VASOREGULATION AND RENAL FUNCTION IN ESSENTIAL HYPERTENSION

Πῇ παρέβην, τί δ' ἔρεξα, τί μοι δέον οὐκ ἐτελέσθη;

Pythagoras.

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PROEFSCHRIFT

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CONTENTS

LIST OF ABBREVIATIONS.

A.	:	arterial
A II.	:	angiotensin II
A.C.T.H.	:	adrenocorticotrophic hormone
A.M.P.	:	adenosine mono phosphate
Art.	:	arterial
A.P.R.C.	:	active plasma renin concentration
%A.R.	:	percentual amount of active renin
B.S.A.	:	body surface area
B.V.	:	blood volume
C_1	:	component 1
% C_1	:	percentual distribution of renal blood flow towards the outer cortex
C_2	:	component 2
C_3	:	component 3
C.B.F.	:	cortical blood flow
C.O.	:	cardiac output
C.O.M.T.	:	catechol-O-methyltransferase
D.B.H.	:	dopamine beta hydroxylase
Diast.	:	diastolic
Dye.	:	dye dilution
E.C.V.	:	extracellular volume
F.F.	:	filtration fraction
G.M.P.	:	guanosine mono phosphate
G.F.R.	:	glomerular filtration rate
H.R.	:	heart rate
H.R.H.	:	high renin hypertension
Ht.	:	haematocrit
Imp.	:	impedance cardiography
I.R.	:	inactive renin

l.	:	liter
L.R.H.	:	low renin hypertension
M.A.O.	:	mono amine oxidase
M.A.P.	:	mean arterial pressure
M.B.F.	:	mean blood flow
M.C.R.	:	metabolic clearance rate
min.	:	minute
ml.	:	milliliter
N.A.	:	noradrenaline
ng.	:	nanogram
Nor.	:	noradrenaline
p.	:	probability
P.A.H.	:	para-amino-hippurate
P.aldo	:	plasma aldosterone concentration
P.max.	:	maximum blood pressure
P.min.	:	minimum blood pressure
P.N.M.T.	:	phenylethanolamine-N-methyltransferase
P.V.	:	plasma volume
r.	:	correlation coefficient
R.B.F.	:	renal blood flow
Ren. fract.	:	renal fraction
R.P.F.	:	renal plasma flow
R.S.R. 100g	:	renin secretion rate per 100 gram
R.S.R. tot.	:	total renin secretion rate
R.V.R.	:	renal vascular resistance
S.D.	:	standard deviation
S.E.M.	:	standard error of the mean
S.N.G.F.R.	:	single nephron glomerular filtration rate
S.V.	:	stroke volume
Syst.	:	systolic
T.P.R.	:	total peripheral vascular resistance
T.P.R.C.	:	total plasma renin concentration
T.R.B.F.	:	total renal blood flow
V.	:	venous
Var.	:	variability of blood pressure
Ven.	:	venous

CHAPTER 1

Introduction

It is well known from population studies that blood pressure tends to increase with age (Master et al., 1950; Hamilton et al., 1954; Zinner et al., 1971; Kahn et al., 1972; Buck, 1973; Kimura, 1973; Miall and Chinn, 1973), at least in Western society. Any upward deviation from this "normal" trend can thus be considered to represent a development into the hypertensive range. A hypertensive individual distinguishes himself by an earlier or steeper increase in blood pressure.

Once a diagnosis of essential hypertension has been established by excluding known causes of elevated blood pressure, the follow-up of these patients is mainly based on repetitive blood pressure readings.

Many studies have been carried out with respect to the epidemiology of hypertension. Such investigations provide information about the incidence and end-points of hypertension but this concerns only the easily accessible part of the disorder.

Although many attempts have been made to elucidate the mechanisms leading to essential hypertension the exact cause of this disease is still unknown.

A certain level of blood pressure always is the result of the interaction between the heamodynamic status, including blood volume and the activity of a number of regulatory mechanisms. Thus, blood pressure is a function of flow and resistance in the arterial system and of the intravascular volume. Alterations in each parameter can result from the modifying impulses of neural or humoral factors. The circulatory control mechanisms and their known interrelations are schematically represented in figure 1. It will be obvious that the isolation of one variable and the study of its function in hypertension can only yield poor information, since this ignores possible adaptations in relation to the other variables. Moreover, questions often arise as to whether abnormal results reflect factors contributing to the hypertensive state or the impact of the increased blood pressure on the organism. This uncertainty can be partly overcome when the duration of the hypertensive process is taken into account. Whereas deviations which are supposed to occur early are likely to be identifiable as factors participating in the elaboration of the hypertensive process, late abnormalities are more probably the result of this process. Unfortunately the duration of hypertension is often unknown since in the majority of patients blood pressure has not been previously measured. The best choice, therefore,

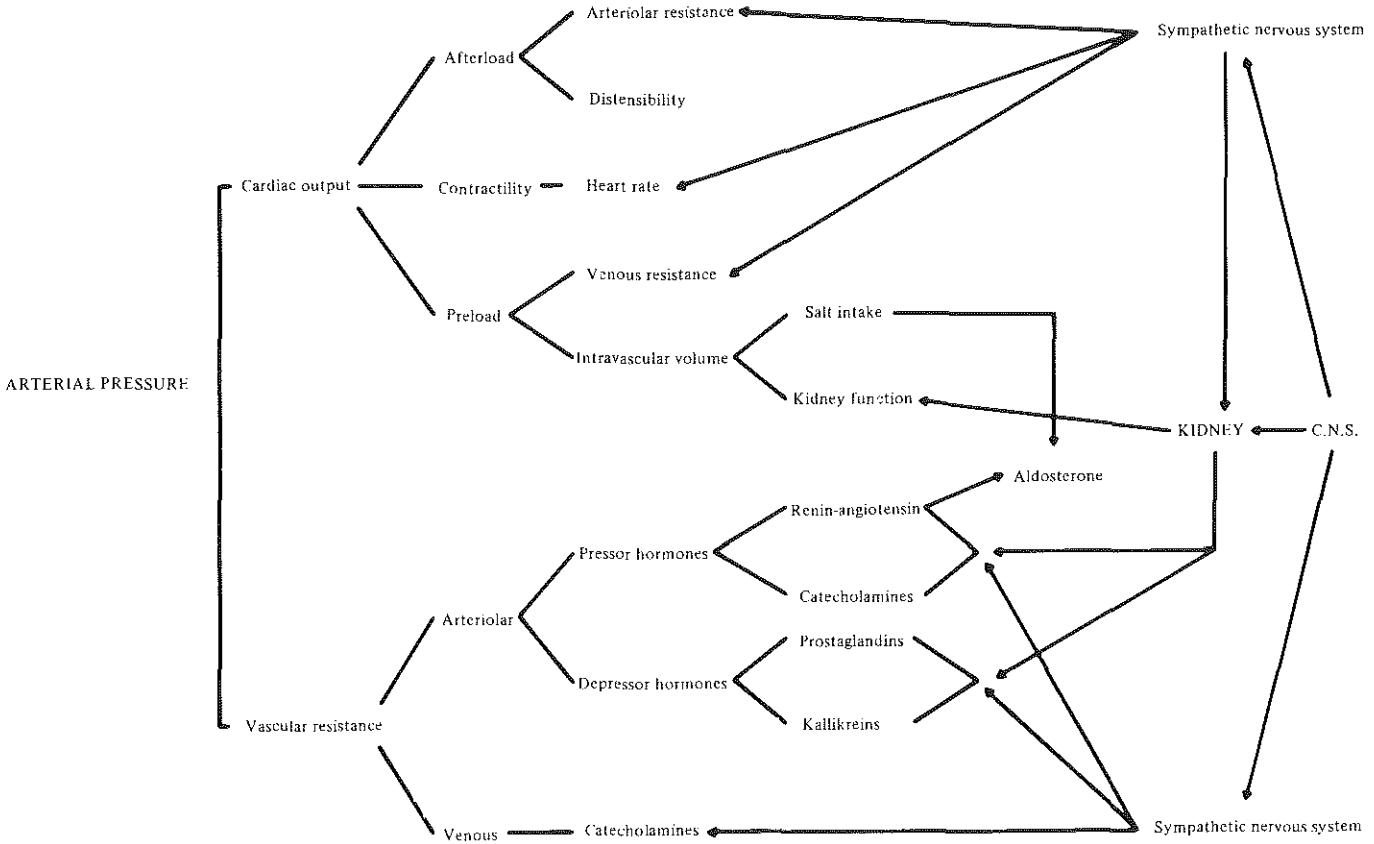

Fig. 1 Schematic representation of the cardiovascular control mechanisms.

in interpreting cross-sectional investigations is to use age as a reference frame. It can be conceived that essential hypertension is rooted in early life (Kass and Zinner, 1969) and although the disorder can arise at any age, it is likely that it has been of short duration in young adults. Another method of appraising the duration of the hypertensive process in cross-sectional studies is to select a variable which is known to change pari passu with time as a consequence of hypertension.
The results of renal function studies use to be applied as such a parameter. Although several studies have been designed in such a manner, most of them deal with patients who have been selected on the basis of one or more of these variables.
The aim of this study is to provide a biophysical profile of essential hypertension. An attempt will be made to interrelate different variables in order to trace the natural history of the disease.
We have directed ourselves to the following questions, which form the basis of this investigation:

1. Which characteristics can be found in the diurnal variations of blood pressure in essential hypertension?

2. Which is the primary haemodynamic abnormality in essential hypertension?

3. Which is the role of the kidney in hypertension relative to exocrine (volume control) and endocrine (production of pressor hormones) function.

4. Which is the role of the adrenergic system in essential hypertension?

The assesment and the reliability of the methods used will be described in the next two chapters.

CHAPTER 2

Subjects and methods

2.1 Introduction

In 1966 a hypertension research program was started at the Department of Internal Medicine in the Zuiderziekenhuis, Rotterdam.
Until now many patients with hypertension have been studied under metabolic ward conditions. In addition, a small number of normotensive control persons could be studied.
One or more of the investigations, mentioned in 2.3 till 2.9, were carried out in 600 subjects. From this group 226 patients with essential hypertension were selected, who fulfilled the criteria of 2.2.
These were 138 men and 88 women. The data obtained in this group will be discussed in chapters 4 to 8. Since methods for determination of noradrenaline and active renin became available only recently, we have selected a second group of 59 patients (40 men and 19 women) in whom specifically these hormones were measured. On most of these patients, the same haemodynamic investigations were carried out as on the original group. The data obtained on this group will be discussed in chapters 8 and 9.
All data presented in this study have been retrieved and recalculated from the original tracings.

2.2. Study protocol

2.2.1. Selection of patients

Patients were selected for the study on an out-patient basis; they were considered hypertensive when their blood pressure exceeded 150 mmHg systolic or 100 mmHg diastolic during at least three consecutive visits.
Although we recognize that such a criterium especially when applied to all age groups, may cause the patient group to become rather heterogeneous, it is hardly possible to make a better selection.
None of the patients were on antihypertensive therapy during the studies. If they had been treated before, drugs were stopped at least two weeks before admission. The initial evaluation included a complete history and physical

examination, determination of blood electrolytes, urea and creatinine concentration, urinalysis, chest film and electrocardiogram.
The diagnosis of essential hypertension was made after exclusion of known causes of hypertension. The screening protocol further consisted of intravenous pyelography, isotope renography and, if necessary, renal arteriography. None of the patients had proteinuria or excess excretion of vanillyl mandelic acid. When other metabolic diseases, such as diabetes, hyperlipidaemia, etc. occurred, subjects were excluded from the study. A further prerequisite for admission was, that hypertension was still being and uncomplicated, fundal changes with a few exceptions being restricted to grade I or II. In none of the patients, central venous pressure, measured indirectly, was elevated. Plasma creatinine in no case exceeded 120μmol/1.

2.2.2 Investigational program

After the initial work-up patients were admitted to a metabolic ward, where they received a standardized diet, containing 60 mmol of sodium per day. This was chosen in view of the feasibility to provide a salt-free diet with 1 gram of sodium chloride per meal added.
Moreover, such mild salt restriction was considered to be an appropriate stimulus to haemodynamic and hormonal adjustments.
Potassium intake could not be controlled.
Usually the patients were in sodium balance on the fourth day of admission. This was checked by 24 hour urinalysis. From there on the haemodynamic and endocrinological studies were performed during recumbency and after an overnight fast. In those cases where plasma volume and extracellular volume were both measured, these determinations were carried out on a separate day.
In 1975 measuring extracellular volume was discontinued. Subsequently plasma volume was measured directly after completing the renal clearance studies.
Cardiac output was measured simultaneously with either the body fluid volumes or renal haemodynamics.
Renal arteriography was performed on a separate day. During these studies renal plasma flow and glomerular filtration rate were determined togehter with the measurement of intrarenal blood flow.

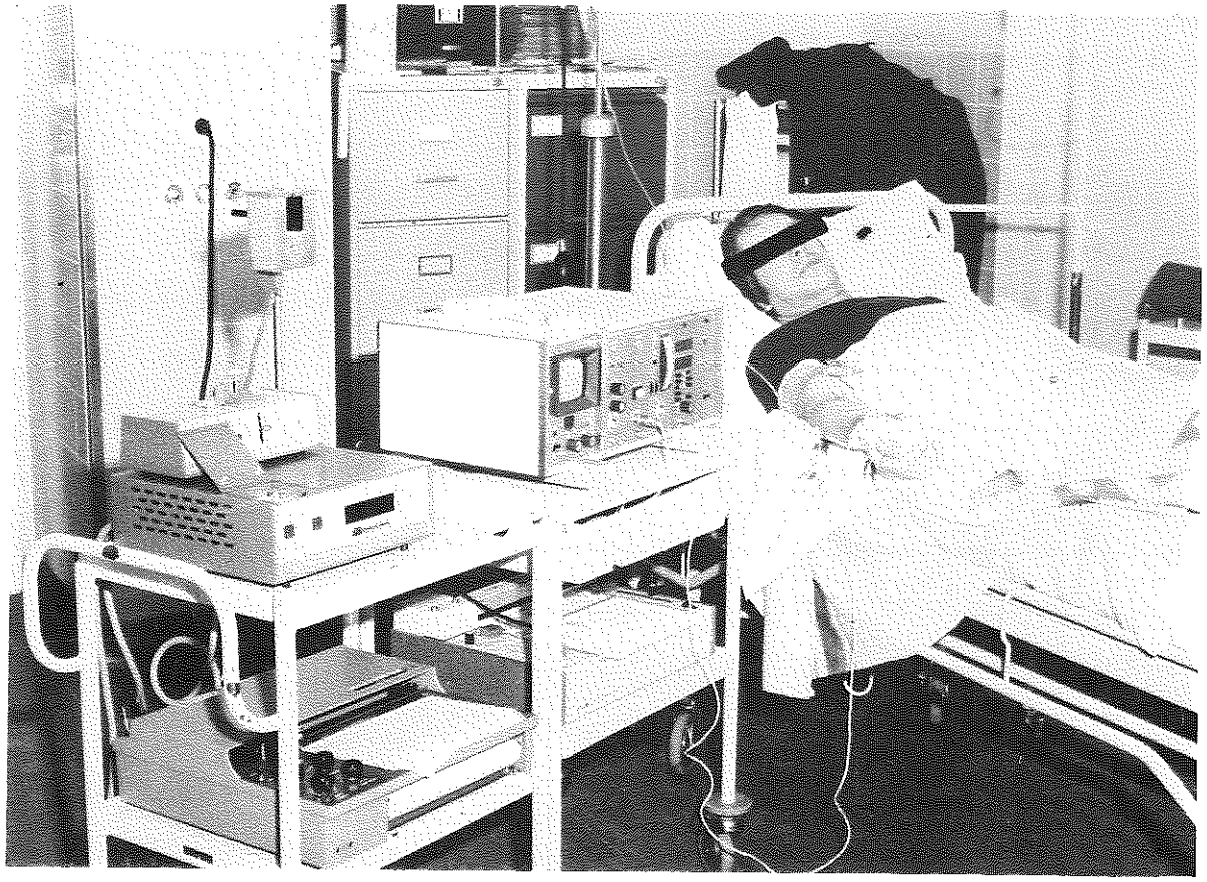

Fig.2 Measurement of intra-arterial blood pressure and cardiac output.

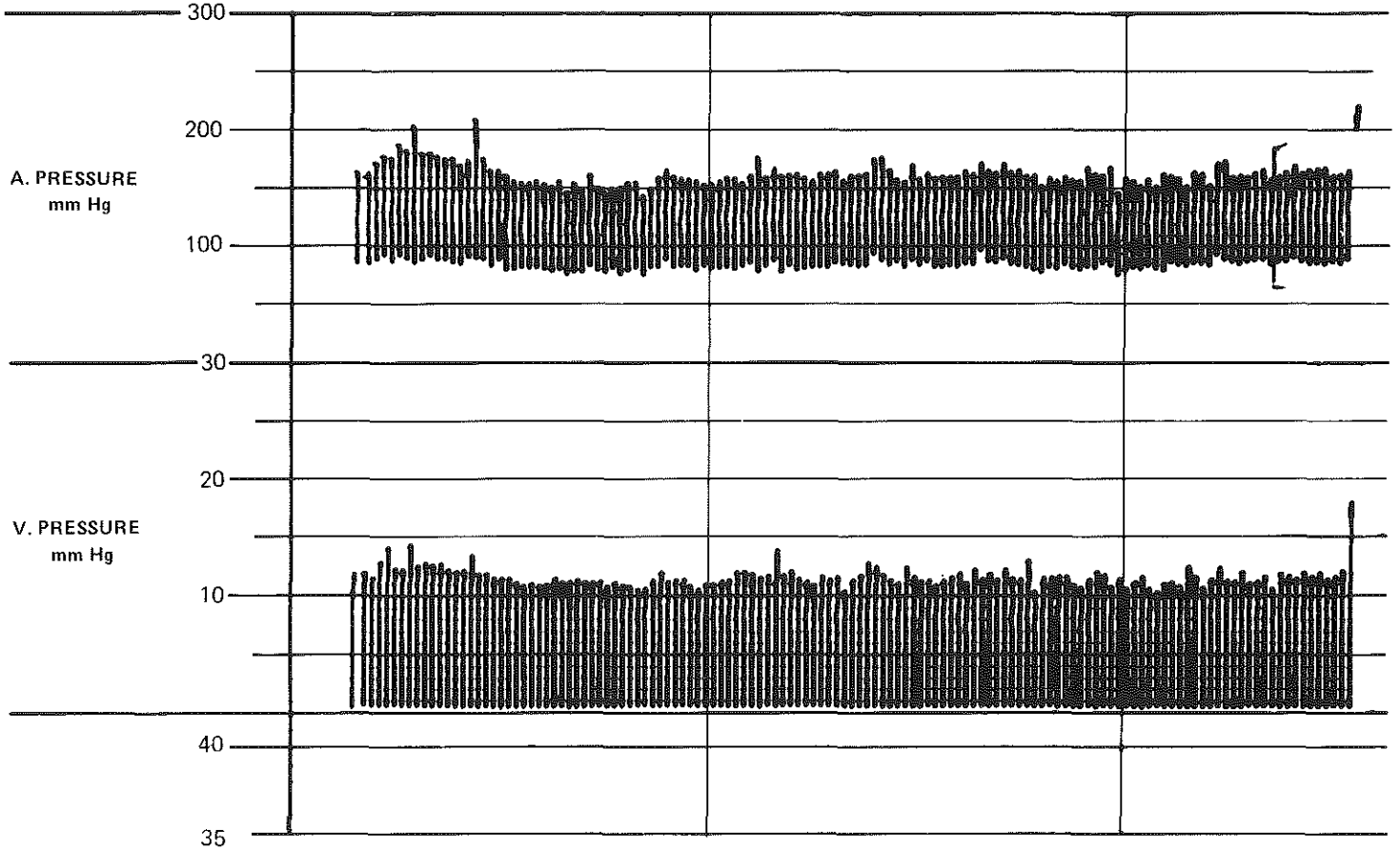

Fig. 3 Example of a direct recording of arterial pressure.

