cardiovascular system (stage I) or with cardiac hypertrophy and without any other evidence of organ damage due to hypertension (stage II). Hypertensive retinopathy grade I or II is acceptable. Severe renal impairment is not allowed. Before the test drug treatment is started, provious antihypertensives are to be replaced by a placebo for a period of maximally 8 weeks. During this wash-out period (A_1 to A_8), the supine diastolic blood pressure (SDBP) must be between 100 and 120 mmHg. A SDBP of 100 to 110 mmHg is considered mildly elevated, and 110 to 120 mmHg moderately elevated. If on placebo

ENTRY

Male + non-pregnant females aged over 18 yrs. Essential hypertension – W.H.O. stage I or II Supine diastolic B.P. 100-120 mmHg. Obtain patient consent for at least 5 month study

EXCLUSIONS

Serious allergy –
Drug hypersensitivity
Recurrent dermatoses.

Significant G.I. disease affecting absorption.

Active history of febrile illness.

Renal impairment with
Creatinine >2 x normal
Creat clearance <50 ml/min/1.73 m^2

Pregnancy or inadequate contraception.

Other sound medical reasons considered relevant by investigator.

RESTRICTIONS

Patient

1. Taking no other vasoactive drug including diuretics, nasal decongestants etc.

2. No tobacco, alcohol or coffee for 2 hours before appointment.

3. Minimal physical activity on day of appointment.

4. Continue pre-study salt programme if relevant.

5. Medication taken at least one hour before or two hours after breakfast and lunch and before bed time.

Investigator

1. Patient seen at same time of day.

2. Visit never less than 3 or greater than 8 hours from time of medication.

3. Blood pressure measured by same investigator each time.

4. Blood pressure taken after patient supine for 10 mins., average of two readings (not differing by more than 5 mmHg).

5. S.D.B.P. taken from disappearance of pulse (Korotkoff V).

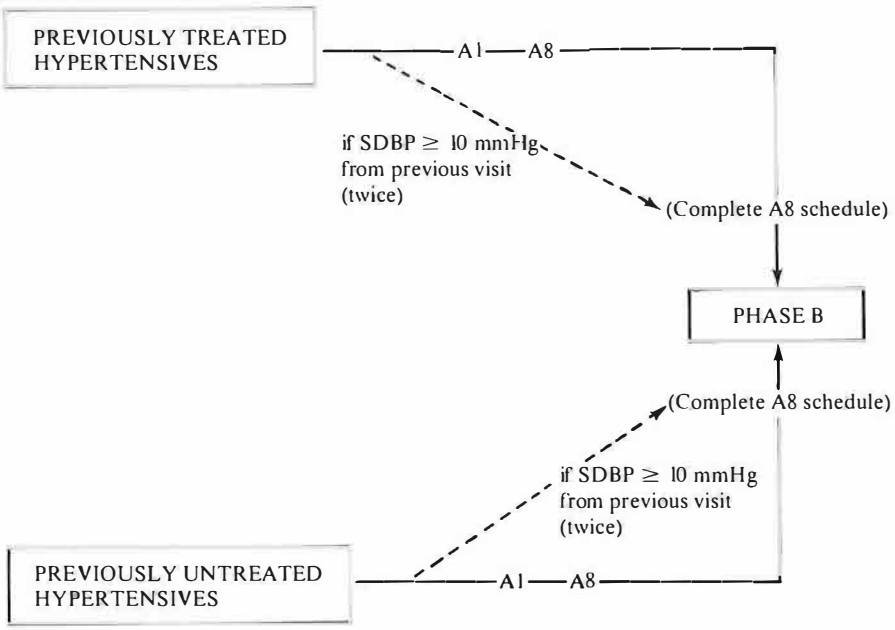
6. Patients with normal fundoscopy acceptable.

PHASE A

Schedule II. Criteria for entry to the placebo period (phase A)

therapy a rise of SDBP of more than 10 mmHg occurs, the start of the test drug treatment is accelerated (schedule III).

Schedule III. The (accelerated) execution of the placebo period A_1-A_8.



Exclude for trial if SDBP is consistently ≤ 100 mmHg or ≥ 120 mmHg.

Patient consent is to be obtained before the patient enrolls the protocol and the approximate duration of the study has been explained. Patients with a medical history of serious allergy or drug hypersensitivity or dermatosis are to be excluded. Also, serious impairment of gastro-intestinal absorption is considered to be a reason not to enter the study. Patients who are, for non-hypertensive reasons, being treated with any vaso-active drug or diuretic are not accepted for entry or disqualified if any of these drugs are prescribed during the study.

Patients participating in this study. The patients (n = 19) were all seen in the outpatient clinic. All but 3 were diagnosed as essential hypertensives (see table I, nr 1-19), the 3 exceptions concerned a patient with polycystic renal disease (nr 9), another had renal parenchymal disease due to tuberculosis (nr 18) and the third patient (nr 17) was a renal transplant patient who appeared to have a chronic rejection of the graft. The latter patient dropped out in the course of the study when transplantectomy became inevitable.

Thus, 12 males and 7 females with an average age of 38½ years (range from 20 to 54 years) participated. The duration of the hypertensive disease was maximally 20 years (nr 18), and minimally known to exist for 3 months. All

but 5 patients (nrs 1, 3, 7, 11 and 15) had been on previous antihypertensive therapy and all adhered to a moderately sodium restrictive diet (containing 100-150 mmol Na^+ per day). Hypertensive retinopathy varied from grade I to II. In 4 patients electrocardiographic signs of left ventricular hypertrophy were present (nrs 3, 11, 15 and 19) and 2 of them (nr 15 and 19) had this confirmed on their chest X-ray film.

Table I Identification of patients. Hypertensive characteristics and treatment just prior to enrollment. Base-line values on placebo (A_8) or during therapy-free interval ('A_8'), prior to initiating treatment with the test drug.

patient number	sex	age (years)	height (cm)	body weight (kg)	diagnosis	duration of hypertension (months)	treatment prior to enrollment	blood pressure on this treatment (mmHg)	dietary sodium intake (mmol/day)	values in A_8 or in 'A_8' initial blood pressure (mmHg)	eye ground (K-W classification)	electrocardiogram	chest X-ray	PRA (nmol A_I/l/hr)	PAC (nmol/l)
1	M	35	182	89	EH	4	none	142/100	150	132/100	I	n	n	0.7	0.31
2	M	54	172	85	EH	12	D β	180/110	150	160/102	I	n	n		
3	M	36	184	80	EH	3	none	162/100	120	160/100	I	LVH	n	0.8	0.45
4	F	41	177	67	EH	8	D	142/100	150	145/101	I	n	n		
5	F	41	173	73	EH	36	D β	141/111	150	165/110	I	n	n	0.2	0.92
6	F	47	168	65	EH	156	D Cl	200/120	150	200/120	II	n	n	0.8	0.47
7	M	37	183	96	EH	60	none	157/104	120	152/109	I	n	n	0.1	0.44
8	M	37	178	85	EH	60	D β	152/100	120	148/100	II	n	n	0.5	0.16
9	M	34	176	82	RPD	14	D β V	134/89	90	151/110	I	n	n	1.7	0.71
10	F	44	161	61	EH	36	D β	138/106	150	160/103	I	n	n	0.4	0.35
11	M	45	173	87	EH	6	none	154/101	120	144/101	I	LVH	n	0.4	0.22
12	M	20	178	67	EH	24	D β	144/95	150	148/101	I	n	n	0.5	0.20

Table I ctd.

patient number	sex	age (years)	height (cm)	body weight (kg)	diagnosis	duration of hypertension (months)	treatment prior to enrollment	blood pressure on this treatment (mmHg)	dietary sodium intake (mmol/day)	initial blood pressure (mmHg)	eye ground (K-W classification)	electrocardiogram	chest X-ray	PRA (nmol A_I/l/hr)	PAC (nmol/l)
										values in A_R or in 'A_R'					
13	M	40	170	78	EH	8	D β	152/101	150	162/103	I	n	n	0.1	0.24
14	M	21	182	66	EH	6	D	143/98	150	148/96	I	n	n	0.8	0.49
15	M	24	168	68	EH	10	none	153/102	120	140/100	II	LVH strain	CM	4.2	1.76
16	F	23	163	58	EH	24	D β	144/103	150	152/103	II	n	n	0.6	0.72
17	F	27	168	66	Tx	120	D β V	150/100	100	150/100	I	n	n	0.3	1.53
18	M	39	180	71	RPD	480	D β α	155/105	50	180/122	II	n	n		
19	M	51	166	75	EH	6	D β V	159/101	120	159/101	II	LVH	CM		
20	M	42	176	74	RVH	24	β V α	220/150	20	225/125	IV	LVH strain	CM	1.7	0.48
21	F	58	169	74,5	RVH	48	D V Cl	160/100	50	240/135	II	n	n	12.3	1.78
22	F	38	159	50	RVH	24	D β	220/130	50	210/120	I	LVH strain	n	1.8	0.85
23	M	55	172	93	RVH	48	β	240/150	50	≠ 215/160	III	LVH strain	CM	3.0	0.78
24	M	32	174	79,5	Tx RVH	34	D β V α Cl	160/100	20	175/125	II	n	n	1.6	0.60
25	F	34	169	59	RVH	12	D β V Cl	200/110	50	210/110	I	n	n	1.9	0.73

Table I ctd.

patient number	sex	age (years)	height (cm)	body weight (kg)	diagnosis	duration of hypertension (months)	treatment prior to enrollment	blood pressure on this treatment (mmHg)	dietary sodium intake (mmol/day)	initial blood pressure (mmHg)	eye ground (K-W classification)	electrocardiogram	chest X-ray	PRA (nmol A_I/l/hr)	PAC (nmol/l)
										values in A_R or in 'A_R'					
26	M	56	187	87	RVH	40	D β V Cl	180/110	20	220/130	II	LVH	CM	1.6	1.90
27	M	57	169	78	RVH	36	D β Cl G	250/115	20	≠ 300/125	II	LVH	CM	2.5	1.55
28	F	18	176	44.5	RPD	15	D β V ClH	150/100	50	200/120	II	LVH	n	5.0	8.92
29	M	53	174	79,5	Tx EH	132	D β V	150/100	100	185/120	II	n	n	0.4	0.64
30	F	47	162	73,5	RVH	48	D β V	200/100	50	210/110	II	LVH	CM	0.5	1.34

Abbrevations:
EH = essential hypertension.
RPD = renal parenchymal disease.
RVH = renovascular hypertension.
D = diuretic
β = beta blocker.
V = vasodilator.
α = alpha-methyldopa.
Cl = clonidine.
G = guanethidine.
ClH = chronic intermittent haemodialysis.
≠ = base-line values obtained in two patients (nrs 23 and 27) in whom complete cessation of beta-blockade was impossible since the blood pressure had increased to life-threatening levels when tapering previous antihypertensive therapy.
CM = cardiomegaly.
LVH = left ventricular hypertrophy
n = normal
M = male
F = female
T_x = renal transplantation

Table II Base-line values reflecting renal function in the placebo period (A_8) or in the therapy-free interval ('A_8'), prior to the start of the test drug. n.d. = not done. – = negative. ± = trace. + = positive.

patient nr	serum creatinine concentration (μmol/l)	creatinine clearance (ml/min)	GFR (ml/min)	ERPF (ml/min)	FF	urinalysis: protein excretion (g/24 h)	urinalysis: glucose (Labstix)	urinalysis: acetone (Labstix)	urinalysis: sediment WBC/hpf	urinalysis: sediment RBC/hpf
1	88	100	n.d.	n.d.	n.d.	–	–	–	0	0
2	71	120	n.d.	n.d.	n.d.	–	–	–	1	1
3	86	95	106	426	0.25	–	–	–	0	0
4	88	115	n.d.	n.d.	n.d.	–	–	–	0	0
5	80	107	113	461	0.25	–	–	–	0	0
6	71	80	94	380	0.25	–	–	–	0	0
7	88	95	123	573	0.22	–	–	–	0	0
8	97	105	105	416	0.25		–	–	0	0
9	137	72	68	210	0.32	–	–	–	0	0
10	71	87	114	454	0.25	–	–	–	4	1
11	71	87	142	492	0.29	–	–	–	0	0
12	80	104	138	454	0.30	–	–	–	1	0
13	71	120	131	476	0.28	–	–	–	2	1
14	94	113	113	426	0.27	–	–	–	1	1
15	90	70	114	477	0.24	–	–	–	0	0
16	82	71	101	375	0.27	–	–	–	3	0
17	224	30	31	139	0.22	0.7	–	–	1	1

patient nr	serum creatinine concentration (μmol/l)	creatinine clearance (ml/min)	GFR (ml/min)	ERPF (ml/min)	FF	urinalysis: protein excretion (g/24 h)	urinalysis: glucose (Labstix)	urinalysis: acetone (Labstix)	urinalysis: sediment WBC/hpf	urinalysis: sediment RBC/hpf
18	304	18	22	75	0.29	2.5	–	–	1	1
19	92	104	104	490	0.21	–	–	–	0	0
20	99	63	97	312	0.31	–	–	–	2	1
21	96	70	62	243	0.26	–	–	–	1	1
22	94	65	99	328	0.30	–	–	–	3	0
23	124	87	87	300	0.29	–	–	–	1	1
24	113	80	90	290	0.31	0.9	–	–	2	1
25	67	90	111	406	0.27	–	–	–	2	3
26	142	78	72	258	0.28	0.5	±	–	1	1
27	113	80	63	230	0.28	–	–	–	2	0
28	272	12	95	41	0.23	–	–	–	2	2
29	90	90	93	326	0.29	–	–	–	0	1
30	110	94	60	248	0.24	–	–	–	0	0

Information on renal function is provided in table II, in which nrs 9, 17 and 18 can be distinguished from the other patients suffering from essential hypertension. General biochemical information is noted in table III and concerns routine haematology and Technicon SMA/c Autoanalyzer measurements.

Management in the outpatient clinic. All patients were seen in the outpatient clinic, started a few years ago exclusively for the treatment of hypertensive patients. It is equipped with trained assistants and a physician, supervised by a

16	14.7	42	4.6	10	6.4	n	160		140	4.1	107	2.38	1.08	23	87	18	16	187	3.2	4.87	–
17	9.8	29	3.6	50	?	n	210		141	4.9	110	2.30	1.25	21	122	25	42	339	3.6	4.01	–
18	13.9	40	5.8	2	8.0	n	255		140	4.6	99	2.55	0.81	24	70	18	11	214	5.86	3.9	–
19	14.7	42	4.8	24	5.5	n	135		141	4.6	104	2.34	0.59	28	99	17	26	194	6.63	4.6	–
20	14.2	42	4.5	2	9.0	n	250		139	4.6	102	2.35	1.06	24	81	15	9	166	5.31	4.5	–
21	13.2	39.2	4.5	6	6.4	n	205	17.5	138	4.2	99	2.24	0.99	23	80	16	26	220	6.17	4.5	+
22	13.1	38.2	4.2	2	7.0	n	220	29.3	141	4.0	104	2.30	1.27	24	33	19	19	202	4.62	4.6	–
23	12.7	35.9	4.1	4	7.1	n	270		139	4.7	103	2.34	0.91	21	67	14	18	179	4.63	5.5	–
24	15.5	47	4.3	14	10.1	n	288		140	4.1	112	2.21	1.12	20	64	20	37	223	5.03	4.1	–
25	12.8	38.5	3.8	10	7.1	n	160		144	3.9	108	2.27	1.12	25	50	18	17	181	4.50	4.2	–
26	17.1	48.4	4.8	8	7.1	n	190		142	4.3	100	2.41	0.74	20	111	22	25	219	6.35	7.2	–
27	15.6	46.0	4.8	8	11.8	n	335		140	5.5	100	2.40	1.08	22	93	18	20	204	6.82	4.5	–
28	8.1	23.0	2.6	2	7.1	n	175		137	2.7	94	2.53	0.98	26	55	14	16	254	7.65	3.6	–
29	14.9	42	4.8	10	7.7	n	245		146	4.0	109	2.28	1.06	22	32	28	44	208	5.31	4.6	–
30	14.6	43.4	4.9	12	5.9	n	125		144	4.0	105	2.31	1.14	21	50	14	10	187	3.22	4.5	–

Table III Haematological and biochemical base-line values in the placebo period (A_8) or in the therapy-free interval ('A_s'), prior to the start of the test drug. n = normal. – = negative. + = positive.

patient nr	Hb (g%)	mH (%)	erythrocytes (x 10^6/mm^3)	reticulocytes (‰)	leucocytes (x 10^3/mm^3)	differential count	platelets (x 10^3/mm^3)	folic acid (nmol/l)	Na (mmol/l)	K (mmol/l)	Cl (mmol/l)	Ca (mmol/l)	P (mmol/l)	HCO_3^- (mmol/l)	AF (U/l)	SGOT (U/l)	SGPT (U/l)	LDH (U/l)	cholesterol (mmol/l)	glucose (mmol/l)	anti-nuclear factors (ANA)
1	15.8	46	4.7	8	5.0	n	250		142	4.5	101	2.40	0.97	25	69	20	34	174	5.59	4.5	—
2	15.7	46	4.7	4	6.8	n	160		140	4.2	101	2.35	0.87	27	54	17	11	175	5.59	4.5	+
3	16.7	51	5.8	4	5.1	n	190	21	141	4.2	102	2.49	0.92	23	88	79	56	268	6.26	4.5	+
4	14.9	47	4.8	1	6.5	n	225		138	4.0	103	2.32	0.93	30	76	13	13	263	6.55	4.1	—
5	14.9	47	4.8	1	6.5	n	250	12.2	138	4.0	103	2.32	0.93	30	76	13	13	263	6.55	4.5	—
6	14.8	44	4.6	1	5.4	n	250		139	4.2	103	2.25	1.23	23	94	17	23	293	7.02	4.4	+
7	15.4	43	4.6	3	5.5	n	160		142	3.5	106	2.35	0.39	25	64	21	36	179	4.26	2.8	—
8	14.9	42	4.2	18	3.7	n	220		140	4.0	104	2.30	0.74	21	61	22	31	222	5.80	3.8	+
9	16.1	43	4.7	4	5.6	n	225		141	4.7	105	2.50	0.81	27	64	25	32	182	5.38	3.8	—
10	12.5	36	4.1	8	5.5	n	250		141	3.5	95	2.25	0.94	28	36	16	7	181	5.17	3.7	—
11	15.2	44	4.7	8	6.1	n	135	18.5	141	4.4	102	2.50	1.00	25	102	21	22	228	4.3	3.95	—
12	15.0	43	4.7	10	4.1	n	170		140	4.4	102	2.40	1.00	24	41	24	14	227	3.4	5.41	—
13	14.5	42	4.7	2	4.6	n	275		138	4.2	103	2.35	1.19	24	73	36	46	272	3.2	6.57	—
14	16.8	50.2	5.5	4	4.4	n	200		141	4.2	103	2.43	1.11	27	70	19	13	189	4.1	4.54	—
15	14.7	43	4.4	0	7.9	n	170		138	4.4	101	2.31	1.34	20	59	15	11	170	4.2	5.52	—

specialist-team consisting of a cardiologist, a nephrologist and a general internist. The assistants performed the blood pressure readings with the London School of Hygiene and Tropical Medicine (LSH) meter and also carried out the necessary haematological and biochemical investigations, and provided numbered bottles containing the appropriate medication sufficient to last until the next visit. Medical history and physical examination, with particular interest in possible side-effects, were the main task of the physician. The patients were asked not to smoke and not to drink coffee or alcoholic beverages for at least 2 hours before measurement of the blood pressure. The time of the day on which measurements were performed was kept as constant as possible, i.e. between 8-10 am. Placebo and captopril tablets were taken 3 times a day, one hour before or 2 hours after each meal. In practice this was approximately at 10 am, 2 pm and 10 pm. However, on days at which the visit to the outpatient clinic coincided with the performance of dose-response curves (with exogenously administered AI, AII or BK: see chapter VI) or renal function tests, the first tablet was taken before breakfast at 8 am. Hydrochlorothiazide was taken at 10 am and 10 pm, respectively, with the same exceptions as mentioned above.

For each patient, a case report form was provided in which every visit was entered. The following features were to be noted: the kind of drugs used, the total daily dose of the test-drug, the number of tablets returned from the bottle provided during the previous visit, the time when the last tablet was taken, the usual times of the day the tablets were taken, and a history of complaints

Schedule IV. Investigations in the consecutive outpatient clinic visits during the placebo period (A1-A8).

Week A1	A2	A3 A4	A5 A6	A7 A8
Entry Visit Dispense drugs for A1 + A2.	1. Complete medication record section. 2. Record vital signs. 3. Record adverse reactions. 4. Record concomitant illness. 5. Dispense drugs for A3 + A4.	As A2 + drug for A5 + A6 Pregnancy Test. Laboratory Tests.	As A2 (1-4) + drug dispensed for A7 + A8.	Full physical examination. Ophthalmological examination. E.C.G. Laboratory tests Dispense drug for B1

attributable to the hypertensive disease, to any side-effect of the drug or to concomitant illness, respectively. Blood pressure and pulse rate after 10 minutes recumbency and after 2 minutes standing were noted at each visit as well as the bodyweight. At certain scheduled visits, a medical history and physical examination, including fundoscopy, were performed. If necessary, laboratory investigations, ECG and an X-ray film of the chest were also performed.

Schedule V. Description of investigations and dose-titration in consecutive visits in the outpatient clinic during the dose-titration phase (B1-B4).

PHASE B – DOSE TITRATION TO DETERMINE EFFECTIVE DOSE

WEEK	B1	B2	B3	B4
	25 mg t.i.d. captopril. *or* 25 mg b.i.d. Hydrochlorothiazide (H.C.T.)	If SDBP ≤ 90 mmHg continue as B1	If SDBP ≤ 90 mmHg continue as B2	If SDBP ≤ 90 mmHg continue as B3
MEDICATION DOSAGE + BLOOD PRESSURE RECORDING		If SDBP ≥ 90 mmHg dispense 50 mg t.i.d. captopril *or* 25 mg b.i.d. H.C.T.	If SDBP ≥ 90 mmHg dispense 100 mg t.i.d. captopril *or* 50 mg b.i.d. H.C.T.	If SDBP ≥ 90 mmHg dispense one bottle 100 mg and one bottle 50 mg dose 150 mg t.i.d. captopril *or* 50 mg b.i.d. H.C.T.
	If SDBP measured at end of any week is either ≥ 120 mmHg or 10 mmHg higher than previous reading, increase daily dose by one step. Review as soon as possible and continue to increase dose in stepwise fashion if SDBP is unresponsive. If SDBP remains elevated despite maximum daily dose (450 mg) enter into Phase C and add hydrochlorothiazide to medication. having performed B4 investigations – do not extend period B.			
	PLEASE MONITOR FOR 2 HOURS BLOOD PRESSURE IN PATIENTS AFTER INGESTION OF FIRST DOSE OF EACH STRENGTH OF THE DRUG			
PROCEDURES	1. Complete medication report. 2. Record vital signs. 3. Record any adverse reactions. 4. Record any concomitant illness since last visit. 5. Dispense medication for B2.	1 - 4 as in B1. 5. Draw blood for haematological evaluation. 6. Dispense for B3.	1 - 4 as in B1 5. Dispense for B4.	1 - 4 as in B1. 5. Physical examination. 6. E.C.G. 7. Laboratory tests. 8. Dispense for weeks C1 and C2.

NOTES

a) Do not increase dose further if resting heart rate (RHR) is ≤ 55 beats/minute or systolic blood pressure ≤ 100 mmHg (standing).
b) Reduce dose by one step if RHR ≤ 45 beats/minute or standing S.B. pressure ≤ 85 mmHg.
c) *Reduce dose by one step if fever ± rash develops.* Monitor closely progress. Stop medication if fever and rash continue. If rash ± fever clears, resume previous (higher) dose. If rash recurs, cut back by one step, and enter patient into Phase C having performed tests at B4.

Schedule VI. Description of investigations, and if necessary the dose titration in consecutive visits in the outpatient clinic during the maintenance period (phase C, C1-C8).

PHASE C – MAINTENANCE OR ADDITIONAL THERAPY

WEEK	C1	C2	C3	C4	C5	C6	C7	C8
If SDBP ≤ 90 mmHg	CONTINUE THE MEDICATION DISPENSED WHICH RESULTED IN 'NORMALISED' SDBP							
If SDBP ≥ 90 mmHg	Add alternative drug i.e., Hydrochlorothiazide (H.C.T.) or captopril. Titrate medication using same time scale and incremental dosages as described in B.							
If SDBP on two consecutive visits ≥ 90 mmHg having been 'normalised' in Phase B	1. Increase test drug stepwise to maximal dosage (i.e., captopril 150 mg t.i.d. or H.C.T. 50 mg b.i.d.) 2. If SDBP does not become 'normalized' – or patient already on maximal dose – add alternative drug and increase as in B until SDBP ≤ 90 mmHg.							
Hypotension, is standing systolic B.P. ≤ 85 mmHg or ≤ 100 mmHg and patient symptomatic	Decrease dose stepwise, ie			*Captopril* First reduce or stop H.C.T. Then if still hypotensive reduce daily dose 450 mg → 300 mg → 150 mg, etc. *H.C.T.* Reduce daily dose 100 mg → 50 → discontinue.				
	C1	C2	C3	C4	C5	C6	C7	C8
PROCEDURES	1. Complete medication record. 2. Attach label. 3. Record vital signs. 4. Record adverse reactions 5. Record concomitant illnesses. 6. Dispense medication for C2.	1-5 as C1. 6. Take blood for haemato-logical assessment. 7. Dispense medication for C3.	1-5 as C1. 6. Dispense medication for C4.	1-5 as C1. 6. Laboratory tests. 7. Dispense medication for C5 & C6.		1-6 as C3. 7. Dispense medication for C7 & C8.		1-5 as C1. 6. Perform physical examination. 7. Eye examination. 8. E.C.G. 9. Take blood and urine for laboratory tests.

Simply, the study was divided into 4 phases. The first (period A) comprised a maximum of 8 weeks and served as a placebo run-in period during which base-line values were obtained (see schedule IV). The second period (B) lasted for 4 weeks during which the patient was titrated onto either captopril or hydrochlorothiazide, having been randomly assigned to one or another drug. The purpose of the dose titration period was to achieve 'nor-

malization' of the blood pressure to a SDBP below 90 mm Hg (see schedule V). The third period (C) lasted for 8 weeks and acted as a maintenance phase of therapy although during period C the alternate drug could be added in cases where the blood pressure had not been normalized on one drug alone (schedule VI). Having completed all 3 periods, the patients then entered a long-term chronic therapy phase which is still in progress. During the A and C periods the patients were reviewed in the outpatient department bi-weekly, whereas during the dose-titration period B they attended the clinic weekly. During the long-term phase they are monitored at monthly intervals, see page 25.

Twice during the placebo period dose-response curves were performed, as well as one renal function study (i.e. GFR and ERPF). During dose-titration with captopril, whether with single drug treatment or with additive therapy, dose-response curves were performed each time before increasing the dosage. Renal function studies were also performed when the patient was on hydrochlorothiazide before captopril had to be added, and on the final captopril dosage (with or without hydrochlorothiazide).

During the whole study the patients adhered to a moderately sodium restricted diet, containing 100 to 150 mmol Na^+ per day, which was checked by determination of sodium and creatinine excretions in 24-hour urine specimens.

b) Captopril emergency protocol (Squibb protocol ≠ 12, 928 - 23)

The purpose of this study is to obtain, in a uniform manner, information on the efficacy and safety of captopril in individual hypertensive patients who are resistant to currently available anti-hypertensive agents (and in whom correctable secondary causes have been ruled out or can not be dealt with immediately).

The ultimate objective is a 'normal' SDBP ($\leq$ 90 mmHg).

Criteria for entry. (Only after expressed approval of the sponsor, concerning each patient separately, individual drug supplies are provided).
The patient must have a SDBP of at least 105 mmHg (measured with a conventional mercury sphygmomanometer after 10 minutes recumbency), the level monitored being the average of 2 consecutive readings not differing by more than 5 mmHg. This level existing despite at least 1 month of multi-drug therapy, referring to a diuretic *plus* a sympathicolytic agent *plus* a vasodilator. Patients are excluded on identical grounds as those described in the first protocol. Tapering of previous anti-hypertensives and the titration of captopril is to be performed stepwise and in-hospital. An attempt should be made to withdraw all previous antihypertensive therapy for at least a 24 hour period during which biochemical baseline values – including PRA and PAC from a venous blood sample taken after overnight recumbency – a renal function

study and dose-response curves can be performed. After this phase captopril is initiated with a 25 mg t.i.d. regimen. Dosages can be increased at 24-hour intervals but may be increased after 8 hours in cases where no blood pressure response is seen at all. Each increasing step (50 mg, 100 mg, 150 mg t.i.d.) can be followed by a dose-response curve, and the final step (i.e., the dose on which an adequate blood pressure is obtained) by a renal function study. If on the maximal captopril dose (150 mg t.i.d.) inadequate blood pressure control is achieved, a diuretic is to be added, which is also followed by a dose-response curve and a renal function study. Finally, a beta-blocker can be added to the previously mentioned regimen if the SDBP persists above 90 mmHg.

The patients participating in this emergency study will be described in detail in chapter VIII. The group of patients (n = 11) consisted of 6 males and 5 females, ranging in age from 18 to 57 years. Renovascular hypertension (RVH) was diagnosed in 9 patients (nrs 20 to 27, and nr 30). One patient (nr 28) had renal parenchymal disease (RPD) due to the haemolytic uraemic syndrome (HUS), whilst another patient (nr 29) was one who had received a renal transplant and had suffered from essential hypertension which was thought to be the cause of the deteriorating renal function prior to dialysis and transplantation. General information on these patients is provided in tables I, II and III.

Management. The patients were hospitalized after their consent had been obtained. A thorough physical examination was performed, including fundoscopy. A chest X-ray film and an electrocardiogram were taken. Measurements of blood pressure (supine after 10 minutes and standing after 2 minutes) and heart rate were performed at least 4 times daily, the body weight was measured daily as well as the body temperature. Daily the 24 hour urine was collected for determination of the volume and the excretion of sodium, potassium, creatinine and protein. Twice weekly a haematogram, antinuclear factors and Technicon SMA/c Autoanalyzer determination and examination of urinary sediment were performed. Daily supine blood samples were drawn for the determination of PRA and PAC after overnight recumbency.

Under close observation, previous anti-hypertensives were withdrawn and captopril was initiated after at least 24 hours without any antihypertensive treatment. In 2 cases however (nrs 23 and 27), an exception to this rule was made because of 'life threatening' high blood pressure levels. The therapy-free interval was used for determination of renal function in all patients and for dose-response curves in some.

Renal function was determined again when the final captopril dose had been reached and the after addition of a diuretic. In 2 patients (nr 21 and 23) the captopril was given more equally than 8 hourly over the day since they remained hypertensive at early morning readings only (i.e. on the maximal interval between 2 dosages).

Each day the patients were seen by the doctor. Their medical status was monitored in a case-report form provided by the sponsor. When blood pressure control had been obtained for at least 4 days, the patients were

discharged from hospital and seen again within 2 weeks in the outpatient clinic. One month after discharge, they entered the long-term study.

c) Long-term treatment study (Squibb protocol ≠ 12, 928 - 15)

The purpose of the long-term study is to undertake a comparison of the long-term efficacy and adverse reactions of captopril and hydrochlorothiazide either alone, or in combination (and if necessary with propranolol). All but one patients from the two previously described studies entered the study, once a new patient consent had been obtained. The duration is scheduled to be maximally 2 years.

Management. Twenty-nine patients from the two previously mentioned studies were enrolled into the long-term phase. They were seen monthly in the outpatient clinic. In general, the management as described in the first protocol (SQ ≠ 12, 928-15A) concerning their attendance and the investigations

Schedule VII. The observations and investigations to be monitored at consecutive visits to the outpatient clinic during the long-term study.

SCHEDULE OF VISITS AND EVENTS
LONG-TERM STUDY

End of Month	Complete Physical Examination	Fundoscopy	ECG	Chest X-ray	Vital Signs	Laboratory Tests
1						
2						
3[a]						
M4					x	x
M5					x	
M6	x	x	x		x	x
M7					x	
M8					x	
M9	x				x	x
M10					x	
M11					x	
M12	x	x	x	x	x	x
M13					x	
M14					x	
M15	x				x	x
M16					x	
M17					x	
M18	x	x	x		x	x
M19					x	
M20					x	
M21	x				x	x
M22					x	
M23					x	
M24	x	x	x	x	x	x

[a] End of three months' treatment = week C8.

undertaken in the outpatient department, were continued (see also schedule VII). By August, 1979 most patients had been treated between 4 to 8 months.

II. INVESTIGATIONAL METHODS

d) Blood pressure measurements were performed using 2 methods. In the outpatient clinic only the London School of Hygiene and Tropical Medicine sphygmomanometer was used (Cinetronics LSH sphygmomanometer) by a trained assistant. The average of 2 consecutive readings, not differing more than 5 mmHg, was recorded. Data mentioned in this study concern only supine blood pressure readings, except when separately mentioned. The readings of the in-patients were measured with the conventional ERKA sphygmomanometers. The level recorded was the same as mentioned above. Only supine blood pressure levels were recorded in the in-patients, except when stated otherwise. Always the diastolic II level (Korotkoff phase V) will be mentioned.

e) Plasma renin activity (PRA) was determined by means of a radioimmunoassay for angiotensin I during incubation of 0.5 ml plasma for 3 hours at pH 6.0 according to a modification of the method of Freedlander et al[1]. Normal upright values at noon for males in the age of 30 years adhering to a 100 mmol Na^+ restricted diet amount to 3.4 ± 0.4 nmol A_1/l/h.

f) Plasma aldosterone concentration (PAC) was measured by a radioimmunoassay according to the method of Pratt et al[2]. Normal upright values for males amount to 0.47 ± 0.03 nmol/l.

g) Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were measured with radiopharmaceuticals according to the method by Donker et al[3]. The coefficient of variation of GFR in the range of 60 to 145 ml/min is 2.2.% and of ERPF in the range of 200 to 600 ml/min is 5%.

h) In order to get an insight in the completeness of the angiotensin I converting-enzyme inhibition by captopril, the influence of the agent was studied with regard to the effects of exogenously administered angiotensin I, angiotensin II and bradykinin on blood pressure, both before and during treatment with incremental dosages of the drug.

Dose-response studies with exogenously administered angiotensin I, angiotensin II and bradykinin were performed between 9 a.m. and noon. The patients were instructed to take their first morning tablet 2 hours in advance. Base-line blood pressure levels in the supine position were determined 30 minutes before the infusions started. Angiotensin I (Squibb), angiotensin II (Hypertensin®, Ciba) and bradykinin (Sigma) were of analytical grade. The fresh substrates diluted in dextrose 5% were infused by means of a constant infusion pump (Braun-Unita II). In order to ensure a sufficient flow of the

chemical into the vein, the initial low rate infusion lasted 10 minutes. Thereafter the pump rate was increased stepwise at six minutes intervals. The responsiveness was defined as the lowest dose of the agent needed to obtain a rise in SDBP of 20 mmHg for angiotensin I and angiotensin II, and or a fall of 10 mmHg for bradykinin. These changes should be present during at least 3 consecutive readings. Furthermore, the responsiveness was considered to increase when a lower dose of the agent was necessary to obtain these changes and to decrease when the infusion rate had to be enlarged. As soon as the ultimate change in SDBP was reached, the pump was switched off until base-line levels had been reached. Sequential dose-response studies were performed with angiotensin I, angiotensin II and bradykinin. The whole procedure took approximately 2 hours.

i) Angiotensin converting enzyme activity was determined according to a modification of the method of Lieberman (normal values 23 ± 6 U/l)[4]. The modification concerns a colorimetric determination of the liberated hippuric acid[5].

j) Statistical evaluations were performed with regression analysis and with the rank test. In those cases where the parameter of interest was supposed to be normally distributed, a Student t test was performed; with regard to paired observations a paired t test was used. All was tested at a significance level of 5 per cent.

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CHAPTER III

BLOOD PRESSURE

In this chapter the antihypertensive effects of the drugs used in this investigation (i.e. captopril, hydrochlorothiazide, or the combination of both) are described. Relationships between the initial mean arterial pressure (MAP_{A8} or $MAP_{'A8'}$*) and the initial log PRA and the FF, respectively, have been investigated and will be given. Also the relationships between the changes in MAP (ΔMAP) on captopril treatment only and the initial log PRA were studied. Finally, an attempt will be made to indicate the maximal daily dose of captopril with which an adequate blood pressure control can be obtained and beyond which a diuretic should be added when no control on captopril treatment alone is achieved.

The in-trial antihypertensive treatment and its effects on blood pressure and supine pulse rate, is summarized in table IV. Three subsequent blood pressure readings in the vertical column indicate the ultimate blood pressure levels – measured in the supine position after 10 minutes recumbency, sitting, and standing for 2 minutes – as established at the conclusion of the study in August, 1979. All supine MAP values are bold printed. The average study duration in August, 1979 was 166 days for all patients, including 2 drop-outs, namely patient nr 6 who was excluded after 105 days because of side-effects and patient nr 17 who underwent a transplantectomy after 46 days.

The average MAP ($\overline{MAP}$) ± SEM of all 30 patients was 134 ± 4 mmHg in the initial (= 'A8') phase (figure 1). With ultimate treatment (in August, 1979; U) practically all patients were under control (see table IV), and the $\overline{MAP}$ was 104 ± 1 mmHg, which was a statistically significant fall ($p < 0.0005$). From the 2 drop-outs the values were taken at the moment when the test drug (in both captopril) was withdrawn.

The $\overline{MAP}_{A8}$ ± SEM of the outpatients who were to be treated with captopril initially (n = 11), was 122 ± 3 mmHg (figure 2). On captopril alone (maximally 150 mg t.i.d.) this value was 106 ± 2 mmHg. The fall in $\overline{MAP}$ was significant ($p < 0.001$). From these 11 patients only one (nr 7) needed the addition of a diuretic to obtain adequate blood pressure control.

The $\overline{MAP}_{A8}$ ± SEM prior to treatment with hydrochlorothiazide initially (n = 8) was 120 ± 3 mmHg (figure 3). On diuretic treatment alone (maximally 50 mg hydrochlorothiazide b.i.d.) a $\overline{MAP}$ of 114 ± 4 mmHg was

* As found in the therapy-free interval 'A8' for the emergency patients.

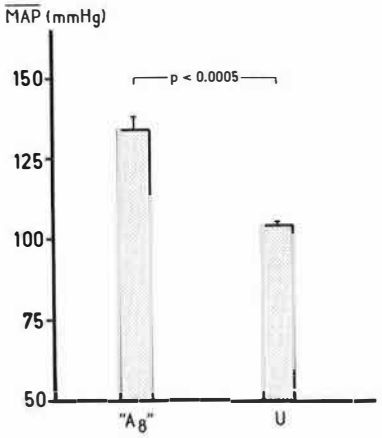


Fig. 1. The average supine mean arterial pressure ($\overline{MAP}$) ± SEM of all patients treated in the study (n = 30). 'A_8' reflects the value prior to the start of the test drugs. U represents the ultimate value as measured in August 1979, either on captopril (n = 20), on the diuretic (n = 3) or on both drugs together (n = 7). Average duration of treatment ± SEM: 166 ± 30 days.

found. The difference was not significant. After the addition of captopril (n = 5), the $\overline{MAP}$ was 98 ± 3 mmHg. Compared to $\overline{MAP}$ on hydrochlorothiazide alone (50 mg b.i.d.), the difference was significant ($p < 0.005$) as was the difference when $\overline{MAP}_{D+C}$ was compared to $\overline{MAP}_{A8}$ ($p < 0.001$). In 2

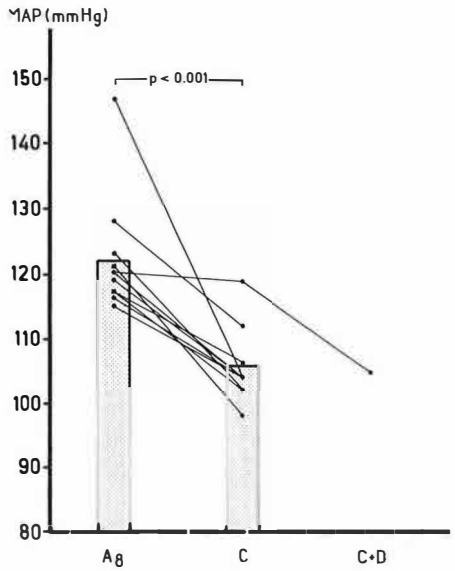


Fig. 2. The supine mean arterial pressure (MAP) in the outpatient group (n = 11) at the end of the placebo period (A_8), on the ultimate captopril (C) dose (n = 11), and after addition of the diuretic (C + D) (n = 1). The bars represent $\overline{MAP}$.

Table IV Supine blood pressure level (BP), mean arterial pressure (MAP) and heart rate (PF) in the placebo period (A_8) or in the therapy-free interval ('A_8'), and during treatment with captopril (C), the diuretic (D), the combined treatment of both drugs (C + D or D + C) and after withdrawing the diuretic (C – D). The duration of captopril treatment (C, C + D, D + C, C – D) and of diuretic therapy alone (D) is mentioned. Three subsequent blood pressure readings in the vertical column indicate the blood pressure levels as ultimately measured in the supine, sitting and standing position in August, 1979.