2.3 Systemic haemodynamics

2.3.1 Blood pressure

At the time of the other investigations, blood pressure was measured either directly by manometry from an indwelling needle or indirectly by an automatic device (fig. 2+3). This will be indicated as the 10^{am} blood pressure. Direct values obtained with a Stetham transducer and a Hellige multicardiotest recording system will be presented as an average of 20 pulses. Average indirect blood pressure data were calculated from 20 recordings over an 2 hour period during determination of the other variables.
For computation of mean blood pressure from indirect recordings the formula of Mc.Intosh et al. (1954) was used: mean arterial pressure = diastolic pressure + one third of pulse pressure.

2.3.2 Variability of blood pressure

The 24 hour blood pressure pattern was recorded by means of an automatic device (fig. 4).
Until 1974 the Godart haemotonograph was used, which is based on the oscillometric phase-shift principle developed by the Dobbeleer (Birkenhäger et al. 1968 Westerman-van der Horst, 1975). From 1974 on, blood pressure was recorded by the Arteriosonde (Roche), which utilizes the Doppler effect (Kazamias et al. 1971).

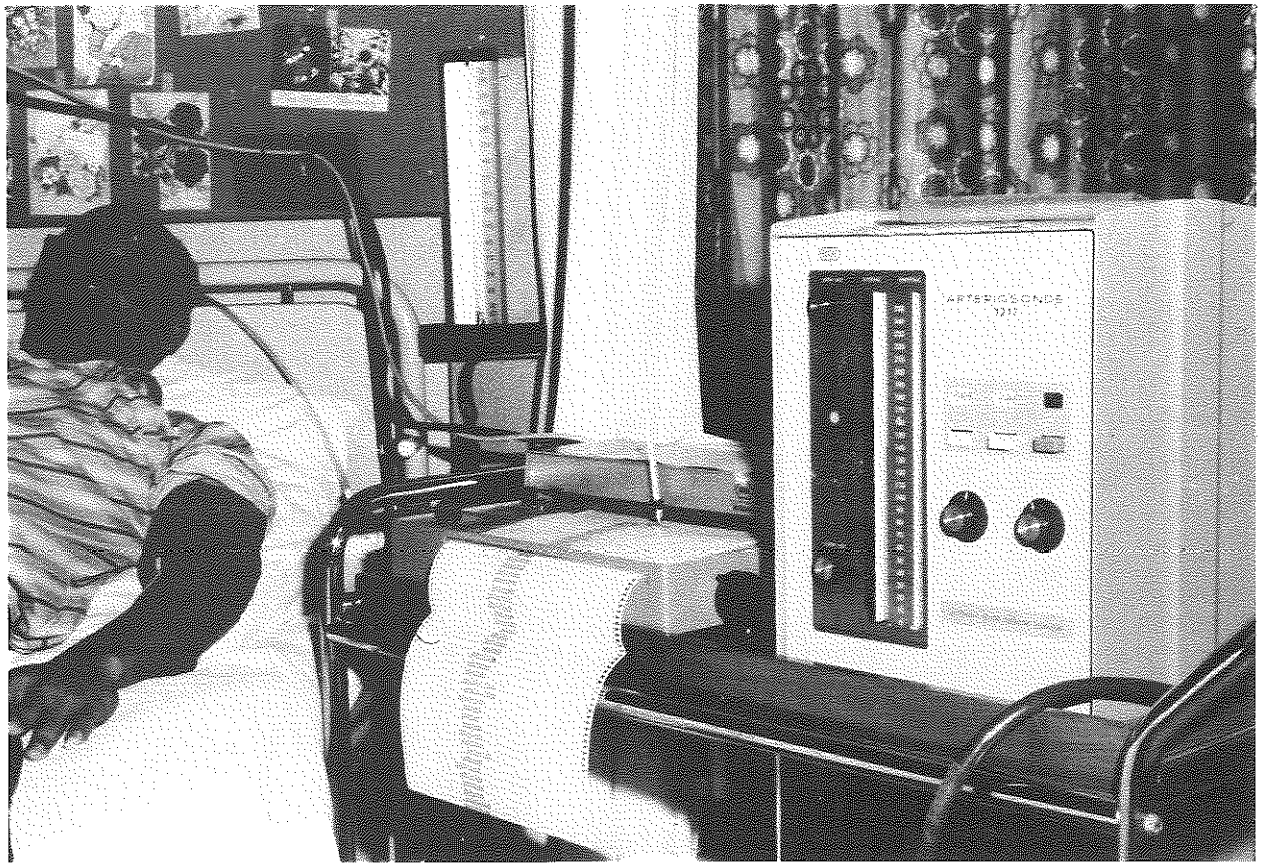

Fig. 4 Indirect blood pressure recording with the Arteriosonde.

Variability of systolic, diastolic and mean blood pressure was calculated as the difference between highest and lowest reading expressed as a percentage of the highest value

$$\left(\frac{P_{max} - P_{min}}{P_{max}} \% \right)$$

Total variability refers to the average of systolic and diastolic variability.
For the computation of mean blood pressure readings the following procedure was developed as proposed by Birkenhäger and Schalekamp (1976). The "basal" blood pressure taken immediately after waking, in accordance with the criterium adopted by Alam and Smirk (1943), was used as a reference. The maximal excursion in daytime blood pressure was noted and the difference from basal blood pressure was termed "pressor range".
The lowest level observed during sleep subtraced from the basal blood pressure yielded the "depressor range". The sum of both ranges corresponds to total variability of mean blood pressure (fig. 5).

Variability studies were repeatedly performed on three consecutive days. The average values from these three days were used for presentation.

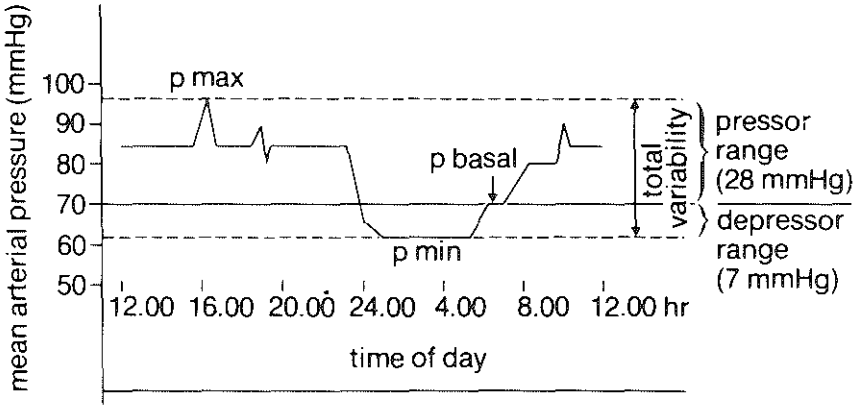

Fig. 5 Schematic representation of the diurnal fluctuations in blood pressure.

2.3.3 Cardiac output and total peripheral vascular resistance

Cardiac output (C.O.) was estimated by the dye dilution technique or impedance cardiography.
The *dye-dilution* technique was carried out according to the Stewart-Hamilton principle (Hamilton et al., 1932). A known amount of indocyanine was injected into an antecubital vein, while arterial blood was drawn with constant speed by a Harvard Pump from the contralateral brachial artery into a Kipp haemodynamic reflectometer. A direct writing micrograph BD_3 (Kipp) recorded the dilution curves (fig. 6). Calibration was performed according to the method of Sparling (1961).

After correction for re-circulation, cardiac output was calculated by planimetric comparison of the circulation curve and the calibration curve (Mulder, 1972).

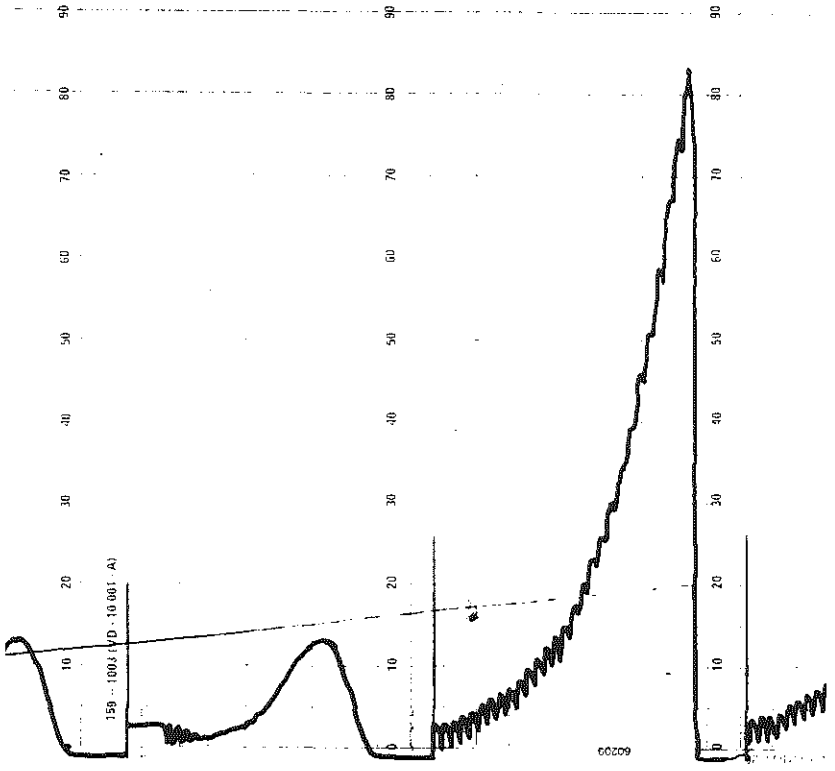

Fig. 6 Example of cardiac output curves (left) and calibration curves (right).

Impedance cardiography was carried out according to the method of Kubichek et al. (1966). Thoracic impedance data were obtained using four electrodes (aluminized tape) and the Minnesota impedance cardiograph model 304 A. Two electrodes are placed circumferentially around the neck, one around the thorax and one around the abdomen. A constant sinusoidal current is applied to the upper and lower electrodes and voltage changes between the two middle ones are measured throughout the cardiac cycle. The change in impedance, indicated by the fluctuations in voltage, is thought to correspond with volume shifts between the two inner electrodes. During end-expiratory breath holding this is entirely due to the ejection of blood by the heart. A phonocardiogram is recorded simultaneously (fig. 7). From the maximum rate of change of impedance, stroke volume can be calculated when basal thoracic impedance, ventricular ejection time and distance between the inner electrodes are known.

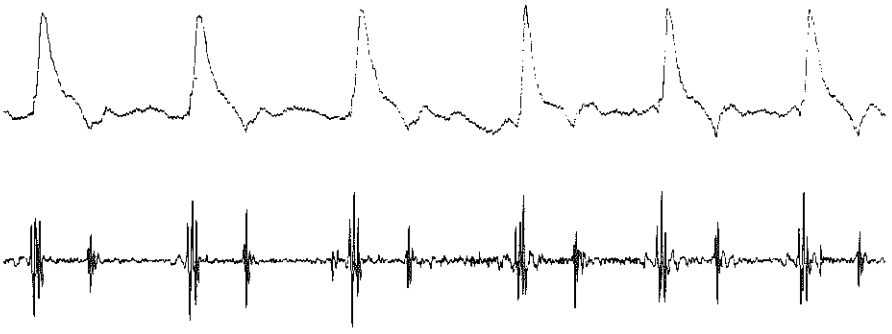

Fig. 7 Example of impedance cardiogram.

In the last ten years several authors have compared this method with the dye dilution or isotope dilution technique, and with a few exceptions, good correlations were reported (Judy et al., 1969; Smith et al., 1970; Baker and Geddes, 1971; Lababidi et al., 1971; Demange et al., 1972; Denniston et al., 1976; Keim et al., 1976).
In our hands the relation was acceptable. In 15 patients from our series cardiac output was measured, using the dye dilution and impedance technique simultaneously.
In addition, we have applied both methods under non-basal conditions (e.g. tilting, saline loading). For the whole group of paired observations a direct relationship ($r=0.66$; $p<0.001$) was found (de Leeuw et al., 1978). There is no significant difference between the regression for the basal and the non-basal determinations. Compared to the dye dilution method, impedance cardiography appears to slightly underestimate cardiac output.

Total peripheral vascular resistance (T.P.R.) was calculated from the following formula:

$$\text{TPR (dyn.sec.cm}^{-5}) = \frac{\text{MAP (mmHg)}}{\text{CO (l/m)}} \times 80$$

In those patients in whom the two methods for cardiac output were used simultaneously, the data from the dye dilution were taken for derivation of peripheral resistance.

2.4 Renal haemodynamics

2.4.1 Clearance studies

Renal plasma flow (R.P.F.) and glomerular filtration rate (G.F.R.) were estimated by clearance techniques. For both measurements a constant infusion was used. The infusion clearance was calculated when plasma samples indicated a steady state between infusion and urinary excretion.
For determining *glomerular filtration rate* (^{57}Co)- cyanocobalamine was used originally. (^{57}Co)-cyanocobalamine is firmly bound to protein; radioactivity of unbound material was determined by subtraction after exhaustive dialysis against 0.9% NaCl.
Later on we switched to inulin clearance. Inulin is measured by fermentation (Wesson, 1969). Both methods were compared in a series of 36 subjects (de Leeuw et al., 1978) and a highly significant relationship was found ($r=0.77$; $p<0.001$).

For determination of *renal plasma flow* (^{125}J)-hippuran was used; the infusion-clearance was divided by the extraction ratio for hippuran. On the basis of data from the literature and from our laboratory a 74% renal extraction was assumed (Pritchard et al., 1965; Dabaj et al., 1966; Houwen et al., 1970; Jago, 1973; Kolsters, 1976).
Total renal blood flow (T.R.B.F.) was calculated from the formula T.R.B.F. = $\frac{\text{RPF}}{\text{1-Ht}}$, where Ht is the venous haematocrit. Renal vascular resistance was then calculated as R.V.R. (dyn. sec. cm^{-5}) = $\frac{\text{MAP (mmHg)}}{\text{RBF (ml/m)}} \times 80.000$.
Filtration fraction was calculated from the quotient $\frac{\text{GFR}}{\text{RPF}}$.

2.4.2 Xenon-washout studies

Intrarenal haemodynamics were assessed by means of the xenon-washout technique (fig. 8) on patients requiring renal arteriography. This method measures intrarenal blood flow distribution and capillary blood flow in each region (Kety, 1951). Its theoretical and practical implications have been the subject of another thesis (Kolsters, 1976).

Percutaneous selective artery catheterization was carried out as described by Seldinger (1953), using Elecath-Cope catheters. Whenever possible, the renal vein was catheterized in the same way. Catheters were kept open by heparinized saline solution.
Renal plasma flow was always measured simultaneously by the clearance and extraction of (^{125}J)-hippuran. In these cases, extraction ratio was calculated from the arterial (A) and venous (V) concentration of hippuran by the formula $\frac{\text{A-V}}{\text{A}}$.

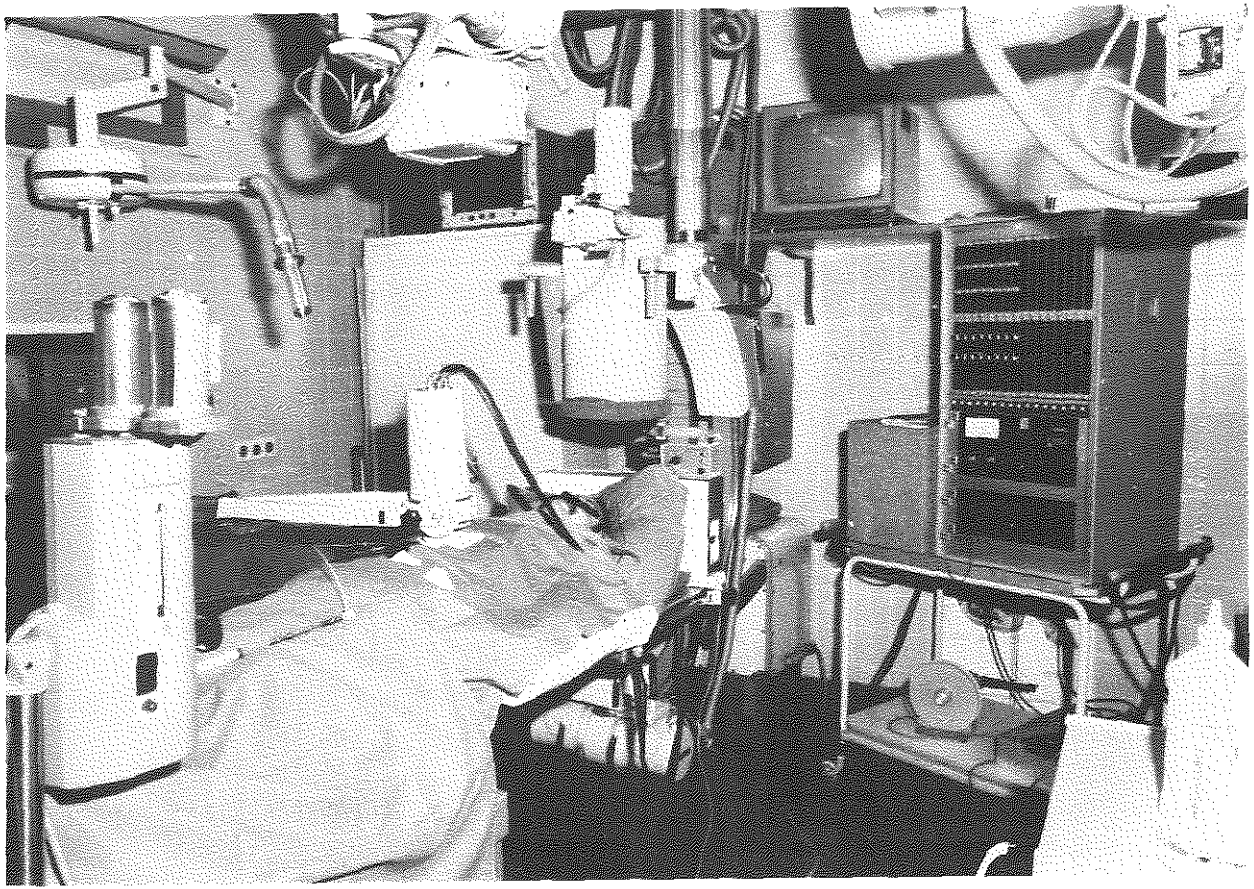

Fig. 8 Set-up of the renal catheterisation laboratory; on the right the Baird Atomic registration instruments.

Blood samples were centrifuged immediately after being drawn. When no angiographic abnormalities were found, the right kidney was used for the washout study.
In order to insure that intrarenal haemodynamics were not affected by contrast material, studies were performed at least 30 minutes after the adminstration of this material (Hollenberg et al., 1968; Rosen et al., 1968).
Subsequently 1 mCi of ^{133}Xe in 2 ml saline was injected into the renal artery in 5 sec.
The disappearance of ^{133}Xe from the kidney was monitored during 20 minutes by external counting with sodium iodide crystals placed in a cylindrical collimator above the kidney. An example of a washout curve is given in fig. 9.

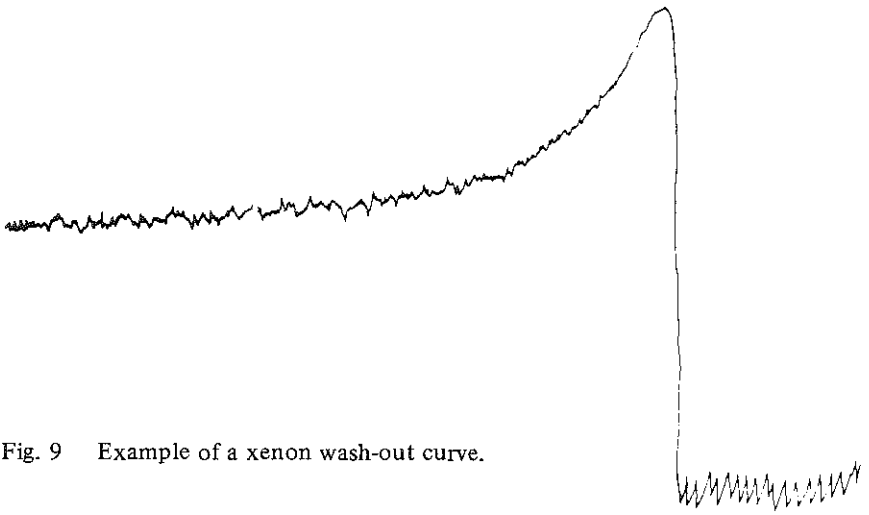

Fig. 9 Example of a xenon wash-out curve.

The mathematical principles on which the measurement of tissue perfusion with an inert gas is based, have been extensively described by Kety (1951). For any substance carried to an organ by the flow of blood, it is evident that the amount (Q_a), which is brought in within a time interval Δt, must equal the amount of the substance which during that time interval leaves the organ (Q_v), plus the amount which is accumulated and metabolized in that organ. In case of an inert unmetabolized substance, like radioxenon, no conversion takes place. Therefore, the total quantity of the substance accumulating in the organ (Q_i) can be described as

$$\frac{\Delta Q_i}{\Delta t} = \frac{Q_a}{\Delta t} - \frac{Q_v}{\Delta t} \quad (1).$$

If it is assumed that flow rates (F) for arterial and venous blood are equal and constant and if the arterial and venous blood represent the only significant pathways of entrance and exit for the organ, then equation (1) can be rewritten as

$$\frac{dQ_i}{dt} = F(C_a - C_v) \quad (2).$$

where C_a and C_v represent the concentration of the indicator in arterial and venous blood. Immediately after the bolus injection of xenon into the renal artery, its concentration in arterial blood is zero and therefore

$$\frac{dQ_i}{dt} = - F \times C_v \qquad (3).$$

Even when assuming very rapid equilibration between blood and tissue, concentrations of xenon in these spaces are not equal due to differences in solubility. Concentration of xenon in tissue (C_i) can be derived from the partition coëfficient

$$\lambda = \frac{C_i}{C_v} \qquad (4).$$

Combining formula (3) and (4) yields

$$\frac{dQ_i}{dt} = \frac{-F \times C_i}{\lambda} \qquad (5).$$

Since $C_i = \frac{Q_i}{V_i}$ (6), where V_i is the total volume of tissue in which the substance is dissolved, equation (5) can be rearranged to

$$\frac{dQ_i}{Q_i} = \frac{-Fdt}{V \times \lambda} \qquad (7).$$

Equation (7) may be integrated to

$$Q_t = Q_o e^{-(\frac{F}{V\lambda})t} \qquad (8).$$

where Q_t and Q_o represent the amount of xenon (Q_i) at times o and t. If the partition coëfficient is known, monitoring the disappearance of xenon from the organ allows calculation of flow per unit volume of tissue ($\frac{F}{V}$).

The equations are valid not only for total organ flow, but also for specific regions within an organ. In case of n parallel open compartments the disappearance curve describes the summation of n different components. Although it is generally accepted that the equation, which describes the xenon washout by the human kidney, contains more than one term, there is uncertainty about the number of terms needed to describe the washout curve. After Ladefoged (1966) and Goluboff et al., (1969), we have chosen for three-compartmental model.
The analysis of the washout data was performed by computer. The analytical program is based on a (iterative) least squares method and is quite similar to the procedure described by Dell et al., (1973). Flow rates per unit volume of

tissue were calculated, partition coëfficients being corrected for haematocrit (Andersen and Ladefoged, 1965). Component 1 (C_1) was considered to represent outer cortical blood flow (Blaufox et al., 1970; Kew et al., 1971; Slotkoff et al., 1971; Kilcoyne et al., 1973; Kinoshita et al., 1974; Hollenberg et al., 1976).
There is very little certainty concerning the physiological meaning of the second and the third component (C_2 and C_3). Although with some reserve, C_2 will be presented here as "subcortical" flow. No significance is attributed to C_3.
Mean blood flow (M.B.F.) was calculated as weighted arithmetic mean as described by Ladefoged (1966). From the distribution of total radio-activity at zero time, the fractional distribution of blood flow to the outer cortex ($\%C_1$) and the "subcortical" region ($\%C_2$) could be calculated (Dobson and Warner, 1957). Absolute cortical blood flow was calculated as $\%C_1 \times$ T.R.B.F.

2.5 Body fluid volumes

2.5.1 Plasma volume (P.V.)

This variable was estimated by determining the dilution of (^{131}J)-ablumin (R.I.S.A.), after 5μCi was injected intravenously. Blood samples were drawn at 10, 20, 30 and 40 minutes. Plasma activity was extrapolated to zero time. Blood volume was calculated with the formula

$$BV = \frac{PV}{1\text{-}Ht}.$$

2.5.2 Extracellular volume (E.C.V.)

This variable was estimated by means of radiosulphate. After intravenous injection of 50 μCi of (^{35}S)-sodium sulphate, blood samples were drawn at 30, 60, 90, 120 and 180 minutes. The zero time value was calculated by semilogarithmic extrapolation.

Interstitial fluid (I.F.) is calculated as E.C.V. - P.V.

2.6 Plasma renin concentration

2.6.1 Assay method

Blood samples for renin determination were taken between 09.00 and 10.00 hours. Chilled E.D.T.A.-containing tubes were used for collecting the blood, which was centrifuged immediately.
Renin was determined according to the method of Skinner (1967).
An excess of exogenous renin substrate prepared from sheep plasma was added to the specimen.

Endogenous renin substrate and angiotensinases were destroyed by dialysis against a buffer solution with Ph 3,3. Following the incubation with renin substrate the amount of angiotensin I generated, was measured by bio-assay in the rat (Skinner, 1967; Schalekamp et al., 1970) or later on, by radio-immuno-assay (Stockigt et al., 1971; Schalekamp et al., 1973).
The two methods were frequently compared. All results were expressed as bio-assay units of A II equivalents (ng/ml. hr.). Since the last year, all results are expressed as micro-units per ml of M.R.C. standard renin (Bangham et al., 1975). In our laboratory 1 μU/ml corresponds to 0.08 ng/ml.hr.

Recently, it has become apparent that there are two forms of renin (i.e. an active and an inactive form).
Since inactive renin is activated when the pH falls below a critical level, the previously described method measures total renin (i.e. active and activated). At pH 4.5 inactive renin is not activated (Derkx) and therefore, at this pH the same method measures only active renin. (Skinner et al., 1975; Derkx et al., 1976). In this thesis, T.P.R.C. (total plasma renin-concentration) will refer to the total amount of renin, while A.P.R.C. (active plasma renin-concentration) stands for active renin only. The difference between the two, indicates inactive renin (Skinner et al., 1975; Derkx et al., 1976).

2.6.2 Renin secretion rate (R.S.R.)

Secretion of renin by the kidney could be determined during the catheterization studies. T.P.R.C. and later also A.P.R.C., were determined in 2 or 3 samples drawn simultaneously from the renal artery and vein. The difference in plasma concentration between the two multiplied by renal plasma flow, yield renin secretion rate by both kidneys together.
Renin secretion rate per 100 grams of kidney tissue (R.S.R.-100 gr.) was calculated by multiplying the arteriovenous concentration difference by mean blood flow (M.B.F.), derived from the xenon-washout curve and the term (1 - haematocrit). This latter term converts M.B.F. to mean plasma flow.

2.7 Plasma aldosterone

Blood was collected in the same way as for the renin assay. After purification by paper chromatography, aldosterone was measured by radio-immuno-assay as described by Fraser et al., (1973).
Recently, we started to use the CIS Aldosterone Radio immuno-assay kit, which provides a sensitive and specific determination of aldosterone on dried extracts of plasma samples without chromatography (Malvano et al., 1976).

2.8 Plasma noradrenaline (NA)

2.8.1 Assay method

Blood was collected in chilled gluthation-containing tubes and centrifuged. Since the stress of venipuncture increases noradrenaline levels (Lake et al., 1976), blood was drawn from an indwelling catheter which had been inserted at least thirty minutes previously. This interval is long enough to bring NA concentration back to basal levels (Lake et al., 1976).
NA concentration was measured by a radio-enzymatic method, based on that described by Henry et al., (1975) and Lake et al., (1976) but with some modifications. Proteins were precipitated by addition of 60% perchloric acid, but we omitted extraction of NA from plasma with alumina.
In this way it is possible to use smaller amoints of plasma. Moreover, the results are more reproducible (Falke et al., in preparation).
Noradrenaline is converted to ^{3}H-adrenaline after addition of highly purified phenylethanol-N-methyl-transferase (P.N.M.T.). In this reaction, added (^{3}H-Me)-S-adenosylmethionine (S.A.M.) serves as methyldonor.
The labeled adrenaline is extracted with alumina and the incorporated label measured in a beta-scintillation counter. Plasma samples are also estimated after addition of 100 picogram internal standard.

2.8.2 Renal NA production

Noradrenaline production by the kidney was assessed in the same way as described for renin secretion.

2.9 Electrolytes, creatinine

Concentrations of sodium and potassium were determined by flame photometry. Creatinine was measured colorimetrically in a S.M.A. 12 apparatus. These procedures were performed both on plasma and on urine.

2.10 Statistical evaluation

For comparisons of data between groups the unpaired Student-t-test was used, while the paired t-test was applied to assess intragroup differences. Regression analysis and calculation of correlation coëfficients were carried out according to standard methods (Snedecor and Cochran, 1967).
Wherever appropriate, partial correlation coëfficients were calculated to measure interdependence. An analysis of variance was applied to test the reproducibility of our methods.
Differences and correlations were considered significant when the t-values exceeded those given for the 5% level of probability (Documenta Geigy, 1970).

2.11 Presentation of data

All test results represent an average of at least three successive determinations. Clearance values were taken as the mean of several samples during a period where the individual samples varied by 5% or less.
Results of biochemical tests were only used for the study when duplicate determinations differed by 10% or less.
Group data will be presented as mean ± S.E.M. (standard error of the mean) except for the reproducibility studies, where they will be presented as mean ± S.D. (standard deviation).

2.12 Radiation doses

Patients who were subjected to all of the described tests, received a radiation dose of approximately 150 mRad (I.C.R.P., 1971; Kolsters, 1976). This value refers to total body radiation dose.
Of the preparations used, only ^{131}J-albumine does not quickly leave the body. When the radioiodine-labeled protein is injected, it first mixes with the intravascular protein pool; subsequently mixing also occurs with the extravascular protein pool. Due to the breakdown of the protein the radio-active label is released in the form of inorganic iodide. Although detailed data about distribution and fate of radio-isotopes in the body are lacking, it is assumed that about 20% of the free label is accumulated in the thyroid.
This organ then receives a radiation dose, which averages 304 mRad (I.C.S.H., 1973). It must be emphasized, however, that this is only an approximation. For all isotopes, used in this study, the total body radiation dose together with the dose on the critical (i.e. most susceptible) organ is given in Table I.

Table I.

Radiation dose of the isotopes used in this study.

Isotope	Dose administered μCi.	Total body radiation dose mRad/μCi	Critical organ	Organ radiation dose mRad/μCi
^{131}J	5	2.0	Thyroid	304
^{125}J	60	0.0002	Kidney	0.04
$^{35}SO_4^{2-}$	50	2.6	Testes	10
^{57}Co	6	0.3	Blood	0.04
^{133}Xe	1000 (1 curve)	0.0004	Bladder Liver	1.5 1.2

All values remain well below the level of the maximum permissible dose for each organ.
Moreover, total radiation is relatively low when compared to the effect of one chest X-ray.
Some controversy still exists about the radiation dose of $^{35}SO_4^{2-}$. Whereas in the table the highest value is given based on a half-life of 90 days, the actual radiation dose probably is considerably less. Moreover, it is not generally accepted that the testes are exposed to $^{35}SO_4^{2-}$.

CHAPTER 3

Assessment of the methods

3.1 Introduction

Prior to any assessment of biologic variables, one should evaluate whether the tests are adequate to register real deviations from the normal pattern. Therefore, two questions arise:

1. What is the variability of the test results obtained on the same subjects with an interval of a few days.

2. What are the normal values and what is the effect of ageing per se on these variables.

Ad 1. In a small number of patients, one or more of the tests, described in Chapter 2, have been performed twice under similar conditions and with an interval of a few days. The data from these paired observations have been compared in order to determine the assay-variability. The individual data from this study are summarized in the appendix (tables A-1 to A-11).

Ad 2. Although some data from out laboratory on normotensives will be presented (table A-12), this study is not a controlled one and our results will be compared with those obtained from the literature on both hypertensive and normotensive subjects.

3.2 Assay variability

For all parameters, calculated means, standard deviations and estimated variation of the differences between the two determinations are summarized in Table II.

Table II. Variability of test results.

Determination	n	Mean±S.D. 1st	Mean±S.D. 2nd	S.D. of difference abs.	S.D. of difference %	Correlation 1 vs 2 r	Correlation 1 vs 2 p
Cardiac output (l/min)	23	5,0±1,1	5,0±1,2	0,5	10	0,82	0,001
Glomerular filtration rate (ml/min)	11	113±28	112±22	9,5	8,8	0,87	0,001
Renal plasma flow-1(ml/min)*	16	498±233	503±242	27	6,8	0,99	0,001
Renal plasma flow-2(ml/min)**	20	481±126	455±105	46	8,8	0,88	0,001
-C_1(ml/min/100 gr)	14	378±97	373±73	35	10	0,83	0,001
Xenon-washout-MBF (ml/min/100 gr)	14	328±97	326±72	29	9	0,89	0,001
-%C_1	14	85±9	88±3	7		0,14	n.s.
Plasma volume (ml)	16	2635±666	2680±707	110	4,2	0,98	0,001
Extracellular volume (l)	5	12,0±4,8	11,1±3,4	1,1	7,1	0,99	0,005
Total renin concentration (ng/ml.hr.)	29	9,2±5,5	8,7±4,6	1,6	16	0,92	0,001
Active renin concentration (μU/ml)	14	24,0±16,6	24,5±18,4	3,0	14	0,97	0,001
Plasma aldosterone (ng/100 ml)	33	12,4±6,6	12,2±5,6	4,5	28	0,46	0,01
Plasma noradrenaline (ng/ml)	12	0,30±0,14	0,31±0,16	0,05	12	0,91	0,001

* Refers to table A-3.
**Refers to table A-4.

3.2.1 Variations in the measurement of arterial blood pressure

Variability of blood pressure over a 24 hour time span constitutes a special problem which will be studied in more detail in the next chapter. During the time the patients spent in the laboratory, fluctuations in blood pressure were demonstrable, albeit of a minor degree.

3.2.2 Variations in the measurement of cardiac output

Since the *dye-dilution* technique requires arterial puncture, it was not felt justified to repeat this invasive investigation without a strict reason. Therefore, we have to make do with data from the literature, which indicate that the variability of this method is about 5%-10% (Brandfonbrener et al., 1955; Lee et al., 1966; Kubichek et al., 1966; Arcilla and Rowe, 1969; Lababidi et al., 1971).
Indeed in 3 patients, in whom we were able to repeat the measurements, the variation remained within this limit.

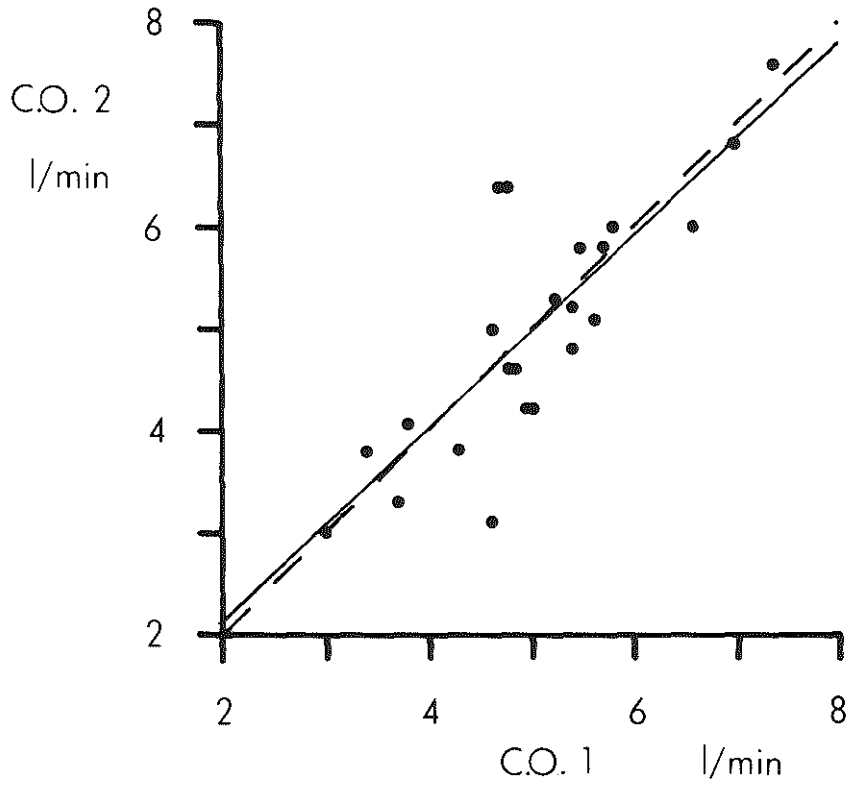

Fig. 10 Comparison between two measurements of cardiac output on separate days.
In this figure and in fig. 11 - 18 the dashed line indicates the calculated regression line, while the dotted line is the line of identity.

Reproducibility of the *impedance method was assessed in 23 patients* (Table A-1). The congruency between the values of the first and the second measurement is given by figure 10. Mean values for the first and the second were 5.0 ± 1.1 and 5.0 ± 1.2. l/min., respectively. A good correlation was found between paired data ($r = 0.82$; $p<0.001$) and variability was 0.5 l/min. or 10%.
Others have reported even better intraindividual reproducibility (Kubichek et al., 1966; Lababidi et al., 1971; Keim et al., 1976).

3.2.3 Variations in clearance measurements

On eleven patients, glomerular filtration rate was determined on two successive occasions (Table A-2; fig. 11). Variation between the measurements was 9.5 ml/min. or 8.8%. This was unrelated to age or average value of G.F.R. There was no difference between the variances of the inulin and the cyanocobalamine measurements. G.F.R. on the first determination averaged 113 ± 28 ml/min. and 112 ± 22 ml/min. on the second. Comparative data from the literature are lacking. However, Davies and Shock (1950[a]) have calculated day-to-day variability for inulin clearance measured by the standard technique; in their series successive measurements had to differ by more than 25.1 ml/min/1.73 m^2 to be significant at the 5% level.