	A8 or 'A8'			C				D				C + D				D + C				C – D			
	BP	MAP	PF	BP	MAP	PF	days	BP	MAP	PF	days	BP	MAP	PF	days	BP	MAP	PF	days	BP	MAP	PF	days
1	132/100	**111**	72					131/88 138/95 128/95	**102**	76	330												
2	160/102	**121**	112	123/85 125/85 130/90	**98**	76	310																
3	160/100	**120**	80					186/115	**139**	64	64					149/82 104/75	**104**	68	103	152/90 159/93 158/98	**111**	60	250
4	145/101	**116**	100					140/96	**111**	100	120					106/80 112/85	**85**	88	45				
5	165/110	**128**	68	163/87 164/91 163/92	**112**	72	270																
6	200/120	**147**	80	136/88 138/95 129/95	**104**	80	220*																
7	152/104	**120**	72	150/103	**119**	64	105					136/89 136/91 127/95	**105**	72	224								
8	148/100	**116**	68	131/90 133/98 136/100	**104**	80	180																
9	151/110	**124**	68					135/105	**115**	80	138					133/84 136/92 128/92	**100**	72	44				
10	160/103	**122**	80					135/87 137/91 138/93	**103**	68	156												
11	144/101	**115**	72	131/90 133/91 138/98	**104**	72	184																
12	148/101	**117**	72	134/86 136/89 133/93	**102**	84	155																

13	162/103	**123**	64	132/87 144/88 140/82	**102**	72	126																	
14	148/96	**113**	84					134/92 135/99 132/96	**106**	88	113													
15	140/100	**113**	88					150/110	**123**	88	6					133/85 130/87 129/89	**101**	84	77					
16	152/103	**119**	64	130/91 142/96 143/97	**104**	68	100																	
17	150/100	**117**	88	145/75 145/80 135/80	**106**	80	48*																	
18	180/122	**141**	84					150/99	**116**	72	33					137/85	**102**	84	16	136/80 144/94 147/100	**99**	92	47
19	159/101	**120**	72	140/86 141/91 145/93	**104**	68	56																	
20	225/125	**158**	76	220/125 134/86	**156**	68	7					123/70	**88**	60	57					161/90 159/93 165/96	**114**	68	125
21	240/135	**173**	80	135/87 133/84 126/86	**102**	72	199																	
22	210/120	**150**	84	141/91 139/93 154/85	**100**	72	203																	
23	215/150	**172**	64	152/86 152/90	**108**	72	188																	
24	175/125	**142**	80	190/105 128/75	**133**	84	3					129/80	**96**	64	132					139/86 145/90 152/91	**103**	68	150
25	210/110	**143**	72	124/86 119/84 172/95	**93**	80	70																	
26	220/130	**160**	84	168/96 173/98	**121**	96	74																	
27	300/125	**183**	64	200/100	**133**	64	11					157/91 135/85	**117**	52	32					166/84 170/87 170/87	**111**	60	61
28	200/120	**147**	80	155/95	**115**	84	15					141/83 142/87 125/89	**102**	64	192								
29	185/120	**142**	64	170/120	**136**	68	4					120/90 127/93 160/76	**101**	56	156								
30	210/110	**143**	72	197/99	**131**	80	21					155/81 153/85	**104**	68	69								

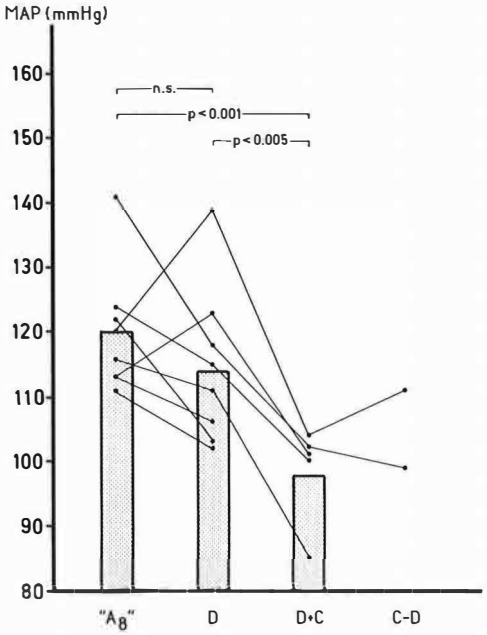


Fig. 3. The supine mean arterial pressure (MAP) in the outpatient group (n = 8) at the end of the placebo period (A_8), on diuretic (D) treatment (n = 8), after addition of captopril (D + C) (n = 5) and after cessation of the diuretic (C – D) (n = 2). The bars represent $\overline{MAP}$.

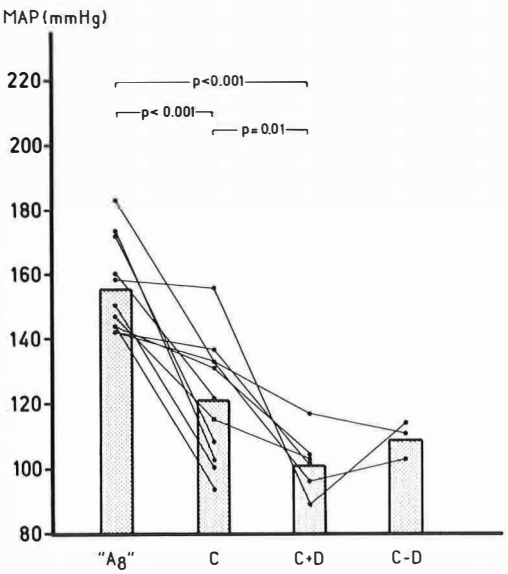


Fig. 4. The mean arterial pressure (MAP) of the emergency patients (n = 11) in the therapy-free interval ('A_8'), on the ultimate captopril (C) dose (n = 11), after addition of the diuretic (C + D) (n = 6) and after discontinuing the diuretic (C – D) (n = 3). The bars represent $\overline{MAP}$.

patients (nr 3 and nr 18) hydrochlorothiazide was withdrawn shortly after captopril had been added, resulting in a further fall in MAP in one patient (nr 18) and a slight rise in the other (nr 3). The latter patient had already shown a marked rise in blood pressure when treated with the diuretic alone.

Comparison of the results of initial single drug treatment to the MAP_{A8} values for captopril and hydrochlorothiazide (outpatient group, n = 19) showed a significant difference in favour of captopril ($p < 0.05$). There existed no statistically significant difference when only essential hypertensives in this group of patients (n = 16) were compared in a similar manner.

The $\overline{MAP}$'$_{A8}$' ± SEM of the 11 patients treated according to the emergency protocol (SQ ≠ 12,928-28) amounted to 156 ± 4 mmHg (figure 4). On ultimate captopril therapy alone, this value was 121 ± 6 mmHg ($p < 0.001$). Addition of a diuretic in 6 patients resulted in a decrease in $\overline{MAP}$ from 134 ± 5 mmHg to 101 ± 4 mmHg. This fall in $\overline{MAP}$ was significant when compared to previous captopril results ($p = 0.01$) and to initial levels ($p < 0.001$). Withdrawal of the diuretic resulted in a further fall of blood pressure in one patient (nr 27) and a slight rise in 2 others (nr 20 and nr 24).

In figure 5 the response of the MAP to single drug therapy when compared to the initial MAP (MAP'$_{A8}$') is plotted for hypertensive patients with renal

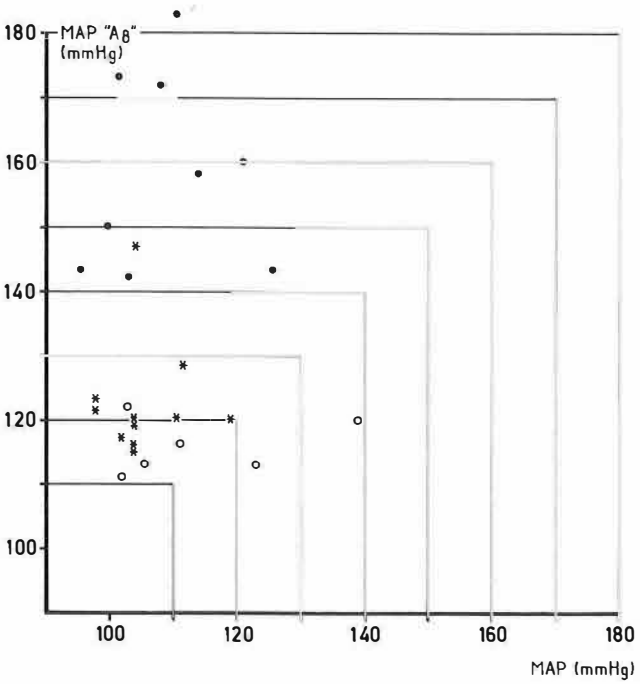


Fig. 5. The response of the supine mean arterial pressure to ultimate single drug therapy (MAP) as compared to the initial MAP in 'A_8'. ° represent renovascular hypertensive patients on captopril (n = 9). * are essential hypertensives on captopril (n = 11) and • represent essential hypertensives on the diuretic (n = 6).

artery stenosis (n = 9), for essential hypertensives on captopril (n = 11) and for essential hypertensives on diuretic treatment (n = 6). It is shown that 2 patients (nr 3 and nr 15) developed a rise in MAP on hydrochlorothiazide alone. Both had a rahter high initial PRA. In patient nr 3 ultimately captopril alone resulted in an adequate blood pressure control. This figure also demonstrates that the hypertensive patients with renal artery stenosis had higher initial MAP levels than the patients with essential hypertension.

A relation was found between the initial MAP and the blood pressure response (Δ MAP) on captopril alone, both for the essential hypertensives ($r = 0.83$; $p < 0.001$) and for the renovascular hypertensive patients ($r = 0.79$; $p < 0.01$). For the 20 captopril treated patients together this coefficient amounted to 0.92 ($p < 0.001$) (figure 6).

Also the initial MAP appeared to be related with the initial log PRA ($r = 0.60$; $p < 0.01$) (figure 7). When testing this relation for the essential hypertensive patients alone (n = 13), no significant relation was found, whereas the renovascular hypertensive patients showed a significant correlation ($r = 0.64$; $p < 0.05$).

The blood pressure response (Δ MAP) on captopril therapy alone for several months (mean 208 days), correlated with initial log PRA ($r = 0.82$; $p < 0.001$; figure 8). This relation however, appeared to be based on the 9 renovascular hypertensive patients in the tested group ($r = 0.86$), whereas the essential hypertensive patients showed no significant relation between Δ MAP and the initial log PRA ($r = 0.31$; n.s.). The above mentioned relation between the initial log PRA and Δ MAP in the renovascular hypertensive

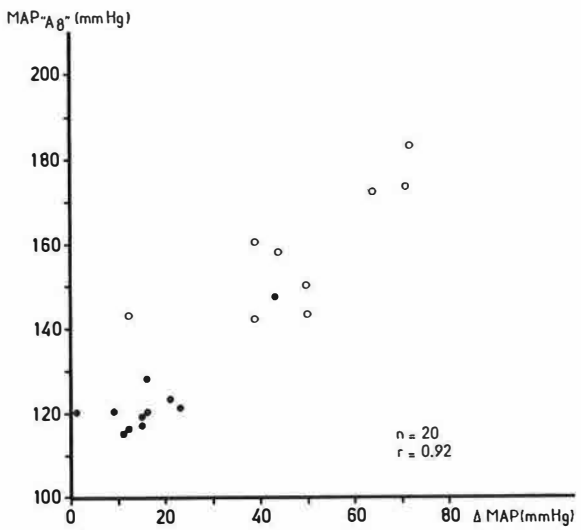


Fig. 6. The blood pressure response (Δ MAP) to ultimate captopril treatment alone, compared with the initial mean arterial pressure ($\bar{MAP}_{A8}$). ⁰ represent renovascular hypertensive patients (n = 9), • represent essential hypertensives (n = 11).

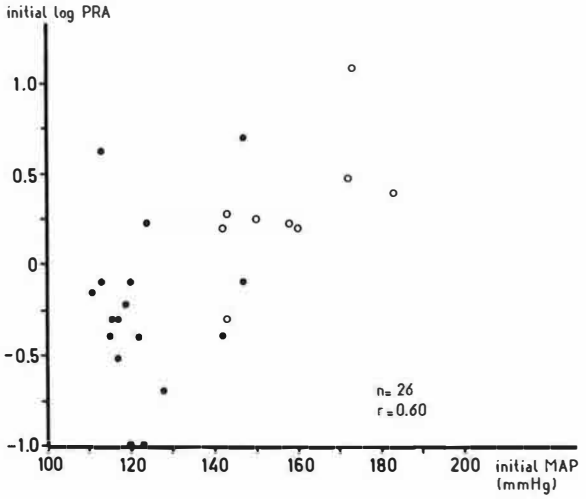


Fig. 7. The initial MAP compared with the initial log PRA. o = renovascular hypertensive patients (n = 9). • = the remaining patients, n = 17 (i.e. patients with essential hypertension, n = 13, and with non-renovascular secondary hypertension, n = 4).

patients after several months of captopril treatment could already be found after 3 to 7 days of captopril therapy ($r = 0.71$; $p < 0.05$; figure 9). This particular relation could not be calculated for the essential hypertensive patients as most of them were seen weekly in the outpatient clinic where no samples for PRA and PAC determinations were drawn.

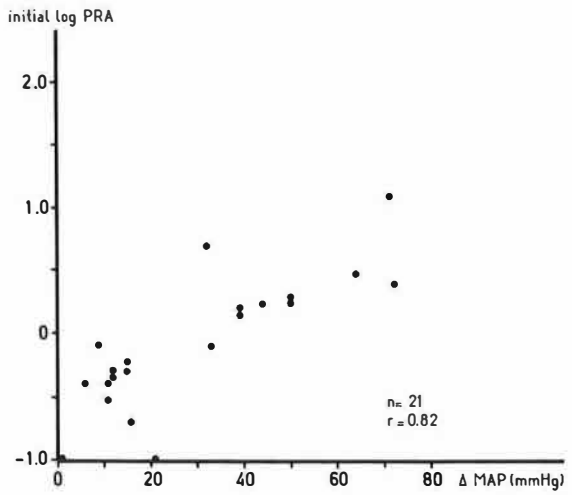


Fig. 8. The long-term blood pressure response (Δ MAP) to captopril treatment alone considered in all patients (n = 21), compared with initial log PRA.

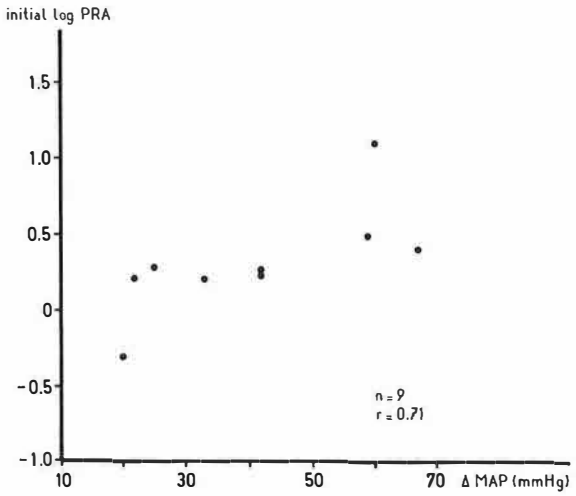


Fig. 9. The blood pressure response (Δ MAP) to captopril alone 3 to 7 days after initiating this drug, compared with initial log PRA in the renovascular hypertensive patients (n = 9).

Of the 22 patients initially treated with captopril, 8 reached the maximal daily dose of 450 mg (150 mg t.i.d.). Five out of these 8 patients needed the addition of a diuretic. However, in 3 (nrs 20, 24 and 27) out of these 5 patients the diuretic was ultimately withdrawn with consistent blood pressure control. Of the outpatients initially treated with captopril alone (n = 11) an adequate blood pressure control was obtained in 10 patients; with 25 mg t.i.d. in one patient, with 50 mg t.i.d. in 4 patients, and with 100 mg t.i.d. in 5 patients. In the single outpatient (nr 7) who reached the maximal captopril dose of 150 mg t.i.d., no 'normalization' in blood pressure could be achieved until hydrochlorothiazide had been added. Therefore it seems reasonable to add a diuretic when inadequate blood pressure control is obtained on the 100 mg t.i.d. captopril dose, after weekly titration.

In summary: in all patients treated in this study an adequate blood pressure control was obtained ultimately, either on captopril (n = 20) or the diuretic alone (n = 3) or, if necessary, with the combination of both (n = 7). The Δ MAP on captopril therapy correlated with the initial mean arterial pressure both for renovascular and for essential hypertensive patients. In renovascular hypertensives log PRA correlated with Δ MAP following both acute and long-term captopril medication. Such a relationship was not found in the essential hypertensive patients.

The maximal dose of captopril on which, as single drug therapy, blood pressure control may be expected in practice seems to be 100 mg t.i.d. When no control can be obtained on this dosage, a diuretic should be added. Withdrawal of the diuretic in the combined treatment may result in a persisting blood pressure control on captopril alone in some patients.

PLASMA RENIN ACTIVITY AND PLASMA ALDOSTERONE CONCENTRATION

In this chapter the changes will be given which have been found in plasma renin activity (PRA) and plasma aldosterone concentration (PAC) during captopril therapy alone and after the addition of diuretics when necessary. The same holds for the serum potassium (K) levels.

As has been mentioned in chapter III there existed in our patients a relation between initial log PRA and the initial MAP (figure 7). Considering essential hypertensive patients and renovascular hypertensive patients separately, there appeared to be no significant relation between initial log PRA and the initial MAP for the former group, whereas in the latter a correlation was found. A positive relation was found when initial log PRA was compared to the change in MAP (Δ MAP) on captopril therapy alone for several months (figure 8). The same held for the renovascular hypertensive patients calculated separately. In the renovascular hypertensives log initial PRA correlated with Δ MAP also 3-7 days after initiating captopril (figure 9).

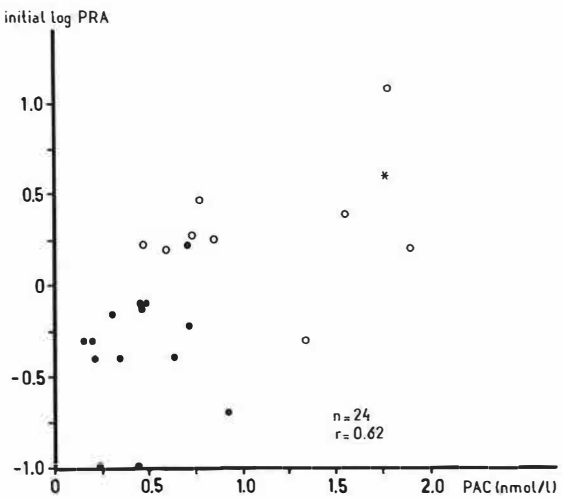


Fig. 10 The relationship between initial log PRA and the initial PAC in 24 patients. o represents renovascular hypertensives (n = 9), ● reflects essential hypertensives (n = 14), * indicates one patient (nr 9) with hypertension due to renal parenchymal disease.

Initial log PRA of 25 patients considered together, correlated with the initial PAC ($r = 0.43$, $p < 0.05$). This group of 25 patients consisted of essential hypertensives (n = 14), renovascular hypertensives (n = 9) and two patients with hypertension due to renal parenchymal disease (nrs 9 and 28). When the latter patient – who was on chronic intermittent haemodialysis prior to the start of captopril – was excluded, initial log PRA correlated better with the initial PAC ($r = 0.62$, $p < 0.01$, see figure 10). Considering the moderately sodium restricted (100-150 mmol Na^+/day) patients (n = 15) separately, the significant positive correlation was also found ($r = 0.56$, $p < 0.05$), which could not be demonstrated for the severely sodium restricted (<50 mmol Na^+/day) patients (n = 9, $r = 0.37$). The latter group actually consisted of renovascular hypertensives only.

The values of PRA, PAC and serum K as measured initially, on maximal captopril dose and on ultimate therapy in July, 1979 are given in table V. On captopril PRA increased significantly ($p < 0.01$) from 1.9 ± 0.7 to 13.7 ± 3.4 nmol A_I/l/h. Only one patient (nr 29) showed a decrease. This patient was also a non-responder regarding the blood pressure. PAC decreased significantly ($p < 0.05$) from 1.31 ± 0.46 to 0.66 ± 0.09 nmol/l and serum K increased significantly ($p < 0.05$) from 4.25 ± 0.08 to 4.41 ± 0.08 mmol/l.

PRA, as measured when maximal captopril dose had been reached and 1-3 months afterwards on the same therapeutic regimen, showed a variable pattern (figure 11). In 5 patients (nrs 8, 17, 20, 21 and 22) a rise was seen and a

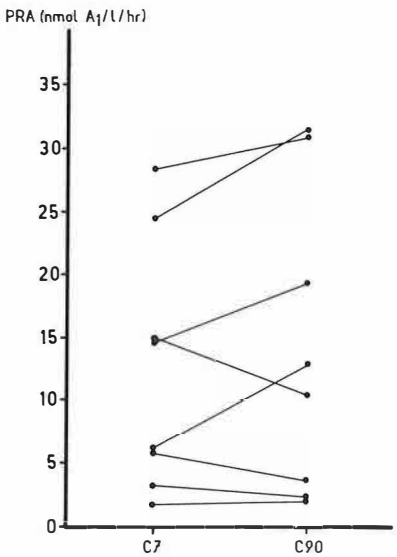


Fig. 11 PRA as measured within 7 days on maximal captopril dose (C7), and approximately 3 months later (C90) on the same therapeutic regimen (n = 8).

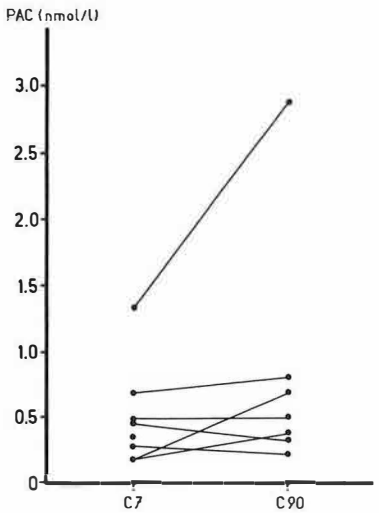


Fig. 12 PAC as found within 7 days on maximal captopril dose, and on the same therapeutic regimen approximately 3 months later (n = 7).

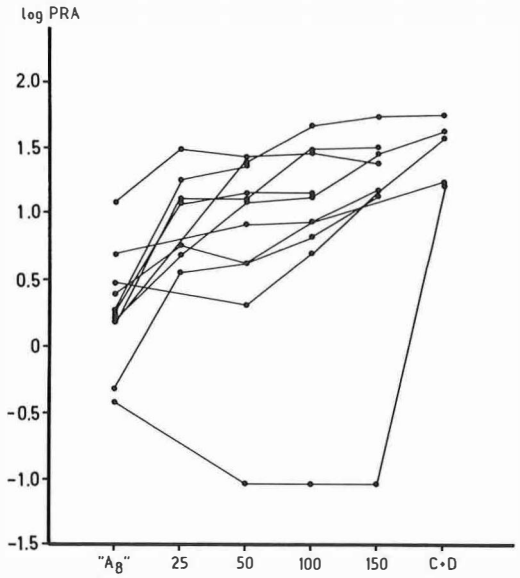
Table V. Plasma renin activity (PRA), plasma aldosterone concentration (PAC) and serum potassium (K) levels as measured in captopril treated patients initially ('A_8'), on their maximal captopril (C) dose (n = 22) and – if performed – on their ultimate treatment after several months (n = 13). Captopril dosages and duration of captopril treatment are given in the 7th, 8th, 12th and 13th column. D in column 12 reflects the diuretic added.

	A8			maximal C					ultimate treatment				
Patient number	PRA	PAC	K	PRA	PAC	K	Max. C dose (mg)	days of C	PRA	PAC	K	ultim. treatm.	days of C
2			4.3	25.6	0.26	4.2	3x150	27		0.24	4.4	3x100C	300
5	0.2	0.77	4.0	0.3	0.70	4.2	3x100	153			4.4	3x150C	260
6	0.8	0.47	4.2	3.1	0.28	4.3	3x50	14	2.2	0.22	4.4	3x50C	105
7	0.1	0.44	3.5	0.2	0.41	3.9	3x150	97	0.4	0.40	4.0	3x150C 50 HCT	111
8	0.4	0.16	4.0	6.0	0.19	4.4	3x50	15	12.8	0.38	4.7	3x50C	145
11	0.4	0.22	4.4	5.7	0.35	4.3	3x50	52	3.6		4.3	3x50C	135
12	0.5	0.42	4.4	1.3	0.24	4.6	3x50	28			4.4	3x100C	145
13	0.7	0.46	4.2			4.5	3x50				4.5	3x100C	126
16	0.6	0.72	4.1			4.5	3x100	99			4.4	3x100C	100
17	0.3	1.53	4.9	1.6	1.33	4.3	3x50	4	2.0	2.88	4.0	3x50C	45
19			4.6		0.13	4.5	3x25	60				3x25C	56
20	1.7	0.48	4.6	28.3	0.18	4.8	3x150	7	30.8	0.68	4.2	3x150C	103
21	12.3	1.78	4.2	24.4	0.68	4.8	4x100	13	31.4	0.80	5.0	4x100C	81
22	1.8	0.85	4.0	14.5	0.48	4.2	3x50	4	19.2	0.50	4.5	3x50C	110
23	3.0	0.78	4.7	14.8	0.45	4.6	5x100	6	10.4	0.33	4.5	5x100C	88
24	1.6	0.60	4.1	53.5	1.25	4.1	3x100	3	25.8	1.59	4.9	3x100C + D	53
25	1.9	0.73	3.9	23.1	0.58	4.3	3x50	6			4.2	3x50C	47
26	1.6	1.90	4.3	32.0	1.23	4.6	3x150	12			4.4	3x150C	74
27	2.5	1.55	5.5	15.3	0.91	5.7	3x150	10	40.2	1.87	4.7	3x150C + D	18
28	5.0	8.92	3.7	8.4	1.21	4.2	3x50	7	17.5	1.46	4.4	3x50C + D	125
29	0.4	0.64	4.0	0.1	0.91	3.8	3x100	3	16.6	2.06	4.2	3x50C + D	11
30	0.5	1.34	4.0	14.0	0.53	4.3	3x150	8		0.38	4.4	3x150C + D	21
Mean	**1.9**	**1.31**	**4.25**	**13.7**	**0.66**	**4.41**							
±SEM	0.7	0.46	0.08	3.4	0.09	0.08							

decrease in 3 others (nrs 11, 16 and23). With regard to the PAC, five showed an increase (nrs 8, 17, 20, 21 and 22) and two showed a decrease (nrs 16 and 23; figure 12). Serum K rose in 4 patients (nrs 6, 8, 21 and 22) and decreased in three (nrs 17, 20 and 23), staying stabile in one (nr 11).

PRA and PAC levels in the in-patients (n = 11) as found initially and after subsequent changes in therapy are given in table VI. PRA rose in all patients on the 25 mg t.i.d. dose of captopril (n = 7, see also figure 13). On the second, third and fourth titration step the pattern became equivocal, though in general a tendency to increasing levels was present. In patient nr 29 (a non-responder), PRA fell but was already low initially, lying very near the lower limit of determination. A marked increase was noticed after the addition of diuretics (figure 13).

Fig. 13 Log PRA prior to captopril, on subsequent dosages of the drug (25, 50, 100, 150 mg t.i.d.) and after addition of a diuretic if necessary. In-patients only.



PAC fell in 9 out of 11 patients on their first dose of captopril (figure 14). One of the 2 patients in whom PAC rose was the non-responder nr 29. On subsequent dosages of captopril there was a tendency to a further fall of PAC. PAC rose after the addition of a diuretic (n = 5, figure 14).

No relation was found between initial log PRA and the PAC response (Δ PAC) on captopril alone (n = 17, r = 0.38). In the 9 renovascular hypertensive patients significant relations between log PRA and PAC were never found: initially (n = 9, r = 0.37), on the first dose of captopril (n = 7, r = 0.49), on the 50 mg t.i.d. step (n = 9, r = 0.05), on the 100 mg t.i.d. step (n = 7, r = 0.44), and on the maximal dose (n = 7, r = 0.53).

	A_8		C 3x25		C 3x50		C 3x100		C 3x150		C + D	
Patient number	PRA	PAC	PRA	PAC	PRA	PAC	PRA	PAC	PRA	PAC	PRA	PAC
20	1.7	0.48	5.0	0.26	12.8	0.21	13.6	0.17	28.3	0.18	42.1	0.51
21	12.3	1.78	30.3	1.48	26.7	1.37	29.0	1.16	24.4	0.68		
22	1.8	0.85	12.1	0.83	14.5	0.48	14.3	0.38				
23	3.0	0.78			2.1	0.72	5.2	0.41	14.8	0.45		
24	1.6	0.60			24.4	0.66	45.9	0.61	53.5	1.25	55.5	1.83
25	1.9	0.73	17.8	0.42	23.1	0.58						
26	1.6	1.90	12.7	0.92	13.2	1.17	30.2	0.96	32.0	1.23		
27	2.5	1.55	5.9	1.12	4.3	0.94	8.9	0.82	15.3	0.91	40.2	1.87
28	5.0	8.92			8.4	1.21	8.9	0.94			17.5	1.46
29	0.4	0.64			0.1	0.83	0.1	0.51	0.1	0.91	16.6	2.06
30	0.5	1.34	3.7	0.66	4.3	0.78	6.9	0.59	14.0	0.53		

Table VI. PRA and PAC levels in the emergency patients (n = 11) as determined initially ('A_8'), on subsequent dosages of captopril (C), and on the combination of captopril with a diuretic (C + D) if necessary. The determinations were performed shortly after changes in therapy.

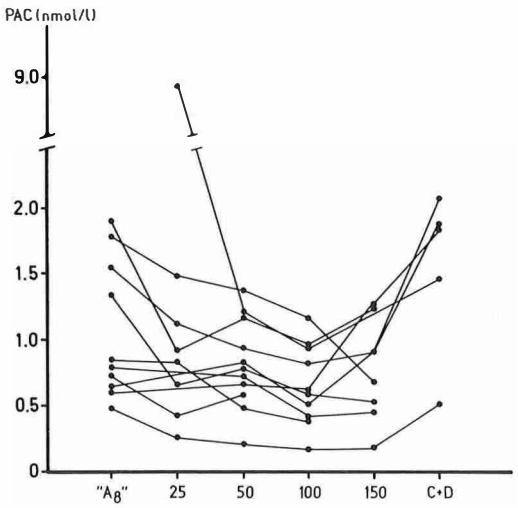


Fig. 14 Plasma aldosterone concentration prior to captopril and on subsequent dosages of the drug and after addition of a diuretic if necessary. In-patients only.

Δ log PRA* was not related with Δ PAC when comparing the changes from the initial levels to the values on maximal captopril dose (n = 17, r = 0.10). In the renovascular hypertensive patients taken separately (n = 9), a significant relationship was not found either (r = −0.54).

In addition no significant relationships were found between the Δ PAC and the change in serum K (n = 17, r = 0.37), nor was Δ MAP significantly correlated to Δ K (r = 0.30). However, Δ MAP and Δ PAC did show a significant positive relation (n = 17, r = 0.59, $p < 0.01$).

In 9 emergency patients the relationship between Δ PAC – compared to the initial levels – and the cumulative sodium balance was investigated. A negative sodium balance was seen in 2 patients only (nrs 20 and 23). No significant relationship between the 2 parameters was found at either dose level of captopril.

In summary: initial log PRA was significantly related to the initial MAP for the whole group (n = 26). Separating the group, a relationship was also found in the renovascular hypertensives (n = 13), but not in the essential hypertensive patients (n = 13). Initial log PRA correlated to Δ MAP after several months on captopril alone. In the renovascular hypertensive patients initial log PRA correlated significantly with Δ MAP both on long-term captopril and also 3-7 days after initiating the drug. Initial log PRA was significantly related to the initial PAC. Under captopril treatment both PRA rose and PAC fell significantly. Serum K rose slightly. On an unchanged captopril dose the ultimate PRA and PAC values became variable when compared to the levels shortly after commencement with the drug. Addition of diuretics always caused an increase in PRA and PAC.

Respective values of PRA and PAC at subsequent captopril dosages could be measured in the in-patients only. The relationship between these 2 parameters and between their changes were not found to be of statistical significance. However, a significant positive correlation was established between the Δ MAP and the Δ PAC. No relationship of statistical significance was present between Δ PAC and the cumulative sodium balance at either step of captopril dosage.

* Δ log PRA = Δ (log PRA_C-log PRA_{A8}).

CHAPTER V

RENAL FUNCTION

In this chapter the influence of captopril, or hydrochlorothiazide or the combination of both drugs on renal function (serum creatinine concentration, GFR, ERPF and FF) will be described.

In table VII the influence of the ultimate therapy on MAP, serum creatinine (both at the time of the last renal function study), GFR, ERPF and FF has been summarized. On ultimate therapy MAP had decreased significantly ($p < 0.0005$) from 134 to 103 mmHg ($n = 30$). The increase in serum creatinine concentration from 110 to 120 μmol/l ($n = 30$) was not significant. The decrease in GFR from 91 to 82 ml/min however was significant ($n = 26$, $p < 0.0025$) as was the decrease in FF from 0.27 to 0.23 ($n = 26$, $p < 0.0005$). The increase in ERPF from 342 to 351 ml/min did not reach statistical significance.

Table VIII shows the differences in the initial serum creatinine level, the initial GFR, the initial ERPF, the initial FF and the initial MAP (A_8 or 'A_8') between the essential hypertensive patients ($n = 12$) and the renovascular hypertensives ($n = 9$). GFR and ERPF have been corrected for standard body surface area (1.73 m^2). The renovascular hypertensive group showed a significant lower GFR ($p < 0.0005$) and a significant lower ERPF ($p < 0.0005$), when compared to the essential hypertensive group. The differences between renovascular and essential hypertensive patients in serum creatinine concentration (106 ± 7 versus 82 ± 3), FF (0.28 ± 0.008 versus 0.25 ± 0.007) and MAP (158 ± 5 versus 121 ± 3) also were significant ($p < 0.0025$, $p < 0.05$, and $p < 0.0005$, respectively).

Initial log PRA was not related to the initial value of the FF ($n = 24$, $r = 0.28$). Equally, the separation of renovascular hypertensive patients ($n = 9$) and essential hypertensives ($n = 11$) did not provide a correlation between these 2 parameters either ($r = 0.06$ and $r = -0.07$, respectively).

In essential hypertensive patients ($n = 9$) captopril alone – after 112 ± 19 days at the time of the renal function study – caused no significant changes in GFR (table IX, panel A). Omitting the non-responder (nr 7), GFR was 116 ± 7 ml/min initially and after captopril 113 ± 7 ml/min. In the non-responder in fact GFR and ERPF increased! However, captopril caused a significant increase in ERPF (from 445 ± 15 to 482 ± 25 ml/min, $n = 8$, $p < 0.05$) and a significant decrease in FF (from 0.26 ± 0.01 to 0.23 ± 0.007, $p < 0.05$).

Captopril alone during 106 ± 24 days did not influence the ERPF in the 9

	serum creatinine (mmol/l)		GFR (ml/min)		ERPF (ml/min)		FF		MAP (mmHg)		Therapy on the day of the final renal function study
Nr	–	+	–	+	–	+	–	+	–	+	
1	88	96	?	117	?	487	?	0.24	111	103	2x25HCT
2	71	76	?	116	?	450	?	0.26	121	96	4x50C
3	86	86	?	124	?	540	?	0.23	120	99	3x100C
4	88	85	?	120	?	443	?	0.27	116	104	3x25C + 1x25HCT
5	80	77	113	101	461	459	0.24	0.22	128	101	3x150C
6	71	88	94	103	380	426	0.25	0.24	147	116	3x50C
7	88	88	123	116	573	591	0.22	0.19	120	101	3x100C
8	97	79	105	106	416	430	0.25	0.24	116	103	3x100C
9	137	147	68	69	210	258	0.32	0.27	124	111	2x25HCT + 3x25C
10	71	60	114	110	454	425	0.25	0.25	122	86	2x50HCT
11	71	82	142	143	492	535	0.29	0.27	115	103	3x100C
12	80	83	138	115	454	560	0.30	0.21	117	114	3x100C
13	71	70	131	136	476	491	0.28	0.28	123	102	3x50C
14	94	91	113	113	426	488	0.26	0.23	113	97	2x50HCT
15	90	89	114	101	477	507	0.24	0.20	113	100	3x 100C + 2x25HCT
16	82	78	101	98	375	397	0.27	0.24	119	109	3x100C
17	224	231	31	30	139	124	0.21	0.24	117	103	3x50C
18	304	339	22	17	75	66	0.29	0.26	141	100	3x25C
19	92	95	104	95	490	455	0.21	0.20	120	99	3x25C
20	99	149	97	56	312	231	0.31	0.24	158	101	3x150C
21	96	123	62	62	243	282	0.26	0.21	173	117	3x100C
22	94	90	99	68	328	286	0.30	0.23	150	89	3x50C
23	124	158	87	57	300	248	0.29	0.23	172	87	4x100C + 3x40P
24	113	164	90	77	290	338	0.32	0.22	142	108	3x100C
25	67	82	111	95	406	370	0.27	0.26	143	125	3x50C
26	142	163	72	58	258	287	0.28	0.20	160	93	3x150C
27	113	183	63	52	230	207	0.28	0.25	183	115	4x50C
28	272	216	9.5	22	41	127	0.23	0.17	147	104	3x50C + 1x40F
29	90	105	93	76	326	299	0.29	0.25	142	100	3x50C + 2x25HCT + 2x50T + 3x20P
30	110	117	60	49	248	244	0.24	0.19	143	108	3x150C + 2x25HCT
Mean	**110**	**120**	**91**	**82**	**342**	**351**	**0.27**	**0.23**	**134**	**103**	
± SEM	10.5	11	6.7	6.5	26.5	27.3	0.006	0.005	4	2	
n =	30		26		26		26		30		

Table VII. The influence of the ultimate therapy (+) – on the day of the final renal function study – on serum creatinine level, GFR, ERPF, FF, and MAP, compared to A_8 or 'A_8' values (–). Abbrevations for therapy: C = captopril, F = furosemide, HCT = hydrochlorothiazide, P = propranolol, T = triamterene. Dosages in mg and in times per day.

renovascular hypertensives (291 ± 18 versus 284 ± 19 ml/min; table IX panel B). However, in this group a significant decrease in GFR (from 82 ± 6 to 65 ± 5 ml/min, $p < 0.01$) and in FF (from 0.28 ± 0.008 to 0.22 ± 0.01, $p < 0.005$) was observed. In figure 15 the difference between the two groups (all with an adequate blood pressure control on captopril alone) is shown.

	Patient nr	µmol/l serum creatinine	GFR (ml/min)	ERPF (ml/min)	FF	MAP (mmHg)
EH group						
	5	80	105	429	0.24	128
	6	71	94	380	0.25	147
	7	88	98	455	0.22	120
	8	97	95	375	0.25	116
	10	71	120	479	0.25	122
	11	71	122	424	0.29	115
	12	80	131	429	0.30	117
	13	71	120	436	0.28	123
	14	94	106	398	0.26	113
	15	90	111	466	0.24	113
	16	82	108	401	0.27	119
	19	92	98	463	0.21	120
n = 12						
mean		**82**	**109**	**428**	**0.25**	**121**
± SEM		3	3	9	0.007	3
RVH group						
	20	99	88	284	0.31	158
	21	96	58	227	0.26	173
	22	94	115	381	0.30	150
	23	124	73	252	0.29	172
	24	113	80	259	0.32	142
	25	67	115	421	0.27	143
	26	142	59	211	0.28	160
	27	113	58	199	0.28	183
	30	110	58	240	0.24	143
n = 9						
mean		**106**	**78**	**275**	**0.28**	**158**
± SEM		7	7	24	0.008	5

Table VIII. The initial values (A_8 or 'A_8') of serum creatinine, GFR, ERPF, FF, and MAP in essential hypertensive patients (n = 12) and in renovascular hypertensives (n = 9). GFR and ERPF are corrected to the standard body surface (1.73 m^2).

In the remaining 4 patients with secondary hypertension (nrs 17, 18, 28 and 29; table IX panel C) captopril alone caused variable changes in GFR, ERPF and FF. Like patient nr 7, the non-responder nr 29 also showed an increase in ERPF.

Hydrochlorothiazide alone (nrs 9, 10, 14, 15, 18) during 64 ± 25 days did not influence GFR significantly (86 ± 18 versus 81 ± 18 ml/min; table X). ERPF remained constant (328 ± 79 versus 328 ± 80). FF fell (from 0.27 ± 0.02 to 0.25 ± 0.01).