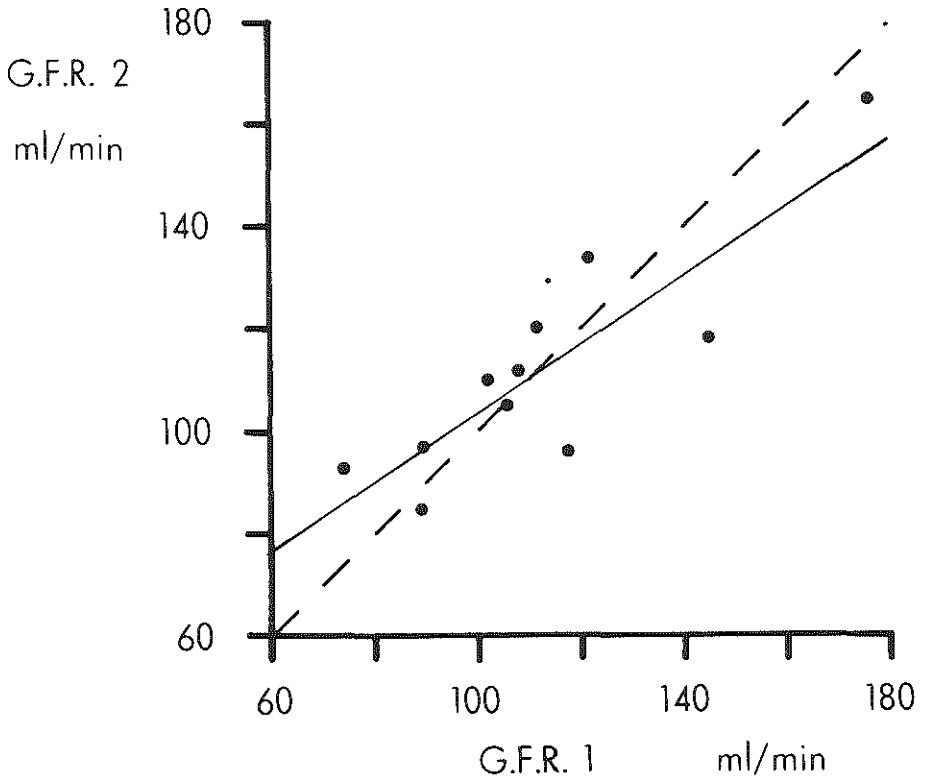

Fig. 11 Comparison between two measurements of glomerular filtration rate on two separate days.

According to Wesson (1969), variations up to 15% are inherent to inulin clearance methods.
Although a simple comparison between their data and ours is not justified, we may conclude that the measurement of G.F.R. by a constant infusion technique in our laboratory, yield quite reproducible results.

In respect to labeled hippuran clearance, variability data are also scarce. In our series the values of the first and the second measurement correlated closely ($n = 16$; $r = 0.99$; $p<0.001$), the averages being 498 ± 233 ml/min and 503 ± 242 ml/min respectively (Table A-3; fig. 12).
Variability was 27 ml/min or 6.8%, which is extremely low when compared to other methods of R.P.F. determination (Davies and Shock, 1950[a]; Smith 1951). Good reproducibility R.P.F. measurements by constant infusion of radio-active hippuran has previously been reported both for the dog (Meschan et al., 1963) and for man (Donker et al., 1977).

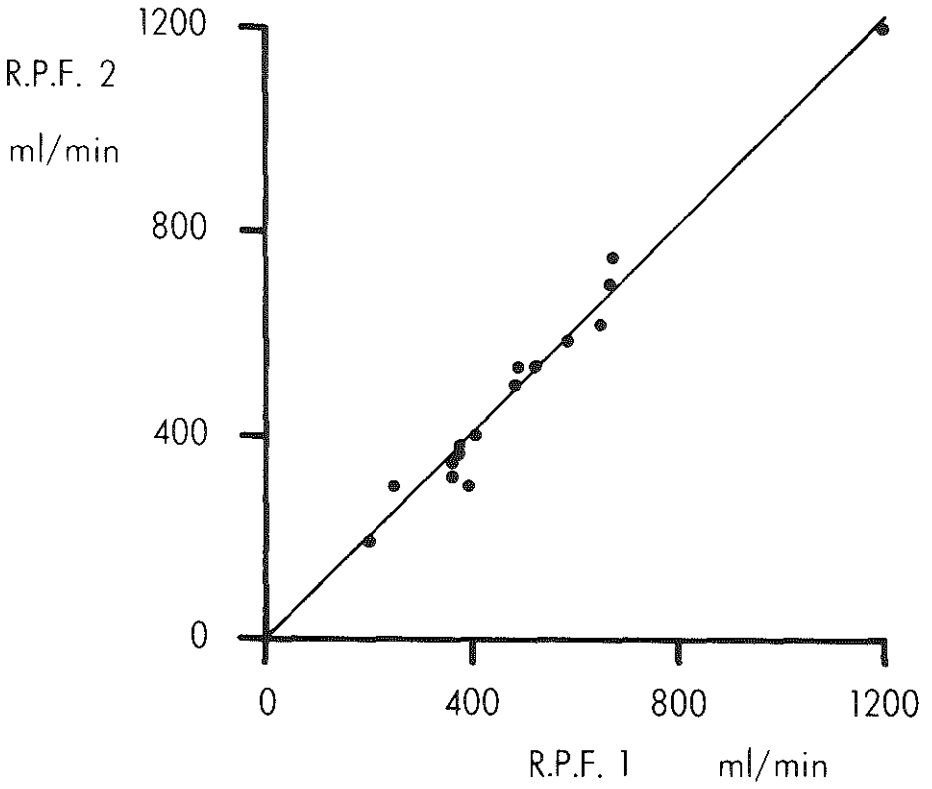

Fig. 12 Comparison between two measurements of renal plasma flow on two separate days.

3.2.4 Variations in intrarenal haemodynamics

In view of the fact that assessment of intrarenal flow rates by Xe-washout requires catheterization of the renal artery, it is obvious that this method is not accessible for routine follow-up measurements. Therefore, it is difficult to determine day-to-day variation in intrarenal blood flow. Especially, uncertainty remains about the effects of the procedure itself, such as stress-induced alterations in renal blood flow or interference by contrast material.
Since most of the renal blood flow passes through the outer cortex, it is to be expected that cortical flow will vary in parallel with changes in total renal blood flow. For this reason, in 20 patients (^{125}J)-hippuran clearance was measured both during the catheterization procedure and on a separate day under otherwise similar conditions. Comparison of the results from both determinations did not show considerably more variation than could be expected on the basis of the data, mentioned in *3.2.3* alone (Table A-4; fig. 13). An important conclusion, derived from this observation is that the contrast material, at least after 30 minutes, does not depress tubular excretion of hippuran.

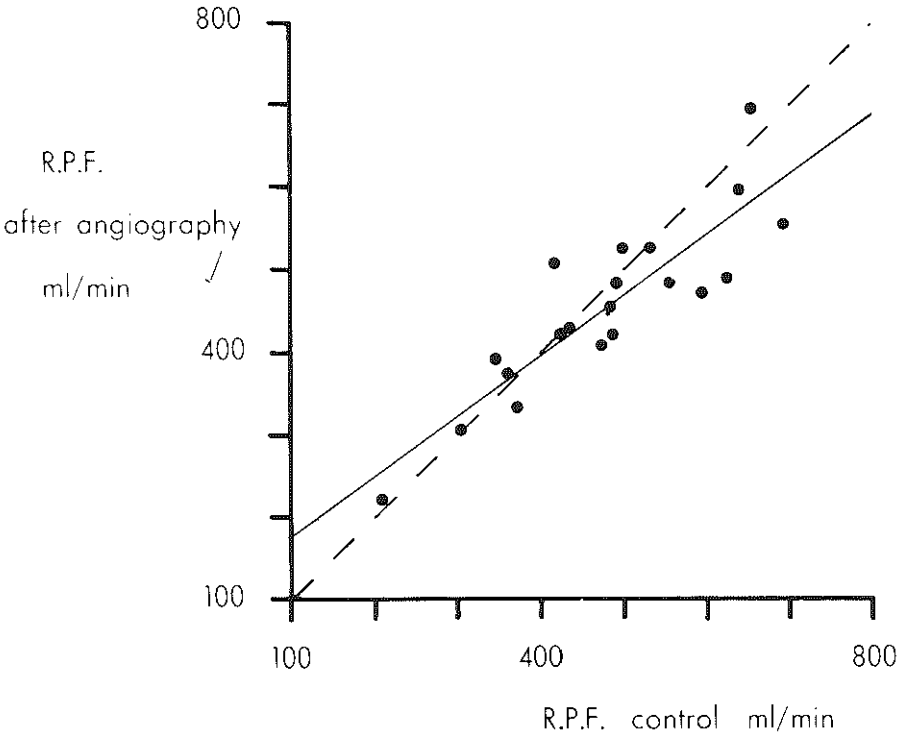

Fig. 13 Comparison of measurements of renal plasma flow as an isolated procedure and after angiography.

Another method of appraising the "stability" of the intrarenal circulation is to measure the flow pattern repeatedly. This has been done with 14 patients. The interval between the end of the first and the start of the second determination was 15 minutes. The results are summarized in Table A-5 and figure 14. It must be emphasized that the variation which was calculated to be 35 ml/min/100 gr, or 10% for C_I and 29 ml/min/100 gr, or 9% for M.B.F., only refers to experimental error during the investigation; % C_I varied by 7% but the error is exaggerated by one patient (nr. 8 in Table A-4).
The results of Ladefoged (1966), obtained with men, are comparable to ours. In his series C_I varied by 20 ml/min/100 gr and % C_I by 5.2%. Variation in M.B.F. was 22 ml/min/100 gr.
A good reproducibility was also reported by Rosen et al. (1968) and Kolsters (1976). In contrast Buchali found a standard deviation of 19%, but this could be due to methodological differences (Buchali et al., 1971). Hollenberg and Adams (1976) found a variability of 37 ml/min/100 gr., in patients with essential hypertension. This was higher than in a control group and explained by vasomotor tone in essential hypertension.

3.2.5 Variations in volume determinations

In sixteen patients variability of plasma volume measurement was estimated. The data from two separate days correlated very closely ($r = 0.98$; $p<0,001$; fig. 15) and the averages of 2635 ± 666 ml for the first and 2680 ± 707 ml for the second determination did not differ significantly (Table A-6). Variation was 110 ml or 4.2%.
Using the same technique Ladegaard-Pedersen (1972) found a variation of 170 ml (4.8%). A good reproducibility has also been reported by Cranston and Brown (1963) and by Huggins et al. (1963).
Other methods usually yield a grater standard deviation (Remington and Baker, 1961; Metcalf, 1961).
Reproducibility of extracellular volume determinations could be assessed in only 5 patients (Table A-7). Variation was 1.1 l or 7.1% with mean values of 12.0 ± 4.8 l and 11.1 ± 3.4 l for the first and second measurements respectively. The values obtained are in reasonable agreement with those from the literature for both the same method (Walser et al., 1956) and for other methods (Hosain and Wagner, 1971; Ladegaard-Pedersen 1972).

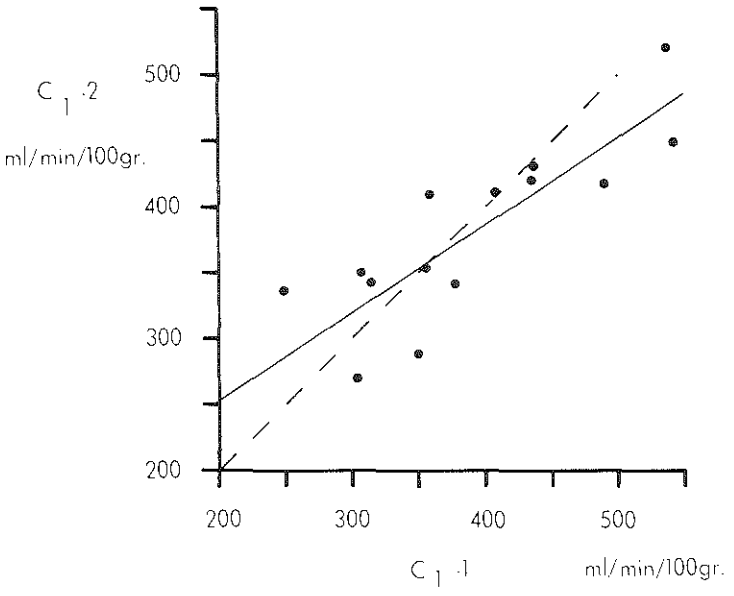

Fig. 14[a] Variation in C_1 flow rate on two consecutive measurements.

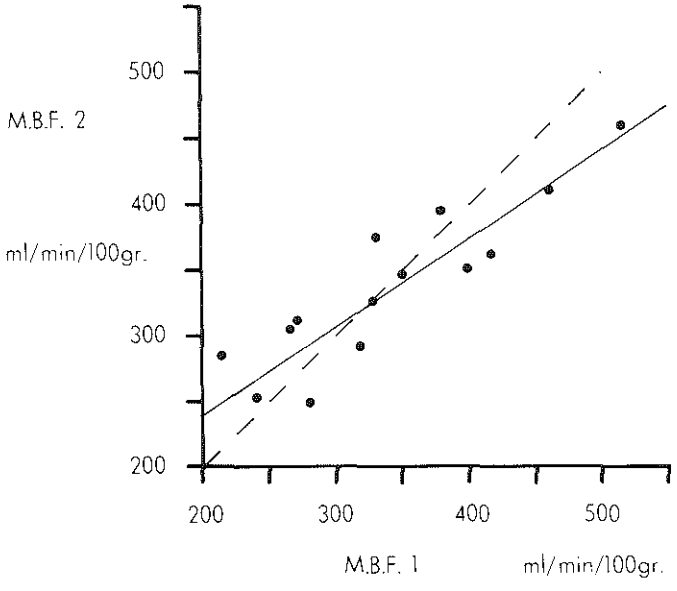

Fig. 14[b] Variation in M.B.F. on two consecutive measurements.

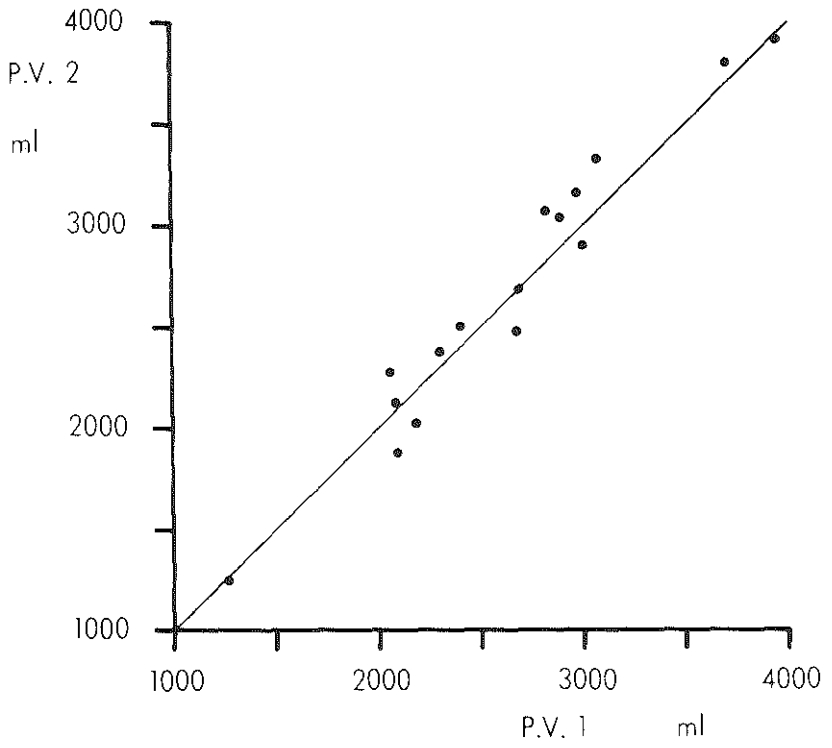

Fig. 15 Comparison of two measurements of plasma volume on two separate days.

3.2.6. Variations in total and active renin concentration

Variability of total and active renin concentration was assessed in 29 and 14 patients respectively. Variation was 16% for T.P.R.C. and 14% for A.P.R.C. In absolute terms this is 1.6 ng/ml.hr (or 20 μU/ml) and 3.0 μU/ml. No differences existed between averages of first and second determination (Table A-8 and A-9; fig. 16). The individual data correlated fairly well both in the T.P.R.C. ($r = 0.92$; $p < 0.001$) and in the A.P.R.C. assay ($r = 0.97$; $p < 0.001$).
The intra-assay variability in our laboratory has changed in the course of time and is at present about 6%.

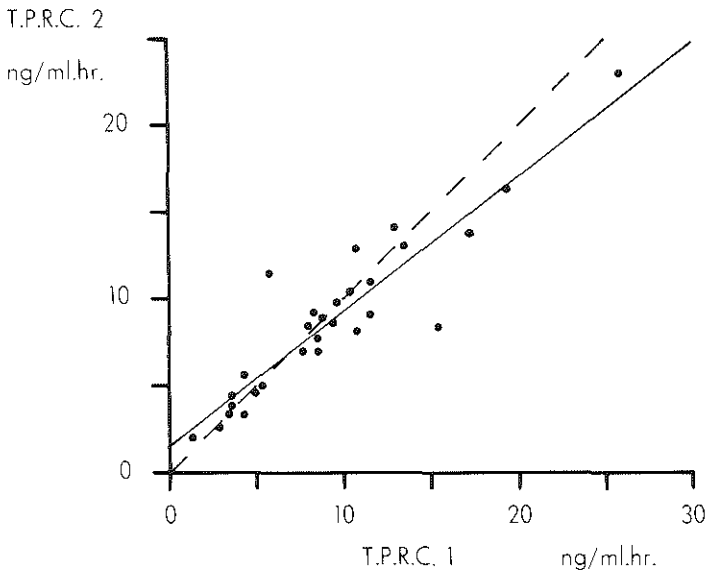

Fig. 16[a] Comparison of two determinations of total renin concentration. The samples were drawn on different days, but at the same time.

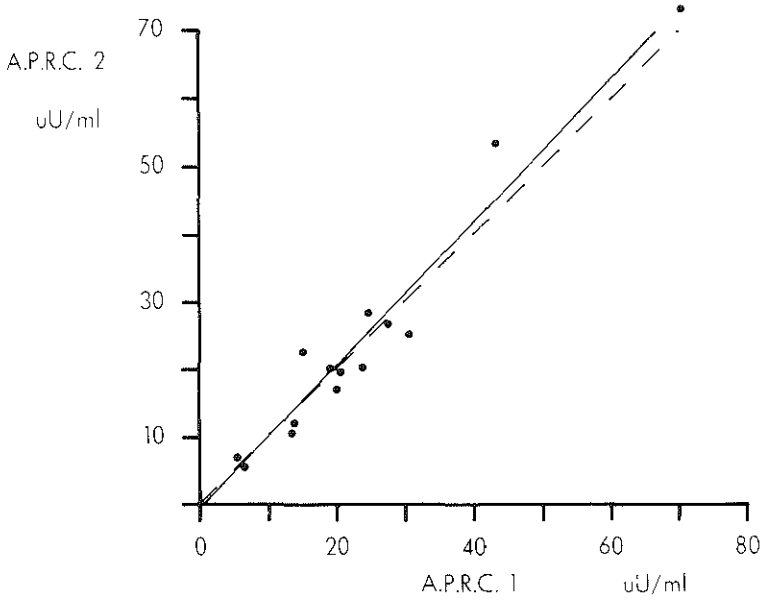

Fig. 16[b] Comparison of two determinations of active renin concentration. The samples were drawn on different days, but at the same time.

3.2.7. Variations in aldosterone concentration

In a total of 33 patients aldosterone concentration was determined twice within a period of 1 week. Although there was a correlation between the respective data, this was rather disappointing ($r = 0.46$; $p < 0.01$; fig. 17).
The average for the first assay was 12.4 ± 6.6 ng/100 ml and for the second 12.2 ± 5.6. Variation between both measurements, however, was as much as 4.5 ng/100 ml or 28% (Table A-10). This exceeds greatly the analytical intra-assay variability, which is only 10%.

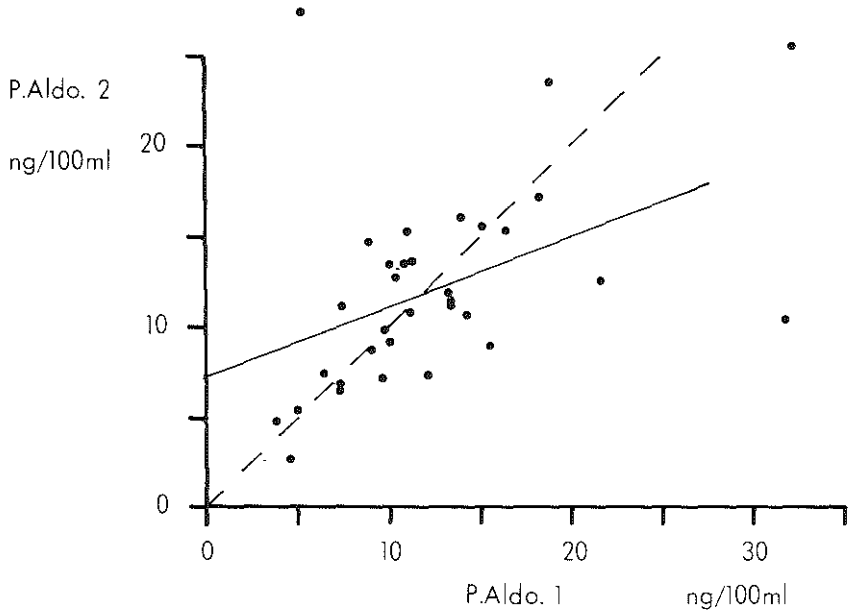

Fig. 17 Comparison of two determinations of plasma aldosterone. The samples were drawn on different days, but at the same time.

3.2.8. Variations in noradrenaline determination

In twelve cases variability of noradrenaline levels was assessed, which was 0.05 ng/ml or 12%. Data from both days correspond well ($r = 0.91$ $p < 0.001$) and average 0.30 ± 0.14 on day 1 and 0.31 ± 0.16 on day 2 (Table A-11; fig. 18).

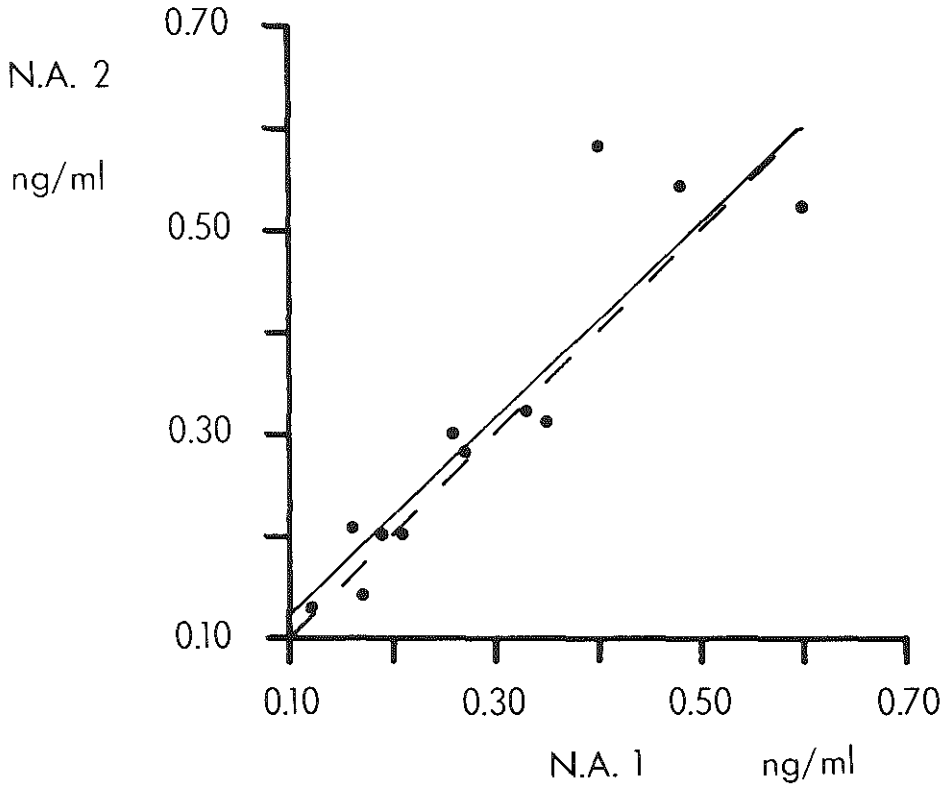

Fig. 18 Comparison of two determinations of plasma noradrenaline levels. The samples were drawn on different days.

3.3. Studies in normotensive control subjects

We have not been able to perform a controlled study, although, at least some experiments could be carried out with normotensive in-patients. The main hindrance was that the selected subjects were often unable to maintain their salt-restricted diet. Nevertheless, there were 76 patients who completed at least part of the study and their individual data are presented in Table A-12. Although the number of observations is too small to serve as a comparison with the study in hypertensives, some characteristics of the material (Table III) could be of interest, especially, where they confirm data in the literature. As is apparent from the table, both renal plasma flow and glomerular filtration rate declined with age in this group. Calculated filtration fraction appeared not to be related to age. No relationship was found between the variables, except for noradrenaline and active ($r = 0.78$) and total ($r=0.79$) renin.

Table III.

Average values for haemodynamic and endocrinological investigations in normotensive subjects.

Type of investigation.	number	mean±S.E.M.
Renal plasma flow. (ml/min)	13	535±51
Glomerular filtration rate. (ml/min)		
-cyanocob.	8	130±5
-inulin	7	100±8
Plasma volume. (ml)	55	2734±57
Extracellular volume. (l)	20	12±0,5
Total renin concentration (μ/ml)	24	185±20
Active renin concentration (μU/ml)	10	33±8
Aldosterone concentration (ng/100ml)	23	10±6
Noradrenaline concentration (ng/ml)	9	0,16±0,01

3.4. Discussion

Variability in the results is caused by several factors, such as errors in the sampling method, handling of the material or reading errors.
In addition, some variation arises from the biochemical and physical analytical methods. Finally, we must consider physiological day-to-day variations occuring in any patient. From the results, presented in 3.2, it can be concluded that the methods used in this study do not appear to be subject to significant experimental error. Despite its importance, relatively little information is available from the literature about such errors. Yet, many studies on pharmacological or follow-up effects are based on the assumed validity of these techniques.
It is shown here that such an assumption is indeed warranted.
An important conclusion which can be drawn when appraising the individual data is that there is no systematic trend between the first and the second measurement. One could anticipate that when a patient is familiarized with the experimental procedure, the stress of the moment decreases. In this case, however, a more directional pattern of the observed difference between test results would be expected.

Reproducibility values of 10 percent or less for biological measurements indicate that the methods are reliable and demonstrate (short-term) stability of the variables studied. In the biochemical determinations the standard deviation was much larger and exceeded the errors inherent to the analytical method.
The larger variability in the levels of hormones may be due to (episodic) alterations in secretion and degradation of these products.
This particularly refers to aldosterone, which is influenced by many factors (see Chapter 8).
These considerations must be taken into account when the results of larger studies are evaluated.

The significance of the findings in normotensives will not be discussed here, since this forms part of the interpretation of the cross-sectional studies, which will be presented hereafter.

CHAPTER 4

Systematic Haemodynamics in essential hypertension

4.1. Introduction

Since blood pressure is basically a haemodynamic phenomenon, it is reasonable to search for a haemodynamic abnormality in hypertension in the first place and to elucidate its cause subsequently.
In this respect, the circulatory control mechanisms which were schematically represented in fig. 1 could serve as a flow sheet for hypertension research.
Arterial pressure is determined by the flow characteristics of the blood stream and the resistance offered by the total of mainly arteriolar vessels.
Thus, hypertension could be caused by either an elevated cardiac output or by an increase in total peripheral vascular resistance or both.
Furthermore, in the modulation of these functions the effect of age should be defined.
As already mentioned in Chapter 2.1, 226 patients could be selected for this study. These were 138 men (age range 17-74 years) and 88 women (aged 19-73 years).
Mean age was 45 years; the distribution of the patients over the various age groups is presented in fig. 19. Since the entire array of determinations was not carried out on all patients, an account is presented in Table IV. All individual data have been recorded in the appendix. In this chapter we will examine the haemodynamic characteristics of the hypertensive patients. First, we will focus on blood pressure itself, including its daily variations and subsequently, turn to the behaviour of cardiac output and vascular resistance.

4.2. Results of the haemodynamic investigations

4.2.1. Relation to age

Blood pressure

Although blood pressure at 10^{am} was measured in all patients, in 41 of them no frequent readings were obtained at the time of the haemodynamic investigations. These patients were omitted from this section. A minority of the

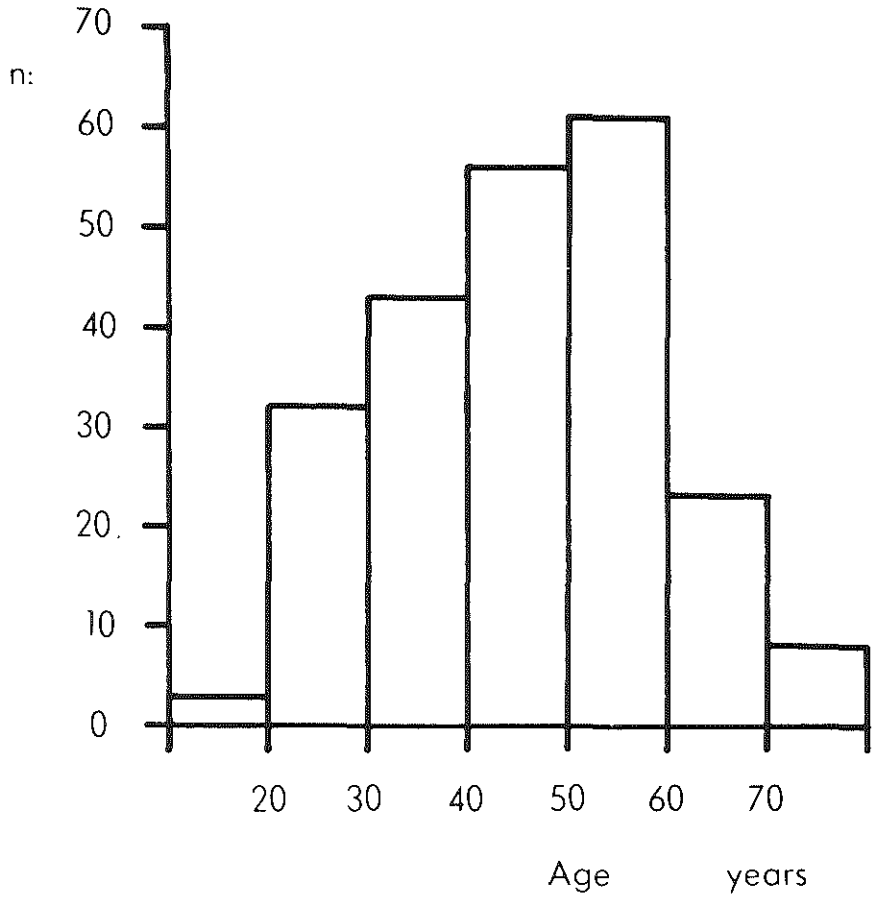

Fig. 19 Frequency distribution of patients in group I.

patients was normotensive at the time of the haemodynamic studies; they represent the group of borderline hypertensives, as defined by Birkenhäger and Schalekamp (1976). When mean blood pressure is plotted against age (fig. 20), a significant positive correlation is obtained ($r = 0.44$; $p < 0.001$). The scattergram comprises 185 patients, in 100 of whom blood pressure was measured intra-arterially.
There is no obvious difference in distribution of data from the direct and indirect estimations.

Total variability of blood pressure was determined in 80 patients and exhibited an inverse relationship with age ($r = -0.28$; $p < 0{,}02$) as shown in fig. 21. When the components of blood pressure variability were analyzed more precisely, the following patterns were found (Table V).
Variability of systolic blood pressure was inversely related to age ($r = -0.22$; $p < 0.05$) but this was only valid for relative values. In absolute terms (mmHg) systolic variability was not related to age ($r = -0.03$; n.s.).

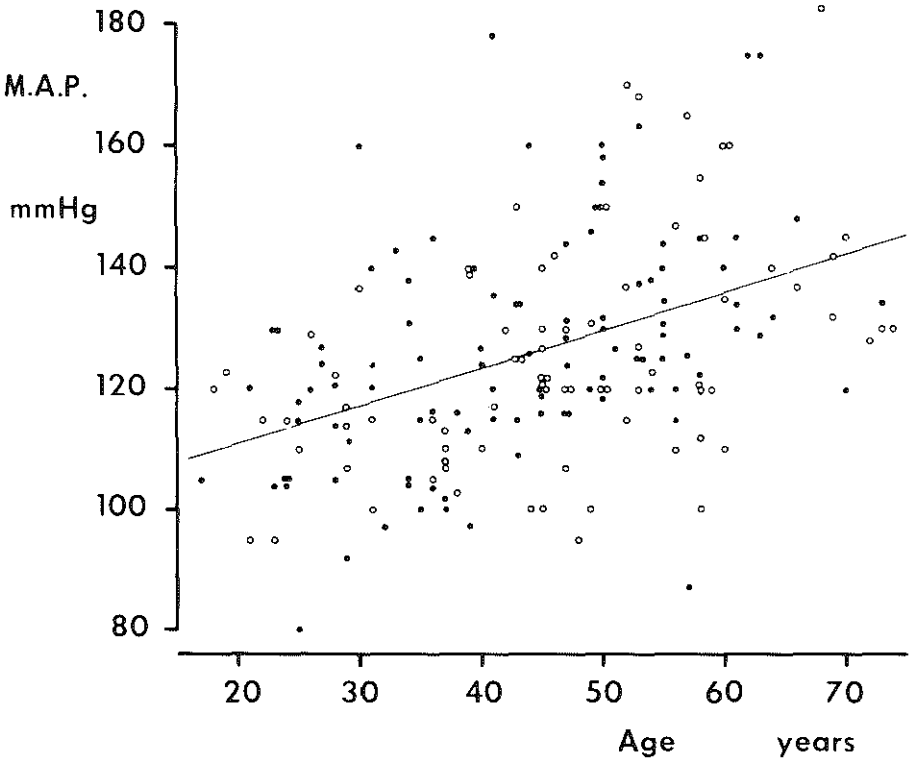

Fig. 20 Relationship between mean arterial pressure and age.
Blood pressure was measured intra-arterially (closed circles) or indirectly with an Arteriosonde (open circles).

Similar results were obtained for variability of diastolic blood pressure. Absolute values were not related to age ($r = -0.14$; n.s.) but in terms of percentage, a significant inverse relation with age was found ($r = -0.27$; $p < 0.02$). Variability of mean arterial pressure was not related to age, either in absolute or in relative terms.

Although rough estimations of basal blood pressure could be made in all patients, in only 55 of them could basal blood pressure be defined exactly. In the other 25, either registrations were incomplete or the moment of wakening was not fully known.

It could be calculated that basal blood pressure is directly related to age ($r = 0.43$; $p<0.001$).

Pressor range in mmHg is inversely related to age ($r = -0.35$; $p<0.01$) and this is also true when pressor range is expressed as a percentage of the basal value ($r = -0.35$; $p<0.01$).

Depressor range tends to increase with age ($r = 0.31$; p. $p<0.025$), but only when this is expressed in absolute terms.

Pulse pressure, measured at 10 AM, also exhibits a positive relationship with age ($r = 0.39$; $p<0.001$).
In fig. 22 the above mentioned results have been summarized in a particular way. For a few parameters, the mean ± S.E.M. for each decade has been plotted on an age scale at the mean age for that decade.

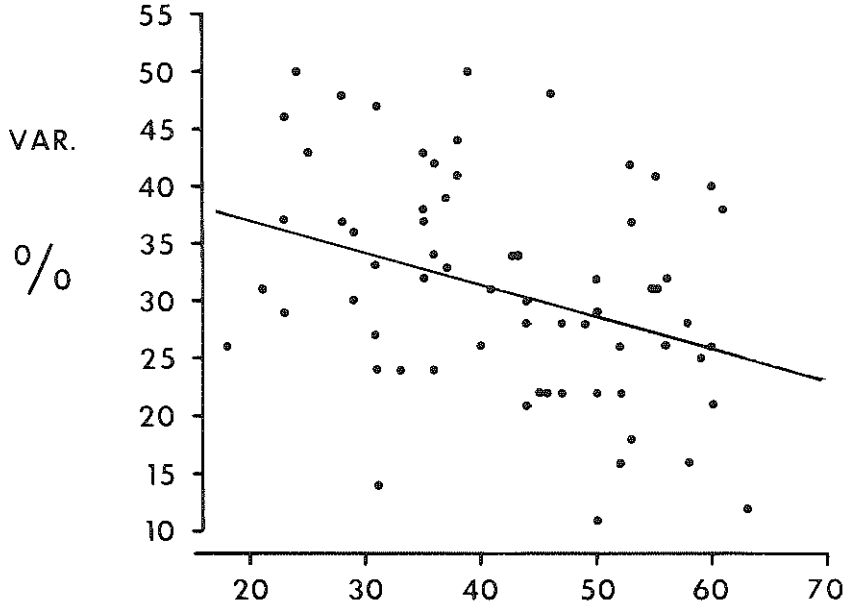

Fig. 21 Relationship between 24-hour variability of blood pressure and age.

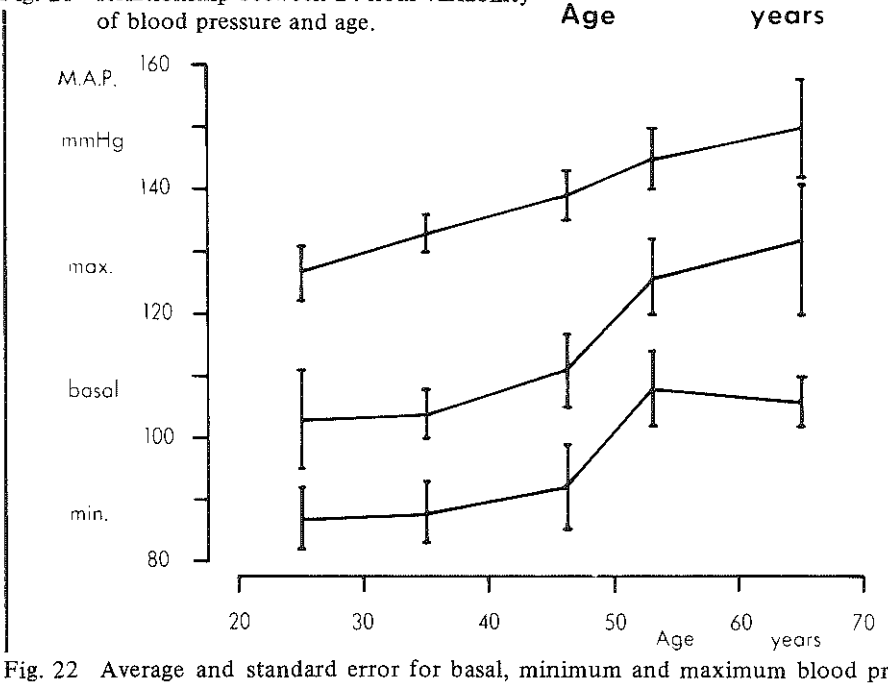

Fig. 22 Average and standard error for basal, minimum and maximum blood pressure at each decade.

Table IV.

Average values for haemodynamic and endocrinological investigations in hypertensive patients (group I).