The addition of captopril to patients, unsuccessfully treated with hydrochlorothiazide alone, increased ERPF (from 278 ± 85 to 320 ± 99 ml/min; table XI). FF fell in 3 out of 4 patients (nrs 9, 15 and 18), whereas the addition of hydrochlorothiazide to the only patient in the out-patient group

	base-line values				on captopril alone				
Essential hypertensive patients	GFR (ml/min)	ERPF (ml/min)	FF	MAP (mmHg)	GFR	ERPF	FF	MAP	days of captopril treatment
nr 5	113	461	0.24	128	101	459	0.22	116	138
6	94	380	0.25	147	103	426	0.24	101	110
7	123	573	0.22	120	143	610	0.23	119	102
8	105	416	0.25	116	106	430	0.24	111	224
11	142	492	0.29	115	143	535	0.27	114	176
12	138	454	0.30	117	115	560	0.21	99	77
13	131	476	0.28	123	141	591	0.24	97	42
16	101	375	0.27	119	98	397	0.24	103	100
19	104	490	0.21	120	95	455	0.20	101	41
mean (n=9)	**117**	**457**	**0.26**	**123**	**116**	**496**	**0.23**	**107**	**112**
± SEM	6	21	0.01	3	7	27	0.007	3	19
mean (n=8)	**116**	**445**	**0.26**	**123**	**113**	**482**	**0.23**	**105**	**113**
± SEM	6.5	15	0.01	4	7	25	0.007	7	64

Table IX, panel A. Renal function and MAP in essential hypertensives (n = 9: omitting the non-responder nr 7: n = 8) prior to captopril (A_8) and on maximal captopril dose. The duration of captopril treatment on the day of the second renal function study is given in the last column.

	base-line values				on captopril alone				
Renovascular hypertensive patients	GFR	ERPF	FF	MAP	GFR	ERPF	FF	MAP	days of captopril
nr 20	97	312	0.31	158	56	231	0.24	117	124
21	62	243	0.26	173	62	282	0.21	89	210
22	99	328	0.30	150	57	343	0.17	85	20
23	87	300	0.29	172	57	248	0.23	108	185
24	90	290	0.32	142	77	338	0.22	125	174
25	111	406	0.27	143	95	370	0.26	93	128
26	72	258	0.28	160	58	287	0.20	115	11
27	63	230	0.28	183	52	207	0.25	120	77
30	60	248	0.24	143	60	254	0.24	111	27
Mean	**82**	**291**	**0.28**	**158**	**65**	**284**	**0.22**	**107**	**106**
± SEM	6	18	0.008	5	5	19	0.010	5	24

Table IX, panel B. Renal function and MAP in renovascular hypertensive patients (n = 9), prior to captopril ('A_8') and on maximal captopril dose.

	base-line values				on captopril alone				
'RDP' patients	GFR	ERPF	FF	MAP	GFR	ERPF	FF	MAP	days of captopril treatment
nr 17	31	139	0.21	117	30	124	0.24	100	7
18	22	75	0.29	141	17	66	0.26	97	53
28	9.5	41	0.23	147	14	89	0.15	120	10
29	93	326	0.29	142	92	350	0.26	92	3

Table IX, panel C. Renal function and MAP in non-renovascular secondary hypertensives ('RPD', n = 4), prior to captopril ('A_8') and on maximal captopril dose.

	base-line values				on diuretic alone				
	GFR	ERPF	FF	MAP	GFR	ERPF	FF	MAP	days of diuretic
nr 9	68	210	0.32	124	70	244	0.29	101	72
10	114	454	0.25	122	106	430	0.24	103	152
14	113	426	0.26	113	113	488	0.23	100	83
15	114	477	0.24	113	105	424	0.25	113	7
18	22	75	0.29	141	13	52	0.26	116	27
mean	**86**	**328**	**0.27**	**123**	**81**	**328**	**0.25**	**107**	**64**
± SEM	18	79	0.02	5	18	80	0.01	3	25

Table X. Renal function and MAP in hypertensive patients (n = 5), prior to hydrochlorothiazide (A_8) and on maximal hydrochlorothiazide dose.

(nr 7), unsuccessfully treated with captopril alone, caused a fall in MAP (from 119 to 103 mmHg), in GFR (from 143 to 116 ml/min), in ERPF (from 610 to 591 ml/min) and FF (from 0.23 to 0.19). The same held true for the non-responder in the emergency group (MAP from 103 to 100 mmHg, GFR from 92 to 70 ml/min, ERPF from 350 to 327 ml/min, and FF from 0.26 to 0.21). The changes in GFR, ERPF and MAP, expressed as a percentage of the initial values, are given in table XII for captopril treated patients with essential hypertension (n = 9) and renovascular hypertension (n = 9). A significant correlation was found between the percentual change in GFR and the percentual change in ERPF (n = 18, r = 0.54, $p < 0.05$, figure 16). This relationship was not present in the 2 groups when considered separately. The same held true for the relation between the percentual change in GFR and the percentual change in MAP (r = 0.19) neither did such a relationship exist correlation between the percentual change in GFR and the percentual change in the product ERPF x MAP was more pronounced (n = 18, r = 0.62, $p < 0.01$ figure 18).

No relation was found between the percentual change in ERPF and the percentual change in MAP (r = + 0.19) neither did such a relationship exist between the percentual changes in MAP and FF (r = 0.37).

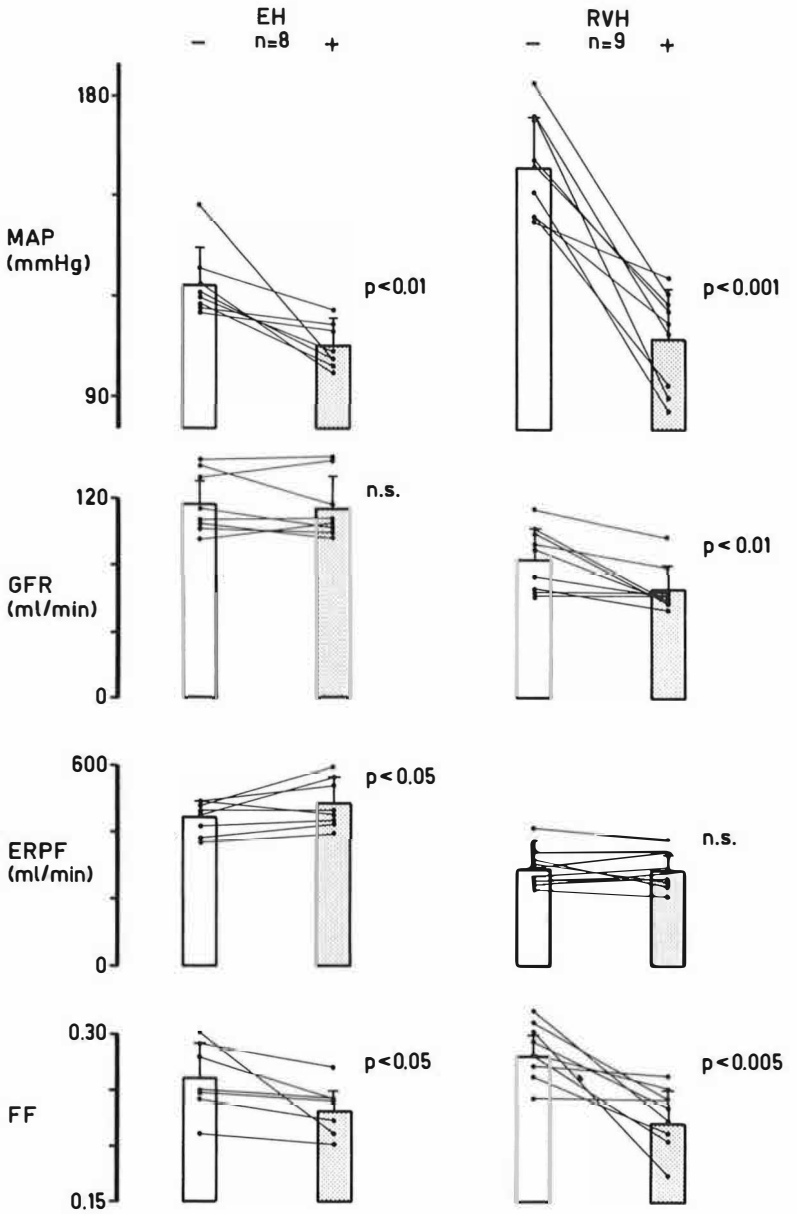


Fig. 15 The influence of captopril alone on MAP, GFR, ERPF, and FF in essential hypertensive patients (n = 8) and in renovascular hypertensives (n = 9). The open bars reflect A_8 or 'A_8' values (−), the closed bars represent on maximal captopril dose (+).

		diuretic alone					diuretic + captopril				
		GFR	ERPF	FF	MAP	D days	GFR	ERPF	FF	MAP	C days
nr	4	98	392	0.25	105	133	120	443	0.27	101	161
	9	70	244	0.29	101	73	69	258	0.27	100	4
	15	105	424	0.25	113	7	101	507	0.20	109	3
	18	13.5	52	0.26	116	27	15.5	70	0.23	102	31
mean		**72**	**278**	**0.26**	**109**	**60**	**76**	**320**	**0.24**	**103**	**42**
± SEM		21	85	0.01	3	24	23	99	0.017	2	34

Table XI. Renal function and MAP in hydrochlorothiazide treated patients prior to (D) and after addition of captopril (D + C) (n = 4). D-days reflect the duration of diuretic treatment on the moment of the first renal function study. C-days represent the duration of captopril therapy on the moment of the second renal function study.

	Percentage of base-line values (mean ± SEM)				GFR vs ERPF	GFR vs MAP	GFR vs ERPF x MAP	ERPF vs MAP
	GFR	ERPF	MAP	ERPF x MAP				
EH (n = 9)	100	108	88	95	r=0.12	0.013	0.102	0.35
± SEM	3.4	3.2	3.1	3.6	NS	NS	NS	NS
RVH (n = 9)	80	99	68	67	r=0.51	0.18	0.465	0.018
± SEM	5.0	4.7	3.5	5.2	NS	NS	NS	NS
All (n = 18)	90	104	78	81	r=0.54	0.46	0.62	0.19
± SEM	3.8	3.0	3.3	4.5	p <0.05	p <0.05	p<0.01	NS

Table XII. The percentual changes in renal function and MAP induced by maximal captopril dose in essential hypertensives (n = 9) and renovascular hypertensive patients (n = 9), and their interrelationships.

Initial log PRA was not related to Δ GFR (n = 18), neither for the captopril treated essential hypertensives (n = 9) nor for the renovascular hypertensive patients (n = 9) when considered separately (r = 0.12, 0.151, 0.104, respectively). The relationship between initial log PRA and Δ ERPF was also not significant for the whole group (n = 18, r = –0.16), neither for the essential hypertensives (n = 9, r = – 0.51) nor for the renovascular hypertensives (n = 9, r = – 0.153). For the 18 patients together, there existed a significant inverse relationship between initial log PRA and Δ FF (r = 0.50, p <0.05). However, when this group was subdivided as previously, no significant correlations were demonstrable (r = – 0.45, and r = – 0.19, respectively).

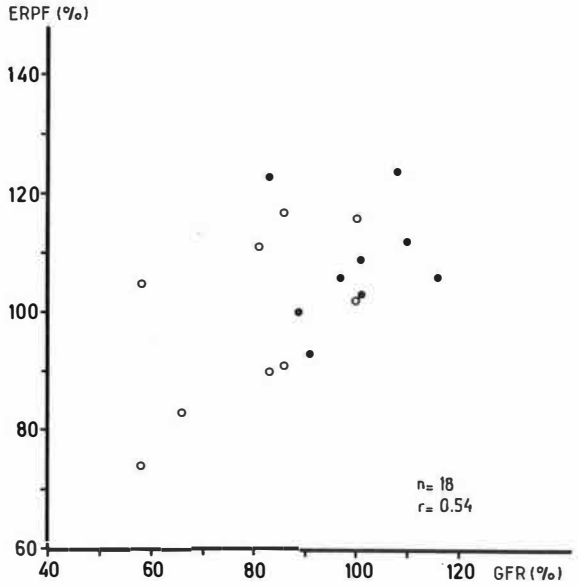


Fig. 16 The relationship between the percentual changes of GFR and ERPF in 18 captopril treated patients. o reflects renovascular hypertensives (n = 9), • represents essential hypertensives (n = 9).

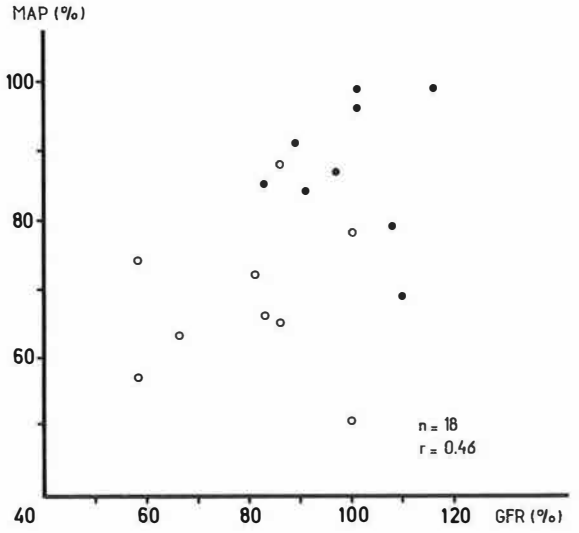


Fig. 17 The relationship between the percentual changes in GFR and MAP in 18 captopril treated patients. o reflects renovascular hypertensives (n = 9), • represents essential hypertensives (n = 9).

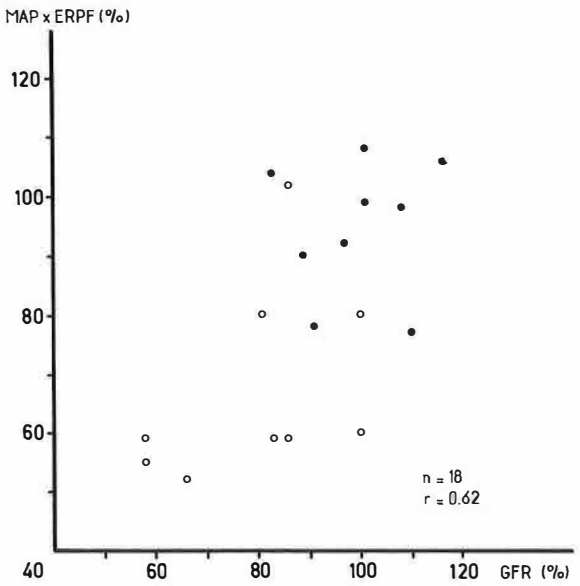


Fig. 18 The relationship between the percentual change in GFR and the percentual change in the product ERPF x MAP in 18 captopril treated patients. o represents patients with renovascular hypertension (n = 9), • reflects patients with essential hypertension (n = 9).

Δ log PRA was not found to be correlated to the ΔGFR in the previously mentioned group of patients (n = 18, r = −0.12), to ΔERPF (n = 18, r = 0.23) and to ΔFF (n = 18, r = −0.32). Separating the overall group into patients with essential and renovascular hypertension in turn failed to demonstrate any significant correlations.

In summary: GFR and FF fell significantly on ultimate therapy (associated with blood pressure under control) in all patients (n = 26). The increase in ERPF was statistically not significant. The GFR and ERPF values – when corrected for body surface – in the renovascular hypertensive patients were significantly lower than in the essential hypertensives; also between these two hypertensive groups, significant differences in serum creatinine levels, FF and MAP were present.

In the essential hypertensive patients treated with captopril alone, GFR did not change significantly. However, ERPF rose and FF fell, both to a statistically significant level.

Captopril caused variable changes in the other non-renovascular hypertensive patients.

In the renovascular hypertensives captopril caused a significant fall in GFR and FF, but did not influence ERPF.

In the diuretic treated patients a fall in FF was observed in 4 out of 5 patients, GFR was variable and ERPF was unchanged. The addition of captopril to the patients unsuccessfully treated with hydrochlorothiazide alone increased ERPF, whereas the addition of the diuretic in 2 patients, unsuccessfully treated with captopril alone caused a fall in MAP, GFR, ERPF and FF.

The percentual change in GFR and the percentual change in ERPF correlated significantly for renovascular and essential hypertensives together. The percentual change in GFR also was related significantly to the percentual change in MAP and to the percentual change in the product ERPF x MAP. Initial log PRA was found to be significantly correlated to ΔFF but not to ΔGFR and ΔERPF. No significant relations were present between the latter 3 parameters and Δlog PRA.

RESPONSIVENESS TO EXOGENOUSLY ADMINISTERED ANGIOTENSIN I, ANGIOTENSIN II AND BRADYKININ

In this chapter the influence of converting-enzyme inhibition by increasing dosages of captopril on the responsiveness to exogenously administered angiotensin I, angiotensin II and bradykinin is described.

Dose-response curves with these agents were performed in 10 patients (6 essential hypertensive patients, 3 renovascular hypertensive patients and one patient with hypertension following renal transplantation) at the end of the placebo period and on captopril 25 mg t.i.d.; furthermore in 7 patients and 4 patients also on a dosage of 50 and 100 mg t.i.d., respectively. The results are shown in figure 19 and in table XIII.

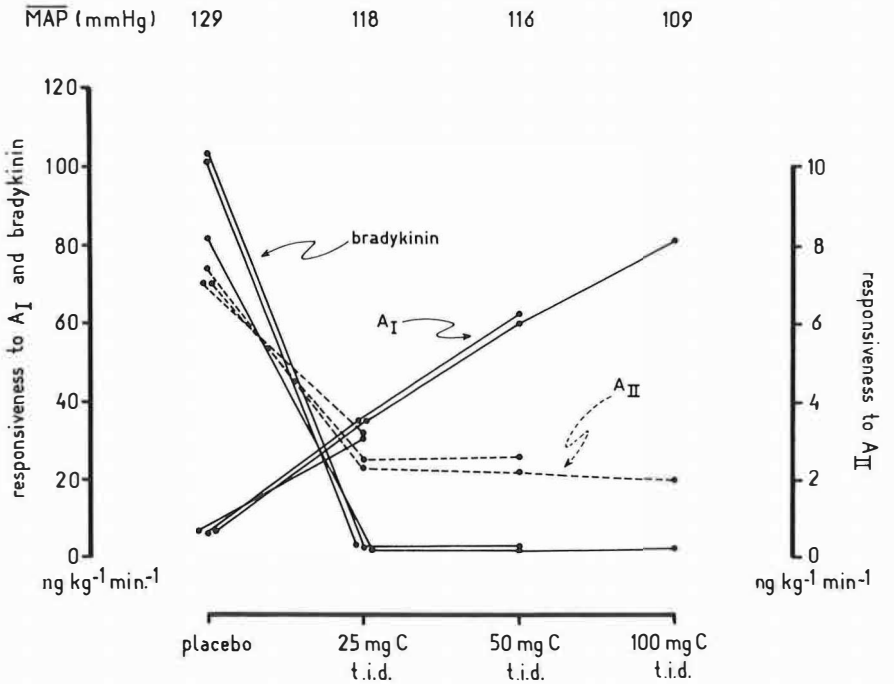


Fig. 19 The changes in responsiveness to angiotensin I, angiotensin II and bradykinin (as expressed by the dosage needed to obtain a 20 mm Hg increase or a 10 mm Hg decrease in diastolic blood pressure, respectively) in 10 patients on different dosages of captopril (C). The subsequent results for the different patient groups (captopril 25 mg: n = 10; 50 mg: n = 7 and 100 mg: n = 4) are separately shown. $\overline{MAP}$ reflects the average mean arterial pressure.

The responsiveness to angiotensin I decreased on captopril therapy. In the placebo period 7.1 ± 0.7 (mean ± SEM) ng/kg/min had to be infused to obtain a 20 mmHg rise in diastolic blood pressure. The same rise was observed at a dose of 30.6 ± 0.6 on a captopril dosage of 25 mg t.i.d. ($p < 0.001$). The infusion rate had to be increased to 62.7 ± 13.2 ng/kg/min at a dosage of 50 mg t.i.d. ($p < 0.05$). A pressor response could be obtained on every dosage of captopril, provided angiotensin I infusion was adapted.

Captopril caused a marked increase of the responsiveness to angiotensin II – induced vasoconstriction as determined by the rise in diastolic blood pressure. The dose of angiotensin II had to be decreased from 7.0 ± 1.1. to 3.1 ± 0.4 ng/kg/min ($p < 0.01$) to obtain the same degree of vasoconstriction on the minimal dosage of captopril. However, at increasing dosages of captopril no further significant enhancement of the vasoconstriction could be obtained.

The angiotensin I-converting enzyme inhibition by captopril resulted in a marked increase of responsiveness to exogenously administered bradykinin. The amount of bradykinin needed for the same degree of vasodilation – i.e. a fall in diastolic blood pressure of 10 mmHg – decreased from 100.2 ± 10.3 to 3.4 ± 0.6 ng/kg/min ($p < 0.001$), at the lowest administered dose of captopril. At incremental dosages of captopril there was no further enhancement of the vascular responsiveness.

The average mean arterial pressure ($\overline{MAP}$) decreased from 129 ± 5 to 119 ± 4 mmHg on the lowest dosage of captopril; at higher dosages no significant further fall was observed.

Table XIII. The responsiveness to exogenously administered angiotensin I, angiotensin II and bradykinin on placebo and on different dosages of captopril (C). The subsequent results for the different subgroups are separately given.

		Placebo		C 25 mg t.i.d.		C 50 mg t.i.d.		C 100 mg t.i.d.	
	N	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Angiotensin I	10	7.1	0.7	30.6***	0.6				
(ng/kg/min)	7			34.9	6.7	62.7*	13.2		
	4					59.8	20.6	80.8	16.2
Angiotensin II	10	7.0	1.1	3.1**	0.4				
(ng/kg/min)	7			2.5	0.2	2.6	0.3		
	4					2.2	0.3	1.9	0.3
Bradykinin	10	100.2	10.3	3.4***	0.6				
(ng/kg/min)	7			2.9	0.7	3.8	0.1		
	4					2.4	1.2	3.1	0.1

* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

CHAPTER VII

SIDE-EFFECTS AND ADVERSE REACTIONS

In this chapter the haematological and biochemical changes on treatment with captopril (if necessary, combined with a diuretic), the observed side-effects and adverse reactions, and the patient's subjective complaints will be described.

In table XIV the haematological and biochemical values as obtained in August, 1979, in routine investigations of blood samples and urine specimens, and the interpretations of the electrocardiograms and the chest X-ray films are given. The table concerns patients on captopril alone (n = 20, mean duration 147 days ± 18) or in combination with a diuretic (n = 7) (130 ± 24 days). Excluding patient nr 27 – who will be described separately – there appeared to be no evident changes in haematological parameters. Base-line folic acid levels were often not available but overall the values found during captopril therapy fell within the normal range (n = 21). Serum levels of sodium, potassium, calcium, phosphate and bicarbonate had not changed; the same held for uric acid, not shown in the table.

Liver function tests were abnormal in 2 patients (nrs 3 and 29). However, patient nr 3 had pre-existing liver function disturbances due to fatty degeneration of the liver, as was demonstrated by histological examination of a liver biopsy specimen. Patient nr 29 developed deterioration in liver function and jaundice after 5 months of captopril therapy. In addition to captopril and diuretics (hydrochlorothiazide and triamterene), this renal transplant patient was treated with azathioprine and prednisolone also. The liver biopsy specimen showed severe morphological changes compatible with viral hepatitis or with drug-induced hepatitis. Infectious causes of the disturbances could be excluded. The patient had no complaints of fever, rash or arthralgia. The eosinophile count was normal, as were the anti-nuclear antibodies. No proteinuria was found. Jaundice disappeared after withholding tramterene and subsequently hydrochlorothiazide, and the liver function normalized completely.

Serum cholesterol and glucose levels remained stable. No evident changes were observed in TSH, LH, or FSH levels. Converting enzyme activity as far as determined ultimately fell during captopril therapy (see table XV).

Initially (A_8 or 'A_8') positive *anti-nuclear antibodies* were found in 5 patients (see also table II: nrs 2, 3, 6, 8, 21); anti-double string-DNA was not present. In

Table XIV. Haematological and biochemical values, electrocardiographic findings and chest X-ray features as obtained in August, 1979*. Panel A concerns patients actually on captopril alone. Panel B concerns patients on captopril plus a diuretic agent. Abbrevations as in Table I.

	patient nr	Hb (g%)	mH (%)	erythrocytes (x 10^6/mm^3)	reticulocytes (‰)	leucocytes (x 10^3/mm^3)	differential count	platelets (x 10^3/mm^3)	eo x ii	folic acid (nmol/l)	Na (mmol/l)	K (mmol/l)	Cl (mmol/l)	Ca (mmol/l)	P (mmol/l)	HCO_3^- (mmol/l)	AF (U/l)	SGOT (U/l)	SGPT (U/l)	LDH (U/l)	cholesterol (mmol/l)	glucose (mmol/l)	ANA	anti DNA	urinalysis: protein excretion (g/24 h)	urinalysis: protein	urinalysis: glucose (Labstix)	urinalysis: acetone (Labstix)	urinalysis: sediment WBC/npf	urinalysis: sediment (WBC/hpf	ECG	chest X-ray
A	2	14.9	43.0	4.5	0	5.3	N	155			140	4.3	103	2.26	1.24	28	51	19	13	174	5.57	5.1	–	–	0	0	0	±	1	1	n	n
	3	15.9	45.2	4.5	10	5.0	N	242	4	12	141	4.2	102	2.40	0.77	26	66	70	98	226	6.12	4.7	–	–	0	0	0	+	1	1	n	n
	5	13.4	41.0	4.6	12	6.7	N	243		7	139	4.2	101	2.44	0.92	23	53	25	8	140	5.60	3.6	–	–	0	0	0	+	0	0	n	n
	6	14.2	41.2	4.1	4	4.8	N	145	10		145	4.0	100	2.17	1.13	21	114	17	19	319	10.97	3.8	–	–	5.1	+	+	+ –	+	5	5	n	n
	8	16.0	45.2	4.5	6	4.8	eo 7%	360		13	140	4.6	101	2.57	1.21	25	74	31	33	241	6.74	4.9	+	–	0	0	0	+	1	1	n	n
	11	15.4	45.2	4.3	14	5.6	N	150		16	140	4.3	105	2.36	0.88	26	101	25	21	204	4.90	4.5	+	–	0	0	0	–	0	0	n	n
	12	14.8	42.8	4.5	4	4.9	N	265		7	141	4.3	106	2.45	0.94	28	43	19	7	190	4.87	3.9	–	–	±	±	0	+	1	0	n	n
	13	16.1	46.9	4.6	4	6.6	N	220		12	137	4.3	98	2.42	1.12	23	69	30	25	284	5.59	4.9	–	–	0	±	0	+	1	1	n	n
	16	14.6	43.1	4.8	10	6.0	N	245		6	141	4.7	104	2.35	0.88	26	85	17	3	203	4.86	3.1	–	–	0	0	0	±	4	0	n	n
	17	9.3	29.0	3.0	11	5.3	N	200	6	12	135	5.4	108	2.35	2.26	26	87	9	16	199	4.81	4.0	–	–	0.8	0	0		2	1	n	n
	18	11.9	35.0	3.5	6	5.8	N	260	9	7	140	5.3	106	2.25	0.98	23	88	17	6	180	5.64	3.2	+	–	4.6	+	+	+ 0	+	1	1	n	n
	19	14.3	41.0	4.6	4	4.5	N	205		8	142	4.0	102	2.33	0.90	23	82	20	20	198	6.08	3.5	–	–	0	0	0	+	0	0	n	n
	20	14.8	44.5	4.5	8	8.5	N	309	10	8	136	4.6	100	2.29	1.02	25	89	23	14	213	6.13	4.2	–	–	0.9	±	0	+	01	0	strain	n
	21	13.6	39.9	4.1	18	4.1	N	175		8	137	5.2	104	2.17	1.23	21	89	21	25	186	6.91	4.2	+	–	0	0	0	+	01	0	n	cm
	22	13.8	41.1	4.1	10	6.1	N	265	3	18	138	4.5	103	2.31	1.08	28	36	17	14	215	5.28	3.8	–	–	0	0	0	+	0	1	n	n
	23	12.8	37.0	3.9	0	5.4	N	205	31	11	138	4.9	99	2.44	1.15	25	55	18	18	194	5.77	4.3	–	–	0	0	0	±	0	1	n	cm
	24	12.0	35.1	3.4	16	9.1	N	320	2	23	142	5.4	107	2.69	1.08	23	49	21	14	241	3.91	5.4	–	–	0	0	0	+	0	1	n	n
	25	13.0	38.5	4.5	2	9.4	N	280			139	4.3	103	2.30	1.01	20	62	19	14	191	5.32	3.0	–	–	0	0	0	+	0	2	n	n
	26	17.3	50.0	5.0	12	6.0	N	200		8	140	4.5	102	2.48	0.82	23	82	26	29	196	5.99	7.0	+	–	0	0	0	+	0	0	n	n
	27	9.0	27.9	3.2	30	11.0	eo 47%	326	200		141	5.1	111	2.25	1.01	26	89	18	21	360	3.90	4.1	+	–	±	±	0	0	1	2	n	cm
B	4	13.8	41.0	4.2	4	6.8	N	179		13	140	3.5	102	2.25	1.00	28	55	21	14	205	6.26	4.2	–	–	0	0	0	+	3	2	n	n
	7	14.8	42.0	4.5	2	4.5	N	310	3		145	3.6	103	2.57	0.67	31	60	30	36	218	4.90	3.5	–	–	0	0	0	+	0	0	n	n
	9	15.8	44.0	4.5	8	5.0	N	210			140	3.7	97	2.49	0.76	23	57	20	18	200	5.40	4.3	–	–	0	0	0	+	3	1	n	n
	15	15.3	43.8	4.6	4	5.7	N	240	3	4	138	3.8	98	2.57	1.07	29	54	16	18	165	6.06	4.6	–	–	0	0	0	+	0	0	strain	n
	28	8.9	23.9	2.5	10	4.2	N	240	9	8	138	4.7	104	2.37	0.98	20	105	25	5	215	5.55	4.0	–	–	0	0	0	+	0	0	n	n
	29	13.7	39.0	3.7	6	7.6	eo 8%	250		14	137	3.6	103	2.38	0.95	20	168	580	335	444	5.23	4.4	–	+	0	0	0	+	1	1	n	n
	30	16.5	47.0	5.2	6	6.9	N	190		18	139	3.8	100	2.48	0.99	28	60	22	21	202	4.80	5.0	–		0	0	0	0	0	0	LVH	cm

* The values as mentioned for patients nr 6 and 17 however, were obtained in May, 1979. See the text.

Table XV. Angiotensin I converting-enzyme activity values, prior ro captopril ('A_8' = base-line levels), and on subsequent dosages of captopril (mg per day).

Patient nr	'A_8'	3x25	3x50	3x100	3x150
5	41	–	32	19	20
7	24	25	27	31	18
8	18	22	14		
11	42	54	34		
12	34		20		
13	44	30	22		
16	34		32	23	
17	20		3		
20	28				9
21	25			12	
22	27		15		
24	15	10	1		
25		31	19		
26		18	5		
27	22			7	7

August, 1979, 8 patients had positive anti-nuclear factors (nrs 8, 11, 18, 21, 26, 27, 29, 30). In one patient (nr 30) anti-double string-DNA was present. Physical examination and additional laboratory investigations (for instance complement levels) revealed no further abnormalities in this patient (though initially a transient rash had occurred), except for a slight proteinuria once (0.5 gr/24 h) in September, 1979. The renal biopsy specimen revealed depositions of IgA and IgM in the glomerular basement membrane (GBM).

Quantifiable *proteinuria* was found ultimately in 6 patients (nrs 6, 17, 18, 20, 27 and 30). Patient nr 17 was a renal transplant patient with previously existing proteinuria, who appeared to have a chronic rejection of the graft. She underwent transplantectomy after discontinuing captopril. Patient nr 18 had pre-existing proteinuria and renal insufficiency caused by renal tuberculosis 20 years previously. Patient nr 20 was a renovascular hypertensive patient in whom the proteinuria was not observed before the ultimate determination in August, 1979. No clinical signs of hypoproteinaemia, hypercholesterolaemia or oedema were present at that time and the body weight was unchanged in these patients.

Patient nr 6 had been on captopril for 8 months without any complaints. Prior to the start of the study, she had been treated with the combination of a diuretic, a beta-blocker and a vasodilator at adequate dosages, however with resulting poor blood pressure control. Secondary causes of hypertension were excluded and the renal function was excellent. An adequate blood pressure control was obtained with 150 mg captopril per day. The patient remained normotensive during regular visits to the outpatient clinic (130/80 mmHg). In April 1979, a *nephrotic syndrome* developed (proteinuria 5 g/24 hr). The

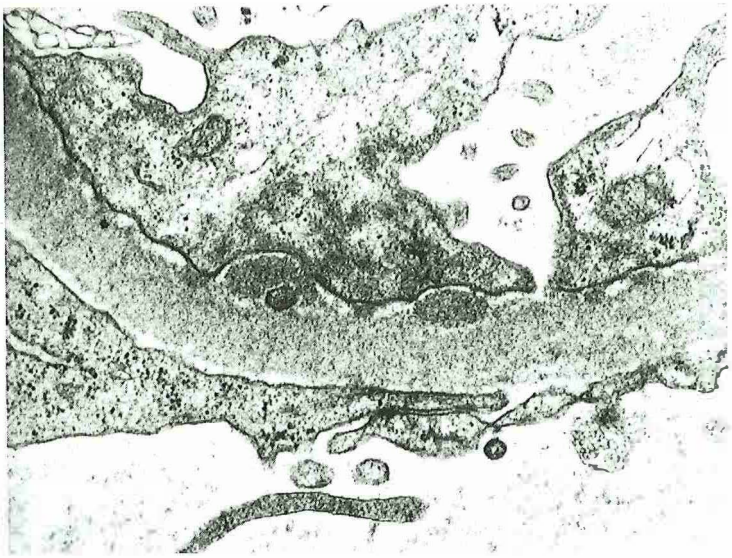


Figure 20. Patient nr 6. Electronmicroscopy of renal biopsy shows electron-dense deposits along sub-epithelial side of GBM (x26600).

anti-nuclear factors were negative and C_{3c} globulin amounted to 124 per cent of the standard serum. In a renal biopsy specimen on light microscopy no proliferative or exudative changes were found. Electron-dense deposits along the subepithelial side of the glomerular basement membrane (GBM) were revealed by electronmicroscopy (figure 20). Immunofluorescence studies showed IgA, IgG, IgM and C_3 distributed in a fine granular pattern in the GBM (figure 21). These findings are consistent with an early stage of membranous glomerulopathy. Under clinical observation captopril was gradually reduced and finally stopped. Investigations performed at that time can

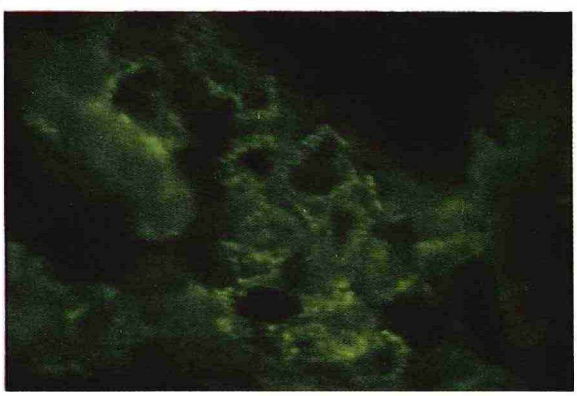
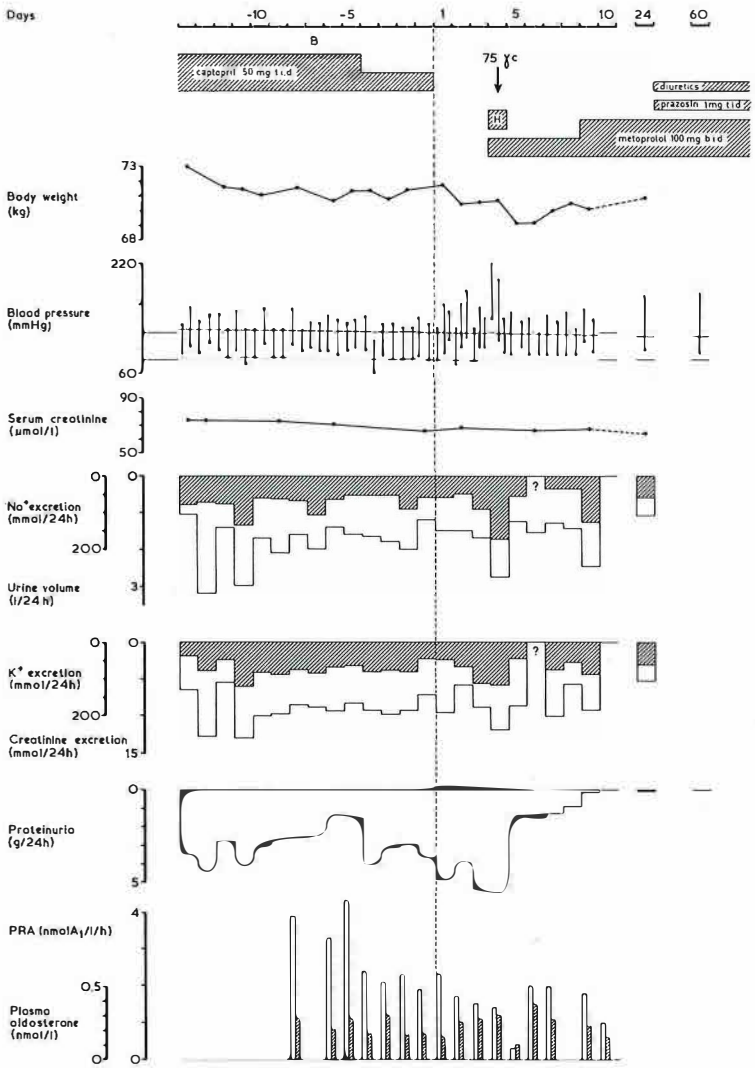


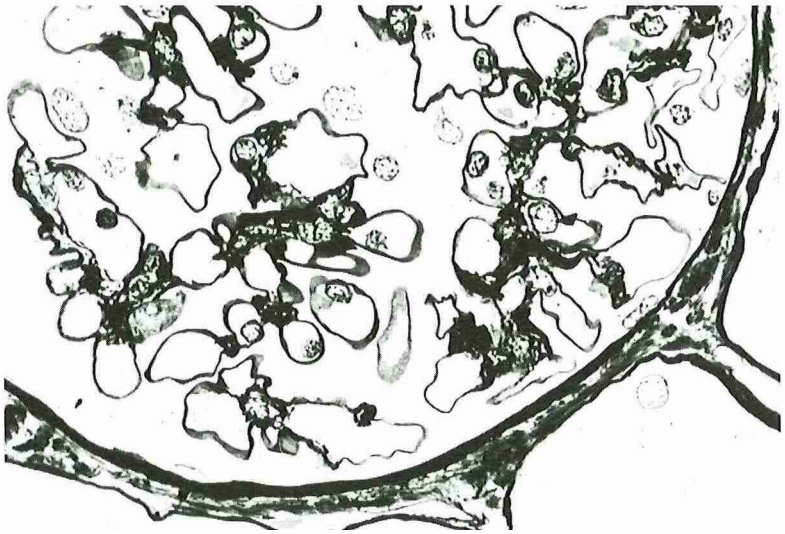
Fig. 21 Patient nr 6. Immunofluorescence microscopy of renal biopsy shows granular pattern of IgG along GBM (x 250).



GFR (ml/min)	103	96	95	88	99
ERPF (ml/min)	426	430	445	460	369
FF	0.24	0.22	0.21	0.19	0.26

Patient nr 6. Diagnostic and therapeutic procedure during withdrawal of captopril and subsequent titration of other antihypertensives. Five days after withholding captopril a sharp decline in proteinuria can be seen. The open bars represent PRA whereas the hatched bars reflect PAC values. See the text.

be visualized from the graph. Blood pressure remained stable despite reducing the captopril dose. After discontinuing the captopril however, a gradual increase in blood pressure to 220/140 mmHg was soon observed, accompanied by severe headaches. Antihypertensive treatment with a beta-



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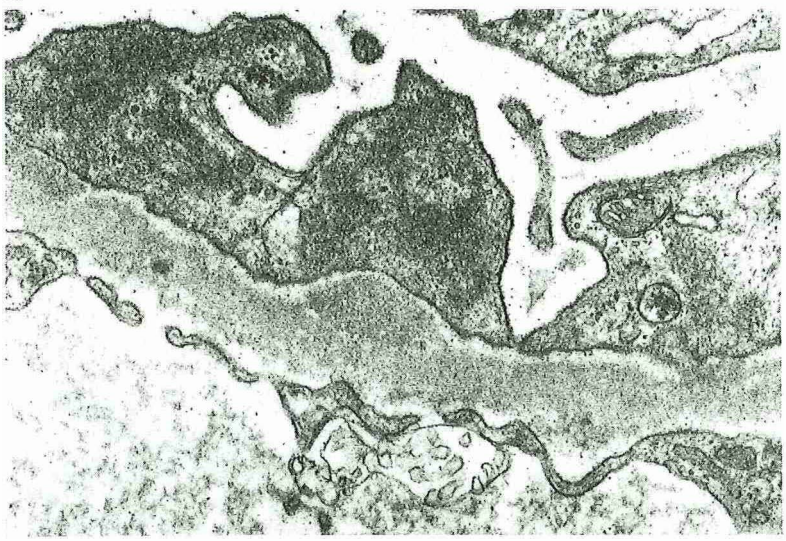


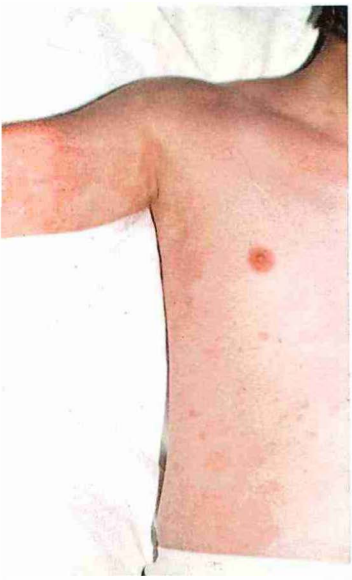
Figures 22 and 23. Patient nr 6. Renal biosy specimen 4 months after cessation of captopril. The light microscopy shows a normal picture (x 160), whereas the electronmicroscopical picture still reveals the presence of electron-dense deposits along the sub-epithelial side of the GBM (x 35,000).

blocker caused a fall in blood pressure though 'normotension' could not be obtained immediately despite increasing the dosage further.