Type of investigation.	number	mean±S.E.M.
Mean blood pressure (mm Hg)	185	126±1
Total variability of blood pressure (%)	80	35±1
Cardiac output (l/min)		
-dye	106	5,7±0,16
-imp.	64	5,0±0,15
Glomerular filtration rate (ml/min)		
-cyano	68	119±3
-inulin	103	109±2
Renal plasma flow (ml/min)	200	497±12
Plasma volume (ml)	194	2835±36
Extracellular volume (l)	96	12±0,3
Total renin concentration (ng/ml/hr)	205	8,8±0,3
Aldosterone concentration (ng/100 ml)	100	14,5±0,9

Cardiac output

Cardiac output was measured in 170 patients. In 106 of them the dye-dilution technique was used, while in 64 patients the impedance method was applied. The relation of cardiac output to age shows a wide variance, there being no difference between the pattern of the dye-dilution and impedance data (fig. 23). Despite the marked variations, a significant inverse relationship exists between cardiac output and age ($r = -0.31$; $p<0.001$).
The decline in caridac output is mainly due to a reduction of stroke volume with age (fig. 24), this relationship being significant ($r = -0.21$; $p<0.02$).

Heart rate and age showed an inverse relationship, bordering on statistical significance ($r = -0.18$; $0.05<p<0.10$).

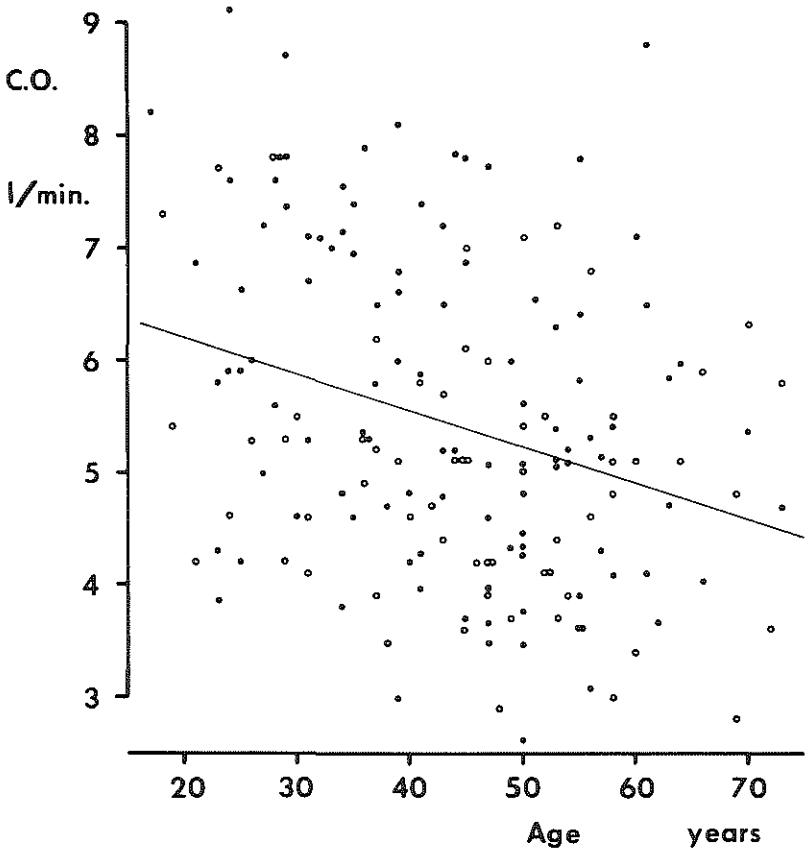

Fig. 23 Relationship between cardiac output measured by dye dilution (closed circles) or impedance cardiography (open circles) and age.

Total peripheral vascular resistance

This variable could be calculated for the 170 patients, in whom cardiac output was measured. In 106 patients intra-arterial blood pressure determinations were available and in the remaining 64 patients the indirect readings from the Arteriosonde were used.
Total peripheral resistance gradually rises with age (fig. 25), the relationship being highly significant ($r = 0.41$; $p < 0.001$).

All values for cardiac output and peripheral vascular resistance are presented here as raw data (i.e. without conversion to a standard body surface area). The same procedure will be followed in the relationships of renal haemodynamics and body fluid volumes against age. The reason for presenting the results as such is based on the observation that correction for body surface area did not disturb the relationships. Moreover, the determination of body surface area is still a speculative matter. For the interrelations between variables, we converted all values to a standard body surface area of 1 m^2 in order to avoid artificial relationships due to body size.

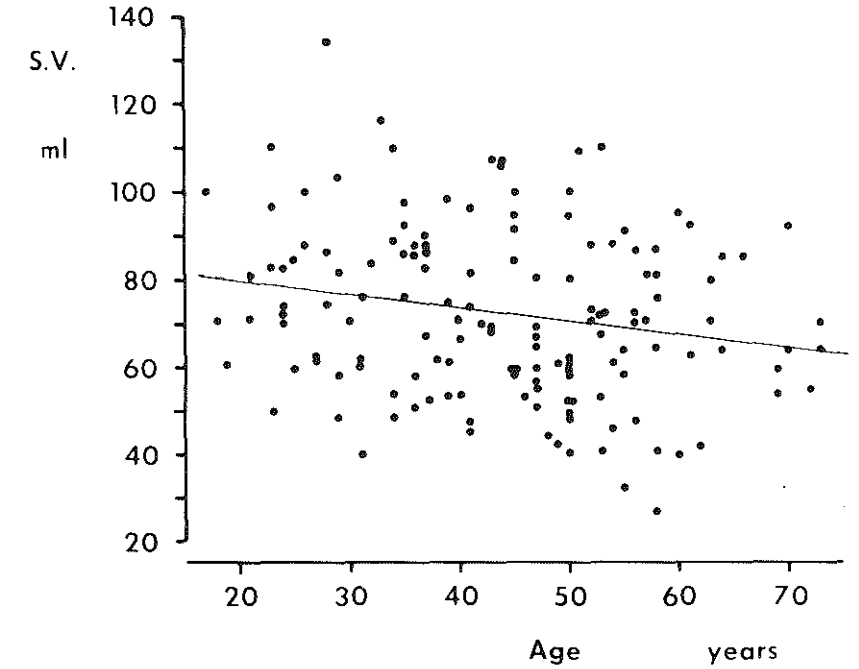

Fig. 24 Relationship between stroke volume and age.

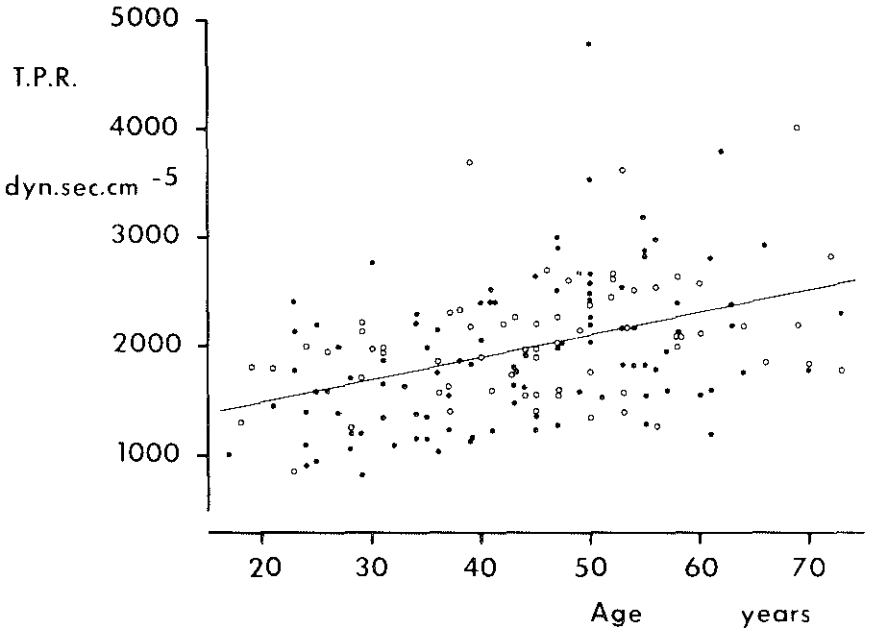

Fig. 25 Relationship between calculated total peripheral resistance and age. Closed circles represent calculations from intra-arterial observations; open circles represent indirect measurements.

4.2.2. Interrelations

Total variability of blood pressure was not related to 10^{am} blood pressure when the effect of age was eliminated. There was, however, a highly significant inverse relationship with basal mean arterial pressure (partial correlation coëfficient ($r = -0.47$; $p<0.001$). Moreover, a direct relationship was found for variability of blood pressure with cardiac output ($r = 0.34$; $p<0.005$) and a negative one with total peripheral vascular resistance ($r = -0.37$; $p<0.005$). These relations are maintained when we correct for the influence of age.
Systolic and diastolic variability when considered apart were not related to cardiac output or vascular resistance and neither were pressor or depressor range.
Basal mean arterial pressure was inversely related to variability of mean blood pressure ($r = -0.32$; $p<0.02$), but this appeared to be the effect of age since partial correlation abolished this relation ($r = -0.23$; n.s.). Elsewhere (de Leeuw et al, 1978) the relation between mean blood pressure and cardiac index is given. At each level of blood pressure cardiac index varies widely, although the range becomes narrower, when the pressure is higher. Furthermore, cardiac index shows an inverse relationships with blood pressure ($r = -0.16$; $p<0.01$) but this again is a pseudo-relation, which disappears when the influence of age is taken into account. Since peripheral resistance is derived from M.A.P. and C.O., it is, strictly speaking, not justified to relate this variable to the other parameters. The best approach to interrelate the two independent variables and the resultant T.P.R. appeared to be drawing them together in a three-dimensional diagram (fig. 26). This figure represents the balance between flow, calculated resistance and the ,,resultant'' pressure. The most intriguing aspect of this figure is the immense variation in the interplay between flow and resistance. The higher blood pressure values tend to be dependent mainly on a high resistance.

4.3. Discussion

An elevated peripheral resistance together with a normal or sometimes low cardiac output has been the hallmark of essential hypertension for many years (Blumgart and Weiss, 1927; Lauter and Baumann, 1928; Burwell and Smith, 1929; Ewig and Hinsberg, 1930; Weiss and Ellis, 1930; Starr et al., 1934; Wiggers, 1938; Goldring and Chasis, 1944; Bolomey et al., 1949; Werkö and Lagerlöff, 1949). However, this finding has been challenged by the observation that especially in young hypertensive subjects, cardiac output can be markedly increased (Liljestrand and Stenström, 1925; Hayasaka, 1927; Wezler and Böger, 1939; Varnauskas, 1955; Hejl, 1957; Taylor et al., 1957; Widimski et al., 1958; Brod, 1960; Fejfar and Widimski, 1961; Rowe et al., 1961; Eich et al., 1962, 1966; Bello et al., 1965, 1967; Finkielman et al, 1965; Sannerstedt, 1966; Lund-Johansen, 1967; Kioschos et al., 1967; Frohlich et al., 1969, 1970; Safar et al., 1970, 1973, 1975; Julius and Schork,

1971; Julius et al., 1971[a, b]; Ellis and Julius, 1973; Tarazi et al., 1974). Although in many of these studies peripheral resistance seems to be normal at first glance, it is actually increased when the data are compared with those of a control group (Birkenhäger and Schalekamp, 1976).

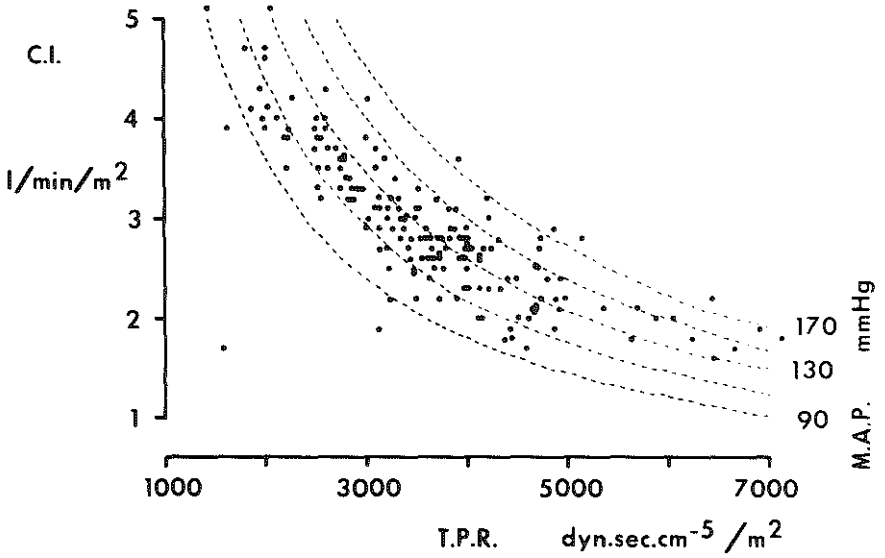

Fig. 26 Nomogram representing the balance between cardiac index, calculated total peripheral resistance and blood pressure.

According to these different haemodynamic patterns hypertensives have been classified in two groups: one with labile or mild hypertension and one with fixed hypertension. The former is characterized by a somewhat hyperkinetic circulation with quite variable levels of blood pressure, while the latter group exhibits a more consistent rise in vascular resistance and blood pressure. Although a minority of patients with labile (borderline) hypertension shows an increased cardiac output, it has been said that this condition is a basic for the future development of hypertension. Epidemiologic studies, indeed, revelaled a higher incidence of sustained hypertension in patients with a previously hyperkinetic circulation (Levy et al., 1944, 1945). However, borderline hypertension per se is already a fairly good predictor of future established hypertension (Julius and Schork, 1971) and it cannot be assumed that this is due solely to the hyperkinetic circulation since this afflicts only part of this population.

Whether the borderline hypertensives should be considered as a distinct group is doubtful. Lability of blood pressure is not a "privilege" of this group since this also been described in patients with more severe hypertension (Ibrahim et al., 1975).

From our studies it is obvious that the degree of hypertension tends to be more severe in higher age groups, even though the same criterium for the diagnosis of hypertension was applied to all age groups. The blood pressure

Table V.

Variability of blood pressure: relationship of its components with age.

	r	p
Syst. maximum	0,37	0,001
Syst. minimum	0,44	0,001
Diast. maximum	0,39	0,001
Diast. minimum	0,39	0,001
M.A.P. –maximum	0,43	0,001
M.A.P. –minimum	0,36	0,005
M.A.P. –basal	0,43	0,001
Var. syst. pressure –mmHg	–0,03	n.s.
– %	–0,22	0,05
Var. diast. pressure –mmHg	–0,14	n.s.
– %	–0,27	0,02
Var. M.A.P. –mmHg	–0,03	n.s.
– %	–0,18	n.s.
Pressor range –mmHg	–0,35	0,01
– %	–0,35	0,01
Depressor range –mmHg	0,31	0,025
– %	0,14	n.s.

profile was based on systematical in-patient readings. When casual readings are taken into account, the relationship with age should be less obvious, since blood pressure is accepted to be more labile in the young. We have assessed variability in a sample of patients, and found indeed an inverse relationship between total variability of blood pressure and age. Even patients with hypertension starting at a higher age apparently do not disturb this general pattern. The regression is linear, there being no apparent distinction between patients with labile or more fixed hypertension. A similar pattern could be detected for both systolic and diastolic variability, buh not for variability of mean arterial pressure. (The latter could be explained by the fact that peak values for systolic pressure do not always coincide with those for diastolic pressure).
However, it must be emphasized that both maximum and minimum values for blood pressure rise with age and it is for this reason that the percentual variability declines, because in absolute terms (mmHg) no relationship with age emerged.
Although total variability seemed to depend in a reciprocal way on casual (10^{am}) blood pressure, this relation could be explained on the basis of age alone.
It is thus apparent that variability of blood pressure in absolute terms is the same in all levels of casual blood pressure and it can therefore be concluded that the relationship of casual blood pressure with age (fig. 20) is a reliable representation of a progressive disorder. Conversely, variability tends to be less when basal blood pressure is higher.
The importance of basal blood pressure was already recognized more than 50 years ago (Addis, 1922).
The concept was adopted and extended by Alam and Smirk (1943), who established a relationship of basal blood pressure with life expectancy (Smirk et al., 1959). From our study it follows that basal blood pressure steeply rises with age, more rapidly than maximum and minimum blood pressure. As a consequence, pressor range declines with age both in absolute terms and as a percentage of the basal pressure. On the other hand, depressor range in mmHg (but not as percentage from basal pressure) increases with age. It can thus be concluded that it is not justified to divide the hypertensive population in subgroups with labile or more fixed hypertension. Furthermore, day time variability is frequently determined by the level of basal blood pressure, as evidenced by the decrease of pressor range with age.
Since in most laboratories, hypertensive patients are studied during the day, it is not surprising that marked lability of blood pressure has been associated with young subjects with early hypertension.
It is tempting to speculate that pressor and depressor responses during day time and sleep depend on vascular tone as already suggested by Shaw et al., (1963) and Richardson et al. (1973[a]). Supportive data for this hypothesis have been obtained in cats by Zanchetti et al (1973) and in man by Bristow et al. (1969).

If we assume that basal blood pressure reflects a certain level of vascular tone, it can be inferred that the lower this tone, the less dilatation will be possible. Conversely, a higher level of resistance in the morning limits further constriction. Our results are compatible with this view, since vascular resis-

tance increase with age (fig. 25). This would imply that in early hypertension variability of mean blood pressure is mainly mediated by vasoconstriction, while in more advanced hypertension this is brought about by vasodilatation. We also obtained relations of total variability with cardiac output, peripheral vascular resistance and basal blood pressure. For the latter, the relationship was most significant, while it was least with cardiac output. This also suggests that vascular tone is the primary factor in determining variability. In view of these relations one is inclined to state that at higher levels of vascular resistance the ability of the vessels to dilate is impaired. This is suggested by the observation that minimal values for mean blood pressure also rose with age. One would have expected that these values were not affected by age when the vascular tree could dilate in the same at all ages. Therefore, our results may indicate that the ability to dilate becomes decreased with age by fixed, organic lesions.

As previously mentioned a higher cardiac output has been recognized in a considerable number of patients, especially in those with only mild elevation of blood pressure. Although it is held by some authors that these patients form a special subgroup, the available data indicate a downward trend of cardiac output during the progression of the hypertensive disease.
It is therefore possible that such patients represent an early stage of hypertension (Pickering, 1968; Birkenhäger et al. 1968).
In most studies, the high cardiac output could be attributed to an increase in heart rate (Eich et al., 1962; Sannerstedt, 1966; Lund-Johansen, 1967; Julius and Schork, 1971; Julius et al., 1971[a,b]; Ellis and Julius, 1973; Safar et al., 1973, 1975; Tarazi et al., 1974), stroke volume being normal. In only one study, an increase in stroke volume together with a normal heart rate was found (Finkielman et al., 1965), but in this study the patients presumably had more advanced hypertension.
Others have stressed an increase both in stroke volume and in heart rate, but in some of these studies, the values for stroke volume in normals are somewhat lower than those reported elsewhere (Bello et al., 1965; Safar et al. 1970, 1973, 1975; Ellis and Julius, 1973; Julius et al, 1975). When excess cardiac function is mainly determined by heart rate, the underlying disorder has been attributed to a combination of sympathetic overactivity and parasympathetic inhibition (Julius et al., 1971[b], 1975; Korner et al. 1973). As a corollary, it may be assumed that these subjects at the time of the (invasive) measurements are more easily upset than their normotensive counterparts. In our laboratory, all measurements are carried out after a sufficient length of time has passed for the patient to become accustomed to the environment. When our determinations of cardiac output in hypertensives are compared with those in normals (adapted from the literature) a marked similarity is found. In fact, the relation between cardiac output and age in this study does not differ much from that in normals, as presented by Brandfonbrener et al. (1955). In his study, equally high values for cardiac output were sometimes observed in young subjects. In fact, the intercept of the regression line, relating cardiac output to age in our study, is even lower than that of Branfonbrener. Although the data of Lee et al. (1966) are more difficult to evaluate, our results do not differ much from theirs. The decline in cardiac output with

age is caused by a reduction of stroke volume, which also occurs in normotensives (Brandfonbrener et al., 1955). Safar et al. (1976[a])found such a decrease only in hypertensives, but in this study mean age was only 28.5 years. The mechanism of this reduction is not clear. Brandfonbrener mentions body size and velocity (force) of flow as possible factors. In our patients no relation of body size with age could be detected. Our data also exclude an inverse relation between afterload and output. So either changes in preload or in contractility (fig. 1) must account for the observed variations. It is reasonable to suggest that contractility decreases with advancing age, since it has been recently established by echo-cardiography that there is an insidious increase in left ventricular wall thickness, associated with a decrease in ejection fraction fiber shortening (Dunn et al. 1977).

In our study, pulse pressure increased with age; in the absecne of an increased stroke volume this points to a reduction in distensibility of the larger vessels. The quotient pulse pressure/stroke volume, as defined by Tarazi et al. (1975) increases with age. Angiographic studies have shown that in human hypertension, aortic volume is increased due to elongation and dilatation (Freis, 1960); this effect is presumably secondary to long-standing hypertension.

The results of our cross-sectional study confirm the positive relationship of total peripheral vascular resistance and age.
When the degree of hypertension is more severe, cardiac output seems to fall in the face of an increase in total peripheral resistance, which is in agreement with other studies (Glazer, 1963; Sannerstedt, 1966; Amery et al., 1967; Lund-Johansen, 1967; 1976; 1977).
It can also be inferred from data in the literature that the natural history of hypertension is characterized by a steady increase in peripheral resistance (Eich et al., 1966; Sannerstedt, 1966; Bello et al., 1967; Birkenhäger et al., 1972; Lund-Johansen, 1973, 1976, 1977).
However, when the haemodynamic studies from various laboratories are examined more closely, it appears that even at a stage when cardiac output is high, peripheral resistance is increased at the same time.
Before discussing the nature of the increased resistance, we will report on our study of the haemodynamic pattern in a single organ, namely the kidney.

4.4. Conclusions

From the data presented in this chapter the following conclusions can be drawn:

1. Variability of blood pressure is demonstrable throughout life; there is no distinction between so called labile and fixed hypertension. The absolute variations are not related to age.

2. Basal blood pressure rises steeper with age than maximal blood pressure. As a consequence, day time lability of blood pressure (pressor range) becomes less with advancing age.

3. It is likely that vascular tone determines the level of pressor and depressor responses. In older age groups the ability to vasodilate is impaired.

4. Even in the younger hypertensives an increase in peripheral resistance rather than a high cardiac output seems to be responsible for the increased blood pressure.

5. In hypertensives cardiac output declines with age just as it does in normotensives. Consequently, the rise in vascular resistance is greater in hypertension.

CHAPTER 5

The kidney in hypertension
I Renal haemodynamics

5.1. Introduction

Ever since the early experiments of Goldblatt et al. (1934), who induced hypertension by clamping the renal artery, the kidney has frequently been implicated in the pathogenesis of essential hypertension.
There are several lines whereby the kidney could exert its hypertensive effect: in the first place, this organ is critically involved in the regulation of extracellular volume. By altering the rate of sodium and water excretion, it plays a key role in the homeostasis of body fluids, which, in turn, could modify intravascular pressure. When renal handling of sodium is affected in such a way that the excretory capacity is compromised, an expansion of plasma volume will be the result. Such a process could be due either to excessive salt intake or to an acquired or inherited intrinsic renal defect.
A second possibility for the kidney to raise blood pressure would be releasing an excess of renin.
This proteolytic enzyme generates angiotensin I, which is converted to angiotensin II, the most potent pressor agent in humans. Angiotensin II, in turn, is involved in the regulation of the sodium retaining hormone aldosterone. Lastly, in view of recent findings, one could argue that the kidney plays its role by interference with other pressor or depressor systems (catecholamines, prostaglandines). In this section, we will deal with the renal circulation and the volume factor, while the renin-angiotensin system is discussed in the next.

5.2. Anatomical features of the renal vasculature

Each kidney is supplied by one or more renal arteries, which originate from the abdominal aorta. Near the hilus the main vessel divides into a number of branches, called the interlobar arteries, which run through the renal columns. At the cortico-medullary junction they branch to form the arcuate arteries; these vessels actually do not form arches, but after running parallel to the

surface of the kidney, they bend and radiate into the cortical tissue as interlobular arteries.
They end as a capillary plexus in and just beneath the renal capsule; some of these vessels pierce the capsule and anastomose with extrarenal vessels (Fourman and Moffat, 1964).
Passing through the cortex the interlobular arteries give rise to smaller intralobular arteries, which ultimately form the afferent arterioles, each of which supplies a glomerulus. The glomerular capillaries rejoin and form the efferent arteriole, which is smaller than the afferent vessel. It has a very thin wall and is practically devoid of muscle cells (Graham, 1956; Barajas and Latta, 1963), and therefore, looks like a thin walled venule. The arrangement of the postglomerular vessels is dependent on their point or origin in the kidney.
There is a total of one million glomeruli in the human kidney (Tisher, 1976); about 20 percent of these are classified as juxta-medullary (deep nephrons), while the others are called cortical (superficial nephrons). The cortical efferent arterioles, having a smaller lumen than the juxtamedullary ones, supply a plexus of peritubular capillaries and, thereafter, form the venules and veins (interlobular, arcuate, interlobar).
The juxtamedullary efferent arterioles, on the contrary, divide in the outer medulla into two types; in both their lumen is often equal or even wider than the supplying afferent arteriole. In the first, less frequent type, the arrangement is similar to the cortical vessels; here, also capillary networks are formed, some laying in the juxtamedullary (or inner) cortex and some laying in the outer medulla. The second type of efferents form the vasa recta spuria, which run (without capillary interposition) directly into the renal medulla. Before reaching the venous system, these vasa recta break into capillary loops (Moffat and Fourman, 1963), also known as inner medullary peritubular capillaries (for survey, see Pomeranz et al., 1968).
It has been recognized that a small amount of blood bypasses the glomeruli through aglomerular shunts (Smith et al., 1938).
It is thought that these shunts, which do not occur in the renal cortex are the result of glomerular degeneration and obliteration, thus forming the vasa recta vera (Ljundquist, 1962, 1963). Their frequency increases with advancing age.
They are not to be confused with the vasa recta spuria, which do have a glomerular circulation, but are, in fact, radially directed efferent arterioles without peritubular capillaries.
Whether there are true arteriovenous shunts in the kidney as suggested by earlier studies (Spanner, 1938; Simkin et al., 1948) has still not been proven.
The process of ageing has a profound influence on the morphology of the renal vasculature.
There is progressive spiralling of the small vessels, especially in the cortex and round the pelvis; collaterals appear to be dilated and elongated (Bellmann et al., 1959). Furthermore, there is constriction of afferent arterioles and progressive loss of glomeruli (Ljundquist, 1962, 1963). In the outer cortex glomerular degeneration is followed by atrophy and fibrosis of both the afferent and the efferent arterioles, rendering this area progressively ischemic.

In the deeper layers of the kidney, the circulation keeps intact, despite a similar loss of glomerular tufts. Here, however, blood is shunted from afferent to efferent arterioles by an anastomosis which is probably already formed in embryonic life.
In hypertension, even in its benign phase, the structural changes are more pronounced. The larger vessels have an irregular calibre with constrictions and dilatations; one can see focal sclerosis and hyperplastic elastosis in many branches (Tellem, 1966). There is more spiralling; there is much more loss of glomeruli than one would expect on the basis of age alone. When the hypertensive process is clinically more severe and in a later stage, more changes are to be seen in the efferent system. In the outer cortex postglomerular vessels of intact nephrons become wider, this being accompanied by intraglomerular dilatation.
While the "efferents" of aglomerular juxtamedullary arterioles show diffuse hyalinosis, the efferent arterioles of intact glomeruli do not appear to be affected by this process.
Kidneys of patients with malignant hypertension have an strongly reduced vascularisation, especially of the cortex. Postglomerular arterioles are very dilated and spiralled. Interlobular and afferent vessels are, at least in part, obliterated.
Good correlations have been reported between the degree of vascular changes in renal biopsy specimens, taken per-operatively, and measurements of renal blood flow; in the early stages of the disease the biopsies did not show much abnormality (Talbott et al., 1943; Castleman and Smithwick, 1948). Other clinical parameters such as cardiac involvement and the fundoscopic appearance also correlate with renal lesions (Salomon et al., 1962).
With modern techniques it has also been demonstrated that the renal vasculature degenerates with increasing age and long-lasting hypertension (Yamaguchi et al., 1969; Hollenberg et al., 1969[a]).

5.3. Innervation of the kidney

The kidney is abundantly supplied with sympathetic nerve fibers; these fibers, which mainly arise from Th 10-Th 12 run along the vessels walls. Their functional significance remains somewhat controversial. In the outer cortical zone, the preglomerular vessels up to the afferent arterioles are heavily innervated; histochemical studies with the dog kidney have shown that the efferent vessels in the cortex are devoid of adrenergic innervation (McKenna and Angelakos 1968[a]). In the juxtamedullary region, the preglomerular arteries are innervated in a similar way as in the cortex, but it is uncertain whether the amount of nerve fibers is comparable.
All these nerves are vasoconstrictor in origin. While the vasa recta in the outer medulla receive some adrenergic and some cholinergic, and perhaps vasodilatory, fibers, there are no such fibers in the inner medulla (McKenna and Angelakos, 1968).
Recently, interest has arisen in the adrenergic innervation of proximal and distal tubular cells, for whic there is both structural (Müller and Barajas,

1972; Barajas and Müller, 1973) and functional (Bello-Reuss et al., 1975, 1976; Nomura et al., 1977) evidence.
Furthermore, the juxtamedullary apparatus is supplied with adrenergic fibers; their role, however, will be discussed in the section on renin release.

It will be apparent that structural-functional correlates in the human kidney could have a profound effect on the results of haemodynamic studies.

5.4. Results of the measurement of renal haemodynamics

5.4.1. Relations with age

In a total of 171 patients glomerular filtration rate was determined, in 68 subjects by means of cyanocobalamine clearance, in 103 with inulin clearance. Glomerular filtration rate tends to fall gradually with age (fig. 27) ($r = -0.21$; $p<0.01$).

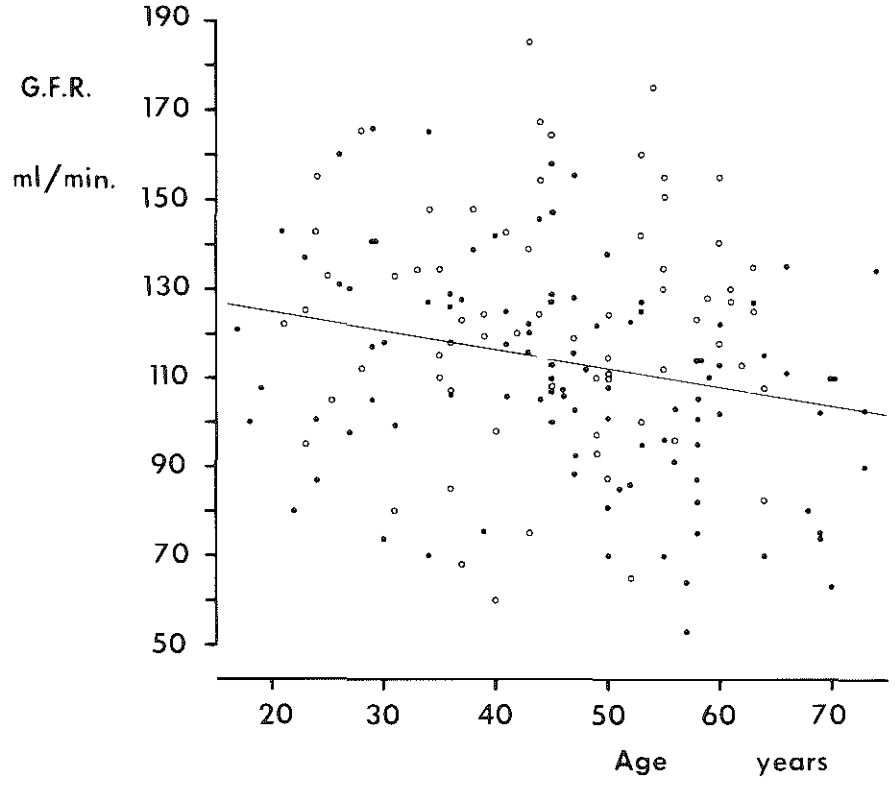

Fig. 27 Relationship between glomerular filtration rate measured by inulin (closed circles) or cyanocobalamine (open circles) and age.

Renal plasma flow and renal blood flow

The results are presented in figure 28. These variables were determined and calculated in 200 subjects. Highly significant inverse relationships were found between renal plasma flow and age ($r = -0.53$; $p<0.001$) and between renal blood flow and age ($r = -0.51$; $p<0.001$).

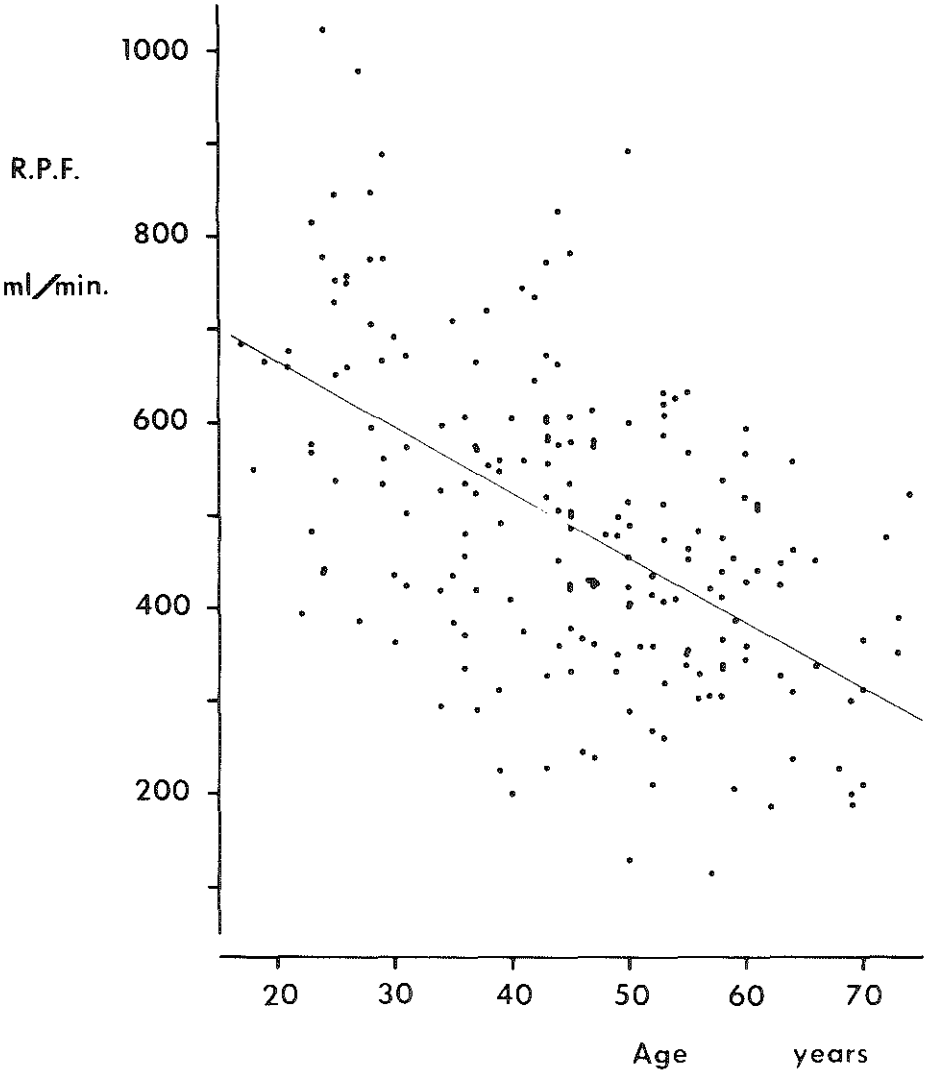

Fig. 28 Relationship between renal plasma flow and age.

It can be inferred from the relations that renal plasma (or blood) flow in the sixth and the seventh decade is reduced until approximately one half of that at the age of 20 years. The renal fraction of the cardiac output also exhibited an inverse relationship with age (fig. 29) ($r = -0.31$; $p<0.001$).

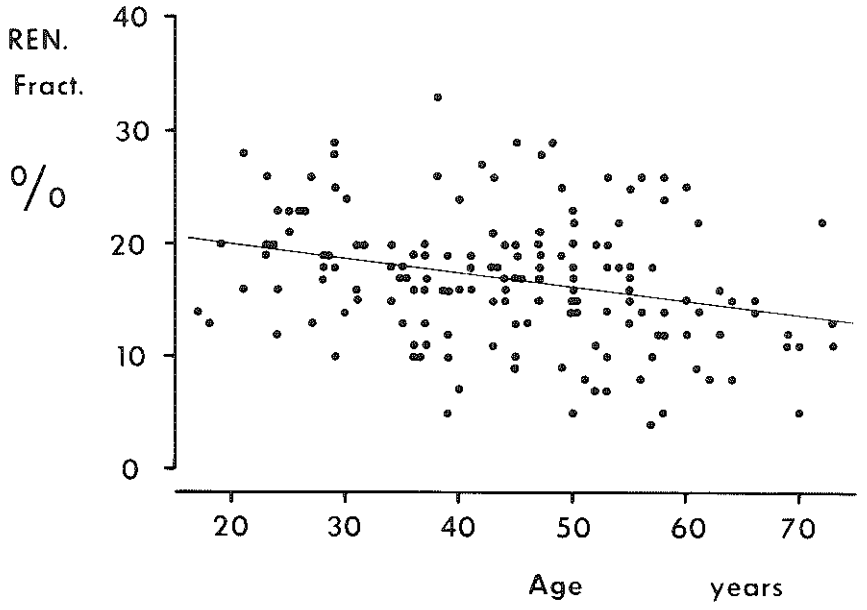

Fig. 29 Relationship between renal fraction and age.

Renal vascular resistance

This variable was calculated for 169 patients. Renal vascular resistance, as shown in figure 30, increased with age ($r = 0.43$; $p<0.001$). There is a suggestion of a curvilinear relationship with a steep increase beyond the age of 50 years. This impression is mainly caused by a small number of patients (all females) exhibiting an extremely high R.V.R.
Besides the exaggerated increase in R.V.R. this group was not shown to have particular characteristics.
Although glomerular filtration rate was low in some, this reduction was not an exceptional one with reference to their age.

Filtration fraction

This was calculated in 168 patients. Again there is a positive relation with age (fig. 31), which is highly significant ($r = 0.51$; $p<0.001$).
Four patients (all women) had filtration fractions which were extremely high. They all belonged to the group with an abnormally high renal vascular resistance, the common denominator being a severely depressed renal plasma flow.