Urinary protein excretion decreased gradually after withdrawing captopril and amounted to 0.1 g/24 hr at discharge. PRA was high during captopril therapy and decreased when the captopril dose was reduced. PAC hardly changed. Discontinuing captopril resulted in a further fall of PRA and a slight increase of PAC. Renal function tests can be read from the last line of the graph. At discharge all features of the nephrotic syndrome had disappeared and the blood pressure amounted to 140/95 mmHg. During regular visits to the outpatient clinic however, the blood pressure appeared to be poorly controlled despite the addition of a diuretic and a vasodilator (180/95 mmHg). The proteinuria had disappeared completely. Renal function remained excellent. The renal biopsy was repeated 3 months after cessation of captopril. The light microscopy, immunofluorescence and electron microscopical studies showed no evident changes, i.e. a fine granular pattern of immunoglobulins and C_3 along the GBM and electron-dense deposits on the subepithelial side of the GBM were still present (figures 22 and 23).

Urticarial rashes were observed in 4 patients (nr 18, 22, 27, 30), none of whom had a previously known history of allergy. In two, the rash developed within 7 to 10 days after the start of captopril. Patient nr 18 developed a rash on his face, upper limbs and chest and also an *angioneurotic oedema* (figures 24 and 25), arising 7 days after initiating captopril. There was no myalgia or fever. The rash and the angioneurotic oedema completely disappeared within 48 hours when the captopril dosage was reduced from 50 to 25 mg t.i.d.. Laboratory investigations revealed no eosinophilia. However, it is noteworthy to mention that the anti-nuclear antibodies which had not been present previously, were found following 30 days of captopril treatment. As the clinical picture had completely returned to normal and the blood pressure remained under control despite reducing the captopril dose, the 25 mg t.i.d. regimen was maintained. At regular visits to the outpatient clinic the patient has remained normotensive and in a good clinical condition.

In patient nr 22 – who will be described in detail in Chapter VIII – myalgia, chills, fever and tachycardia developed on the 10th day of captopril treatment. Twenty-four hours later, an urticarial rash had developed on the face, upper limbs and chest, spreading slowly over the body (figure 26). Blood pressure had come under control during the previous days on a captopril 100 mg t.i.d. regimen. Eosinophilia was not present, the anti-nuclear factors were negative and there existed no proteinuria. Captopril was then gradually withdrawn and within 24 hours the rash had disappeared. As the rash and fever had been accompanied by hypotension and impairment of renal function (see the patient's graph, Chapter VIII) saline was infused, resulting in a 'normal' blood pressure. However, within 72 hours of discontinuing captopril, the blood pressure began to rise. Captopril was then titrated again. The blood pressure remained under control on a 50 mg t.i.d. dose and there was no recurrence of the rash.



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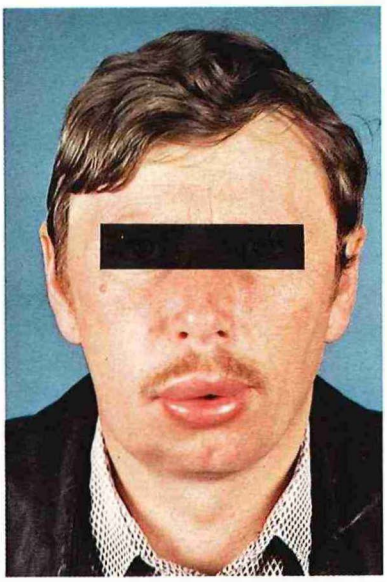

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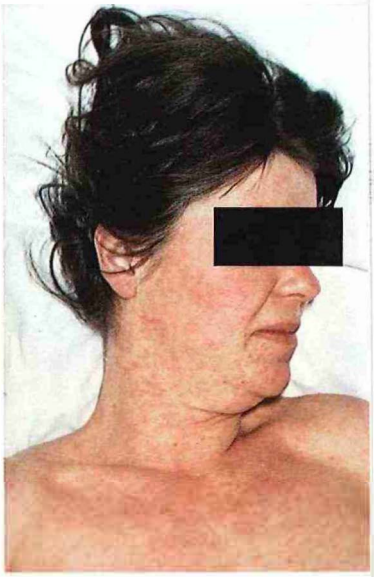

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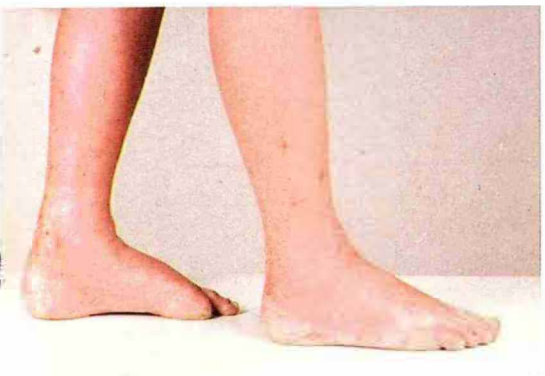

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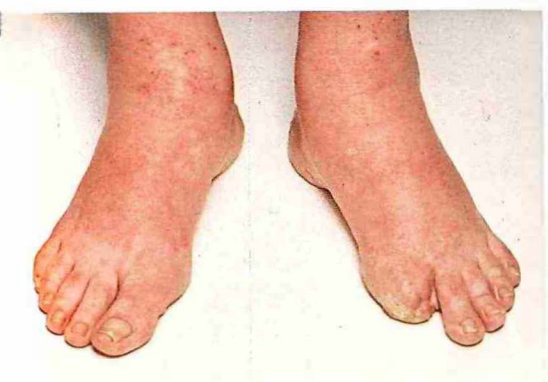

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Fig. 24 Patient nr 18. Urticarial skin rash on the chest and upper limbs, developing after 7 days of captopril treatment. Actual dose: 50 mg t.i.d.

Fig. 25 Patient nr 18. Angioneurotic oedema after 7 days of captopril treatment.

Fig. 26 Patient nr 22. Exanthema on face and chest developing 10 days after initiating captopril. Actual dose: 100 mg t.i.d.

Fig. 27 and 28 Patient nr 27. Exanthema, oedema and epidermal necrolysis of the lower limbs. The left hallux was amputated after trauma in 1957.

Patients nr 27 and 30 will also be described in detail in Chapter VIII. Nr 27 developed eosinophilia (34 per cent in the differential count) without physical abnormalities when the captopril was initiated. Five weeks after commencing captopril however, an urticarial rash developed on the upper limbs and the chest, slowly spreading over the body surface. There were no complaints of chills, fever or myalgia. Renal function had already become 'impaired' during captopril treatment alone, but deteriorated progressively when hydrochlorothiazide had been added in order to obtain an adequate blood pressure control (see the patient's graph, Chapter VIII). Hydrochlorothiazide had been withdrawn one week before the rash started. The antinuclear factors were negative. The urinary sediment was normal and there existed no proteinuria. Reducing the captopril dose from 150 mg t.i.d. to 50 mg t.i.d. resulted in a slow disappearance of the rash. As the blood pressure had risen slightly the captopril dosage was again increased to 50 mg q.i.d., and this resulted in a good blood pressure control. Meanwhile, the renal function had improved, but the eosinophilia persisted though at a lower level and the dermal reaction (generalized rash comprising a maculo-papular exanthema with oedema and epidermal necrolysis; see figures 27 and 28) returned 2 weeks after restarting the 50 mg q.i.d. dose, this time associated with arthralgia, fever and a generalized lymphadenopathy. Proteinuria was noted (0.9 g/24 h). Anti-nuclear factors were positive, anti-double string DNA negative. C_{3c} globulin was 102 per cent of the standard serum; C_1-esterase inhibitor 920 U/l (normal value 860 ± 280). Renal function had become 'impaired' again as well (blood pressure 120/80 mmHg) and the patient was readmitted. The renal biopsy revealed a granular deposition of immunoglobulins along the GBM. Captopril was gradually withdrawn resulting in rise in blood pressure, in an improvement of renal function and in a disappearance of the rash. The eosinophilia decreased to 13 per cent. Further information on this patient will be given in Chapter VIII (case report nr 27).

In patient nr 30 thirty minutes after ingesting the very first tablet of captopril (25 mg) a transient, short lasting (30 minutes) rash on the face developed without any other clinical features. The second dose (7 hours later) was tolerated without any rash. However, the third dose (still 25 mg) again caused an urticarial rash on the face, upper limbs and chest, disappearing within 30 minutes. The laboratory investigations revealed no abnormalities. Subsequent increasing dosages were tolerated well. It is noteworthy to mention that this patient was very sensitive to exogenously administered bradykinin in the therapy-free interval, when compared to the other patients. Furthermore, in this patient positive anti-nuclear factors and a positive anti-double string-DNA were ultimately found, as mentioned previously.

In two patients (nrs 24 and 27) *hyponatraemia* was observed. Both patients will be described in detail in Chapter VIII. Patient nr 24 adhered to a 20 mmol sodium restricted diet and was in complete sodium balance (also when using diuretics). The captopril dose was titrated stepwise in 3 days to the maximal dose (150 mg t.i.d.) without the blood pressure being distinctly lowered (see

this patient's graph in Chapter VIII). There was no increased natriuresis in this phase. The addition of hydrochlorothiazide resulted in a fall in blood pressure, and also in an increased natriuresis and isosthenuria. The natriuresis was not accompanied by a clear fall in body weight, and gave rise to a state of hyponatraemia and uraemia. The state of salt depletion became even more marked after the addition of furosemide (given since adequate blood pressure control had not been achieved on the previous combination). Cessation of the diuretics did not influence the normotensive state that had been achieved. Further, the blood pressure did not increase when additional sodium was provided and the salt restriction was lifted allowing a 100 mmol sodium containing diet. The biochemical values of sodium, urea and creatinine did return to previous levels after salt repletion.

Patient nr 27 (see also the patient's graph in Chapter VIII) had a 20 mmol sodium restricted diet and was in complete sodium balance before captopril was initiated. Captopril was titrated stepwise to the maximal dose (150 mg t.i.d.) over a 7 days period but adequate blood pressure control was not obtained. Natriuresis had increased slightly. The addition of hydrochlorothiazide in this patient also resulted in a marked natriuresis, giving rise to hyponatraemia and uraemia. Urinary osmolality was not determined. The hyponatraemia persisted when the diuretic was withdrawn and the captopril dosage was reduced to 100 mg t.i.d.. An urticarial rash developed during the succeeding days and hence the captopril dose was further reduced to 50 mg t.i.d.. Since hyponatraemia and uraemia persisted, additional sodium was given intravenously and the dietary salt restriction was expanded to 100 mmol sodium per day. This resulted in a gradual improvement of the above mentioned biochemical values whilst the blood pressure remained under control.

One patient (nr 22) developed a Raynaud phenomenon 4 weeks after initiating captopril. Plethysmography showed an evident decreased blood flow when repeated in cold water (4°C). Two other patients complained of *cold fingers and/or toes* (nrs 11 and 23). In patient nr 23 propranolol had been continued (80 mg t.i.d., see Chapter VIII). Four weeks after the start of captopril this patient complained about cold fingers, independent of the outside temperature. His general practitioner reduced the propranolol dose to 40 mg t.i.d., and the complaints diminished but did not disappear completely. Two other patients had vague complaints of paraesthesia in some fingers (nrs 21, 29). The complaints were not present at every visit to the outpatient clinic in patient nr 21, and started after 7 months treatment in patient nr 29.

Increased pulse rate or a history of *palpitations* was noticed in 4 patients (nrs 22, 25, 26, 29). Each had received beta-blocker therapy prior to the commencement of captopril. Patient nr 22 had a transient increase in pulse rate which rose from 60 beats per minute in the therapy-free interval to 92 b/min on captopril (and was 80 b/min 6 months later). Patient nr 25 had had palpitations prior to captopril treatment and appeared to have an intermittent sinustachycardia (120 b/min) associated with stress and anxiety. She therefore was treated with propranolol 20 mg t.i.d.. Patient nr 26 had no physical

complaints but his pulse rate increased from 66 b/min in the therapy-free interval to 100 b/min on captopril, this was still present after 4 months treatment. Patient nr 29 had ventricular ectopic beats and was successfully treated with propranolol 20 mg t.i.d.

One patient (nr 30) noticed olphactory hallucinations 8 months after the start of captopril.

At each visit to the outpatient clinic and during hospitalization, the patients were carefully questioned about any complaints. Apart from the ones mentioned above, no other features have been observed. Especially no *loss of taste* (ageusia) was noted at any phase of captopril therapy.

CHAPTER VIII

CASE REPORTS

In this chapter the case histories of the 11 emergency patients will be described. Nine suffered from renovascular hypertension due to renal artery stenosis. Five patients (nrs 21, 22, 25, 26, 30) had unilateral renal artery stenosis, associated with fibromuscular dysplasia in two (nrs 22, 25). In three patients (nrs 20, 23, 27) bilateral renal artery stenosis was present. One renal transplant patient (nr 24) had a stenosis of the graft artery. In the other renal transplant patient (nr 29) secondary causes of hypertension were not found. Patient nr 28 suffered from renal insufficiency and hypertension due to a haemolytic uraemic syndrome.

Patient nr 22, a 38 year old female.

Her medical history was negative until by chance hypertension (220/130 mmHg) was found in an epidemiological survey. Although she had been using an oral contraceptive for 10 years, her blood pressure had never been checked. She used to eat a considerable amount of liquorice daily.

Both the oral contraceptive and liquorice were discontinued. Until she visited our outpatient clinic in November, 1978, she had been treated with various anti-hypertensive agents. When first seen by us, her blood pressure was 220/140 mmHg on a therapeutic regimen consisting of propranolol and a moderately sodium restricted diet. The cardiovascular history was normal. She used to suffer from migraine and perspiration on the 3rd and 4th day of menstruation until she stopped the 'pill'. The perspiration was never accompanied by flushing or pallor. Twice during the past 10 years she had had a urinary tract infection. Her two pregnancies had been uncomplicated. There was no family history of hypertension. Physical examination revealed a normal heart size and no vascular bruits could be heard, especially not over the renal region. Fundoscopy demonstrated normal fundus with only a slight decrease in vessel diameter. Electrocardiography showed left ventricular hypertrophy and signs of strain. A chest X-ray revealed no abnormality. The rapid sequence IVU showed a small right kidney (10x5 cm) and a normal left one (13x6.5 cm). Nephrography and excretion were symmetric. No irregularities of the renal cortex were present. The calyces and the outflow tract were also normal. In the standing position, the left kidney had a mobility of 1½ vertebra, on the right side 1¼. The laboratory investigations revealed normal values of haematogram, anti-nuclear factors and serum levels of sodium, potassium, chloride, calcium and phosphorus. Urea was 5.9 mmol/l and creatinine was 74 μmol/l. The liver function tests were also normal. The creatinine clearance amounted to 62 ml/min. Urinalysis revealed neither proteinuria nor glucosuria. No cells were seen in the sediment. Urinary excretions of 5-HIAA and VMA were normal.

For 3 months, she was treated with an anti-hypertensive regimen of hydrochlorothiazide, metoprolol and hydralazine. When admitted to the hospital in order to change therapy to captopril, her blood pressure was 220/140 mmHg. Medical history and physical examination revealed no new data. Renal angiography was performed and showed no signs of atherosclerosis. The left

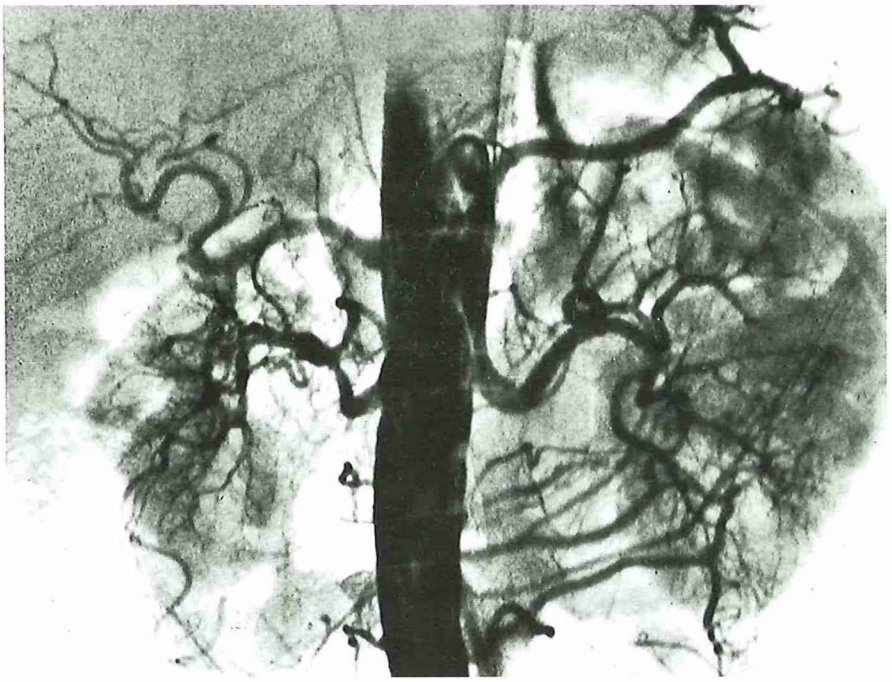


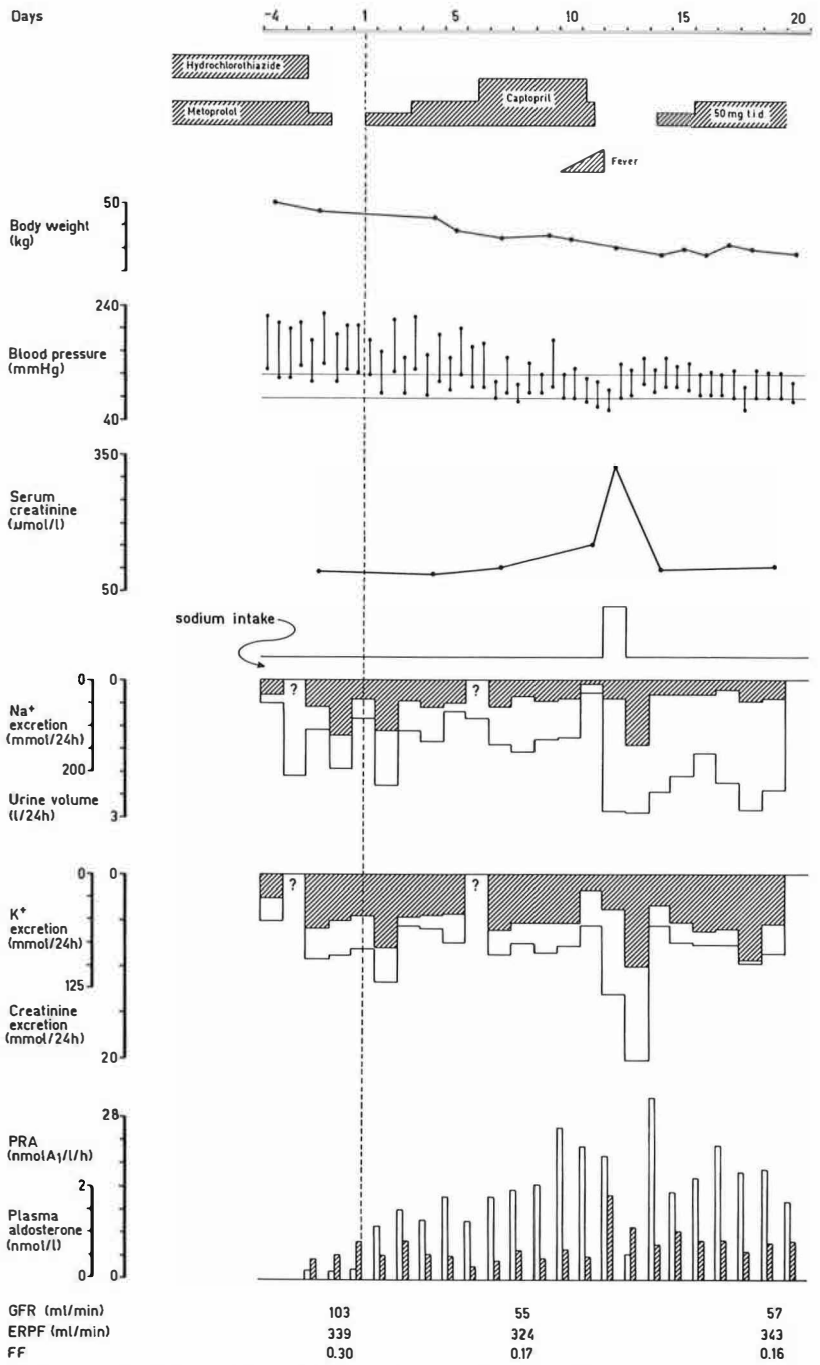
Figure 29. Patient nr 22. Renal angiography shows a normal vascular pattern of the left side. Contralaterally, a renal artery stenosis is present 1.5 cm from the origin, with a post-stenotic dilatation. The right kidney is smaller (10 x 5 cm) than the left one (13 x 6.5 cm).

renal artery was normal. In the right renal artery a stenosis was observed 1½ cm from its origin, with a poststenotic dilatation (see figure 29). Beyond this, a second stenosis was also present. The picture resembled that of fibromuscular dysplasia. It was concluded that a severe renovascular hypertension existed without evidence of serious damage to the end-organs.

The procedure followed is shown in the graph. Under careful monitoring of blood pressure and body weight, and regular measurement of PRA, PAC, serum electrolytes, urea and creatinine, and the 24 hour excretion of sodium, potassium and creatinine the previous therapy was withdrawn. Renal function studies were performed without therapy and on captopril. Dose response curves were performed without therapy and at each increasing dose of captopril.

The graph shows blood pressure levels being unacceptably high during treatment with hydrochlorothiazide and metoprolol, ranging from 185 to 225 mmHg systolic and from 110 to 140 mmHg diastolic. She adhered to a 3 g sodium containing diet. Measured on the therapy-free day, the GFR was 103 ml/min and the ERPF 339 ml/min. The filtration fraction was high (0.30). Blood pressure on this day amounted to 205/125 mmHg. The sensitivity for exogenously administered A_I was 2⅔ ng/kg/min, for A_{II} 5 ng/kg/min and for BK more than 100 ng/kg/min. PRA was 1.3 nmol A_I/l/h and PAC amounted to 0.62 nmol/l.

Treatment with captopril was initiated at a total daily dose of 75 mg. An evident, though inconstant fall in blood pressure was noted. After 48 hours the dose was increased to 150 mg per day which was followed by a further fall in blood pressure. Following a further 72 hours the dose was increased again to 300 mg per day, since an adequate blood pressure control had still not been achieved. On the 10th day of treatment, the temperature began to rise to 38°C. The patient felt cold and the skin was wet. Specific complaints, apart from myalgia and a disgust for hospital food,



Patient nr 22. Diagnostic and therapeutic procedures during withdrawal of previous antihypertensives and subsequent titration of captopril. The open bars represent PRA, the hatched bars reflect PAC values. For details see the text.

were not volunteered. There was no loss of taste. During the night of the 10th day a maculo-papular rash developed, first in the face and on the chest, later also on the extremities (see figure 26, Chapter VII). Locally, the rash had an urticarial property. There was no prutitus, oedema or joint pain. The temperature rose to 39.8°C in the next 24 hours. Influences, other than captopril responsible for fever and rash were ruled out as far as possible. Since hypotension was evident, the captopril was discontinued after a stepwise decrease in the dosage. On the next day she showed a normal temperature, the rash having disappeared almost completely. However, the blood pressure remained low and since her renal function proved to have deteriorated, an infusion of 1500 ml NaCl 0.9% was given. The transient, steep rise in serum creatinine was apparently of pre-renal origin, since the administration of saline was immediately followed by an increase in diuresis and in the urinary excretion of creatinine, resulting in a fall of the serum level. The supplemental sodium was interestingly excreted within one day. A negative sodium balance during captopril treatment has not been observed. The blood pressure initially returned to normal, but later rose to elevated levels again. After 2 days of withholding captopril, the drug was reinstituted and finally, a dosage of 50 mg t.i.d. was found to maintain acceptable blood pressure levels. The patient tolerated the drug well after the above mentioned episode.

During hospitalization the body weight fell from 50 to 45.2 kg and remained constant thereafter. The explanation of this loss must be in the fact that the patient ate far less than at home.

The inhibition of angiotensin-II formation by captopril was demonstrated by the rise in PRA (open bars), and by the decrease in PAC (hatched bars). It is noteworthy to mention that at the same time as the test drug had been discontinued, the PAC increased markedly. PRA decreased on sodium and volume repletion but increased again after excretion of this load.

The renal function tests showed a decrease in GFR from 103 to 55 ml/min but no evident change in ERPF. Since there was a fall in the filtration fraction, this indicated a decrease of intra-renal vascular resistance. The responsiveness to exogenously administered angiotensin I decreased on captopril. The responsiveness to exogenously administered A_{II} remained high and the responsiveness to exogenous bradykinin increased markedly. Seven days after reinstituting the test drug, the patient left the hospital in a good condition without any sign of adverse reaction. Her blood pressure which had previously been unsuccessfully controlled then was 120/80 mmHg.

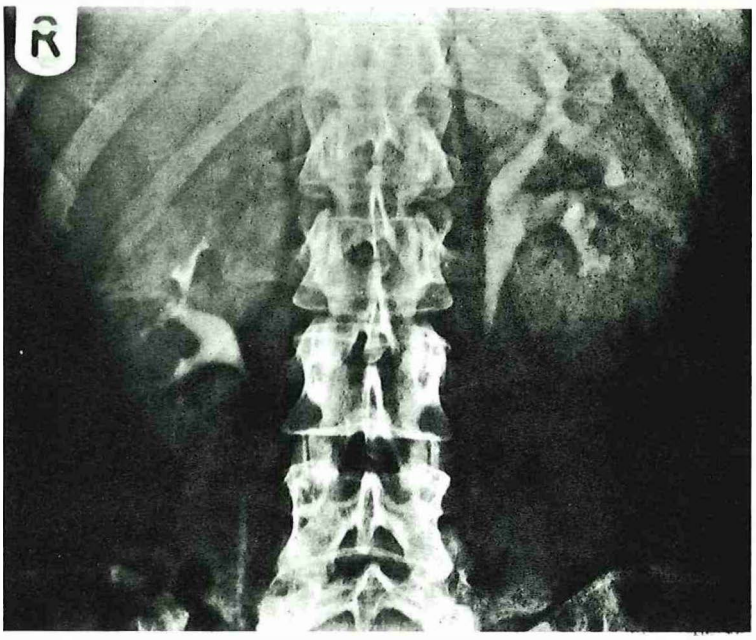
The patient was seen regularly in the outpatient clinic. Her blood pressure remained under control. The body weight increased slightly to 47 kg. Six weeks after initiating captopril, she started to complaint of cold and white fingers. Plethysmography showed a decreased blood flow in the fingers and toes when held in cold water (see Chapter VII). However, since the complaints were not severe, and tolerable to the patient, the therapeutic regimen was left unchanged (captopril 50 mg t.i.d.). In August, 1979, – six months after starting captopril – her blood pressure was 130/95 mmHg. Her renal function was acceptable (GFR 68 ml/min, ERPF 286 ml/min), serum creatinine concentration being 90 µmol/l. Urinalysis gave normal results. The anti-nuclear factors were negative.

In summary: In a 38 year old female with intractable unilateral renovascular hypertension, probably due to renal artery stenosis associated with fibromuscular dysplasia, blood pressure normalized on captopril therapy (100 mg t.i.d.). However, fever, myalgia and an urticarial rash developed after 10 days. A reduced captopril dose was tolerated well, and the blood pressure remained under control.

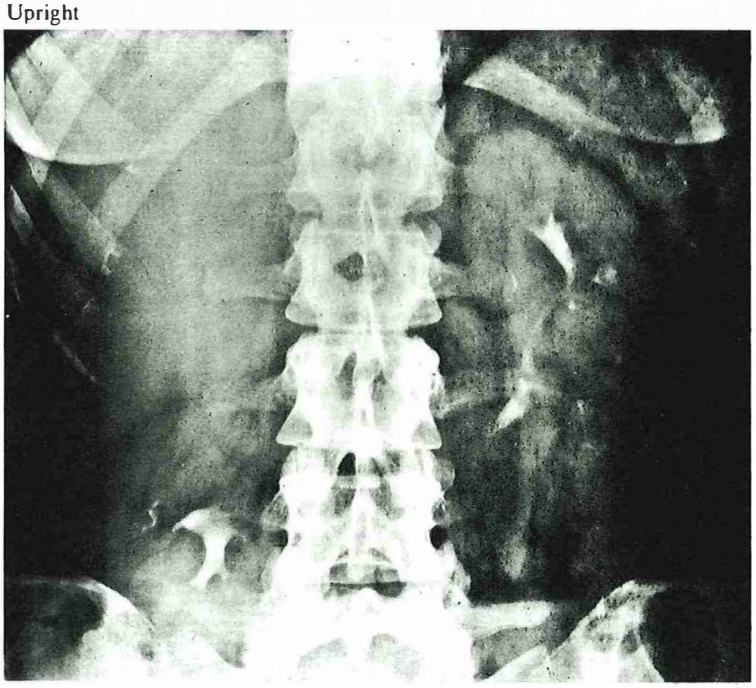
Patient nr 25, a 34 year old female.

In 1965 this patient was suspected to have post-traumatic seizures due to a trafficaccident. She has used phenobarbital medication since that time. In 1972 a breast adenoma was extirpated. Her general practitioner noticed hypertension in 1978 and treated her with hydrochlorothiazide, triamterene, beta-blockade and hydralazine. Because of inadequately controlled hypertension on this regimen, she consulted our outpatient department in 1978. Blood pressure was 200/135

Supine

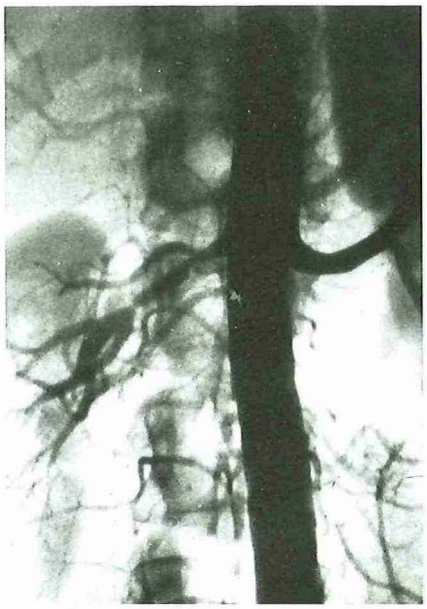


Upright

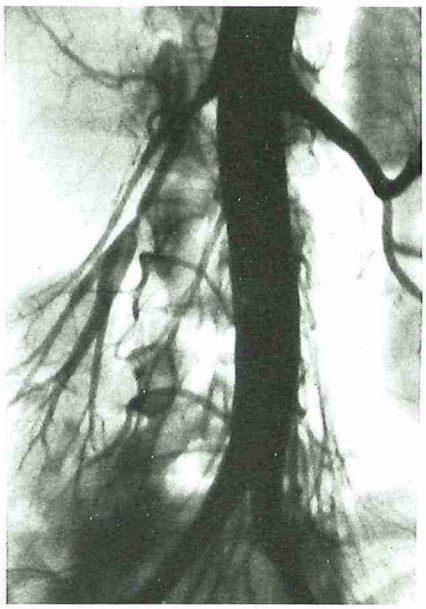


Figures 30 and 31. Patient nr 25. The IVU shows nephroptosis of the right kidney.

Supine



Upright

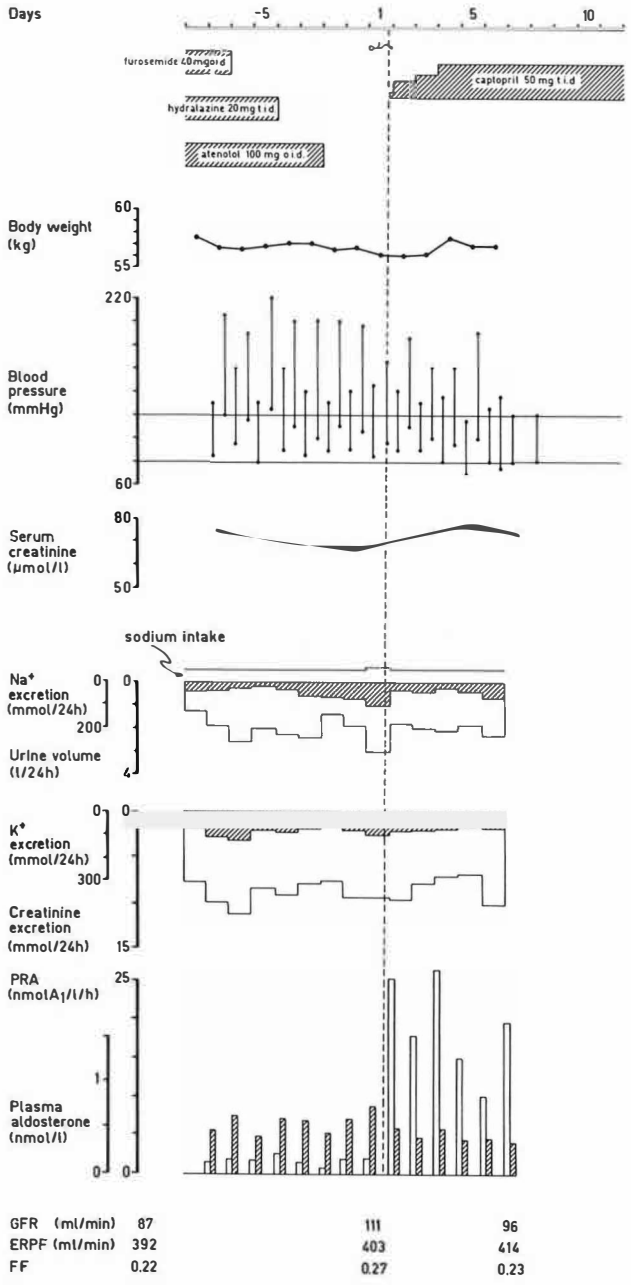


Figures 32 and 33. Patient nr 25. Renal angiography reveals a renal artery stenosis on the right side on 2 locations. In the upright position also narrowing of extrarenal and intrarenal arteries can be seen on the right side.

mmHg. On the ECG signs of left ventricular hypertrophy were present. Rapid sequence IVU revealed nephroptosis on the right side but no other abnormalities (see figure 30, 31). Renography showed lateralization. Renal angiography was found to be suspect for fibromuscular dysplasia with stenosis at two locations in the right renal artery. In the standing position a narrowing of the extra- and intrarenal arteries and the ptosis were especially impressive (figure 32, 33).

In this phase, all anti-hypertensive treatment was transiently withdrawn in order to perform 3 studies, the first 2 at the same time. Firstly, renal function was studied in the supine position. This was subsequently repeated when the patient had been upright for 2 hours. GFR supine was 87 and upright 65 ml/min, ERPF 392 and 227(!) ml/min, and FF 0.22 and 0.28, respectively. Secondly, determinations of PRA and PAC were performed. PRA levels were 2.8 and 14.5 nmol A_I/l/h supine and upright, respectively. PAC values were 1.50 and 2.20 nmol/l, respectively. The third study was the determination of PRA in blood samples obtained by selective renal vein catheterisation. PRA in the right renal vein was 3.9 nmol A_I/l/h, in the left renal vein 3.2 nmol A_I/l/h, the arterial sample being 2.7 nmol A_I/l/h.

Treatment with furosemide, atenolol, hydralazine, and clonidine resulted in poor blood pressure control. At admission in May, 1979 she complained about occipital headaches, general fatigue and bilaterally diminished eyesight. The consultant ophthalmologist found no abnormalities. She had palpitations often occuring without clear provoking circumstances. Her blood pressure was 200/110 mmHg when she had been out of bed for some time, but early morning readings revealed normotensive levels (see the graph). Reducing the previous antihypertensive treatment did not influence the blood pressure levels. After a 36 hour non-treatment period, during which renal function studies and dose-response curves were performed to obtain base-line values, captopril treatment was started. The dose was titrated according to the blood pressure response, and this was found to be acceptable on 50 mg t.i.d. (blood pressure 135/70 mmHg supine and after standing,



Patient nr 25. Diagnostic and therapeutic procedures during withdrawal of previous anthypertensives and subsequent titration of captopril. The open bars reflect PRA, whereas the hatched bars represent PAC values. See the text.

early morning values). Orthostatis was not noted in the early morning findings at this dosage. During the observation period, body weight and serum creatinine levels did not change much. PRA (open bars) rose immediately when captopril treatment was initiated and PAC (hatched bars) fell. GFR decreased and ERPF increased slightly, resulting in a decreased FF. The responsiveness to exogenously administered A_I decreased from 6.6 ng/kg/min to 40 ng/kg/min on the 25 mg t.i.d. and to 53.3 ng/kg/min on the final dosage (50 mg t.i.d.). The responsiveness to A_{II} increased from 10 ng/kg/min to 2 ng/kg/min on both the 25 mg t.i.d. and the 50 mg t.i.d. dosages, respectively. Bradykinin sensitivity increased from more than 100 ng/kg/min to 2.0 ng/kg/min on the first dosage and to 1.33 ng/kg/min on the final captopril dosage.

After discharge, the patient was seen regularly in the outpatient clinic. She tolerated the drug well and her blood pressure remained under control (128/75 mmHg). Renal function studies (August, 1979) showed a GFR of 95 ml/min and an ERPF of 370 ml/min (supine) and a GFR of 58 ml/min, ERPF 249 ml/min (upright). The serum creatinine level amounted to 82 μmol/l. Urinalysis was normal. She had negative anti-nuclear factors. However, complaints of palpitations persisted and were due to sinus tachycardia. Therefore, propranolol was prescribed (20 mg t.i.d.) resulting also in a further fall in blood pressure (110/75 mmHg). The captopril dose was thus reduced to 25 mg t.i.d.. On this regimen no complaints were mentioned and the blood pressure remained under good control (145/80 mmHg).

In summary: a 34 year old female with intractable renovascular hypertension associated with nephroptosis and unilateral renal artery stenosis (fibromuscular dysplasia) was treated successfully with captopril. No complications have been observed.

Patient nr 21, a 58 year old female.

This patient had an extensive medical history: colonic diverticulosis, cholecystectomy (gallstones), anteroseptal myocardial infarction, chronic obstructive respiratory disease, recurrent urinary tract infections in the presence of an urethrastenosis (normal IVU in 1963, 1965 and 1969), and spondylarthrosis. Her behaviour was suggestive of the existence of a hyperaesthetic-emotional syndrome. At periodic consultations by a number of specialists a moderate hypertension (170/100 mmHg) and obesity was noted. Since she had already rather extense 'pulmonary' medication, the primary approach to the hypertension was conservative, i.e. an attempt to decrease body weight with a calorie (and sodium) restricted diet. However, in the course of 1978 the blood pressure rose to 200/110 mmHg. Fundoscopy revealed grade I-II hypertensive changes. Cardiac and pulmonary findings were within normal limits. The electrocardiogram showed a consolidated myocardial infarction. GFR was 60 ml/min, ERPF 267 ml/min and FF 0.22. Rapid sequence IVU revealed normal sized kidneys but nephrography was more intense on the left side as compared to the contralateral side. Also the excretion of contrast was delayed on the left side. There were no signs of obstruction. The renogram also confirmed delayed functions on the left side. Angiography demonstrated widespread atherosclerosis and a clear stenosis of the left renal artery was noticed (see figure 34). On the right side a minor stenosis was also seen. Renovascular hypertension was thus diagnosed and a therapy was instituted consisting of a sodium restricted diet, hydrochlorothiazide and clonidine. Since the blood pressure rose after a few weeks, hydralazin was added.

Upon admission in January, 1979, her 'pulmonary' medication was left unchanged, consisting of thiazinamium, oxyphenomium bromide and promethazine. She also continued the 50 mmol sodium restricted diet. Apart from frontal headaches, she had no physical complaints. In particular visual, cardial, pulmonary and urogenital complaints were absent. Blood pressure was 160/100 mmHg supine and 160/110 mmHg upright. No vascular bruits over the abdominal aorta or kidneys were heard. The laboratory investigation revealed a normal serum creatinine level and a creatinine clearance of 70 ml/min. Positive anti-nuclear factors were present, anti-double string DNA was negative. No cells were found in the urinary sediment and the urine culture showed no bacterial growth. The electrocardiogram was unchanged.

The diagnostic and therapeutic procedures during hospitalization can be read from the graph. The blood pressure increased to 240/140 mmHg whilst the previous antihypertensive medication

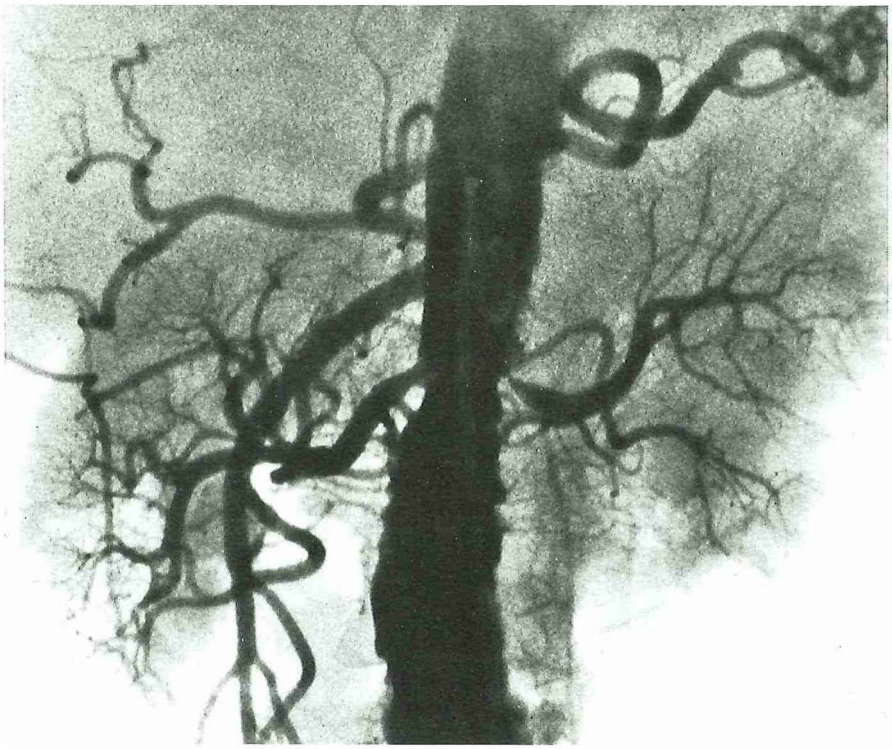


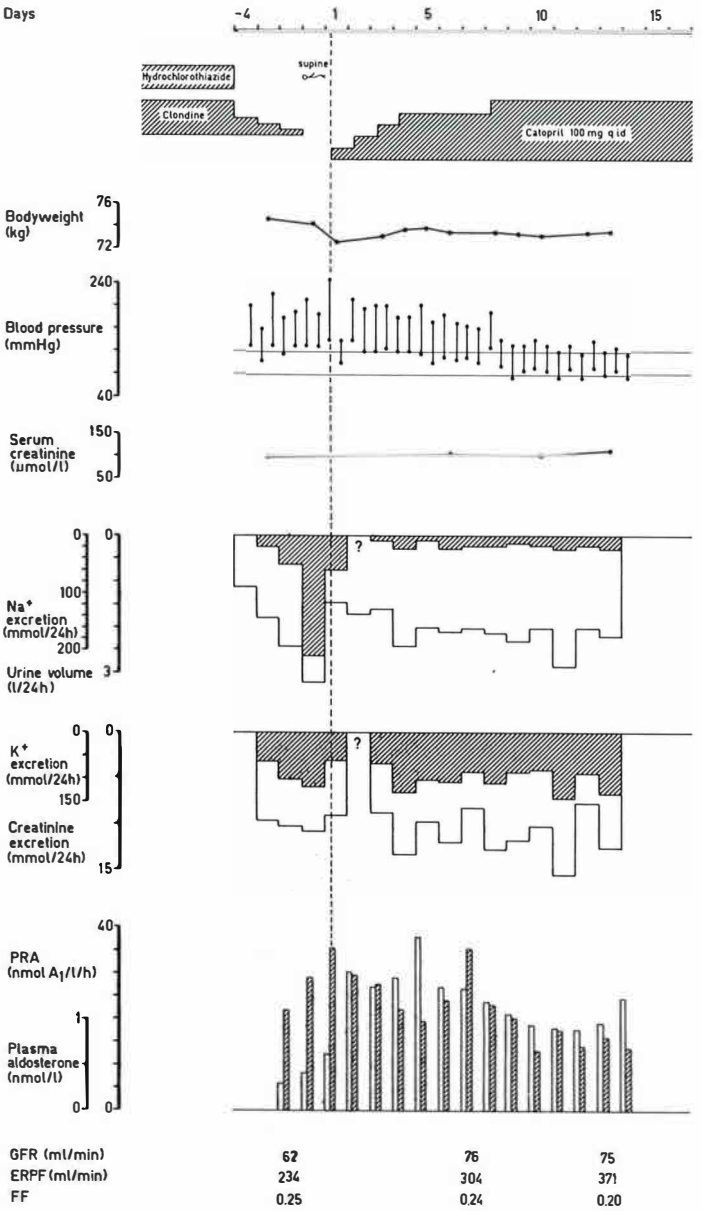
Figure 34. Patient nr 21. Renal angiography. Extensive atheroscerotic degeneration of abdominal aorta and bilateral renal artery stenosis.

was being withdrawn. In this phase, PRA (open bars) and PAC (hatched bars) were elevated. When kept in a supine position for one day before captopril treatment was initiated, a markedly increased urinary volume and sodium excretion resulted in a clear fall in body weight. Immediately on the first captopril dose (25 mg) a sharp, however transient, fall in blood pressure was observed. PRA rose and PAC decreased gradually. The blood pressure was finally adequately controlled on a 100 mg q.i.d. dosage of captopril. Both GFR and ERPF increased and FF fell.

The patient tolerated her medication well and was discharged in a good general condition. She was seen regularly in the outpatient clinic. Her blood pressure remained under control. A few weeks after discharge, renal vein catheterization was performed with collection of blood samples for PRA determination. In the right renal vein PRA was 14.1 nmol A_I/l/h and left 43.3 nmol A_I/l/h, the arterial sample being 16.2 nmol A_I/l/h.

In August, 1979, her treatment consisted of captopril 100 mg t.i.d. and she had sometimes complained of paraesthesia in some fingers. The blood pressure was 134/86 mmHg. The renal function was good (GFR 62 ml/min, ERPF 282 ml/min). The serum creatinine level was normal (96 μmol/l). The positive anti-nuclear factors which had been found prior to captopril treatment, persisted. The urinalysis was normal.

In summary: a 58 year old female with extensive atherosclerosis and unilateral renal artery stenosis was successfully treated with captopril. No complications were observed.



Patient nr 21. Diagnostic and therapeutic procedures during withdrawal of previous antihypertensive therapy and subsequent titration of captopril. The open bars represent PRA, the hatched bars reflect PAC values. See the text.

Patient nr 26. a 56 year old male.

From 1940 to 1945 this patient was treated because of pulmonary tuberculosis. In 1976 he was hospitalized because of congestive heart failure and malignant hypertension (275/140 mmHg).

Renography showed a decreased uptake of radioactivity in the right kidney. On rapid sequence IVU no excretion from the right kidney was observed; the length of the kidneys was 11.5 cm on the right side and 15.5 cm on the left side. Angiography showed extensive atherosclerotic involvement of the abdominal aorta and iliac arteries. Renal angiography revealed a 5 cm long stenosis of the right renal artery (figure 35). The left renal artery was normal. The creatinine clearance amounted to 56 ml/min. Treatment was started with clonidine, hydralazine and digoxin together with a sodium restricted diet. When first seen in our outpatient clinic in 1977 blood pressure was 250/140 mmHg. Fundoscopy revealed grade I-II hypertensive changes. The electrocardiogram showed signs of left ventricular hypertrophy and strain. A Frederickson hyperlipoproteinaemia type IV was found in addition to obesity. Renal vein catheterization was performed during the treatment as mentioned above. PRA was 2.4 nmol A_I/l/h in the right renal vein and 2.8 nmol A_I/l/h in the left, the arterial sample being 1.8 nmol A_I/l/h. Hydralazine had to be discontinued because of (transient) liver function disturbances. No abnormalities could be found in the liver biopsy. In February, 1979, his blood pressure was 180/130 mmHg on a therapeutic regimen consisting of hydrochlorothiazide,metoprolol, prazosin, clonidine and digoxin combined with a carbohydrate and 20 mmol sodium restricted diet.

In May, 1979 the patient was hospitalized in order to start captopril treatment according to the protocol. There were no physical complaints. His family history was negative. Physical examination demonstrated a blood pressure of 200/110 mmHg. Fundoscopy again showed grade

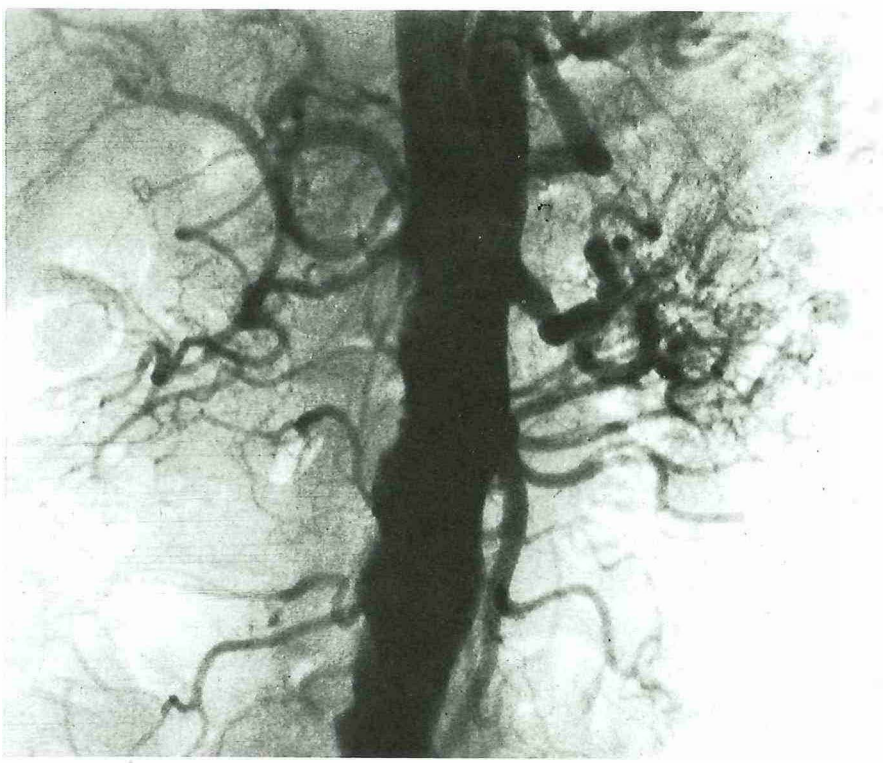
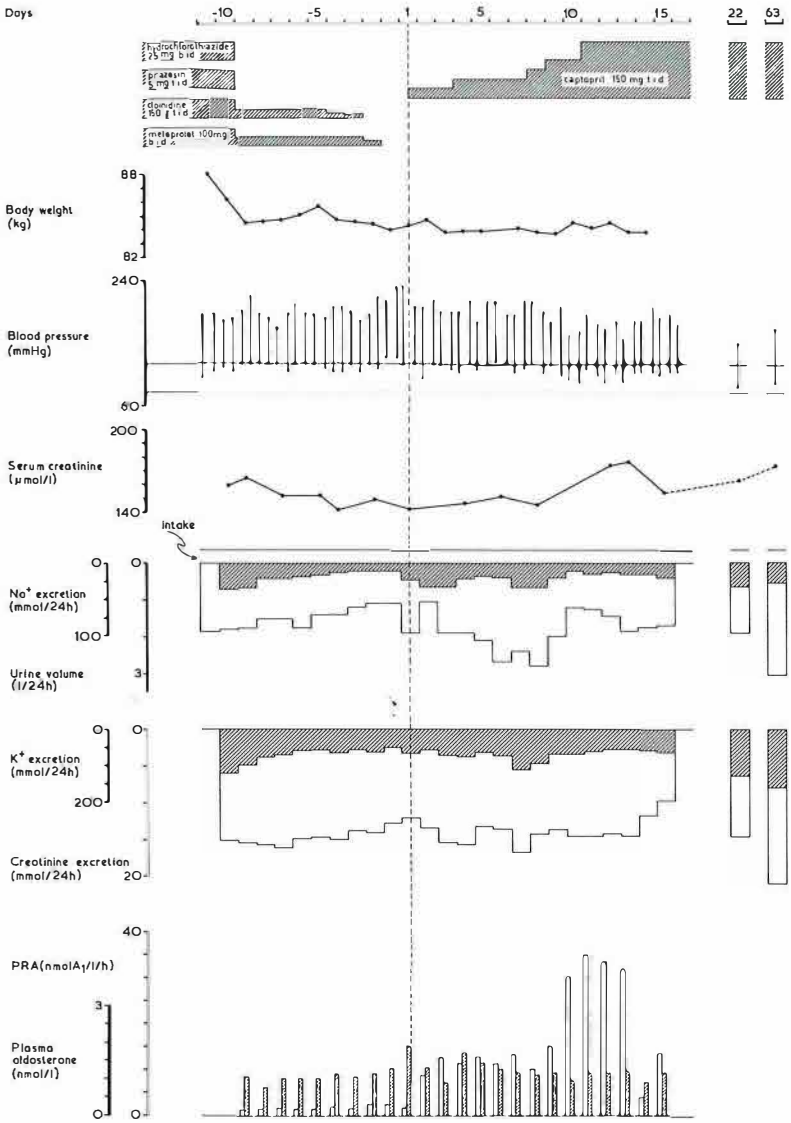


Figure 35. Patient nr 26. Renal angiography. Extensive atherosclerotic degeneration of the abdominal aorta. The right renal artery shows a long stenosis. The size of the right kidney is 11.5 cm, and of the left 15.5 cm.



GFR (ml/min)	72	76	58
ERPF (ml/min)	258	315	287
FF	0.27	0.24	0.20

Patient nr 26. Diagnostic and therapeutic procedures during withdrawal of previous antihypertensives and subsequent titration of captopril. The open bars represent PRA and the hatched bars PAC values. See the text.

I-II hypertensive changes. The heart size was not enlarged. Vascular bruits were heard over the femoral and popliteal arteries. The laboratory investigations revealed normal haematological values. The serum levels of urea and creatinine were 11.4 mmol/l and 160 µmol/l. respectively.

Creatinine clearance was 63 ml/min. The liver function was normal. In the 24 hour urine a minimal protëin excretion of between 0 to 1.2 g was noticed. Vectorcardiography showed clear signs of left ventricular hypertrophy without strain. The X-ray film of the chest showed no cardiomegaly; the picture was similar to previous films of the past 2 years.

The diagnostic and therapeutic procedures can be read from the graph. Renal function studies, performed without antihypertensive treatment and on captopril 150 mg t.i.d., showed a decrease in GFR from 72 to 58 ml/min. ERPF rose from 258 to 287 ml/min. Consequently, FF fell. The initial dose-response curve was performed with only exogenous bradykinin because of the high blood pressure level once the previous therapy was withdrawn. The responsiveness increased from 100 ng/bradykinin/kg/min to 2 ng/kg/min on the lowest captopril dose (25 mg t.i.d.). Subsequent increase of the dosage (50 mg, 100 mg and 150 mg t.i.d., respectively) caused a slight further increase in responsiveness to 1.3, 1.0, and 0.83 ng/kg/min, respectively. The sensitivity for A_I could be determined from the lowest captopril dose on and was 80 ng/kg/min and on subsequent dosages over 100 ng/kg/min. The responsiveness for exogenous A_{II} (also measured on captopril only) was 5 ng/kg/min on all dosages.

The patient tolerated the treatment well. His blood pressure at discharge was 150/90 mmHg supine and 140/90 mmHg upright, without orthostatic complaints. The treatment consisted of captopril 150 mg t.i.d. and digoxin in combination with a 20 mmol sodium restricted diet.

During regular outpatient visits his blood pressure remained well controlled (September, 1979: 155/88 mmHg; captopril 150 mg t.i.d.). He mentioned no complaints. The GFR was 58 ml/min and the ERPF 287 ml/min. The serum creatinine concentration amounted to 163 µmol/l. Urinalysis revealed normal values. The anti-nuclear factors however, appeared to be positive 3 months after the start of captopril.

In summary: a 56 year old male with previously intractable hypertension due to atherosclerotic unilateral renal artery stenosis, was treated successfully with captopril 150 mg t.i.d.. Positive anti-nuclear factors developed during treatment, but the patient remains in an excellent clinical condition.

Patient nr 30, a 47 year old female.

This patient's medical history is suspect for pyelonephritis in 1970. In 1974 she was admitted to a hospital because of 'essential' hypertension (blood pressure 250/130 mmHg). Renal function seemed to be normal according to the serum levels of urea and creatinine. The IVU was described as normal. She was treated with a 50 mmol sodium restricted diet and propranolol. In 1976 the patient was readmitted because of inadequate blood pressure control despite propranolol and guanethidine therapy. Renal function was normal. According to the description of the renal angiography, a minor renal artery stenosis on the left side was present. The renogram gave a symmetric picture. There proved to be a bad patient compliance with regard to medication and to sodium restriction. In June, 1976, she was admitted to our clinic with a blood pressure of 220/130 mmHg. Fundoscopy revealed grade I-II hypertensive changes. Renal function was unchanged. A 10 kg overweight and a Frederickson type IV hyperlipoproteinaemia was noticed. The renogram again was symmetric and the rapid sequence IVU demonstrated only minor bilateral nephroptosis. All other findings were within normal ranges. Renal vein catheterization in September, 1976 gave no evidence for a functional stenosis. In February, 1978, again it was noted that the patient did not keep her sodium restricted diet. The therapeutic regimen then consisted of hydrochlorothiazide, triamterene, propranolol, hydralazine and clonidine. The blood pressure was 230/130 mmHg. On her own decision, the patient stopped all antihypertensive medication in November, 1978. Two weeks later she was sent in by her general practitioner with a blood pressure of 300/200 mmHg and she was instantly readmitted. Fundoscopy revealed grade IV hypertensive changes. A saralasin infusion caused a fall in blood pressure from 300/200 to 240/160 mmHg, suggesting that the blood pressure was – at least partly – angiotensin II dependent. This effect was reached on a dose of 1½ µg/kg/min saralasin; enlargement of the saralasin infusion rate caused no further fall in blood pressure. PRA before saralasin administration amounted to 19.0 nmol A_I/l/h and rose to 66.9

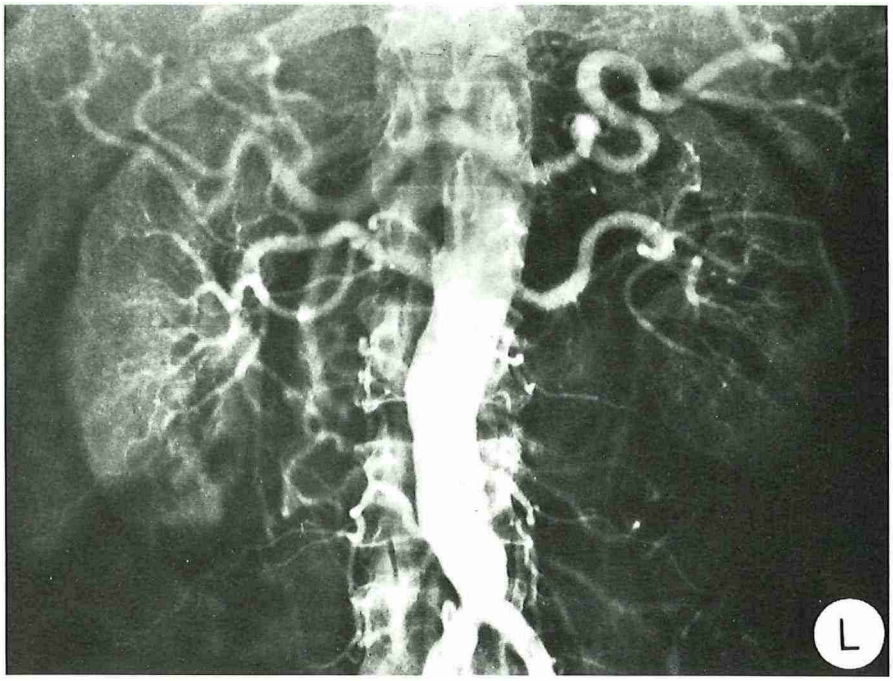
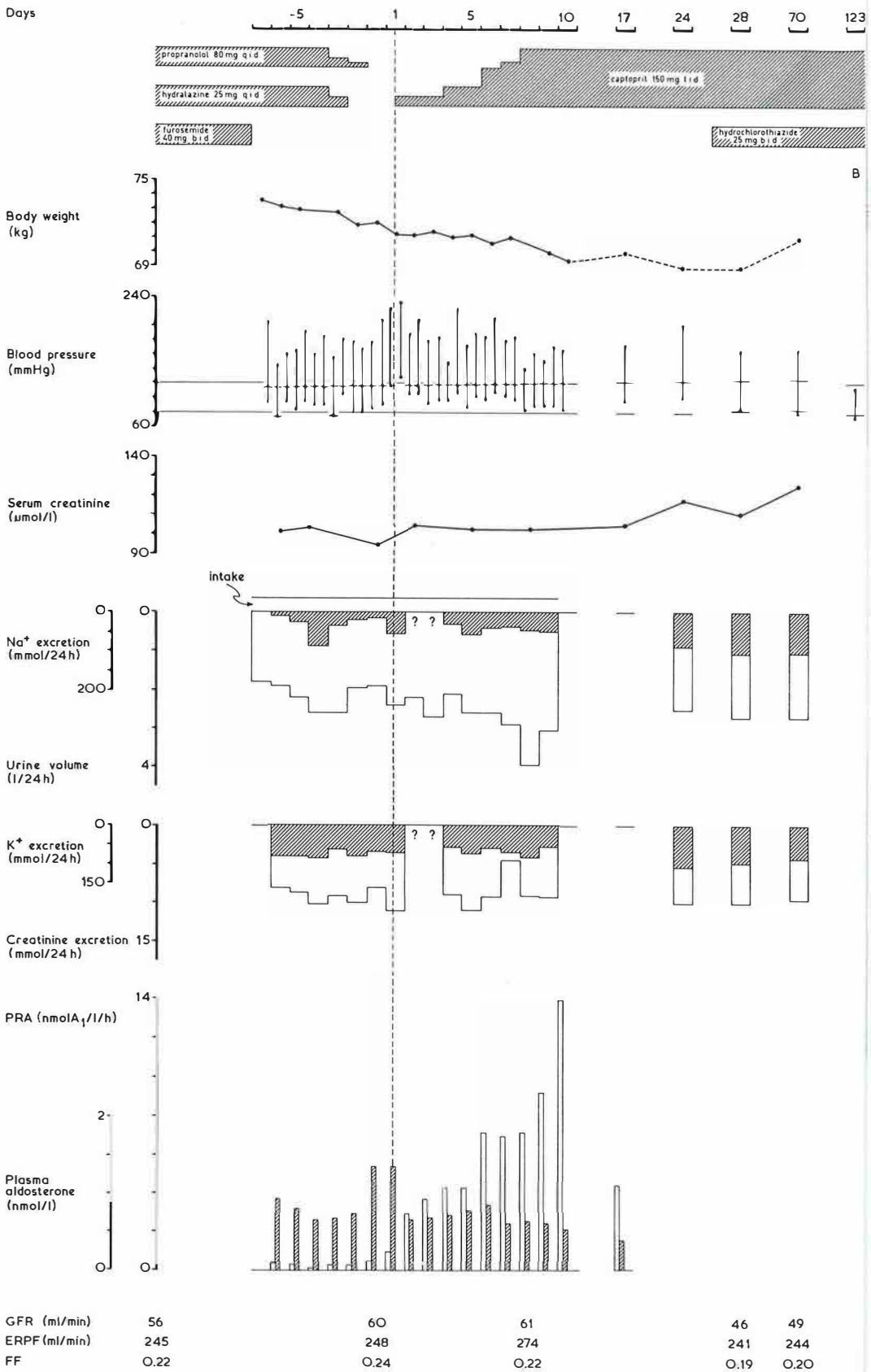


Figure 36. Patient nr 30. Renal angiography. Extensive atherosclerotic changes of the abdominal aorta and iliac arteries. A stenosis of a minor degree is present in the left renal artery.

nmol A_I/l/h thereafter. PAC values were 3.27 and 2.76 nmol/l, respectively. On the X-ray film of the chest the heart size was increased. The electrocardiogram revealed evident signs of left ventricular hypertrophy and strain. The IVU appeared to be unchanged. Aortography revealed atherosclerotic degeneration of the abdominal aorta and the communal iliac arteries. Selective renal angiography (figure 36) showed a stenosis of a minor degree in the left renal artery. The right renal artery was normal. The renogram now did demonstrate lateralization, compatible with the angiographic findings. Serum creatinine level was 116 µmol/l, and the creatinine clearance amounted to 50 ml/min. A renal function study (performed under medication consisting of furosemide, propranolol and minoxidil) showed a GFR of 56 ml/min, and an ERPF of 245 ml/min. When discharged from the hospital, the blood pressure was 170/90 mmHg on a therapeutic regimen consisting of furosemide and propranolol, together with a sodium (20 mmol) and calorie-restricted diet. When seen in the outpatient department, the blood pressure soon appeared to rise again to 230/100 mmHg. The 24 hour sodium excretion amounted to 60 mmol Na^+ without signs of hyponatraemia. Again sodium restriction was emphasized and hydralazin was added to the regimen.

In May, 1979, the patient was readmitted to the hospital in order to start captopril treatment according to the emergency protocol. There were no physical complaints. Her family history revealed severe hypertension in 4 siblings; two had died from myocardial infarction. At physical examination she appeared obese (height 1.62 m, body weight 73.6 kg). The heart was enlarged. No vascular bruits were heard. Fundoscopy revealed grade II hypertensive changes. The ECG now showed signs of severe left ventricular hypertrophy and strain.

The diagnostic and therapeutic procedures can be read from the graph. Previous antihypertensives were gradually withdrawn, resulting in an increase of the blood pressure. Initiating



GFR (ml/min)	56	60	61	46	49
ERPF (ml/min)	245	248	274	241	244
FF	0.22	0.24	0.22	0.19	0.20

captopril caused a slight fall at first but on the maximal dose (150 mg t.i.d.) an acceptable blood pressure was achieved. During hospitalization the body weight fell which can be the result of the severe calorie-restriction. An increased natriuresis was not seen in this phase. PRA during previous antihypertensive agents was low and increased when all had been withdrawn, as did PAC. A marked increase in PRA was seen when captopril was initiated, which was more pronounced at increasing dosages, and PAC fell.

GFR hardly changed on captopril alone (from 60 to 61 ml/min). However, ERPF increased from 248 to 274 ml/min.

Dose-response studies were performed in the therapy-free phase. The sensitivity for exogenous A_I was 8 ng/kg/min, for A_{II} 5 ng/kg/min and for bradykinine 40 ng/kg/min. On the lowest captopril dose (25 mg t.i.d.) these values were 53.6, $2^2/3$, and 1 ng/kg/min, respectively. On captopril 50 mg t.i.d. the sensitivities were 100, $2^2/3$ and 0.83, respectively. On both the 100 and the 150 mg t.i.d. dosages, the sensitivities were 100 ng/kg/min for A_I, 2 ng/kg/min for A_{II} and 0.83 ng/kg/min for bradykinin.

Thirty minutes after the first captopril tablet (25 mg) was administered, patient developed a short lasting (30 min) rash on the face and forearms. She was not hypotensive. The rash was not accompanied by fever, chills, arthralgia or myalgia. The laboratory investigations showed similar and normal results as previous to captopril administration. The following tablet was tolerated well. However, after the third tablet again the transient urticarial exanthema was noted in the face, forearms and upper part of the chest. All features had disappeared within one hour. Subsequent tablets and increasing dosages were tolerated well.

At discharge the patient was in a good general condition. The blood pressure was 165/85 mmHg. Her medical treatment consisted of captopril 150 mg t.i.d., digoxin, oral iron suppletion and a 50 mmol sodium and calorie-restricted diet. When seen in the outpatient clinic two weeks afterwards, the blood pressure was 155/100 mmHg. Sodium excretion was increased (90 mmol/24 hours), so it was decided to add hydrochlorothiazide to the regimen. Two weeks later, the blood pressure was 145/90 mmHg. The renal function study was repeated under this treatment in August, 1979, and showed a GFR of 49 ml/min and an ERPF of 244 ml/min. The blood pressure remained under control (160/76 mmHg). No complaints were mentioned. Urinalysis revealed proteinuria (0.9 g/24 h). Anti-nuclear antibodies and anti-double string DNA had developed 3 weeks after initiating captopril.

On September, 26, a renal biopsy was performed. The immunofluorescence study of the biopsy specimen revealed depositions of IgA and IgM along the GBM. However, the clinical condition of this patient remained excellent and no change in the therapeutic approach has been introduced so far.

In summary: In a 46 year old female with intractable hypertension and unilateral renal artery stenosis, blood pressure control was achieved with combined treatment consisting of captopril and a diuretic, together with a sodium restricted diet. Anti-nuclear factors, anti-double string DNA and proteinuria developed during this treatment. The renal biopsy specimen revealed despositions of IgA and IgM in the GBM. At the very start of captopril, a short-lasting urticarial rash was observed, possibly related to a pre-existing increased sensitivity to exogenous bradykinin.

Patient nr 20, a 42 year old male.

In 1977 hypertension (blood pressure 230/145 mmHg) was established when this patient was hospitalized for observation of abdominal complaints. Causal factors for his original complaints could not be found. Fundoscopy revealed grade III hypertensive changes. Electrocardiography showed clear signs of left ventricular hypertrophy and strain. The creatinine clearance amounted to 140 ml/min and the IVU was normal. Renography revealed that the right kidney had a lower uptake than the left. Renal angiography demonstrated extensive atherosclerotic changes and a complete blockade of the right renal artery. The right kidney seemed to be supplied only by

◀ Patient nr 30. Diagnostic and therapeutic procedures during withdrawal of previous anti-hypertensive therapy, the subsequent titration of captopril and the addition of a diuretic. The open bars represent PRA, whereas the hatched bars reflect PAC values. See the text.

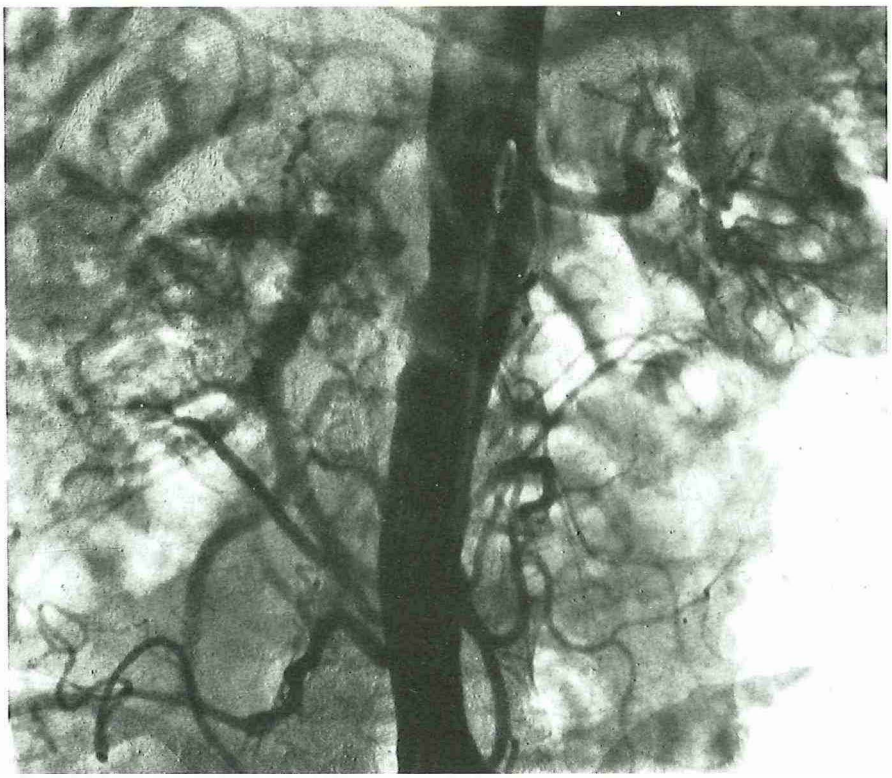


Figure 37. Patient nr 20. Renal angiography. The right main renal artery has a complete stop.

collateral vessels alone. He was treated with alpha-methyldopa, metoprolol and clonidine, combined with a 20 mmol sodium restricted diet. To evaluate corrective surgical possibilities, he consulted our outpatient clinic in 1978. At that time the patient had no physical complaints. His blood pressure amounted to 210/120 mmHg and therefore diazoxide was added to the above mentioned therapy. Since the origin of the renal arteries could not be seen adequately on the previous angiograms, this investigation was repeated. This time oblique films were also taken. Extensive atherosclerotic vascular degeneration was again seen in the abdominal aorta. The renal arteries appeared to have unequal origins. The lower poles of both kidneys were seperately vascularized. Since the main renal artery had a complete blockage (figure 37), vascularization of the right kidney was almost totally dependent upon the accessory vessels (figure 38). The left renal artery had a less severe stenosis. Because of the difficult surgical reconstruction of the unequal position of the main renal arteries, a conservative approach was chosen. The blood pressure was 190/110 mmHg on the treatment extended with diazoxide. In September, 1978, renal vein catheterization was performed after discontinuing metoprolol a few days earlier. PRA levels were 1.4, 2.2, and 1.8 nmol A_I/l/h in the upper, middle, and lower right renal veins, respectively. The following values were received from the left upper and lower renal veins, respectively: 1.3 and 1.7 nmol A_I/l/h.

When admitted to the hospital in April, 1979, the blood pressure was 210/130 mmHg. The antihypertensive treatment at that moment consisted of metoprolol, diazoxide, alphamethyldopa, and a 20 mmol sodium restricted diet. The patient had no physical complaints. The family history was negative concerning hypertension or cardiovascular disease. Physical examination revealed

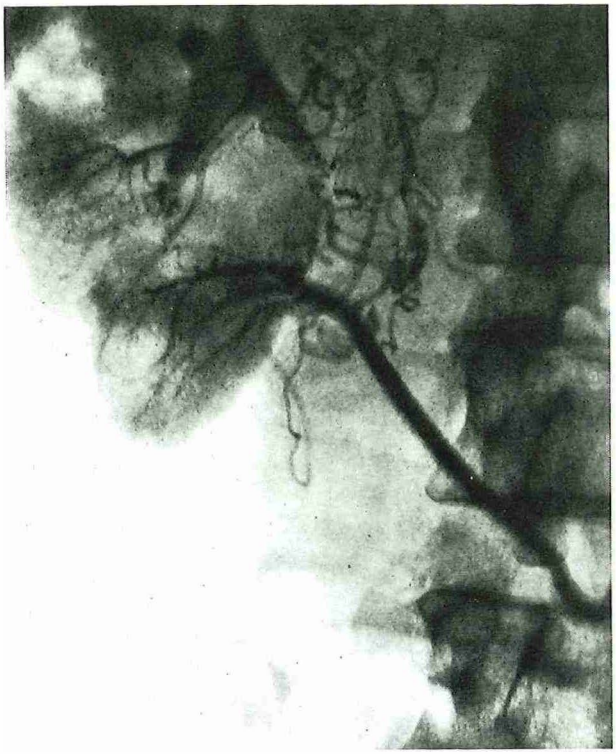
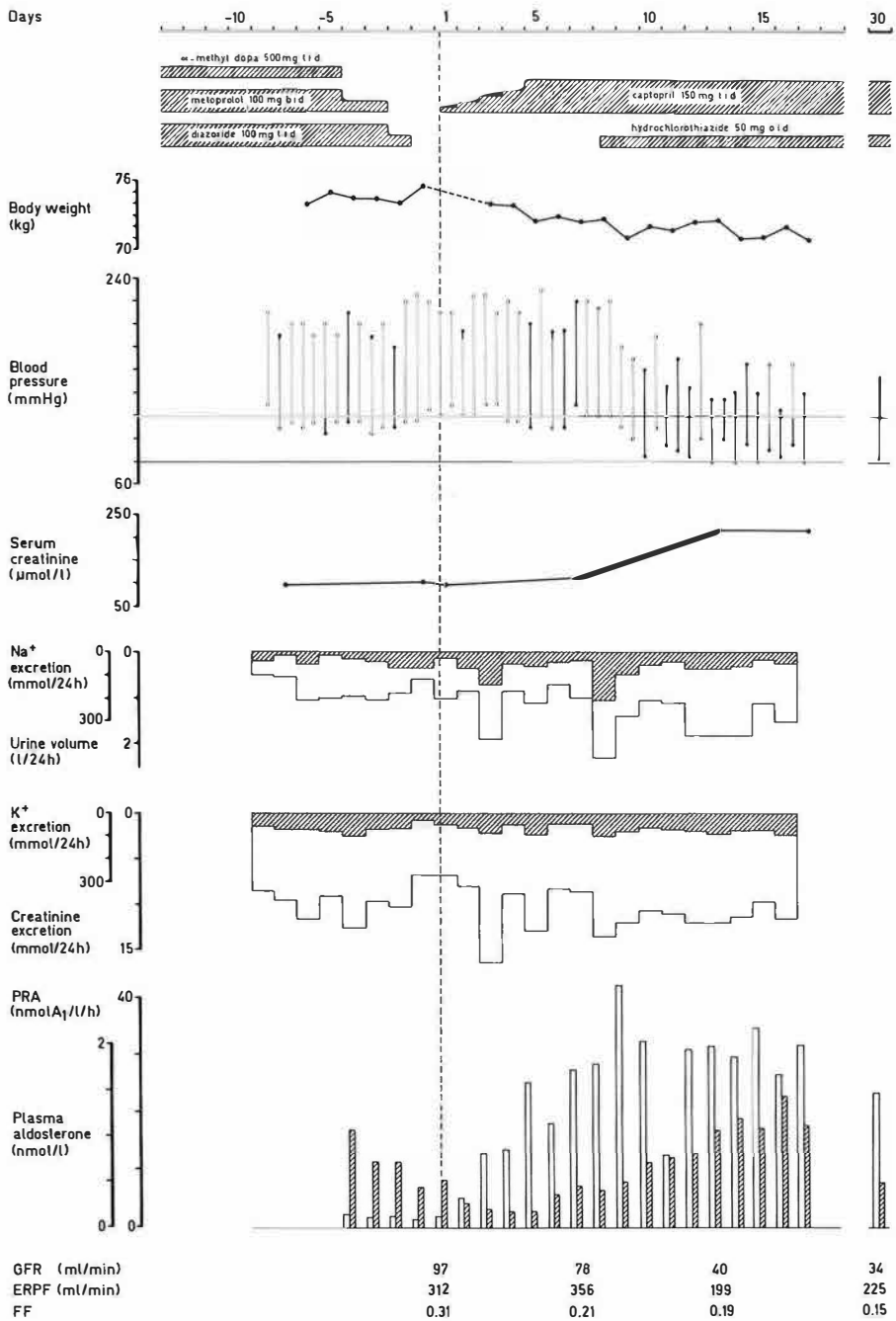


Figure 38. Patient nr 20. Renal angiography (detail). The right kidney is vascularized by collateral vessels and an underpole artery.

vascular bruits over both femoral arteries. Fundoscopy demonstrated grade III hypertensive changes. Laboratory investigations revealed a serum creatinine level of 99 μmol/l. The creatinine clearance was 63 ml/min. The urinary sediment was normal. The ECG showed signs of left ventricular hypertrophy and strain. On the chest X-ray cardiomegaly was seen.

The diagnostic and therapeutic procedures can be read from the graph. When previous treatment was withdrawn the blood pressure rose. During this phase, the PRA (open bars) was low and the PAC (hatched bars) fell slightly. Initiating captopril treatment and increasing the dose subsequently, had no marked effects on the blood pressure. PRA however, immediately showed a clear increase and PAC fell. Reaching the maximal dose of captopril was attended without providing adequate control of the blood pressure, hydrochlorothiazide was added, which resulted in normotension and an increase in PAC.

During captopril treatment alone, serum creatinine was constant but rose once the diuretic had been added. It finally remained stable on approximately 210 μmol/l. The renal function studies showed a decrease in GFR from 97 to 78 ml/min and an increase of the ERPF from 312 to 356 ml/min on captopril alone. FF fell from 0.31 to 0.21. After adding hydrochlorothiazide, GFR fell to 40 ml/min, ERPF to 199 ml/min and FF to 0.19. Repeating the renal function study 2 weeks later showed a further fall in GFR but an increase in ERPF, the FF being 0.15.



GFR (ml/min)	97	78	40	34
ERPF (ml/min)	312	356	199	225
FF	0.31	0.21	0.19	0.15

Patient nr 20. Diagnostic and therapeutic procedures during withdrawal of previous antihypertensives, subsequent titration of captopril and the addition of hydrochlorothiazide. The open bars represent PRA and the hatched bars PAC values. See the text.

Because of the high blood pressure level when the initial treatment was withdrawn, dose-response curves were performed with exogenous bradykinin only. The amount of bradykinin necessary to abtain a 10 mmHg fall in blood pressure decreased from over 100 ng/kg/min to 1.33 ng/kg/min on 25 mg captopril t.i.d. Further increases in captopril dosage did not cause an corresponding increase in responsiveness to exogenous bradykinin. When the diuretic was added, the sensitivity rose to 1.0 ng/kg/min.
At discharge from the hospital, the patient had a blood pressure of 125/85 mmHg. The treatment consisted of captopril 150 mg t.i.d. and hydrochlorothiazide 50 mg o.i.d., in combination with a 20 mmol sodium restricted diet. He tolerated this treatment well. Because of the decrease in renal function following the addition of a diuretic, this drug was withdrawn 3 weeks after discharge. When seen again 2 weeks afterwards, his blood pressure remained under control (145/93 mmHg) on captopril alone (150 mg t.i.d.). The serum creatinine level had fallen to 154 µmol/l. Repeating the renal function study in August, 1979 showed a GFR of 56 ml/min, and an ERPF of 231 ml/min. Ultimately a trace of proteinuria was found. Urinalysis revealed no abnormalities in the sediment. The anti-nuclear factors however, were positive.

In summary: In a 42 year old male with intractable renovascular hypertension due to atherosclerotic degeneration, the blood pressure was treated successfully with captopril and additional hydrochlorothiazide. Withdrawal of the diuretic did not appreciably alter the achieved blood pressure control.

Patient nr 23, a 55 year old male.

His medical history revealed pancreatitis and cholelithiasis in 1974, for which a cholecystectomy was performed. In 1975 he consulted a cardiologist because of hypertension (blood pressure 200/130 mmHg). No primary cause for the elevated blood pressure was found, although generalized atherosclerosis was noticed. Treatment with a diuretic and metoprolol was started but normotension could not be achieved. In 1975 patient was seen by an internist because of dysbasia intermittens of his left leg for which conservative treatment was advised. Blood pressure amounted to 200/140 mmHg on a therapeutic regimen consisting of a diuretic and metoprolol, combined with a sodium and calorie-restricted diet, because of his obesity. The creatinine clearance was 71 ml/min. The X-ray film of the chest revealed slight cardiomegaly. The IVU was normal. Renography showed no lateralization. However, the scintigram revealed a slightly less active right kidney when compared to the left side. The diagnosis was made of 'essential hypertension'. During the next 2 years the patient was treated with alpha-methyldopa, clonidine and propranolol.

On admission to our hospital in March, 1979, the medical history revealed nocturnal dyspnoea, but no nocturia or overt oedema. Sleeping flat did not provoke dyspnoea. He had no further complaints of dysbasia. Headaches were frequent but there were no complaints concerning his vision. At physical examination the heart was found to be enlarged.

Posteriorly over the right renal area a systolic bruit was heard, though not reproducable over the abdominal renal tract. The legs showed varicosites and slight static oedema. Vascular bruits were heard over the femoral tracts, and distally beyond the popliteal level no arterial pulsations could be felt. Fundoscopy revealed grade II-III hypertensive changes. The X-ray film of the chest showed cardiomegaly; there were no signs of pulmonary oedema. A 90 per cent obliterating stenosis of the right renal artery was demonstrated with angiography, whereas the left renal artery showed a less extensive stenosis (figure 39). Renal vein catheterization was performed *after* the patient had been put on to captopril in association with propranolol. Determination of PRA demonstrated 3.2 nmol A_I/l/h in the right renal vein, 2.1 nmol A_I/l/h in the left one, the arterial PRA being 1.5 nmol A_I/l/h. Plethysmography and Doppler technique investigation revealed minor organic vascular degeneration in both legs. When hospitalized, treatment with hydrochlorothiazide, propranolol, hydralazine and clonidine was inadequate (highest blood pressure values being 240/160 mmHg at the time clonidine was added). It was decided to withdraw previous hypertensive treatment and to initiate captopril therapy (see the graph). Complete cessation of the propranolol was impossible because of unacceptably high blood pressure values occurring during the discontinuation of this

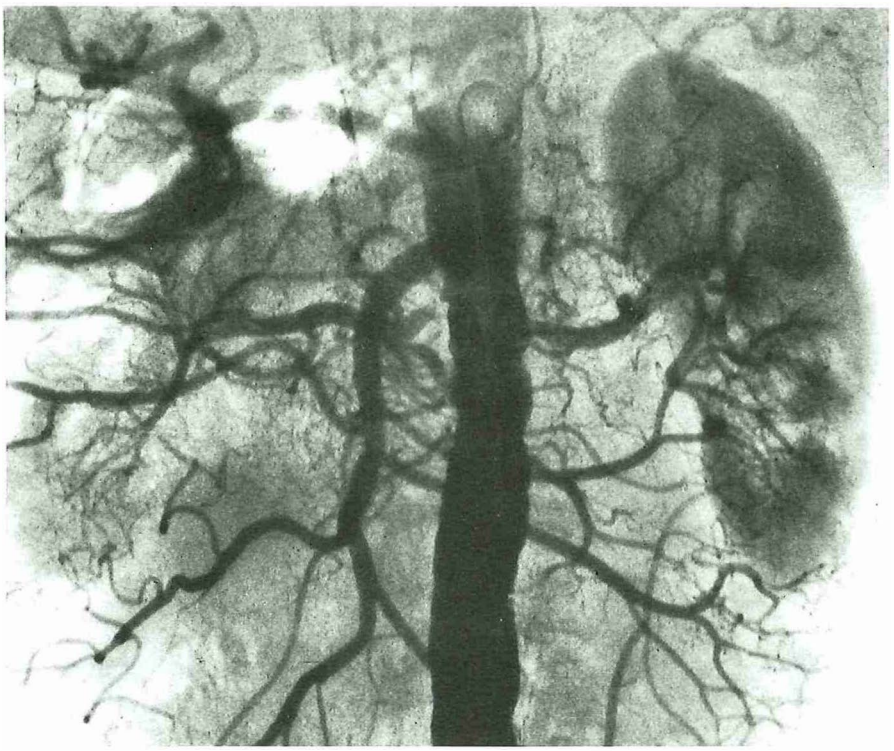


Figure 39. Patient nr 23. Renal angiography. Extensive atherosclerotis of abdominal aorta. Bilateral rena artery stenosis, more pronounced on the right side.

drug. Captopril reduced the blood pressure although early morning levels remained high. An adequate blood pressure control was finally obtained by a better spread of the 24 hour dose (100 mg five times a day).

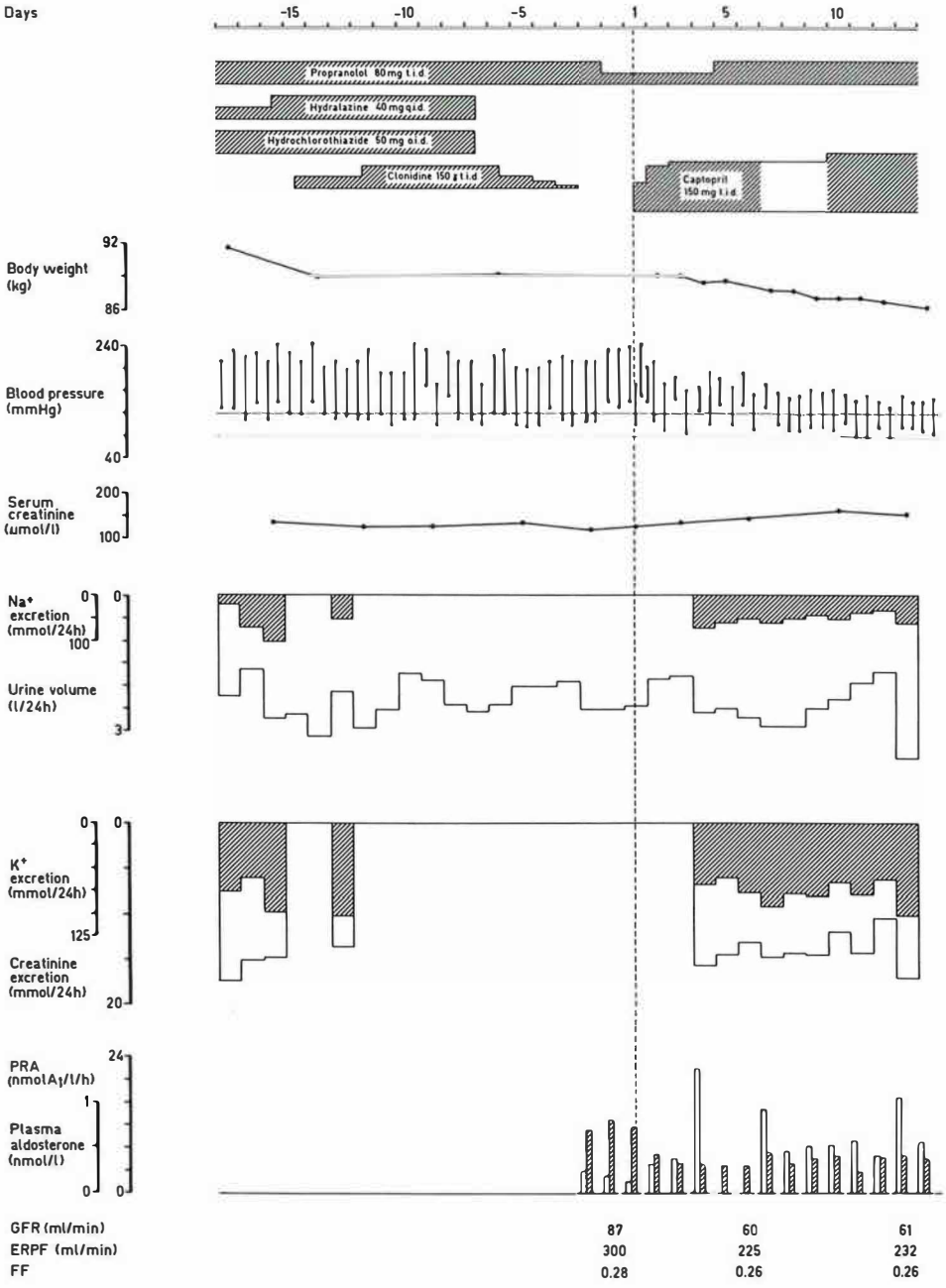
Body weight showed a gradual decrease on the calorie-restricted diet. Serum creatinine levels increased when the blood pressure fell.

PRA levels (open bars) increased during converting-enzyme inhibition together with a slight decrease of PAC (hatched bars). Both GFR and ERPF showed a fall as did FF.

The patient was discharged from the hospital in a good clinical condition and has since visited the outpatient clinic regularly. He tolerated the treatment well despite complaints of white and cold fingers, which were not strictly dependent upon the ambient temperature. Because of this phenomenon, his general practitioner halved the propranolol medication following which his complaints became less severe. In June a successful attempt was made to reduce the captopril regimen to 100 mg q.i.d. and blood pressure levels remained acceptable.

In August, 1979, his blood pressure was 154/85 mmHg on captopril 100 mg q.i.d., and propranolol 40 mg t.i.d. combined with a 50 mmol sodium restricted diet. Urinalysis revealed no abnormalities. The serum creatinine level was 158 μmol/l, GFR amounted to 57 ml/min and ERPF to 248 ml/min. Anti-nuclear factors were negative.

In summary: In a 55 year old male with previously intractable renovascular hypertension due to atherosclerosis, treatment with captopril was successful. Complaints of cold extremities were mentioned.



Patient nr 23. Diagnostic and therapeutic procedures during withdrawal of previous antihypertensive treatment and subsequent totration of captopril. Propranolol had to be continued because of inacceptable high blood pressure levels when reducing the dose. The open surface in the captopril bar reflects a more equal spread of the 450 mg dose over the day. PRA is represented by open bars, PAC by hatched bars. See the text.

Patient nr 27. a 52 year old male.

In January, 1977,this patient was seen by a neurologist because of an 'essential' tremor of the hands wich had started one year previously. A blood pressure of 180/105 mmHg was noticed. After institution of propranolol 80 mg t.i.d. the tremor disappeared. In January, 1978, he was seen by an internist because of 'essential hypertension'. The chest X-ray film revealed slight cardiomegaly. The IVU was described as normal. Electrocardiographic signs of left ventricular hypertrophy or strain were not present. The serum creatinine and urea level amounted to 105 µmol/l and to 9.0 mmol/l. respectively. Treatment with furosemide, propranolol, clonidine and guanethidine, in combination with a sodium restricted diet was inadequate (supine blood pressure 280/130, upright 260/120 mmHg). Therefore the patient was admitted to our hospital in May, 1979. His medical history at admission revealed gonarthrosis, and a splenic cyst for which a splenectomy had been performed. The family history revealed that his mother had suffered from hypertension. He had no physical complaints. On physical examination a slightly obese (height 169 cm, body weight 78.3 kg) man was seen. Supine blood pressure was 250/115 mmHg, standing 215/115 mmHg, under the above mentioned medication. A grade II retinopathy was recorded. Vascular bruits were meard over the carotid arteries. The heart was 1 cm enlarged and a systolic ejection murmur could be heard. Vascular bruits were noticed bilaterally over the femoral arteries. The arteries distally from the popliteal level were not palpable. The chest X-ray film on admission did not show signs of cardiomegaly. Electrocardiography revealed clear signs of left ventricular hypertrophy without strain. Revision of the IVU of April, 1979, showed a symmetric, though delayed nephrography. The length of the right kidney was 13.5 cm, the left was 15 cm. Renography showed a compatible, symmetric picture. Angiography disclosed diffuse atheroscleritoc degeneration of the abdominal aorta. Bilaterally a renal artery stenosis was present (figure 40), with a post-stenotic dilatation of the right renal artery.

During hospitalization, but prior to the patient's participation in the captopril study, an effort was made to control blood pressure by expanding the existing therapeutic regimen. However, treatment consisting of hydrochlorothiazide 50 mg o.i.d., propranolol 80 mg t.i.d., hydralazine 60 mg q.i.d. and clonidine 0.300 mg t.i.d. in combination with a sodium restricted (20 mmol) diet, was ineffective. Blood pressure remained high (250/115 mmHg). With the patient's consent, the medication then was gradually reduced. The relevant parameters can be read from the graph. The high blood pressure levels did not permit a complete cessation of all drugs and captopril was initiated despite a concomittant propranolol 80 ml t.i.d. therapy. The dose was increased stepwise but did not cause a considerable fall in blood pressure. PRA, however, rose immediately after starting captopril and the PAC fell. On the maximal captopril dose, hydrochlorothiazide was added, resulting in acceptable blood pressure levels (170/100 mmHg) in view of the renal blood flow. The renal function studies in fact showed a change in GFR from 63 ml/min on propranolol alone (blood pressure 260/110 mmHg), to 72 ml/min when combined with captopril 150 mg t.i.d. (blood pressure 215/100 mmHg) and finally to 23.5 ml/min on the ultimate therapy (blood pressure 175/100 mmHg). Because of the high blood pressure levels, no dose-response curves could be performed.

No adverse reactions were noticed, although from the start of the diuretic, serum urea rose from 8.8 to 18.2 mmol/l and serum creatinine from 130 to 187 µmol/l. Furthermore, the eosinophils in the differential count increased from 6 to 34 per cent. The addition of hydrochlorothiazide caused an increased natriuresis and at discharge the serum sodium concentration had fallen to 128 mmol/l. Apart from this, the patient was in a good clinical condition. At discharge his blood pressure was 160/85 mmHg.

When seen at weekly intervals in the outpatient department, a further fall in the serum sodium concentration, together with an increased deterioration of the renal function as expressed by the serum levels of urea and creatinine was noticed. The hydrochlorothiazide was therefore gradually withdrawn and captopril dose was reduced to 100 mg q.i.d.. Blood pressure remained under control in this phase, but the above mentioned laboratory findings deteriorated progressively.

Thirty-seven days after captopril treatment had been initiated, an exanthematous rash developed on the face, trunk and limbs. There was no associated history of myalgia, chills or fever. The captopril dose was gradually reduced to 50 mg t.i.d.. The rash disappeared slowly and could no

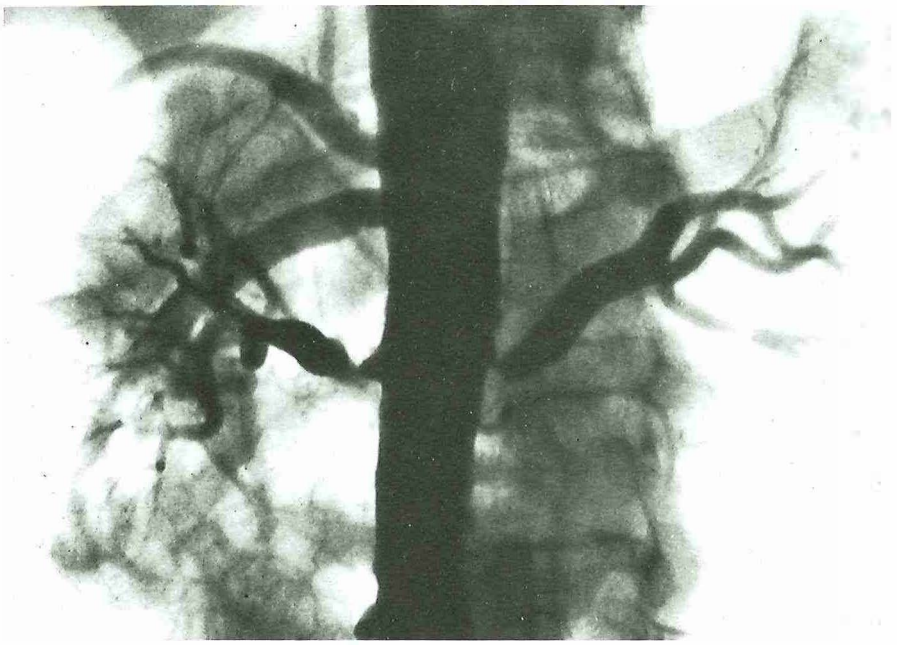
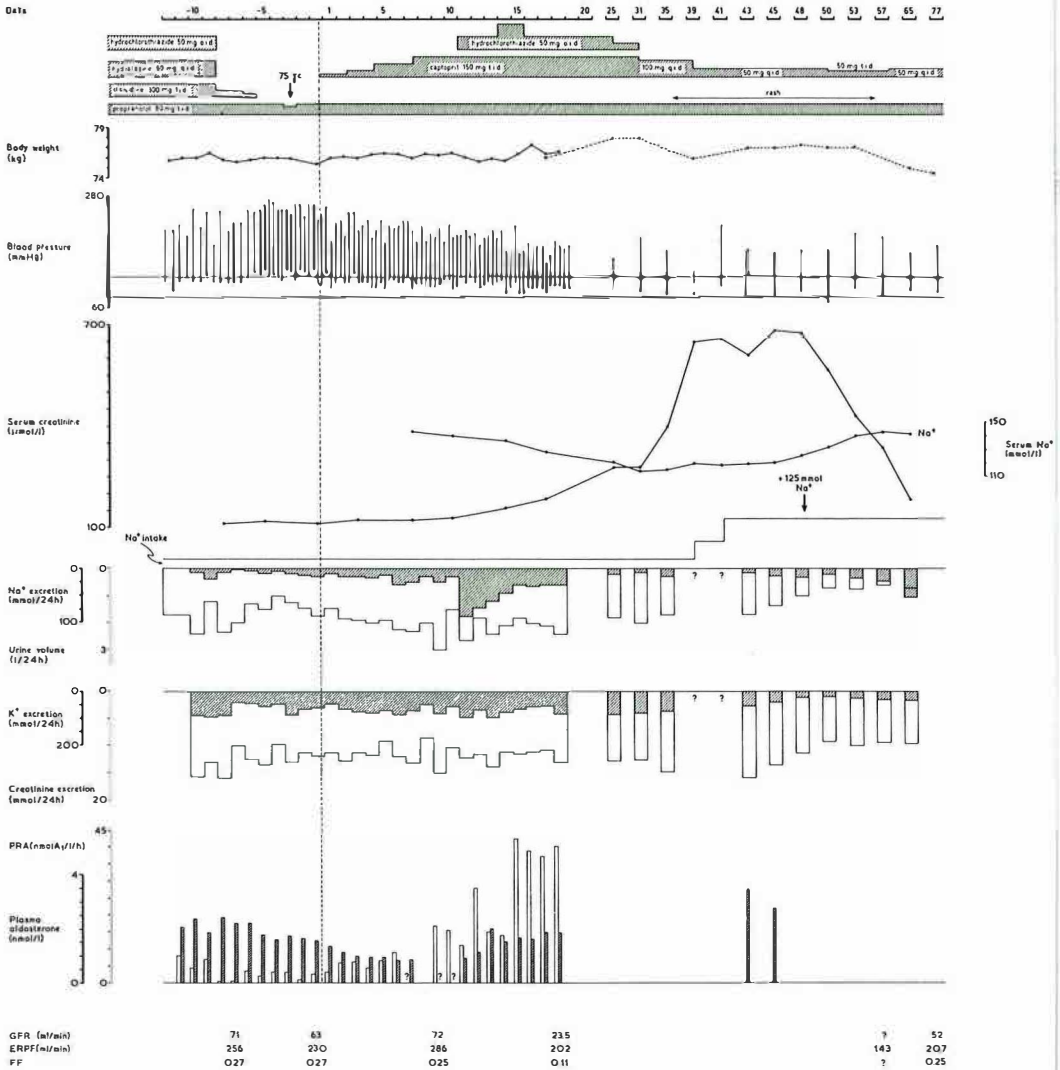


Figure 40. Patient nr 27. Renal angiography. Diffuse atherosclerosis of abdominal aorta. Bilatteral renal artery stenosis.

longer be found on the 20th day after onset, but the eosinophilia remained present (30 per cent). The renal function deterioration was thought to be due to sodium depletion, therefore the dietary sodium restriction was reduced from 20 mmol to 80 mmol sodium/day. At one stage, 130 mmol sodium was administered intravenously. Under this regimen the serum concentration of sodium normalized, whereas the urea and creatinine levels fell more slowly. In this phase a slight rise in blood pressure to 200/95 mmHg was observed on the 50 mg t.i.d. captopril dose. Subsequently, captopril treatment was increased once more to 50 mg q.i.d.. A renal function study performed on the 77th day after the start of therapy (August, 1979) showed a GFR of 52 ml/min, and a ERPF of 207 ml/min, blood pressure being 165/90 mmHg.

The eosinophilia however, increased to 44 per cent and the rash re-occurred within 2 weeks of reinstituting the 50 mg q.i.d. captopril dose (September, 1979). There also existed fever, generalized lymphadenopathy, oedema and epidermal necrolysis of the feet (see figures 27 and 28, Chapter VII). Renal function was again 'impaired'; the creatinine clearance had fallen to 26 ml/min and a trace of proteinuria (0.4 g/24 h) was found. Ultimately positive anti-nuclear factors were recorded but anti-double string DNA remained negative. C_3 globulin amounted to 102% of the standard serum. C_1-esterase was 920 (normal value 860 ± 280 U/l). LDH was elevated (378 U/l). Fibrin degeneration products were present (20-30 μg/ml). Transient microscopic haematuria was noticed once.

A renal biopsy and skin biopsy were performed. Histological examination of the former specimen showed signs of severe arteriolosclerosis. Immunofluorescent studies revealed granular depositions of immunoglobulins and complement along the GBM. Electronmicroscopy showed electron-dense deposits along the subepithelial side of the GBM. In the skin biopsy, light microscopy showed non-specific perivascular infiltration with lymphocytes and plasma cells in the dermis. The immunofluorescent microscopy revealed no depositions of immunoglobulins or complement.



Patient nr 27. Diagnostic and therapeutic procedures during withdrawal of previous antihypertensives, the titration of captopril and the short-term administration of hydrochlorothiazide. PRA is represented by open bars and PAC by hatched bars. For details see the text.

For obvious reasons cessation of captopril treatment was now considered the only choice left. Captopril was gradually withdrawn, and the blood pressure rose within 48 hours. Treatment consisting of hydrochlorothiazide 50 mg o.i.d., propranolol 80 mg t.i.d. and minoxidil 5 mg t.i.d. resulted in an acceptable blood pressure level (160/80 mmHg). Meanwhile, the creatinine clearance had improved to 67 ml/min. The eosinophilia decreased to 13 per cent in the differential count 14 days after the withdrawal of captopril and at that time the rash had disappeared

completely. Proteinuria however, persisted (0.2 g/24 hr), and is still present at the time of writing.

In summary: In a 52 year old male with intractable renovascular hypertension, blood pressure could be controlled by captopril, initially only in combination with hydrochlorothiazide. After discontinuing the diuretic, blood pressure remained under control. Withdrawal of captopril became inevitable because of an allergic reaction. In the renal biopsy specimen granular depositions of immunoglobulins and complement were found along the GBM.

Patient nr 24, a 32 year old male.

This patient has a medical history of recurrent urinary tract infections due to a hydronephrotic right, and a hypoplastic left kidney. Because of recurrent infections and deteriorating renal function, nephrectomy of the right kidney was performed in 1974, and chronic intermittent haemodialysis (CIH) was started. During this period the patient was normotensive. A renal

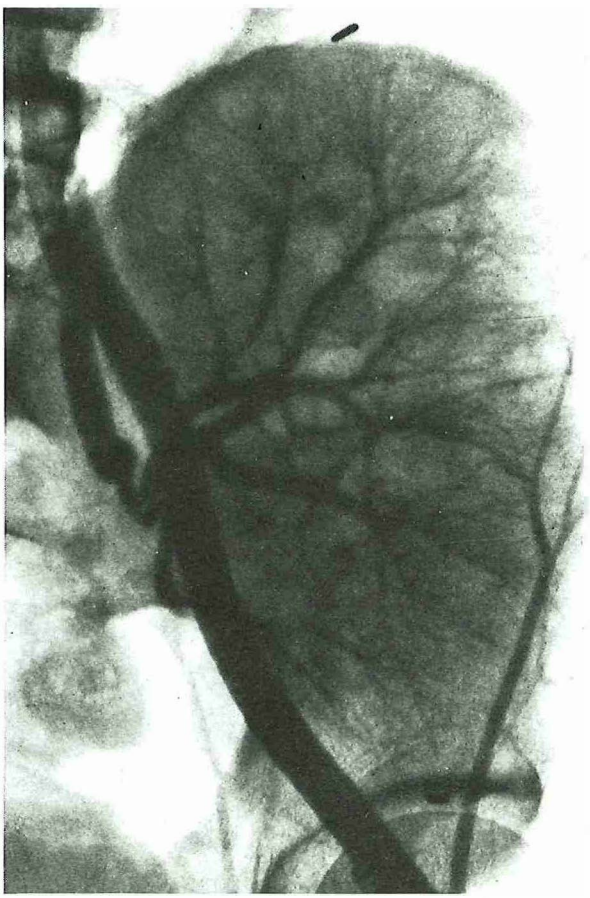


Figure 41. Patient nr 24. Angiography of renal graft shows an end-to-end anastomosis of the renal artery to the left internal iliac artery. The main renal artery is stenosed at its origin and has a post-stenotic dilatation.

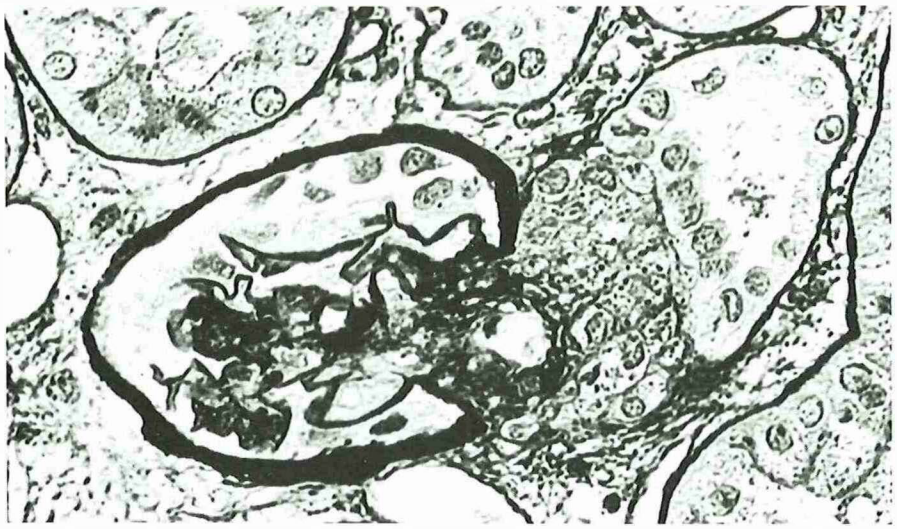


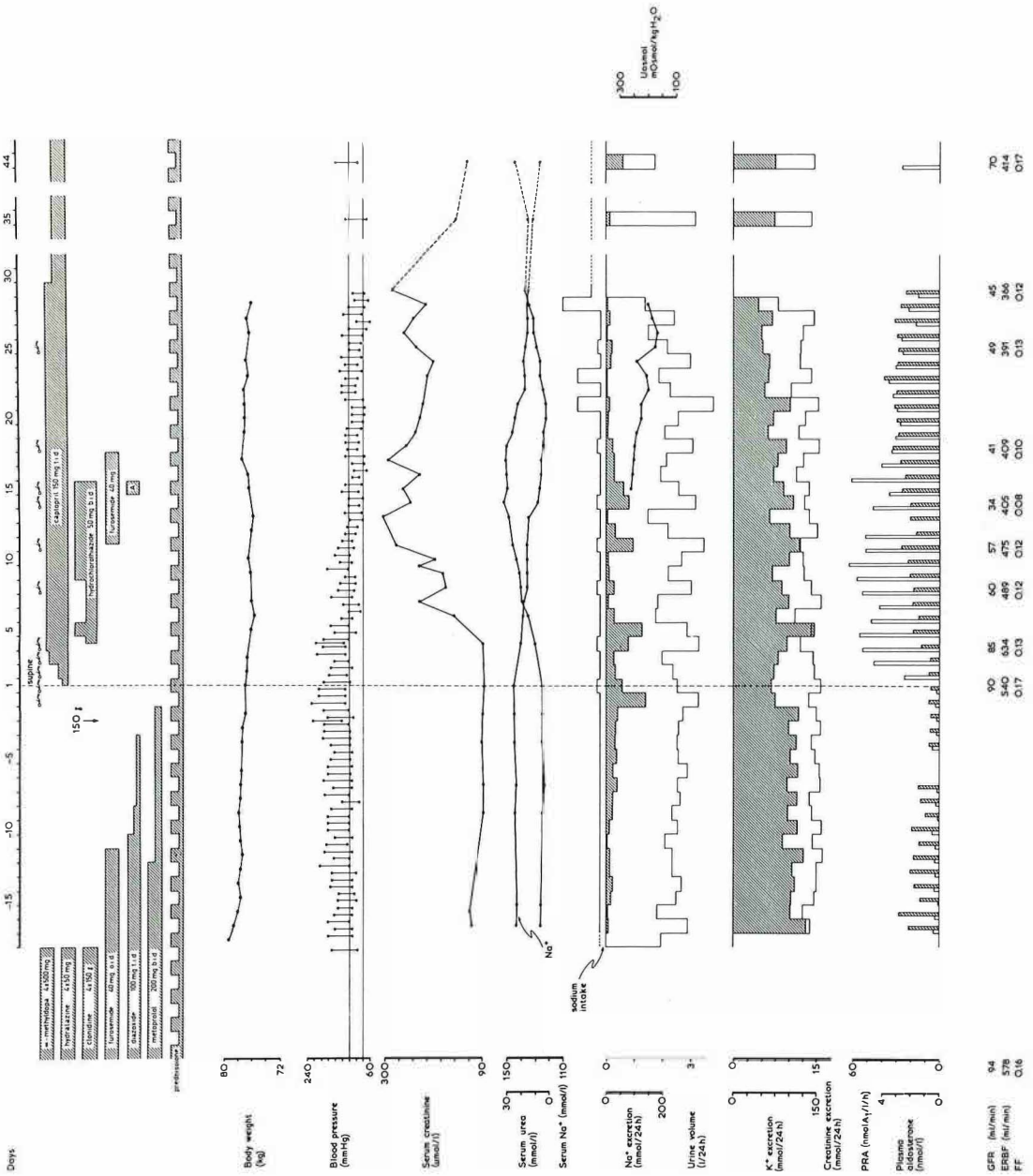
Figure 42. Patient nr 24. Light microscopical picture of a bopsy specimen taken from the upper pole of the transplanted kidney. The glomerulus shows ischaemic changes. The hypertrophy of the juxtaglomerular apparatus is striking (x 700).

transplantation was performed in July, 1976, with a graft from a 9 year old donor. Total ischaemic time amounted to 27 hours. Two renal arteries on a patch were anastomosed end-to-end to the left hypogastric artery. The post-operative phase was complicated by a displaced ureter splint, necessitating operative correction. At discharge, the patient had moderate hypertension (160/100 mmHg) and a vascular bruit was heard over the grafted kidney. ERPF at discharge was 103 ml/min, GFR 35 ml/min, FF being 0.36.

At regular visits to the outpatient clinic, a steady increase in blood pressure was noted, which finally could not be adequately controlled with an antihypertensive regimen consisting of beta-blockade, hydralazine, and clonidine. In September, 1976, he was readmitted to the hospital, with signs of malignant hypertension and 3 periods of seizures. Blood pressure was controlled by intravenously administered diazoxide. The creatinine clearance at that time was 54 ml/min. Angiography showed a stenosis with poststenotic dilatation in the main renal artery (figure 41). An operation was performed and a small, barely patent and tortuated artery of the lower pole was ligated. Surgical reconstruction of the main artery was technically impossible. A biopsy taken from the upper pole revealed slight ischaemic changes in the glomeruli and a marked hypertrophy of the juxtaglomerular apparatus was also noted (figure 42).

One week after the operation a cholecystectomy had to be performed because of biliary colic due to gallstones. During this operation the left hypoplastic kidney was removed. An uneventful recovery followed. However, hypertension persisted which could be controlled with alpha-methyldopa, clonidine, hydralazine, beta-blockade and a diuretic. In December, 1976, renal function studies demonstrated a GFR of 94 ml/min, ERPF of 318 ml/min and FF 0.29. A rise in blood pressure in this phase was treated with the addition of oral diazoxide and the patient was normotensive for almost a year. At the end of 1978 however, the blood pressure rose again (190/130 mmHg) despite the extended combination.

On admission to the hospital in February, 1979, a 20 mmol sodium restricted diet was prescribed. The anti-hypertensive medication was gradually withdrawn (see the graph), but the azathioprine and prednisone were continued. The withdrawal of the previous therapy resulted in a manifest rise in blood pressure. A 3 kg loss in body weight was noticed during this period, due to sodium and



Patient nr 24. Diagnostic and therapeutic procedures during withdrawal of previous antihypertensive treatment, subsequent titration of captopril and short-term administration of diuretics. PRA is reflected by open, and PAC by hatched bars. See the text for details.

water loss after withholding diazoxide. PRA (open bars) and PAC (hatched bars) decreased to normal values. GFR did not change and effective renal blood flow (ERBF) decreased slightly.

Administration of captopril caused a slight, transient fall in blood pressure. PRA increased immediately, PAC initially did not change. ERBF increased and GFR showed a slight fall. Because there was no substantial fall in blood pressure on the maximal dose of captopril, hydrochlorothiazide and later on furosemide were added, resulting in a gradual fall in blood pressure to normal values. However, the addition of diuretics resulted in isosthenuria, uraemia, a hyponatraemic hypochloraemic alkalosis, and paradoxic aciduria. PAC rose steadily in this situation of sodium depletion, though the combination of high PRA, the increased sensitivity to exogenously administered A_{II}, and a low converting-enzyme activity (CEA) (from 15 before captopril to 1 U/l during converting-enzyme inhibition) suggested an almost complete inhibition of the enzyme. GFR decreased but ERBF fell to a lesser degree, resulting in a low FF.

Because of these serious complications of the combined therapy, the diuretics were withdrawn. Surprisingly this did not result in a rise of blood pressure. After changing the daily sodium intake to 100 mmol/24 h, the serum sodium concentration and the ability to produce a diluted urine returned to normal. GFR rose to 70 ml/min, ERBF to 414 ml/min and FF to 0.17.

The patient was discharged in a good general condition. At periodic visits to the outpatient clinic he remained normotensive and showed no adverse reactions due to the treatment. In August, 1979, his blood pressure was 139/86 mmHg on an antihypertensive regimen consisting of captopril 100 mg t.i.d. in combination with a 100 mmol sodium restricted diet. Renal function was as folllows: GFR 77 ml/min, ERPF 338 ml/min. The serum creatinine concentration amounted to 164 μmol/l. Urinalysis gave normal results. The anti-nuclear factors were negative.

In summary: this 32 year old male had intractable renovascular hypertension due to a stenosis of the graft artery. His blood pressure became under control when diuretics were added to the regimen of captopril and a sodium restricted diet. However, a state of severe hyponatraemia was induced. Discontinuing diuretics and an increased sodium intake led to normalization of the serum sodium concentration, and surprisingly, maintenance of good blood pressure control.

Patient nr 29, a 53 year old male.

An elevated blood pressure was found in 1968 during a medical examination. Being a physician, the patient treated himself with guanethidine. In 1971 he was seen by an internist because of general fatigue and blurred vision: a blood pressure of 250/150 mmHg was found. Fundoscopy revealed haemorrhages and exudates. Creatinine clearance amounted to 6 ml/min. The chest X-ray showed cardiomegaly and the electrocardiogram signs of left ventricular strain. Hypertension was initially successfully treated with reserpine, bethanidine and chlorthalidone (blood pressure 200/110 mmHg supine, 140/95 mmHg upright). The renal insufficiency was treated with a protein restricted diet. In the following months the blood pressure rose despite additional therapy with clonidine. A seizure due to hypertensive encephalopathy occurred once. The renal function deteriorated further and chronic intermittent haemodialysis (CIH) started without any effect on blood pressure. The plain X-ray film of the abdomen had revealed bilateral small kidneys. One month after initiating CIH, bilateral nephrectomy was performed. The blood pressure was under control for only a few months and soon antihypertensive treatment was restarted.

At the end of 1972 a renal transplantation was performed. A donor kidney from a 17 year old male was anastomosed end-to-end to the left hypogastric artery. Blood pressure remained elevated and was for the next 7 years treated with various antihypertensive drugs.

In January, 1979 the patient was hospitalized. He had no complaints. The blood pressure was 200/120 mmHg. Fundoscopy revealed grade II retinopathy. On the electrocardiogram no signs of left ventricular hypertrophy or of strain were present. There was no evidence of cardiomegaly on the chest X-ray. Selective angiography of the renal graft demonstrated no stenosis (see figure 43).

The therapeutic and diagnostic procedure during hospitalization can be read from the graph. Whilst discontinuing the previous treatment, the blood pressure rose to 200/130 mmHg and there was a slight increase in body weight, possibly due to cessation of chlorthalidone therapy. The start

and subsequent stepwise titration of captopril therapy induced no obvious changes in blood pressure. However, the addition of a diuretic in combination with a sodium restricted diet, produced 'normotension'. Because of hypokalaemia, triamterene was added to the therapeutic regimen. The captopril dosage was reduced after a few days because of orthostatic complaints. Thereafter, the therapy was tolerated well, but the ECG revealed the existence of ventricular ectopic beats; therefore propranolol in low dosage was prescribed with benificial effects.

On previous anti-hypertensive treatment with propranolol, PRA (open bars) and PAC (hatched bars) were low, and without change when this therapy was interrupted. PRA and PAC did *not* further change during captopril treatment alone. It was only after the addition of hydrochlorothiazide, that the PRA rose to high levels (followed by a minor increase in PAC).

Renal function studies showed no change in GFR during captopril therapy alone, when compared to the pre-treatment value. However, there was a decrease in FF, due to a small increase in ERPF. Once the diuretic had been added, both GFR and ERPF fell. The FF also decreased.

The dose-response curves with exogenously administered bradykinin in this patient showed a sharp increase in sensitivity for bradykinin at a small dosage of captopril already (see figure 44). The sensitivity for A_I decreased gradually at each captopril dosage. The sensitivity for exogenous A_{II}, which was already high before captopril was administered, did not change.

The patient was dismissed from the hospital in a good general condition and was seen monthly in the outpatient clinic. After 7 months of captopril treatment (August, 1979) his blood pressure was 125/88 mmHg. The therapeutic regimen consisted of captopril 50 mg t.i.d., triamterene 50 mg b.i.d., hydrochlorothiazide 25 mg b.i.d., prednisolone 10 mg o.i.d., and azathioprine 100 mg o.i.d..

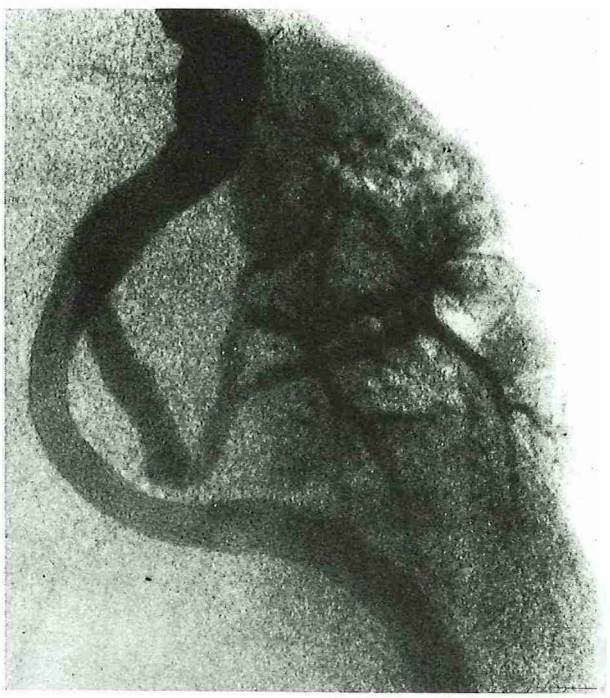
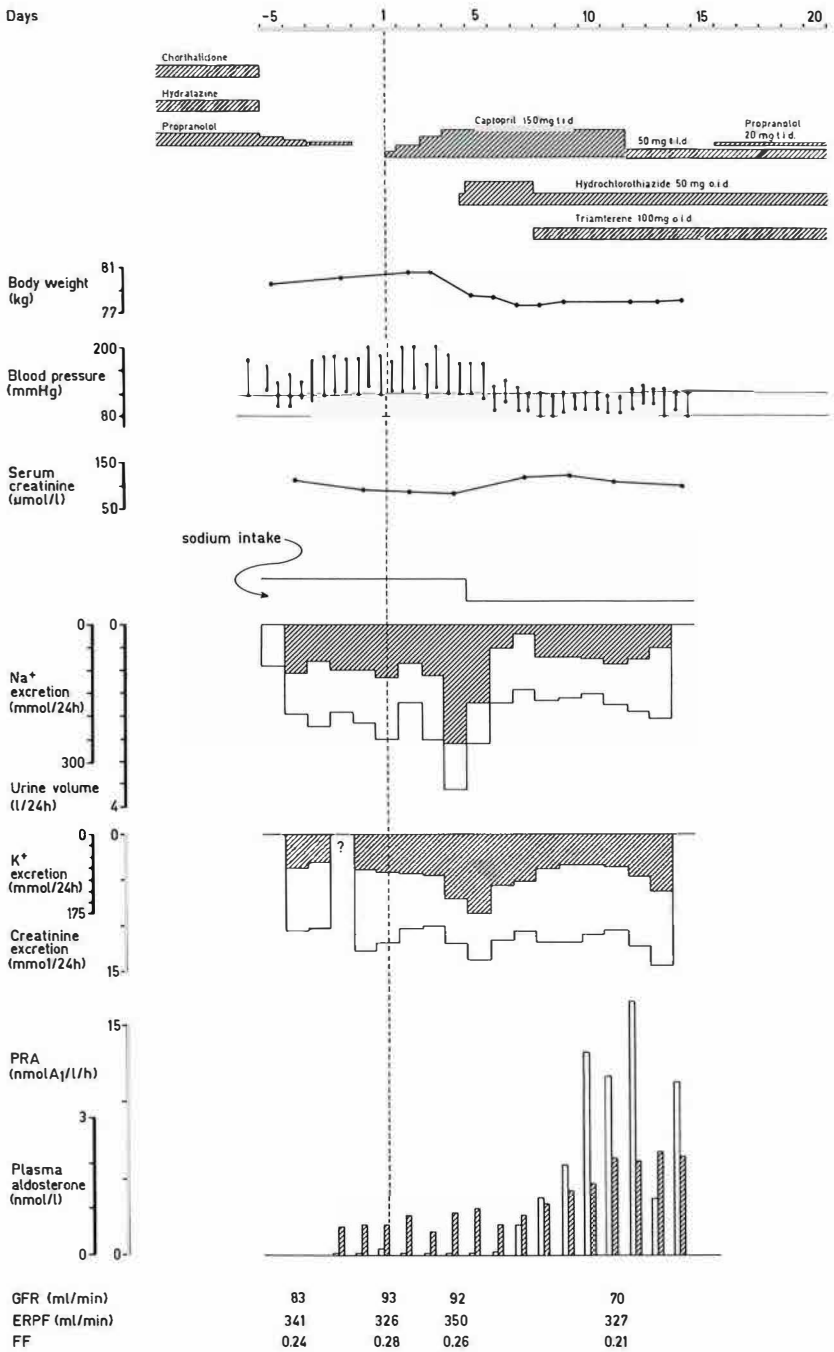


Figure 43. Patient nr 29. Renal angiography of transplanted kidney. Although this picture may be suggestive for a stenosis of the end-to-end anastomosis of the renal artery to the left hypogastric artery, oblique shot films showed neither a stenosis nor a post-stenotic dilatation.



Patient nr 29. Diagnostic and therapeutic procedures during withdrawal of previous antihypertensives, subsequent titration of captopril and ultimately the addition of diuretics. The open bars represent PRA, the hatched bars reflect PAC values. See the text.

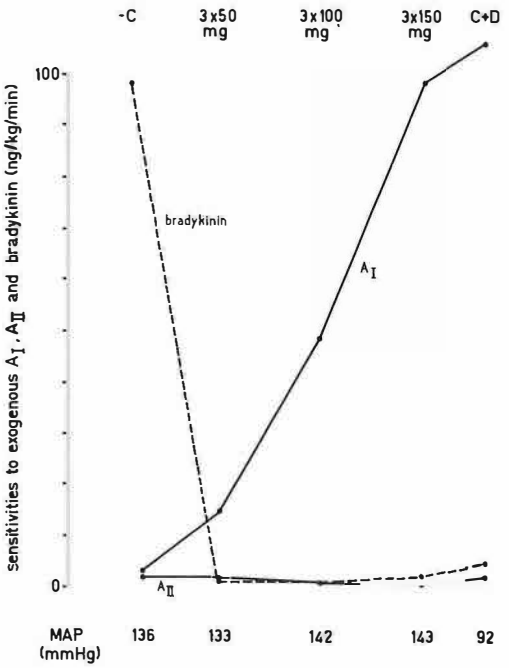


Figure 44. Patient nr 29. The sensitivity to exogenously administered angiotensin I (A_I), angiotensin II(A_{II}) and bradykinin on different dosages of captopril (C). The patient had low initial PRA levels which did not change during captopril alone. Only when hydrochlorothiazide was being added to captopril, the mean arterial pressure fell from 143 to 92 mm Hg.

In August, 1979, he had noticed mild paraesthesia of his fingers, which had lasted for 2-3 weeks. On physical examination the patient appeared to be jaundiced. The laboratory investigation revealed liver function disturbances, suggestive for hepatitis. The patient was hospitalized and a liver biopsy was performed. Microscopy of the liver biopsy specimen showed a picture compatible with viral hepatitis or drug-induced hepatitis. Infectious causes could be excluded. With bed rest, jaundice and liver function restored completely when triamterene (and subsequently hydrochlorothiazide) was withdrawn. Captopril dose was left unchanged and the blood pressure rose to 180/120 mmHg. After addition of chlorthalidone, normotension (110/70 mmHg) was reached again. The anti-nuclear factors were negative and urinalysis was normal.

In summary: In a 53 year old male with intractable 'low renin hypertension' in whom both kidneys had been removed and a renal transplantation had been performed previously, initiating captopril caused no decrease in blood pressure. PRA did not change. However, the addition of a diuretic caused an immediate blood pressure control and was accompanied by an impressive rise in PRA. The hepatitis-like clinical picture, developing 7 months after treatment with captopril probably has been induced by the diuretic treatment (i.e. triamterene).

Patient nr 28, an 18 year old female.

From October, 1977, to March, 1978, this patient was hospitalized because of a haemolytic uraemic

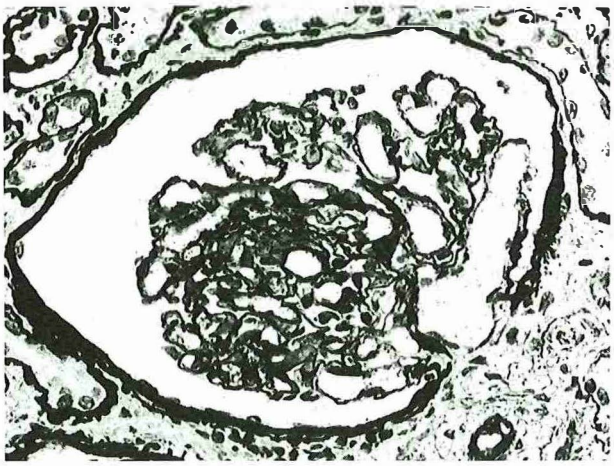


Figure 45. Patient nr. 28. Renal biopsy specimen. Light microscopy shows glomerular ischaemia and interstitial damage (x 700).

syndrome (HUS) complicated by (partially reversible) renal failure. The creatinine clearance finally amounted to 12 ml/min. In the acute phase, malignant hypertension developed which together with the renal failure, necessitated intermittent haemodialysis (CIH). Although renal function had recovered to some extent, it appeared inevitable that we would have to continue dialysis because of repeated overhydration and persistent hypertension. Fundoscopy (January, 1978) demonstrated hypertensive changes grade III-IV. Once she had a seizure due to hypertensive encephalopathy. The renal biopsy specimen in December, 1977, had revealed glomerular ischaemia and interstitial atrophy due to vascular damage resulting from the HUS (figure 45). Renal angiography in May, 1978, disclosed bilaterally small kidneys with cortical atrophy and no signs of aneurysmatic dilated vessels (figure 46). No renal artery stenosis was found. Plasma renin activity before dialysis appeared to be high (15.9 nmol A_I/l/h). A renal function study in September, 1978, (blood pressure 190/125 mmHg, anti-hypertensive treatment consisting of hydrochlorothiazide, metoprolol and hydralazin) showed a GFR of 9 ml/min and a ERPF of 59 ml/min, FF being 0.15. With the hydrochlorothiazide discontinued and the blood pressure varying from 130/90 (after dialysis) to 170/110 mmHg (before dialysis), the GFR was 10.5 ml/min, ERPF 68 ml/min and FF 0.15. Under this regimen, a pre-dialysis saralasin infusion showed a fall in blood pressure (see figure 47), indicating that blood pressure before dialysis was still angiotensin II dependent. The sensitivity for saralasin was about 0.3 µg/kg/min. Increasing the infusion rate caused no further fall in blood pressure. Withdrawal of this agent was followed by a return of the blood pressure to previous levels. PRA at the end of A_{II}-receptor blockade had increased from 15.9 to 42.2 nmol /A_I/l/h.

From September, 1978, the patient was treated with furosemide, metoprolol and minoxidil combined with a 50 mmol sodium and a 1000 ml fluid restricted diet. Twice weekly dialysis was performed for 7 hours. On this regimen, the blood pressure was under control (150/100 mmHg) but a progressive hirsutism due to the minoxidil grew intolerable for this teenage girl and made her socially very handicapped (figure 48).

On admission in January, 1979, her cardiovascular history was negative. She had a bad appetite and complained of nausea every morning. On days of dialysis, she tended to vomit after meals. On physical examination a tall (height 1.76 m), lean (body weight 44.6 kg) girl with severe hirsutistm was seen. Blood pressure was 150/100 mmHg. Fundoscopy revealed grade II retinopathy. Electrocardiography showed signs of left ventricular hypertrophy without strain. Laboratory investigations revealed a haematocrit of 23 per cent and normal white blood cell and platelet counts. The differentiation leucocyte count showed a slight lymphopenia. Values of serum

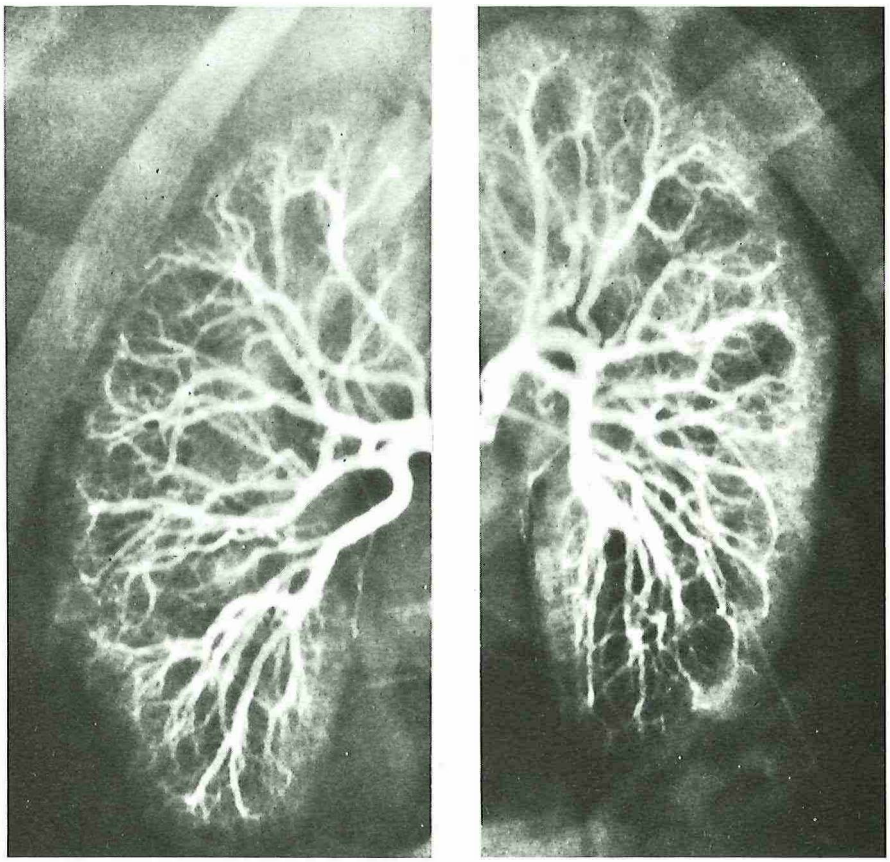
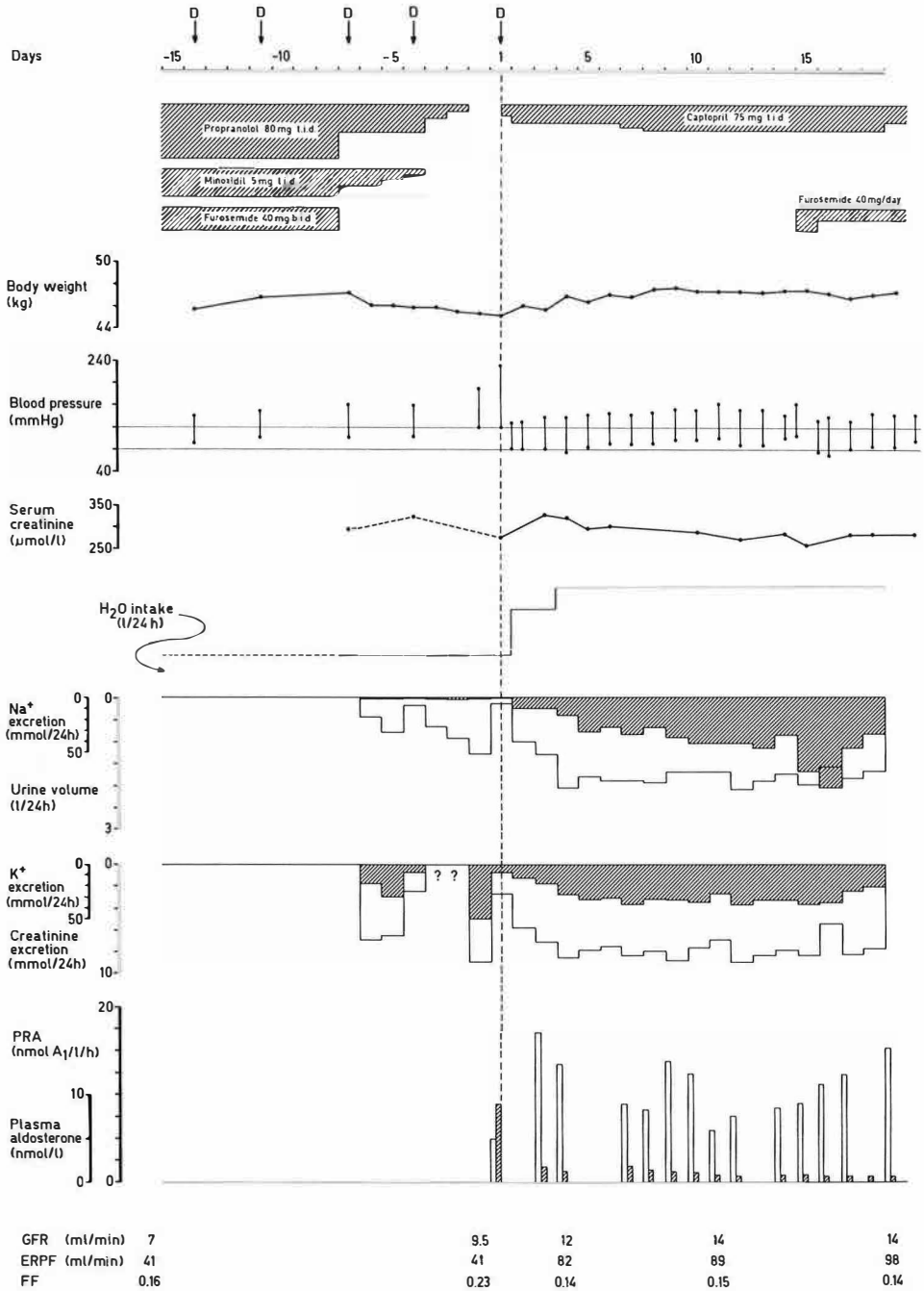


Figure 46. Patient nr. 28. Selective renal angiography shows bilateral small kidneys and cortical atrophy. No signs of aneurysmatic dilated vessels.

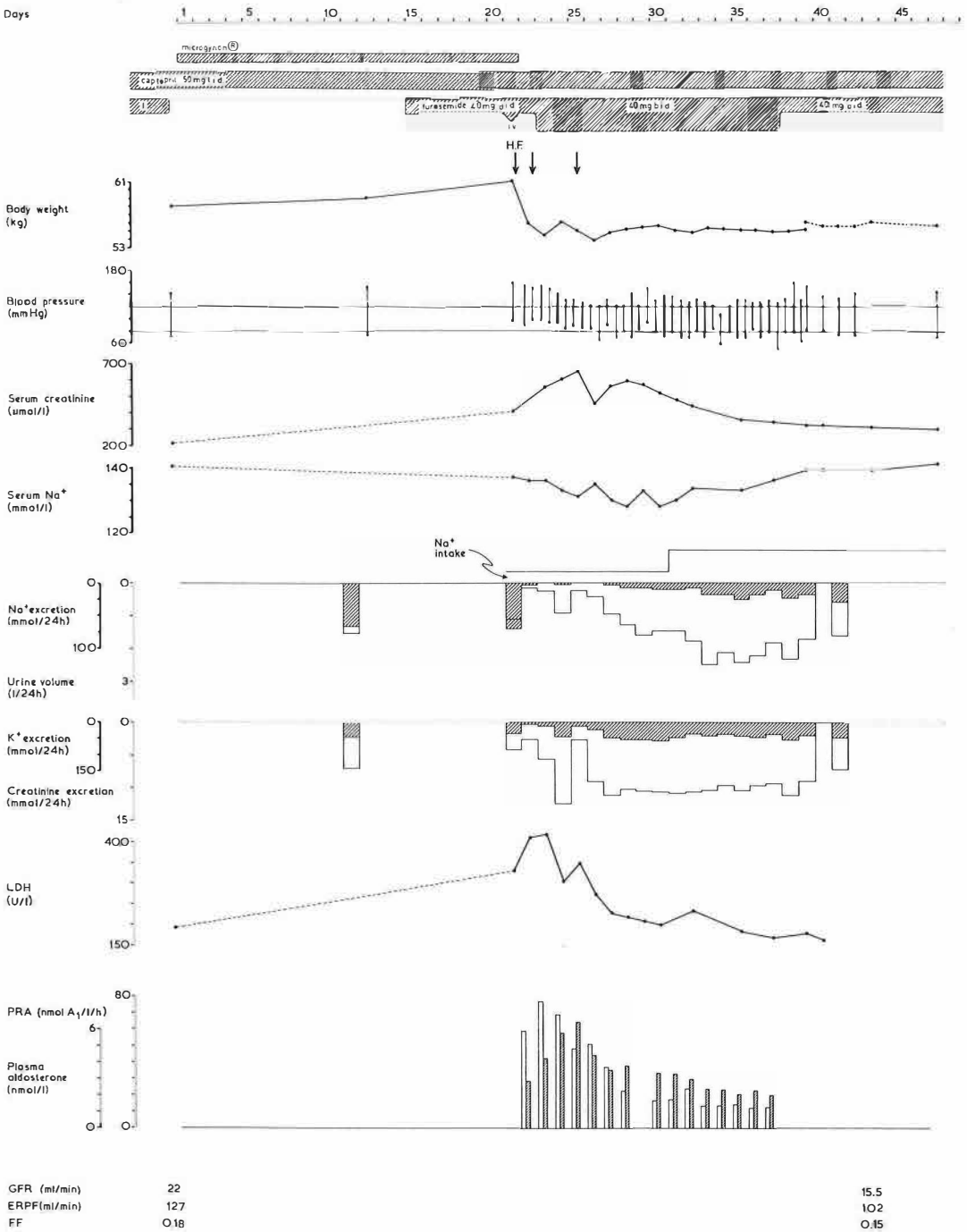
electrolytes were all within normal ranges. Urea amounted to 20.7 mmol/l and creatinine to 272 μmol/l before dialysis. The LDH was 254 U/l (normal range 80-200 U/l).

The therapeutic and diagnostic procedures during hospitalization are shown in the first graph. Under close observation of blood pressure, body weight and 24 hour urinary excretion of sodium, potassium and creatinine, and with regular determination of serum electrolytes, urea and creatinine levels, the antihypertensive treatment was withdrawn in a stepwise manner. Supine PRA (open bars) and PAC (hatched bars) were measured almost daily from the morning of the last dialysis (D). Renal function studies were performed on the previous medication, without therapy and during dose-titration with captopril.

The patient was without any kind of therapy for 36 hours. Her blood pressure increased to 240/110 mmHg. PRA was 13.2 nmol/A_1/l/h, and PAC 8.93 nmol/l. Immediately after the last dialysis, captopril therapy was started which caused a marked decrease in blood pressure. It then was decided to increase the fluid intake after which an increase in urinary volume was observed. The patient never showed signs of hypovolaemia or hypotension. The serum creatinine concentration initially increased to 350 μmol/l, but subsequently fell to 250 μmol/l. The sodium excretion paralleled inversely the increase in body weight and ultimately was constant until a diuretic had been added. A few days after the last dialysis had been performed, the creatinine and potassium excretions showed only slight variations, the first indicating an accurate sampling of 24 h urine.



Patient nr 28.1. Diagnostic and therapeutic procedures during withdrawal of previous antihypertensive therapy – including dialysis (D) – titration of captopril and ultimate addition of furosemide. PRA is represented by open bars and PAC by hatched bars. See the text.



GFR (ml/min)	22	15.5
ERPF(ml/min)	127	102
FF	0.18	0.15

Patient nr 28.II. Diagnostic and therapeutic procedures during readmission. HF = haemofiltration. See the text for details.

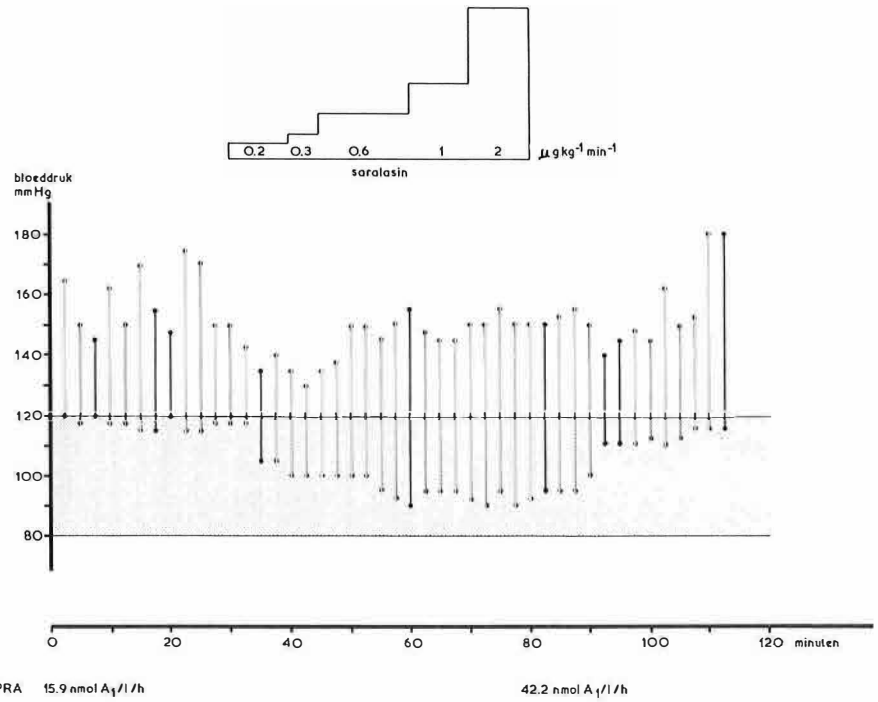


Figure 47. Patient nr. 28. Saralasin infusion prior to haemodialysis shows a fall in blood pressure which is optimal on the 0.3 µg/kg/min rate. Stopping the infusion resulted in an increased blood pressure. Supine PRA, already high prior to saralasin, more than doubled on the maximal saralasin infusion rate.

The rise in PRA and the fall in PAC, respectively, indicated an effective inhibition of angiotensin II generation. When the body weight increased, PRA was slightly depressed, to rise again after furosemide was administered.

The addition of a diuretic to the therapeutic regimen was considered because the increased fluid intake and on captopril 75 mg t.i.d., gave rise to only poor blood pressure control. A total daily dose of 225 mg captopril was considered to be the maximum for this patient with renal insufficiency. Thus, furosemide was added, resulting in acceptable blood pressure levels again, a slight fall in body weight, and a further increase in PRA.

The renal function studies showed an increase in GFR when the blood pressure increased after discontinuing previous therapy. ERPF remained constant. Starting captopril therapy decreased blood pressure, however, the GFR rose to 14 ml/min and ERPF to 89 ml/min. As a consequence, the filtration fraction fell, indicating a decrease in intrarenal vascular resistance.

The dose response curves of exogenously administered angiotensin I showed a decrease in sensitivity from 16.7 to 80 ng/kg/min (50 mg t.i.d.) and to 133 ng/kg/min (75 mg t.i.d.). For angiotensin II there appeared to be an increase. The bradykinin infusions showed a marked increase in sensitivity from more than 106 ng/kg/min to 4.2 ng/kg/min (both on 50 mg t.i.d. and 75 mg t.i.d.).

At discharge the patient had the following therapeutic regimen: captopril 50 mg t.i.d., furosemide 40 mg o.i.d., oral iron supplement, aluminium hydroxide, calcium carbonate, allopurinol, and a 3 g sodium restricted 2500 ml fluid containing diet. The blood pressure was 130/85 mmHg.

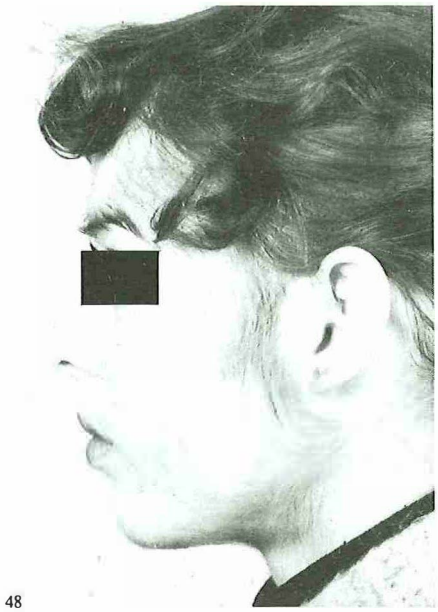
The patient was seen regularly in the outpatient clinic and showed an improvement of the general condition, amongst other things expressed as a gradual gain in body weight. The hirsutism had disappeared (figure 49). The renal function study was repeated in May, 1979, when she had a blood pressure of 140/80 mmHg. The serum creatinine level had decreased to 246 μmol/l and the GFR had increased to 22 ml/min, the ERPF to 127 ml/min. The therapeutic and dietary regimen were left unchanged.

At the end of June, her blood pressure was 135/73 mmHg and her body weight 58 kg. The serum creatinine level was 216 μmol/l. With her blood pressure under control and with improving renal function, it was decided to withdraw furosemide. Twelve days later, her blood pressure was 149/73 mmHg; body weight had increased to 59 kg. Urinary volume in 24 hours was 1500 ml. No laboratory investigations were performed. When seen again 7 days later, she complained of severe headaches frontally and occipitally. Her medical history was suspect for a viral respiratory infection. Two days before the control visit she noticed a reduced urinary volume and noctural dyspnoea, hence she started furosemide again (40 mg/day). Until this visit, it was unrecognised that for 3 weeks she had been taking her oral contraceptive again. On physical examination, her blood pressure was 160/98 mmHg and her body weight had increased with another 2 kg to 61 kg. Her face looked puffy but there were no signs of oedema. Over the lungs basal rales were heard. A chest X-ray showed pulmonary oedema and an increased heart size. The laboratory values were as follows: haematocrit 24 per cent, leucocytes 7200/mm^3, thrombocytes 185.000/mm^3, without fragmented erythrocytes in the blood smear. Clotting time was more than 15 min. FDP amounted to between 20-30 μg/ml. Fibrinogen was 400 mg%. Prothrombin and cephaline time were within the normal ranges. Serum concentrations of electrolytes were normal, the serum urea amounted to 29.7 mmol/l and the serum creatinine had increased to 400 μmol/l. The liver function tests were normal. The LDH was 332 U/l. The haptoglobin level was 4 mg/100 ml (normal values 100-300 mg/100 ml). C_3 globulin had decreased to 60 per cent, and the C_4 amounted to 154 per cent of the standard serum. The antinuclear factors were negative. The urinary sediment contained 20 red blood cells/hpf. Proteinuria of 1.4 g/24 h was initially present. The electrocardiogram was unchanged and normal.

The clinical picture at first resembled as a volume overload, possible due to cessation of the furosemide. However, an eventual role of the oral contraceptive (which was the same she had been using prior to the start of the HUS), or a provocative role of any viral infection was also considered. Finally, the captopril itself could have been responsible for initiating the deterioration in renal function which might have led to the oliguria and subsequently, to an increase in body weight and in blood pressure. The therapeutic and diagnostic procedures during this last hospitalization can be read from the second graph.

Initially, 40 mg furosemide was administered intravenously, which was followed by a 150 ml urine output in the next 2 hours. Another furosemide injection (150 mg) was given, together with 0.5 mg digoxin, and in the next 2 hours 50 ml of urine were passed. It was concluded that cessation of the furosemide could not have been the only causal factor in this situation. In order to obtain a normal extracellular fluid volume and adequate blood pressure levels, the patient was haemofiltrated for 4 hours. Her body weight decreased by 4 kg. The expected fall in blood pressure during haemofiltration however, did not occur although 25 mg of captopril twice was administered (before and immediately after the procedure).

Haemofiltration was repeated the following day. Although her body weight had decreased by another 1.5 kg the captopril was continued (50 mg t.i.d.), and an evident decrease in blood pressure again was not observed. The therapeutic regimen at that time was: captopril 50 mg t.i.d., furosemide 40 mg b.i.d., aluminium hyxdroxide 2 g t.i.d., calcium carbonate 500 mg o.i.d., allopurinol 100 mg o.i.d., and dihydrotachysterol 0.2 mg o.i.d., combined with a 20 mmol sodium, 30 g protein, and 1500 ml fluid restricted diet (initially the fluid intake had been limited to 800 ml/24 h). In the following days, the blood pressure decreased to 135/95 mmHg. Urinary volume increased although fluid balance had not yet been achieved since the body weight slowly increased again. As serum urea and creatinine levels had increased meanwhile, a haemodialysis was performed, which was then followed by an evident fall in blood pressure (lowest level 110/55 mmHg).



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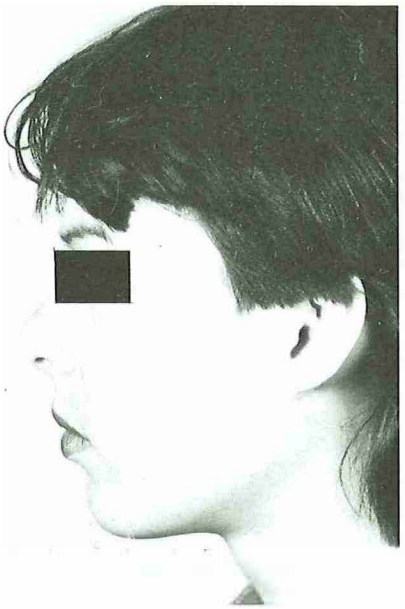

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Figure 48. Patient nr 28. Hisutism developed during minoxidil treatment and made this teenager socially very handicapped.
Figure 49. Patient nr 28. Four months later hirsutism had disappeared completely.

The therapeutic and dietary regimen was left unchanged and again the urinary volume increased, until a state of fluid balance existed. Since hyponatraemia became apparent after the haemodialysis, the sodium restriction was extended to 50 mmol/24 h. The fluid intake was temporarily reduced. This resulted in a normalization of the serum sodium concentration, in an increased urinary volume together with a fall in body weight to 54.8 kg, and in a further fall in serum urea and creatinine levels. Four weeks after the onset of symptoms the patient was discharged with a normal blood pressure. The serum concentration of urea had fallen to 13.0 mmol/l, and of creatinine to 299 μmol/l. LDH had decreased to normal (162 U/l), the same held for FDP. After the fourth day of hospitalization the urinary sediment showed no red blood cells anymore. The therapeutic regimen was kept unchanged except for a reduced furosemide dosage (20 mg b.i.d.). It was concluded that a relapse of HUS – possibly provoked by the recently restarted oral contraceptive – was the most probable diagnosis. Since the blood clotting time remained prolonged no renal biopsy could be performed.

After discharge the patient was seen regularly in the outpatient clinic. Creatinine and urea levels decreased further and remained ultimately constant (October, 1979) at a level of 275 μmol/l, and 15.3 mmol/l, respectively. Creatinine clearance had increased from 12 ml/min four days after the haemodialysis, to 26 ml/min four weeks later. Renal function studies showed a GFR of 19 ml/min an ERPF of 125 ml/min, FF being 0.15. The body weight was 56 kg. The blood pressure remained satisfactory controlled (134/76 mmHg).

In summary: This 18 year old girl had suffered from HUS complicated by malignant hypertension and renal insufficiency. Overhydration and hypertension necessitated continuation of chronic intermittent haemodialysis (CIH) when renal function had recovered to some extent. The antihypertensive treatment was ineffective in gaining an adequate blood pressure control. After initiating captopril therapy, the blood pressure response was satisfactory. In addition, an

improvement in renal function was observed and CIH was withheld successfully from the start of captopril. This observation of effective treatment with captopril of malignant hypertension and renal insufficiency (due to HUS) is compatible with the reversal of vascular and renal crises in 2 patients with scleroderma during treatment with captopril, recently reported by Lopez-Ovejero et al*.

When the patient took her oral contraceptive again the clinical picture of a HUS reoccurred, with impairment of renal function and volume overload. A possible provocative role in the development of HUS by oral contraceptives has been mentioned before**. Other possible factors involved could be ruled out. This especially concerned captopril, as continuation of this drug was possible. Withdrawing the contraceptive agent and restoring a normal state of hydration were sufficient to overcome the above mentioned features, and again an acceptable blood pressure control was achieved.

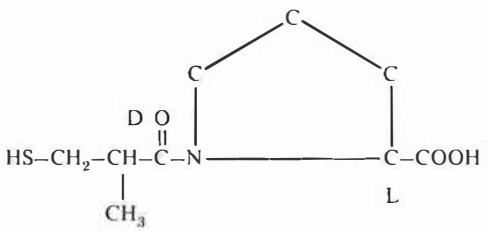
* Lopez-Ovejero JA, Saal SD, D'Angelo WA et al, (1979) Reversal of vascular and renal crises of scleroderma by oral-angiotensin-converting-enzyme blockade. N. Engl. J. Med. *300*:1417

** Brown CB, Clarkson AR, Robson JS, et al (1973) Haemolytic uraemic syndrome in women taking oral contraceptives. Lancet *I*: 1479

CHAPTER IX

DISCUSSION AND CONCLUSIONS

Captopril (SQ 14, 225), is designated chemically as 1– (D–3– mercapto–2– methyl–1– oxopropyl) –L– proline (S, S isomer) and has the following structure:



The empirical formula is $C_9H_{15}NO_3S$ and the molecular weight amounts to 217.29.

The drug is very soluble in water (about 10 per cent on a weight base) and appears as a white, fine, free-flowing crystalline powder with a sulphur-like smell. Data on file from the Squibb Institute for Medical Research indicate that SQ 14,225 is stable in a light box for one month (900 foot candles) and at storage temperatures from –20°C up to 50°C for the time periods studied (six to twelve months at –20°, 5°, 33° and 50°C, respectively).

Renal excretion provides the principal mode of captopril elimination from the body. Since the captopril metabolites still contain a C = O group, the urine gives a positive acetone reaction (see also table XIV). From a study of Singhvi et al[1] it appeared that the excretion of captopril in the urine was relatively rapid, as demonstrated by recovery of almost half of the radioactive dose (^{35}S-labeled captopril) in the first 4 hours after administration of both 100 mg dry-filled capsules and 100 mg compressed tablets to healthy subjects. In the 0 to 24-hour urine collection, captopril accounted for more than half of the total radioactivity; most of the remaining radioactivity was found in unidentified polar metabolites. The disulfide dimer of captopril (SQ 14,551), accounted for less than 2 per cent of the radioactivity in urine.

From another internal Squibb report[2] it appeared that when captopril-^{14}C was administered as 100 mg tablets to healthy male volunteers (n = 12) in a two-way crossover study, in which the subjects were either fasting or provided with a standard meal immediately prior to dosing, substantial decreases in

absorption of radioactivity and bioavailability of the drug could be observed in the postprandial state. Both the absorption of total radioactivity and the bioavailability of captopril were decreased approximately 35 to 40 per cent after a meal (based on blood level and urinary excretion data).

Excretion of the radioactive dose in urine and faeces (from 0 to 72 hours), as established by Willard et al[2], is summarized below:

Total radioactivity as % of dose (mean ± SEM)

	urine	faeces	total recovery
fasted state	75.7 ± 1.7	15.6 ± 1.8	91.3 ± 2.0
fed state	49.0 ± 1.5	41.5 ± 2.9	90.5 ± 2.2

Excretion in the urine was again found to be relatively rapid, as was evident by recoveries of about one-half and one-third of the radioactive doses in the first 4 hours after drug administration to fasted and fed subjects, respectively. In the fed subjects, more than half of the radioactivity excreted in urine was recovered in the first 4 hours. In the 0 to 24-hour period, 74.3 ± 1.7 per cent (fasted) and 47.7 ± 1.4 (fed) of the radioactive dose was excreted in the urine. In the same period (0 to 24 hours), unchanged captopril accounted for 38.0 ± 1.9 per cent (fasted) and 25.3 ± 1.1 per cent (fed) of the dose, whereas SQ 14,551 accounted for only 4.7 ± 1.2 per cent (fasted) and 1.3 ± 0.2 per cent (fed) of the dose. The remainder of the radioactivity in urine was attributed to metabolites more polar than SQ 14,551 (based on Rf values in thin-layer chromatograms).

Using ^{35}Sulphur-labeled captopril, it had been noticed that the average time to reach peak plasma concentrations of radioactivity was 1.4 hours. Biphasic plasma elimination was observed, with a half-life ($t_{1/2}$) value of 4.5 hours for total radioactivity in the terminal phase (5 to 12 hour interval after drug administration).

Willard et al could not detect captopril in blood 6 hours after oral administration of 100 mg of captopril-^{14}C. Since semilogarithmic plots of blood concentration of unchanged captopril versus time showed no terminal linear phase, they could not calculate $t_{1/2}$ values. It was not possible to determine whether the non-linearity was directly attributable to the time course of unchanged captopril, or whether minor metabolites (as yet undetected) might have caused some interference in the assay. It was also possible that the limit of quantitation of the method employed did not permit definition of the terminal phase of the drug. In all blood samples analyzed, they found considerably lower concentrations of SQ 14,551 than of captopril. Intersubject variability was present.

From the results of two other Squibb investigations (protocols 12,928-3 and 12,928-4) it appeared that sodium-replete normotensive subjects tolerated captopril well in doses ranging from 10 to 1200 mg for 3 to 10 consecutive days. In these normotensive patients no consistent or dose-related response on

blood pressure or heart rate were noted. However, the drug caused dose-related increases in plasma renin activity (PRA), presumably due to the removal of the negative feedback exerted by angiotensin II on the renin release. Plasma aldosterone concentration (PAC) decreased, the greatest decreases often coinciding with maximal increases in PRA. In sodium-depleted subjects blood pressure did tend to fall although no clear evidence of orthostatic hypotension was observed.

From the results of Squibb protocol 12,928-5C it became apparent that captopril (alone or in combination with a diuretic) decreased blood pressure in 88 per cent of patients (n = 145) with moderate to severe hypertension. Our experience in 27 patients with hypertension is in agreement with this finding. All patients became 'normotensive' on captopril, alone or in combination with a diuretic. This also fits in with data of other investigators[3,4,5,6,7]. The need for sodium depletion (either by a severe sodium restricted diet or by means of diuretics) has also been mentioned[3,4,5,6,7]. However, in contrast to the latter findings Gavras[8] found that – even in patients with very low plasma renin activity – on captopril a marked fall in diastolic blood pressure to the target value of ≤95 mmHg occurred in all patients (n = 12). These patients adhered to a 100 mmol sodium containing diet, but they received much higher doses of captopril (from 400 to 1000 mg daily) than is advised presently by the manufacturer (i.e. a maximal daily dose of 450 mg). Using the same high doses of captopril, also combined with a 100 mmol sodium restricted diet, Bravo[3] reported the need for additional sodium depletion in 3 out of 5 patients. The contrasting results of both investigators suggest that to obtain satisfactory blood pressure control with captopril, other factors, in addition merely to dosage, may be important. Many of these factors still have to be evaluated.

In our hands there appeared to be a positive relationship between the initial MAP and the initial PRA. This relationship seemed to be particularly true in the renovascular hypertensive patients, as opposed to the essential hypertensive patients taken separately where no significant relation between these parameters could be demonstrated.

The lack of correlation between the initial PRA and the maximum observed fall in blood pressure (ΔMAP) in our *essential hypertensive patients* suggests that the antihypertensive effect of captopril may not depend entirely on suppression of plasma angiotensin II levels. Many[7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21], though not all[5, 22, 23, 24, 25, 26, 27, 28] investigators share this opinion and it can be explained since – although in normal man the pulmonary circulation has the highest capacity for angiotensin I conversion[29] and bradykinin inactivation[30] – the converting-enzyme is widely distributed along the endothelium of many vascular beds[31,32] and is also present in renal tubular cells[33] as well as in other tissues such as the pituitary gland and the central nervous system[34,35] and in fluids like plasma[36] and renal lymph[37]. Therefore, it is possible that accumulation of bradykinin – primarily a local hormone – in vascular smooth muscles may add to the effects of reduced plasma angiotensin II levels, despite normal or reduced plasma bradykinin

concentrations[38]. Additionally, according to Sullivan and co-workers[16], accumulation of bradykinin via activation of phospholipase A_2 can result in release of arachidonic acid and enhanced synthesis of prostaglandins[39,40,41,42,43]. In vascular smooth muscle, the major compound formed in response to arachidonic acid is the vasodilator prostacyclin (PGI_2)[44], but activation of the arachidonic cascade can result in the formation of PGE_2 in blood vessel walls, which can cause an impaired norepinephrine release at the nerve endings[45]. However, captopril neither influences plasma norepinephrine concentrations[46,47] nor sympathetic nervous activity[48]. The complexity of converting-enzyme inhibition was recently shown by Vinci and co-workers[30]: depressor response to the nonapeptide SQ 20,881 correlated better with alterations in urinary kinins and prostaglandin E than with changes in plasma levels of angiotensin II! Furthermore, converting-enzyme inhibition interferes also with other peripheral peptide systems such as enkephalins[49].

On the other hand, in our *renovascular hypertensive patients* the captopril-induced suppression of angiotensin II levels seems to be the major explanation for the antihypertensive action of the drug, since a good correlation was established between base-line PRA and ΔMAP, both after 3-7 days and after several months of captopril. Thus, the variable contribution of the captopril-induced inhibition of angiotensin I conversion and of bradykinin inactivation may explain the controversy with regard to the correlation between the initial PRA and ΔMAP. However, both the decrease in circulating (or locally formed) angiotensin II — a vasoconstrictor — and/or the increase in locally formed (or circulating) vasodilators, will lead to a reduced peripheral resistance. In fact it has been found after the administration of captopril that despite a significant decrease in blood pressure, the cardiac output did not change[46].

That the hypotensive response to converting-enzyme inhibition does not reflect only reduced angiotensin II formation, has recently been shown by Man in 't Veld et al[15] who reported evident hypotensive responses following captopril administered to 7 anephric patients after dialysis. Furthermore, in 7 responders to SQ 20,881 the plasma angiotensin II level (angiotensin II exogenously administered) required to return the blood pressure to control levels, was 45 ± 15 pg/ml higher than the control plasma angiotensin II concentration[50]. This suggests that some other factor(s), bradykinin and/or enkephalins, are also responsible for the hypotensive response in the presence of converting-enzyme inhibition. Fouad et al[23] reported that in 20 patients treated with captopril base-line PRA related to ΔMAP initially ($r = -0.83$); after prolonged treatment a significant correlation was no longer demonstrable. On the other hand, Améry and co-workers[24] established a significant negative correlation between ΔMAP and initial log PRA (and initial log plasma angiotensin II concentration!), both initially and after 2 months of captopril therapy. As mentioned previously, the latter relationship was also found in our renovascular hypertensive patients: the relationship between initial log PRA and ΔMAP did not change after months.

The additive effect of diuretics to converting-enzyme inhibition – and vice versa – has been generally accepted. In the two-kidney, one clip hypertension model, Ribeiro et al[51] noticed a diminished action of captopril during high sodium intake. In our experience, diuretics should be added when administration of captopril 100 mg t.i.d. for at least one week, does not result in a decrease in blood pressure. This experience is supported by the observation of Brunner and colleagues[52] that increasing the dosage to more than 25 mg t.i.d. only prolongs the duration of the blood pressure fall.

In renovascular hypertensive patients sometimes the diuretic could be withdrawn a few weeks later without causing an increased blood pressure. These particular patients however, continued on a sodium restricted diet. Zweifler et al[53] observed the best results with a combination of captopril (450 mg per day), hydrochlorothiazide (100 mg per day) and propranolol (360 mg per day), especially in intractable hypertension.

After long-term administration, the antihypertensive effect of captopril has been reported to outlast the angiotensin I converting-enzyme inhibition[54]. Finally, Antonaccio and co-workers[55] found that captopril had no effect on the blood pressure following bilateral nephrectomy in spontaneously hypertensive rats. These investigators suggest that the administration of captopril apparently results in a release of a (non-prostaglandin) vasodilator from the kidney rather than in the removal of a pressor substance.

PLASMA RENIN ACTIVITY AND PLASMA ALDOSTERONE CONCENTRATION

The most extensive report on the long-term effects of captopril on hormone levels has recently been published by Johnston and colleagues[17]. Captopril, given as a single drug in essential hypertension, induced a significant and sustained fall in plasma angiotensin II concentration, without changes in angiotensin I levels. Plasma renin activity doubled, but circulating levels of (venous) bradykinin were unchanged. After the addition of a diuretic definite and sustained increases were observed in plasma renin activity, angiotensin I and angiotensin II, whereas treatment with a diuretic alone was associated with significant and sustained increases in plasma angiotensin II and renin levels, but not with changes in angiotensin I (or bradykinin). When captopril was added to the diuretic regimen, plasma angiotensin II concentration fell significantly but renin and angiotensin I levels rose. The changes in the renin-angiotensin system were reflected in the levels of urinary aldosterone excretion and of plasma potassium in the two groups. Hydrochlorothiazide alone increased urinary aldosterone excretion and caused hypokalaemia. Captopril alone was associated with no change in serum potassium and with a small decrease in aldosterone excretion. When hydrochlorothiazide was added to captopril, urinary aldosterone excretion rose in parallel to the changes in plasma angiotensin II. All of these hormonal changes which remained constant over a period of 8 months demonstrated that the in vivo inhibition of converting-enzyme by captopril is indeed sustained.

Overall, our results are in agreement with the results of Johnston et al. Initial log PRA was significantly (positive) related to initial PAC. Captopril alone increased PRA and decreased PAC. These captopril-induced changes were sustained for several months. Moreover, the decrease of PAC in our patients was accompanied by a slight but significant increase in serum potassium concentration. Addition of diuretics to the captopril treatment increased PRA and PAC.

Interestingly, in the 2 non-responders to captopril alone (patients nr 7 and 29) – with a simultaneous low pre-treatment PRA – captopril did not change our parameter of renin release. Therefore, we doubt if the increase in PRA during converting-enzyme inhibition in the responders is only due to an interruption of the angiotensin feed-back mechanism on renin release. The increase in PRA during successful captopril treatment can also be explained by a baroreceptor-mediated stimulation of the juxtaglomerular apparatus. A similar observation (and interpretation) was made previously with saralasin, an angiotensin II analogue[56]. In responders (with regard to the blood pressure) PRA rose, but in the non-responders the PRA remained unchanged or even decreased. In this respect, it has to be mentioned that recently we observed orthostatic hypotension in a successfully treated patient when propranolol was added to captopril therapy, which induced a decreased PRA. Therefore, also a sympathetic nervous system mediated renin stimulation is possible, although the fact that no changes in plasma norepinephrine and epinephrine levels during converting-enzyme inhibition have been reported[46,48]. Probably plasma catecholamines do not reflect accurately sympathetic activity. In tilt studies, an enhanced increase in plasma norepinephrine during tilt in captopril-treated hypertensives has been described[48]. Tilting increased PRA *and* PAC during converting-enzyme inhibition, although blood pressure was maintained during the procedure[48].

The sodium balance could only be studied in our emergency patients. Most of them were sodium-depleted due to previous diuretic therapy and adherence to a sodium restricted diet. This could explain why we observed a natriuretic action from captopril in only two patients.

An extensive and accurate study of the captopril-induced changes in sodium and potassium balance has been made by Atlas et al[25]. They found a captopril-induced blood pressure fall in 22 of 23 patients studied, reaching a nadir after 7-10 days of therapy. Plasma aldosterone and urinary aldosterone excretion fell in all but one patient, who had a low base-line renin activity. Aldosterone secretion remained suppressed despite progressive potassium retention and increased plasma potassium concentrations. Concurrently, captopril produced a negative sodium balance in most patients, although in 4 patients – three of whom had renal artery stenosis – significant sodium retention developed when the blood pressure was reduced. The changes in blood pressure, aldosterone secretion and potassium balance were greatest in patients with high PRA and least in the low-renin patients. After 7 days of maintenance treatment, the changes in MAP were also directly related to changes in aldosterone excretion ($r = 0.73$).

In accordance with our observations, Bravo et al[19] could not establish a relationship between pre-treatment PRA and ΔPAC.

We also found a significant positive relationship between ΔMAP and ΔPAC (r = 0.59), although we could not demonstrate a significant correlation between ΔMAP and ΔK. We agree with Atlas and co-workers that these findings suggest that reductions in blood pressure during captopril treatment result to a great extent from blockade of angiotensin II formation, since enhanced sodium excretion can be due to kinin-induced renal vasodilation but this mechanism is unlikely to induce potassium retention.

An increase in serum potassium concentration during captopril treatment has also been observed by Morganti et al[48] and by Omae and colleagues[18].

RENAL FUNCTION

From renal and glomerular haemodynamic studies in anaesthesized hydropenic dogs with renal arterial pressures reduced to a range of 85-90 mmHg, it appeared that converting-enzyme inhibition with SQ 20,881 can cause an increase in renal blood flow (by 13 per cent) without a change in GFR[57]. No significant alterations in single nephron GFR, proximal tubule pressure, peritubular capillary pressure or estimated glomerular pressure have been established[57]. Neither the ultra-filtration coefficient (K_f) nor effective filtration pressure are altered. In essential hypertensive sodium-restricted man, SQ 20,881 increased the creatinine clearance, especially in patients in whom an initial reduction was evident and hypertension was more severe[58]. Moreover, an immediate increase in sodium excretion was observed, far too quick to be attributed to a fall in the effect of aldosterone on the kidney. In 2 patients with advanced bilateral renal artery stenosis and a reduced creatinine clearance however, such a rise in GFR was not noticed.

In pentobarbital anaesthesized dogs, Duchin and Steinbacher[59] found a captopril-induced fall in renal artery pressure whilst the renal blood flow increased and inulin clearance remained constant. Despite renal vasodilation, the sodium and potassium excretion did not change. In another series of acute experiments, these investigators noticed an increase in urinary sodium (and potassium) excretion with captopril when the renal artery pressure was kept constant. Their data suggested that the natriuretic effect of captopril may be due to a depressed tubular reabsorption secondary to renal vasodilation.

In man, Mimran et al[60] observed a decrease in FF in sodium replete normal subjects after the ingestion of 50 mg captopril. In patients with essential hypertension, also on a normal sodium intake, 50 mg captopril induced a significant increase in ERPF (by 12 per cent) whereas the GFR did not change. De Bruyn et al[46] reached similar conclusions. In 8 patients with uncomplicated essential hypertension who were successfully treated with captopril for up to 12 weeks, an increase in ERPF by 14 cent without a significant change in GFR was observed.

Our results with regard to the influence of captopril on GFR and ERPF in

essential hypertension are in striking agreement with the above mentioned observations. In essential hypertension with normal renal function, captopril caused an increase in ERPF (by 9 per cent) without a change in GFR. Also an increase in ERPF was noticed when captopril was added to a diuretic regimen. On the other hand, captopril caused a decrease in GFR in most of the renovascular hypertensive patients while ERPF did not change. For the latter observation several explanations are possible. First, the renovascular hypertensive patients had a more severe hypertension and a greater fall in blood pressure during treatment than the essential hypertensive patients. Secondly, these patients had unilateral or bilateral renal artery stenosis, which itself causes a decrease in renal blood flow, especially when the blood pressure normalizes. Thirdly, these patients adhered to a sodium restricted diet and were, in general, sodium depleted. In our moest recent experiences in this category of patients with elevated PRA, captopril increased GFR and ERPF markedly when the drug was initiated after sodium repletion!

No significant correlation could be established between initial log PRA and ΔERPF. Therefore, the intrarenal concentration (or action) of angiotensin II possibly does not parallel the PRA peripherally, or alternatively, captopril exerts an additional effect on the renal blood flow, for instance by potentiating (renal) bradykinin. In this respect it is noteworthy that in 2 patients (nrs 7 and 29) with a low PRA, who both did not respond to captopril alone with a fall in blood pressure and an increase in PRA, an increase in ERPF and a fall in FF were observed. Moreover, Carretero et al[61] noticed that SQ 20,881 induced an increase in renal blood flow – especially in the inner cortex – during continuous blockade of angiotensin II receptors with an angiotensin II antagonist. They also suggested that part of the effect of converting-enzyme inhibition on renal blood flow is mediated through kinin potentiation.

An antihypertensive agent which effectively lowers blood pressure without affecting GFR and yet increases renal blood flow, is rather unique[62]. Only hydralazine may increase clearance values when given in a single dose[63]. The increase in renin release however, diminishes the favourable effect of this drug. Normally, the fall in blood pressure caused by antihypertensive agents depresses the GFR and enhances tubular reabsorption of sodium and water. An exception to the latter effect is produced by the beta-adrenergic receptor blocking agents, probably due to a suppression of renin release.

Indeed, we found a relationship between the percentual change in GFR and the percentual change in MAP. Since the dependence of GFR on renal plasma flow has been known for many decades[64], the finding of a correlation between the percentual change in GFR and the percentual change in ERPF in the 18 captopril-treated patients was not unexpected. Thus, captopril-induced changes in GFR seem to depend on changes in blood pressure and on changes in ERPF. This is demonstrated by the significant correlation between percentual change in GFR and the percentual change in the product ERPF x MAP (illustrating the 3-variable correlation between GFR, ERPF and MAP two-dimensionally). However, in the essential hypertensive patients GFR was

maintained completely by the increase in ERPF but in the renovascular hypertensive patients, the decrease in GFR – due to a decrease in blood pressure – was only opposed by renal vasodilatation as expressed by a preserved renal blood flow. In both groups of patients FF fell, also pointing to a decrease in renal vascular resistance (being a part of the total peripheral resistance which indeed decreases during captopril treatment[16,46]).

We never noticed sodium retention in our patients successfully treated with captopril. In fact a slight natriuretic action has been described[25,65].

THE RESPONSIVENESS TO EXOGENOUSLY ADMINISTERED ANGIOTENSIN I, ANGIOTENSIN II AND BRADYKININ

The results of Ferguson et al[9] suggest that smaller doses of the drug than are generally used almost completely block the conversion of angiotensin I to angiotensin II. As little as 2.5 mg captopril produced considerable inhibition of the pressor response to exogenous angiotensin I. Recently, Brunner et al[52] reported that increasing the dosage beyond 25 mg t.i.d. did not enhance its initial hypotensive effects.

Administration of the converting-enzyme substrate angiotensin I, revealed a blunting of the vascular responsiveness on incremental dosages of captopril as is shown in Chapter VI. However, a pressor response could be obtained at every dosage of the drug. The mere observation of a pressor response gives evidence to conversion of angiotensin I to angiotensin II since angiotensin I has no inherent vasoconstricting properties[66,67]. As mentioned previously, angiotensin I converting enzyme-inhibition has been shown to elevate endogenous angiotensin I plasma levels[17,68]. The results of our study demonstrate that exogenous angiotensin I – in combination with the increased endogenous plasma levels – can effectively compete with captopril for the active binding sites of converting-enzyme, since incremental quantities of angiotensin I during increasing dosages of captopril had to be administered in order to obtain the same rise in blood pressure.

An increase of the vascular responsiveness to exogenously administered angiotensin II during captopril treatment in human hypertensives has not been described before. No change in vascular responsiveness to angiotensin II during angiotensin I converting-enzyme inhibition has been found in normotensive sodium replete humans[9]. Since angiotensin II levels decrease during converting-enzyme inhibition (both in sodium replete normotensive persons and in hypertensive patients[69]), the enhancement of the vascular response to angiotensin II in our patients cannot be fully explained by a decreased angiotensin II generation and a diminished occupancy of the angiotensin II receptors. A decrease of the receptor availability and the arteriolar smooth muscle responsiveness may also have played a role in the increase of the angiotensin II-induced vasoconstrictor response, since captopril is reported to have natriuretic properties[25,65]. Furthermore, accumulation of bradykinin or other vasoactive peptides may affect angiotensin II

responsiveness. Evaluation of the increased responsiveness to angiotensin II induced by captopril through assessment of the shape of angiotensin II dose-response curve and the position on this curve of the endogenous prevailing angiotensin II plasma concentration therefore seems mandatory.

The blood pressure response to exogenous bradykinin during captopril therapy was markedly enhanced. This observation is in agreement with the captopril-induced potentiation both in magnitude and duration of hypotensive effects produced by exogenous bradykinin in rabbits and rats[70,71]. Pulmonary clearance for bradykinin is very effective as this potent vasodilator has a strong affinity to angiotensin I converting-enzyme – at least 10 times the affinity of angiotensin Ito converting-enzyme[72]. The decreased amount of bradykinin required to obtain the same blood pressure response (by vasodilation) during converting-enzyme inhibition when compared to the base-line level, points to an inhibited clearance of this kinin in the lung. However, the degree of increase in vascular responsiveness may depend at the same time on other factors such as prevailing endogenous bradykinin and angiotensin II levels, and a stimulated renal prostaglandin synthesis[71].

The effects of both exogenously administered bradykinin and angiotensin II were already maximally enhanced at the lowest captopril dosage (25 mg t.i.d.). As the antihypertensive effect of this dose, according to Brunner[52], is similar to the effects observed when higher doses of captopril are given, the inhibition of angiotensin I converting-enzyme presumably is maximal at this low dose of captopril. Increasing the dosage beyond 25 mg t.i.d. probably only prolongs the duration of the blood pressure response and the duration of the inhibition of converting-enzyme. A study concerning time-relationships between plasma levels of captopril, its antihypertensive action and the effects of exogenously administered vasoactive substances such as angiotensin II and bradykinin could provide useful information for therapeutic guidelines to a rational use of captopril, the importance of which is emphasized since at least some side-effects of the drug seem to be dose-related[5].

ADVERSE REACTIONS AND SIDE EFFECTS

Anti-nuclear antibodies (ANA) generally are determined by means of an indirect immunofluorescence technique using rat liver slices as antigen substrate. With human foetal fibroblasts from tissue cultures both the titre can be quantified and the pattern of fluorescence can be recognized. Both methods are in use in our immunological laboratory. Anti-nuclear antibodies in low to moderate quantities may, amongst other things, be drug-induced. Moreover, in healthy women aged over 60 years ANA may be present in 10-20 per cent. The finding of (low titre) ANA prior to captopril therapy in 5 patients is not unexpected, since all had been taking antihypertensive treatment before enrollment in this study. Three of the initially ANA-positive patients appeared to have become negative during the study; on the other hand, in 6 patients ANA developed while on captopril. The fact that in one patient (nr

30), apart from – as moderately quantified – ANA, also anti-double string-DNA developed during captopril therapy, may indeed be of more serious pathological significance. The development of ANA and the anti-double string-DNA during captopril treatment has not been described in the medical literature previously. This is of particular interest when considered in conjunction with the observations in the renal biopsy specimens obtained in 3 patients, and with regard to the proteinuria, as occurring in some of our patients during the treatment. We have reported the proteinuria observed in patient nr 6 recently[73] and have suggested that a drug-induced membranous glomerulopathy (MGP) had developed. Presently however, we have observed the presence of immune-complexes – as is evident from the presence of electrondense deposits on electronmicroscopy and of granular depositions in the immunofluorescence technique – along the glomerular basement membrane (GBM) in 2 other patients (nrs 27 and 30). Both patients had ANA (in moderate quantities), the latter patient also developed anti-double string DNA. An immunological mechanism appears to be active in the 3 patients mentioned, but the way in which captopril induces an immune-complex nephropathy is still unclear. The allergic reaction to captopril in patient nr 27 showed a resemblance to 'serum sickness'. The clinical picture consisted of fever, generalized maculopapular exanthema with oedema and epidermal necrolysis, generalized lymphadenopathy, and leucocytosis with marked eosinophilia. Microscopic haematuria was seen once and there existed a slight proteinuria. The renal biopsy specimen revealed granular depositions of immunoglobulins along the GBM. A similar type of allergic reaction induced by carbamazepine has been described by Houwerzijl[74]. Lymphocyte transformation tests as well as patch tests appeared to be of diagnostic value.

We thus face the fact that in at least 3 out of our 27 successfully captopril treated patients an immunological reaction to captopril appears to have developed. The presence of circulating immunecomplexes in all 3 patients seems possible, although we do not know the antigen involved in the formation of these complexes. The results of the lymphocyte transformation tests and patch tests with captopril will reveal whether cellular immunity to this drug exists. A key question will then be whether the origin of this immunity is due to the chemical properties of the drug or due to the consequence of its pharmacological action. Considering the first possibility, the similarity of captopril to penicillamine with regard to chemical properties and the spectrum of side-effects is striking. Both drugs are sulphur-containing derivates of aminoacids. The incidence of MGP in patients using penicillamine is high. Early allergic reactions, angioneurotic oedema, loss of taste and the occurrence of ANA are common side-effects to penicillamine. Similar observations have been noticed in this study and are in striking agreement with those mentioned by other investigators using captopril. Rashes (and fever) were common findings[4,5,7,8,17,18,19,20,75], occurring in 10 per cent of the patients treated. These reactions seem to be dose-dependent as they disappear when the captopril dose is decreased. Continuing a lower dose then often is

tolerated well. Other features reported were hypotension[26,75] (as in our patient nr 22), tachycardia[75], and fatigue[75]. In our patients we did not find taste disturbances (ageusia), which also have been reported[17,47,75]. However, olphactory hallucinations as observed in one patient (nr 28), have not been previously described. The mechanisms involved in the latter findings are a matter of speculation[76]. Complaints of cold and white fingers are quite common during beta-blocking therapy, for example with propranolol. This suggests that these complaints are due to the blood pressure lowering effect of captopril rather than to an intrinsic property of the agent.

Impaired renal function, as expressed by a marked increase in serum creatinine concentration or by a severe depressed GFR, was found in some of the – previously intractable – hypertensive patients (nrs 24 and 27), especially when diuretics were added to captopril treatment. The primary reason for this impairment in renal function seems to be the dramatic fall in blood pressure associated with the existence of stenosis. It can also be found when this kind of patients is already sodium depleted[19] or in the case of a high renin-hyponatraemic state[77,78,79]. In these circumstances extreme caution is warranted[79]. A (reversible) renal failure due to captopril, as also described by Farrow and Wilkinson[80] and by Collste et al[81], does not seem to be caused by a nephrotoxic effect of the drug[80] since Collste et al observed the same transient deterioration in the renal function in their patient during successful minoxidil treatment.

The state of hyponatraemia and uraemia after the addition of diuretics to the captopril therapy in our patients nrs 24 and 27 has not been documented previously. Normally, hyponatraemia due to diuretic therapy alone is rarely seen. It is caused by an impaired free water clearance. Since captopril interferes with renal homeostatic mechanisms (such as intrarenal angiotensin II formation, renal vascular resistance, ERPF, GFR, and aldosterone secretion) and therefore possesses natriuretic properties itself, the combination of captopril with sodium restriction and diuretics such as hydrochlorothiazide will more likely lead to this undesirable situation. Interestingly, in these 2 patients with a 'one-clip, one kidney' hypertension the blood pressure remained under control after sodium repletion. In both patients blood pressure probably became completely renin-dependent after sodium and water depletion and this renin-dependency apparently could not be offset by a secondary subtle sodium and water retention when diuretics were withdrawn but captopril was continued.

As a final conclusion, it is our opinion that captopril provides antihypertensive properties which overshadow the results obtained with currently available therapeutics. At this moment however, it seems wise to reserve this agent for intractable hypertensive patients until definite data on the observed side-effects are available.

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SAMENVATTING

In Westerse landen is verhoogde bloeddruk een veel voorkomende ziekte en een belangrijke factor in de sterfte ten gevolge van hart- en vaatziekten. Wanneer hypertensie behandeld wordt, blijken mortaliteit en morbiditeit af te nemen. Adequate behandeling is daarom wenselijk, maar de behandeling zal meestal aspecifiek zijn aangezien bij het merendeel van de patiënten geen oorzakelijke factor kan worden aangetoond. Inzicht in (patho)fysiologische processen van belang bij de regulatie van de bloeddruk zal kunnen leiden tot een méér doelgerichte therapie. Eén van de mechanismen die een rol spelen bij het reguleren van de bloeddruk is het renine-angiotensine-aldosteron (RAA) systeem, waarin veel onderzoekers zich het laatste decennium hebben verdiept. In hoofdstuk I wordt aangegeven op welke wijzen men getracht heeft de rol van dit systeem in de bloeddrukhomeostase en bij pathologisch verhoogde bloeddruk te onthullen. Zo won de ontdekking van het angiotensine I converting-enzyme – dat het niet-vasoactieve angiotensine I omzet in het vasoconstrictieve angiotensine II – aan betekenis, toen bleek dat een mengsel van peptiden uit het slangegif van de *Bothrops Jararaca,* naast het vermogen om de afbraak van bradykinine te remmen ook de eigenschap bezat de omzetting van angiotensine I naar angiotensine II te voorkómen. Tegenwoordig wordt algemeen aangenomen dat het angiotensine I converting-enzyme (het peptidyl peptidase) identiek is aan het enzym dat bradykinine afbreekt. De bloeddrukverlagende werking van remmers van angiotensine I converting-enzyme kan dus het gevolg zijn van een verminderde vorming van het vasoconstrictoire angiotensine II enerzijds, en van een verminderde afbraak van het vasodilaterend bradykinine anderzijds.

De ontdekking van de remmende eigenschappen van de peptide-mengsels van de *Bothrops Jararaca* op het converting-enzyme opende nieuwe mogelijkheden om het RAA systeem te onderzoeken. Eén van de vervolgens ontwikkelde remmers is het teprotide (SQ 20,881) waarmee veel dierexperimenteel en klinisch onderzoek is verricht, maar dat geen practisch-therapeutische waarde blijkt te bezitten. Het prepraraat kan namelijk alleen intraveneus worden toegediend en heeft slechts een korte werkingsduur.

De ontwikkeling van het potente, oraal werkzame captopril (SQ 14,225) maakte het mogelijk om naast het bloeddrukverlagende effect zelf, verschillende bloeddrukregulatiemechanismen gedurende langere tijd te bestuderen. Van deze mogelijkheid werd in het beschreven onderzoek gebruik gemaakt.

Negentien patiënten werden poliklinisch ingesteld op captopril of hydrochlorothiazide of, bij onvoldoende effect op de maximale dosis, op een combinatie van beide. Elf andere patiënten met ernstige hypertensie, tevoren zonder succes met verschillende antihypertensiva behandeld, werden klinisch ingesteld op captopril, zonodig met toevoeging van een diureticum. Van deze 30 patiënten konden er 29 gedurende langere tijd vervolgd worden.

In hoofdstuk II worden de patiënten kort beschreven en de behandelingsprotocollen en onderzoeksmethodieken vermeld. Van de 30 patiënten hadden 17 essentiële en 9 renovasculaire hypertensie; bij 4 patiënten was de hypertensie het gevolg van een intrinsiek nierlijden (respectievelijk cystenieren, chronische rejectie van een donornier, niertuberculose, hemolytisch uremisch syndroom).

In hoofdstuk III worden de resultaten van de eerder genoemde therapie op de bloeddruk behandeld. Uiteindelijk werd bij alle 30 patiënten een normotensieve toestand bereikt, hetzij met captopril (n = 20) of met hydrochlorothiazide alleen (n = 3), hetzij met een combinatie van beide (n = 7).

De daling van de gemiddelde arteriele bloeddruk (Δ MAP) bleek zowel bij renovasculaire als bij essentiële hypertensie patiënten gecorreleerd te zijn met de initiëel gevonden MAP. Bij de patiënten met essentiële hypertensie werd geen correlatie gevonden tussen de initiële logarithme van de plasma renine activiteit (PRA) en de Δ MAP tijdens captopril, hetgeen suggereert dat het bloeddrukverlagende effect van captopril niet alleen afhankelijk is van een verlaging van de angiotensine II spiegels. Accumulatie van bradykinine, eventueel locaal, is hierbij mogelijk een factor van betekenis. Bij de renovasculaire hypertensiepatiënten echter, lijkt de verlaging van angiotensine II spiegels wel de meest waarschijnlijke verklaring te zijn voor het bloeddrukverlagende effect van captopril. Zowel na enkele dagen als na maanden werd een goede correlatie gevonden tussen de initiële log PRA en de Δ MAP. De waargenomen verschillen tussen de twee groepen patiënten duiden erop dat zowel de afname in circulerend (of plaatselijk gevormd) angiotensine II, als de toename van plaatselijk gevormde (of circulerende) vasodilatoren zoals bradykinine, een (wisselend) aandeel hebben in de verlaging van de perifere weerstand.

Het additionele effect van diuretica bij converting-enzyme inhibitie en vice versa wordt ook in de literatuur algemeen onderschreven. In hoofdstuk III wordt tenslotte voorgesteld om diuretica aan de therapie toe te voegen als captopril in een dosering van 100 mg 3x daags gedurende minstens één week, geen verlaging van de bloeddruk teweegbrengt.

Bij sommige patiënten met renovasculaire hypertensie kon het diureticum overigens enkele weken na toevoeging aan captopril gestaakt worden – onder continuering van het zoutbeperkte dieet –, zonder dat daarna de bloeddruk steeg.

In hoofdstuk IV wordt het effect van converting-enzyme inhibitie met captopril op de PRA en de plasma aldosteron concentratie (PAC) beschreven. Captopril alléén veroorzaakte een stijging van de PRA en een daling van de PAC. Deze veranderingen bleken zowel kort na instellen, als na maanden aanwezig te zijn. De daling van de PAC ging bij onze patiënten gepaard met een lichte, doch significante stijging van de serumkaliumconcentratie. Toevoeging van diuretica aan captopril deed zowel de PRA als de PAC stijgen.

Of de stijging van de PRA tijdens captopril alléén het gevolg is van het onderbreken van het angiotensine-terugkoppelingsmechanisme op de renine afgifte wordt in twijfel getrokken. Bij twee patiënten die op captopril alléén geen verandering van de bloeddruk vertoonden en bij wie tevens lage initiële PRA waarden gevonden waren, werd namelijk geen stijging van de PRA gezien tijdens captopril. De stijging van de PRA tijdens effectieve behandeling met captopril zou ook verklaard kunnen worden door stimulatie van de baroreceptoren in het juxtaglomerulaire apparaat.

De gevonden relatie tussen ΔMAP en ΔPAC steunt de in de literatuur geuite veronderstelling dat de bloeddrukdaling tijdens captopril gebruik toch voor een aanzienlijk deel het gevolg moet zijn van een verminderde angiotensine II vorming.

In hoofdstuk V wordt de invloed van captopril op de nierfunctie beschreven. Bij patiënten met essentiële hypertensie gaf captopril een stijging van de effectieve renale plasma doorstroming (ERPF) te zien, terwijl de glomerulaire filtratie snelheid (GFR) onveranderd bleef. Bij patiënten met renovasculaire hypertensie veroorzaakte captopril een daling van de GFR, zonder verandering van de ERPF. Een verklaring voor de verschillen tussen deze 2 groepen is, dat ten eerste de renovasculaire hypertonici een hogere uitgangsbloeddruk en een grotere daling ervan onder captopril hadden dan de essentiële hypertensie patiënten. In de tweede plaats hadden de renovasculaire patiënten een unilaterale of bilaterale nierarteriestenose, die op zich al een verlaging van de renale bloeddoorstroming veroorzaakt, vooral wanneer de bloeddruk normaliseert. Ten derde gebruikten de renovasculaire hypertonici een strenger zoutbeperkt dieet en waren zij in het algemeen in een toestand van zoutdepletie.

De afwezige relatie tussen de initiële log PRA en ΔERPF die werd vastgesteld, suggereert dat de intrarenale angiotensine II concentratie (of actie) niet de perifere PRA weergeeft, òf dat captopril een additioneel effect op de renale bloeddoorstroming oproept, bijvoorbeeld door potentiering van (renaal) bradykinine. De bevinding van een stijging van de ERPF bij de twee eerder genoemde patiënten met lage initiële PRA, die evenals de bloeddruk niet veranderde tijdens captopril toediening – is met deze laatste veronderstelling in overeenstemming.

De procentuele veranderingen van de GFR en van de MAP bleken gecorreleerd te zijn. De afhankelijkheid van de GFR van de renale doorbloeding is reeds lang bekend en de gevonden correlatie tussen de procentuele verande-

ring van de GFR en van de ERPF was dan ook niet onverwacht. De gehandhaafde filtratie, respectievelijk de eventueel door captopril geïnduceerde veranderingen in de GFR lijken derhalve samen te hangen met veranderingen in bloeddruk én in ERPF, hetgeen wordt geïllustreerd door de significante correlatie tussen de procentuele verandering in GFR en de procentuele verandering van het product ERPF × MAP.

De invloed van captopril op de gevoeligheid voor exogeen toegediend angiotensine I, angiotensine II en bradykinine wordt beschreven in hoofdstuk VI. Bij stijgende doseringen captopril werd een afname van de gevoeligheid voor exogeen angiotensine I gezien. Het bleek echter steeds mogelijk om door ophogen van de hoeveelheid toe te dienen angiotensine I toch een bloeddrukstijging te veroorzaken, hetgeen aangeeft dat omzetting van angiotensine I naar angiotensine II altijd nog mogelijk was. Het demonstreert de competitie tussen angiotensine I en captopril om de actieve bindingsplaatsen van het converting-enzyme.

De waarneming dat de gevoeligheid voor exogeen toegediende angiotensine II op stijgende doseringen captopril toeneemt is bij hypertensieve personen nog niet eerder beschreven. Aangezien endogene angiotensine II spiegels tijdens converting-enzyme inhibitie dalen, kan de versterkte vasculaire reactie op toegediend angiotensine II bij onze patiënten verklaard worden door een verminderde angiotensine II vorming en daardoor een verminderde bezetting van angiotensine II-receptoren. Een afname van de receptor beschikbaarheid en van de gevoeligheid van het gladde spierweefsel der arteriolen kan echter òòk een rol spelen bij de verhoogde vasoconstrictiviteit, aangezien captopril natriuretische eigenschappen bezit. Ook de accumulatie van bradykinine of andere vasoactieve peptiden zouden de gevoeligheid voor toegediend angiotensine II kunnen beïnvloeden. Nadere evaluatie door het vastleggen van dose-response curves van angiotensine II èn de positie daarop van de op dat ogenblik endogeen voorkomende plasma angiotensine II concentraties lijkt daarom zeer wenselijk.

De toegenomen gevoeligheid voor exogeen toegediend bradykinine wijst op een verminderde klaring van dit kinine (in de long). Op de toegenomen gevoeligheid kunnen tegelijkertijd andere factoren – zoals de bestaande endogene bradykinine en angiotensine II spiegels, en een gestimuleerde renale prostaglandine synthese van invloed zijn.

Aangezien de effecten van zowel exogeen toegediend bradykinine als van angiotensine II reeds maximaal waren op de laagste dosis captopril (25 mg, 3x daags), en volgens mededelingen uit de literatuur het bloeddrukverlagende effect van deze dosis gelijk is aan dat van hogere doses, lijkt de remming van angiotensine I converting-enzyme op deze lage dosis al maximaal te zijn. Verhoging van de dosis verlengt waarschijnlijk slechts de duur van de remming van converting-enzyme en van de bloeddrukverlaging. Onderzoek naar tijdsrelaties tussen plasma spiegels van captopril, het antihypertensieve effect ervan en de effecten van exogeen toegediende agentia als angiotensine II en

bradykinine zou waardevolle informatie kunnen verschaffen, die kan leiden tot een rationele dosering en toepassing van captopril.

In hoofdstuk VII wordt ingegaan op de nadelige gevolgen en bijwerkingen van captopril zoals die bij onze patiënten zijn waargenomen. Deze worden vergeleken met wat hierover in de medische literatuur bekend is. Bij 6 patiënten werden tijdens captopril gebruik antinucleaire factoren aangetoond; bij één patiënte ontwikkelde zich daarbij anti-dsDNA. Deze waarneming is bij captopril gebruik niet eerder beschreven en verdient met name aandacht omdat in de nierbiopten van 3 patiënten – van wie er 2 positieve antinucleaire factoren hadden – bij electronenmicroscopisch onderzoek en immuunfluorescentie het beeld van een membraneuze glomerulopathie bleek te bestaan. Bij deze 3 patiënten lijkt een immunologisch mechanisme actief te zijn. De wijze waarop captopril een immuuncomplex nefropathie lijkt te induceren dient nader te worden onderzocht. Bij één van de bovengenoemde 3 patiënten vertoonde het klinisch beeld gelijkenis met de z.g. 'serumziekte': koorts, gegeneraliseerd maculopapuleus exantheem met oedeem en epidermolyse, gegeneraliseerde lymfadenopathie, en leucocytose met evidente eosinofilie. Een soortgelijke allergische reactie is eerder beschreven bij gebruik van carbamazepine. Lymfocyten-transformatie testen en huidtesten zullen voor een nadere evaluatie waardevol kunnen zijn.

De bij verschillende patiënten waargenomen huidreactie is uit de literatuur bekend en komt bij 10 % van de behandelde patiënten voor. De huidreacties lijken dosis afhankelijk te zijn, aangezien de verschijnselen kunnen verdwijnen als de captoprildosering wordt verminderd. Een lagere dosis wordt daarna vaak goed verdragen.

Bij enkele, tevoren onbehandelbare, patiënten werd een toenemende nierfunctiestoornis gesignaleerd tijdens gebruik van captopril, vooral na toevoegen van een diureticum. Primair lijkt hieraan de dramatische daling van de bloeddruk, tezamen met de aanwezigheid van een nierarteriestenose, ten grondslag te liggen. Verslechtering van de nierfunctie is uit de literatuur bekend bij renovasculaire hypertensie patiënten die tevoren in een toestand van zoutdepletie waren of ingeval van een z.g. 'high-renin hyponatraemic state'. Onder zulke omstandigheden is grote waakzaamheid vereist. De reversibele nierinsufficientie bij captopril, zoals ook enkele malen in de medische literatuur beschreven, lijkt niet te wijten aan een nefrotoxisch effect van het geneesmiddel.

Na toevoeging van diuretica aan de bestaande captopril therapie ontstond bij 2 patiënten een 'urémie par manque de sel'. Hyponatremie wordt zelden gezien bij diuretica alléén en is dan in het algemeen een gevolg van een gestoorde vrije waterklaring. Omdat captopril met de renale homeostase mechanismen interfereert (zoals renale angiotensine II vorming, renale vaatweerstand, ERPF, GFR, en aldosteron) en daardoor zelf natriuretische eigenschappen heeft, zal de combinatie van captopril met zoutbeperking en

diuretica aanleiding kunnen geven tot het ontstaan van hyponatremie ten gevolge van èn een gestoorde vrije waterklaring èn een werkelijk zouttekort.

Geconcludeerd wordt tenslotte dat captopril bloeddrukverlagende eigenschappen bezit welke die van tot dusver toegepaste antihypertensiva overtreffen. Het lijkt echter aangewezen het middel te reserveren voor onbehandelbare hypertensie patiënten tot meer duidelijkheid over de aard en de omvang van de waargenomen bijwerkingen verkregen is.