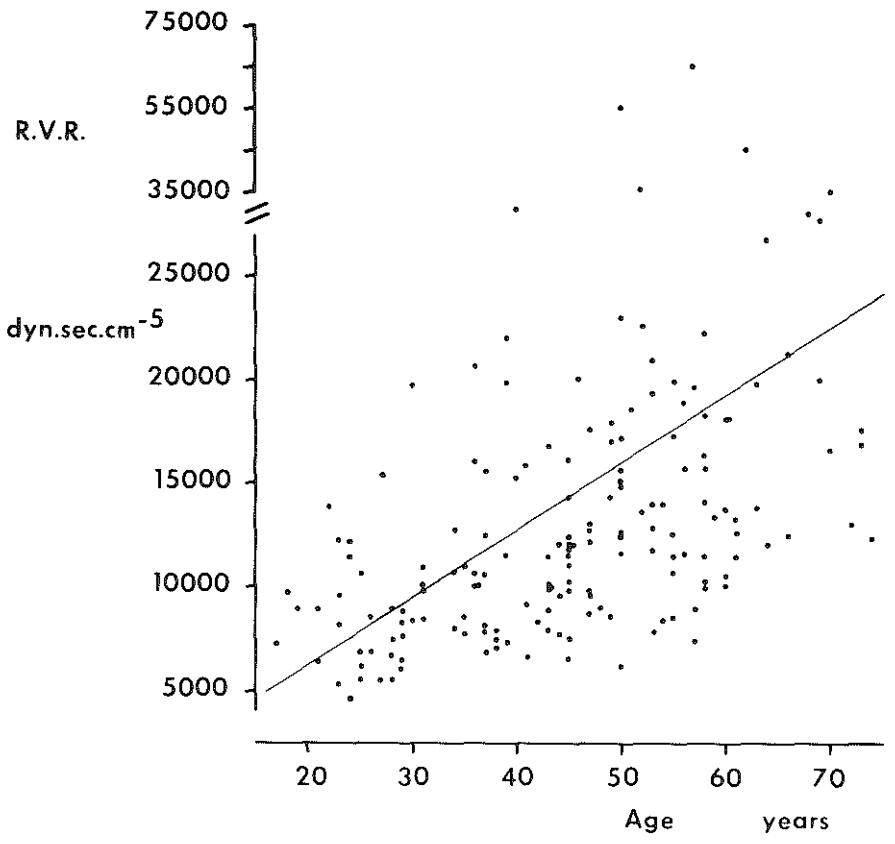

Fig. 30 Relationship between renal vascular resistance and age.

Intrarenal haemodynamics

The measurement of intrarenal haemodynamics has been the subject of a thesis by Kolsters (1976). He clearly demonstrated that, in the kidney, outer cortical blood flow declined with age both in normotensives and in hypertensives. Cortical flow appeared to be diminished already in the younger age groups.

These studies have now been extended and confirmed. Moreover, we have been in the exceptional situation to re-study three subjects in whom intrarenal blood flow was measured four to six years earlier. Their data are presented in the appendix.

Component I flow rate decreased in the course of time in all subjects, although in one patient the reduction was only minor and hardly to differentiate from spontaneous fluctuations in cortical blood flow (Fig. 32).

No consistent changes were observed for C_2.

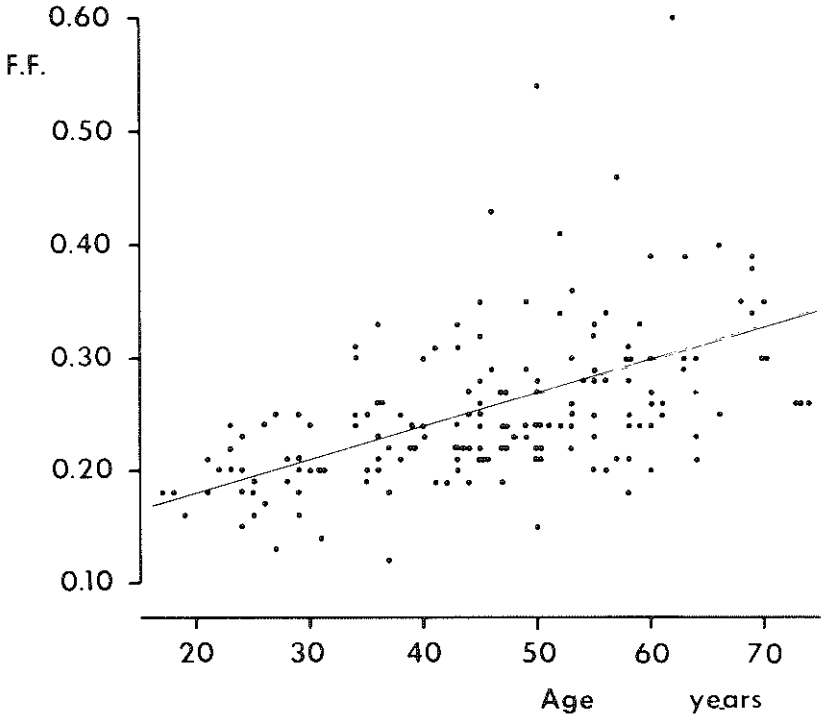

Fig. 31 Relationship between filtration fraction and age.

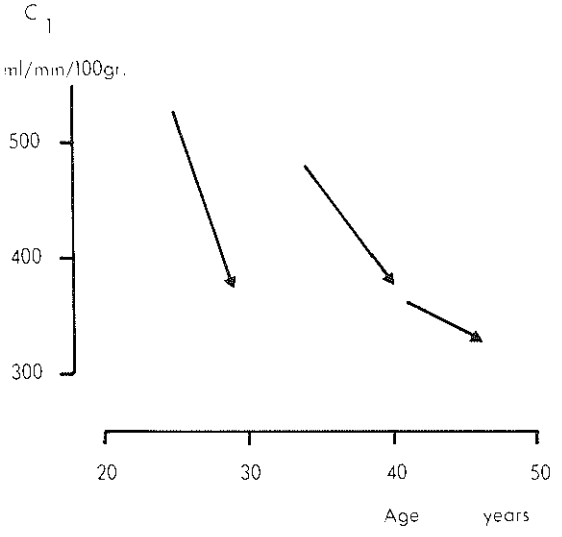

Fig. 32 Reduction in C_1 flow rate during follow-up. Arrows indicate the magnitude and direction of the decrease in C_1.

5.4.2. Interrelations

Renal haemodynamics

Glomerular filtration rate in a particular way is directly related to renal plasma flow (fig. 33). When R.P.F. is lower than approximately 300 ml/min/m^2, the regression is linear ($r = 0.62$; $p<0.001$), but above that point the slope of the regression line almost parallels the X-axis, which means that at these higher flow rates G.F.R. is practically independent of renal plasma flow. G.F.R. is inversely related to R.V.R. ($r = -0.57$; $p<0.001$), as shown in figure 34. These relations remain in partial correlation after eliminating the effect of age.

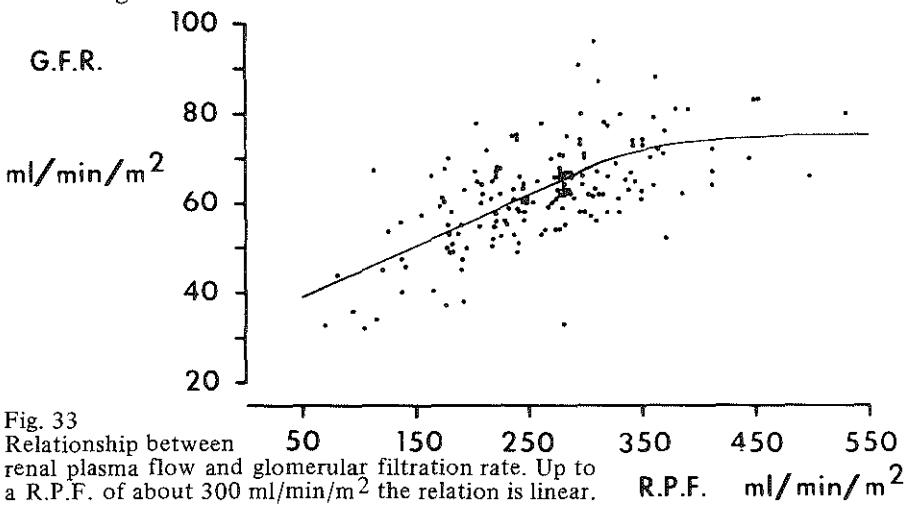

Fig. 33
Relationship between renal plasma flow and glomerular filtration rate. Up to a R.P.F. of about 300 ml/min/m^2 the relation is linear.

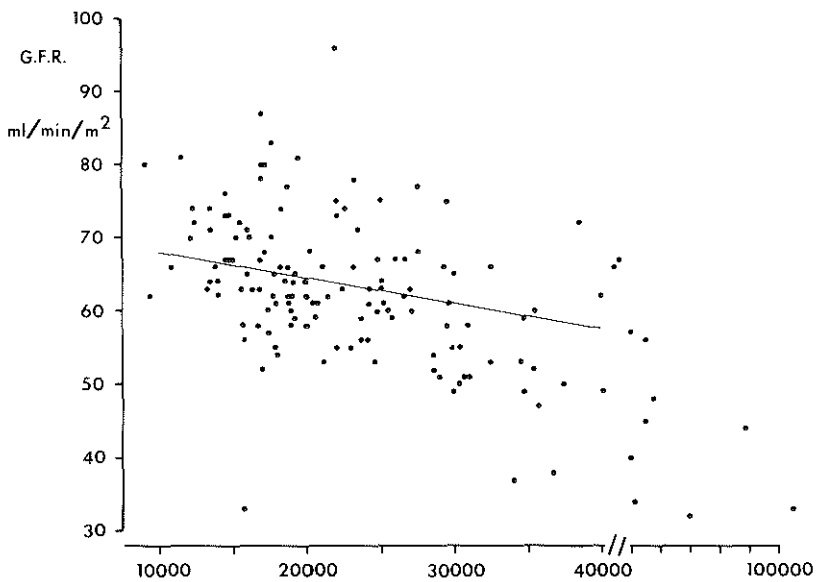

Fig. 34 Relationship between renal vascular resistance and glomerular filtration rate.

No comparisons were made between the other parameters of renal function because they are interdependent.
Nevertheless, pressure-flow relationships may be clarified by presenting the data on arterial pressure, renal blood flow and derived resistance values in one diagram (fig. 35). As in systemic pressure-flow relationships, a wide spread is observed.

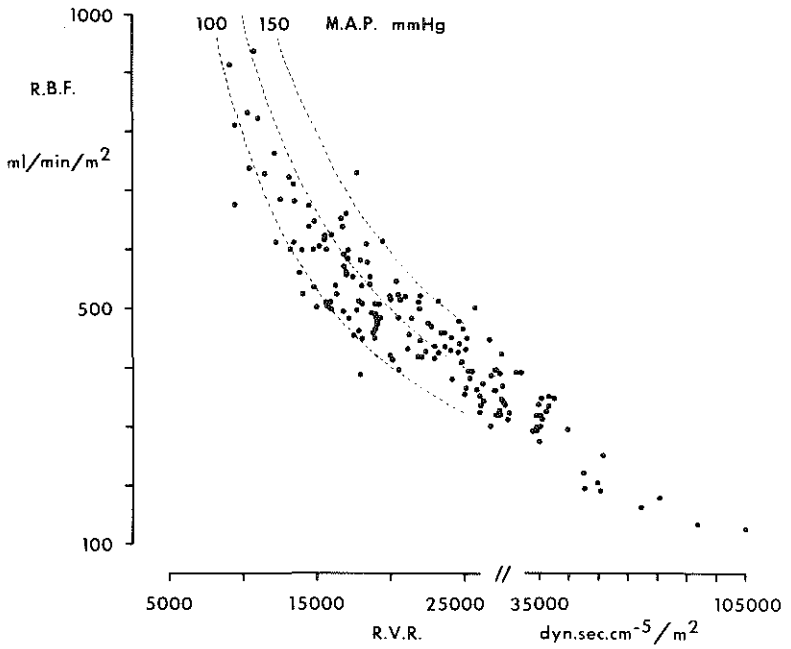

Fig. 35 Nomogram representing the balance between renal blood flow, calculated renal vascular resistance and blood pressure.

Systemic haemodynamics versus renal haemodynamics

There appears to be a significant inverse relationship between mean arterial pressure and renal plasma flow ($r = -0.39$; $p<0.001$; fig. 36), which is independent of age (partial regression: ($r = -0.23$; $p<0.01$).
To a lesser degree such a relationship was also found with respect to mean blood pressure and glomerular filtration rate ($r = -0.23$; $p<0.01$), but this appeared to be an age-related phenomenon. Filtration fraction was directly related to mean blood pressure ($r = 0.45$; $p<0.001$; fig. 37), even after correction for age ($r = 0.30$; $p<0.001$). Cardiac output and renal blood flow were found to be positively related ($r = 0.27$; $p<0.005$; fig. 38), but this was due to age. Glomerular filtration rate and filtration fraction were not clearly proportionate to cardiac output.

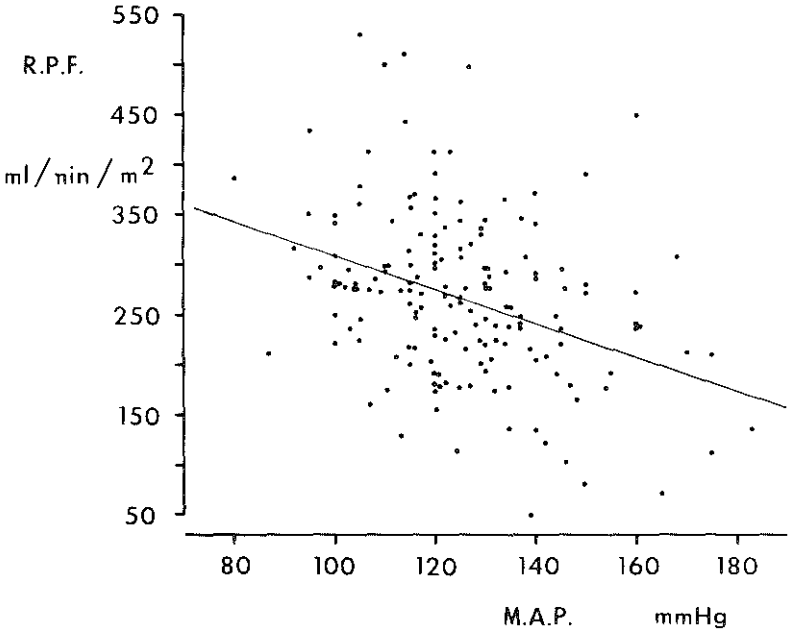

Fig. 36 Relationship between mean arterial pressure and renal plasma flow.

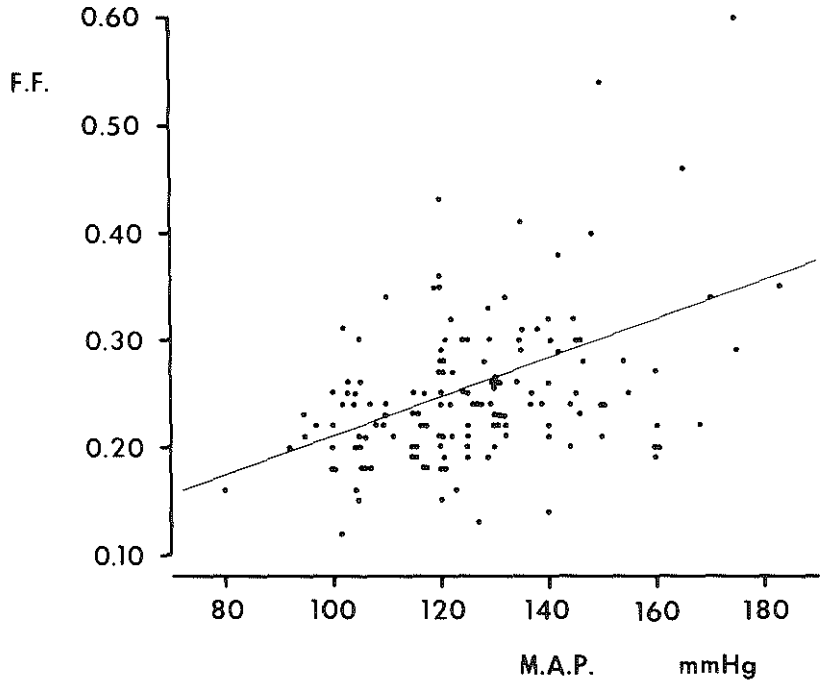

Fig. 37 Relationship between mean arterial pressure and filtration fraction.

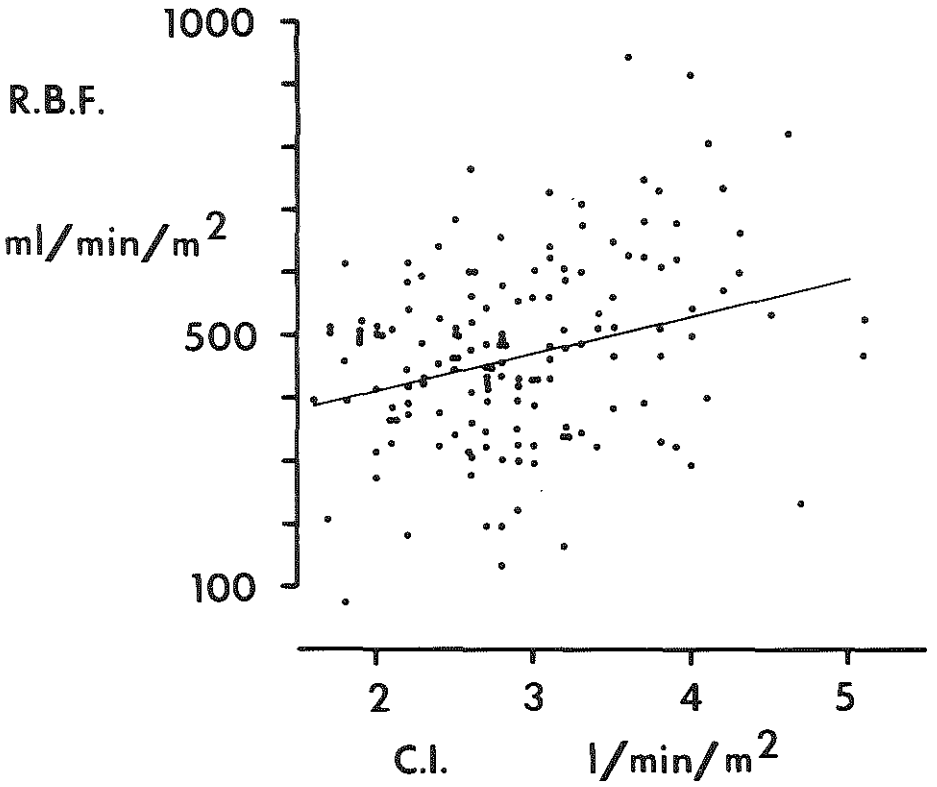

Fig. 38 Relationship between cardiac index and renal blood flow.

5.5. Discussion

Renal blood flow in essential hypertension

Several studies have revealed that in normal man renal blood flow as well as glomerular filtration rate tend to decline with age, usually more so beyond the age of 40 (Shock, 1945, 1946; Davies and Shock, 1950b; Klütsch et al., 1962; Lee et al., 1966; Wesson, 1969; Hollenberg et al., 1973, 1974a). Glomerular filtration rate is maintained for a longer period than renal blood flow; this means that the filtration fraction (F.F.) which is defined as the quotient of G.F.R. and R.P.F. has a tendency to rise with age. Tubular function, as assessed by the maximal tubular transport capacity for diodrast or P.A.H. (Smith et al., 1938) is also diminished in the older age groups.
The reduction of renal blood flow with age is only partially understood. Renal mass decreases by 10 to 20 percent between the fourth and the eighth decade (Bell, 1950; Rao and Wagner, 1972). Thus one could argue that the depression of renal plasma flow is related to tubular inability to extract the test substance used in renal blood flow studies. However, when renal perfusion is measured by the inert gas washout technique, which is independent of

tubular function, it is apparent that the reduction in flow exceeds the reduction in renal mass (Hollenberg et al., 1974[a]). Therefore, a limited blood supply is the primary factor. Thus, a small rise in renal vascular resistance with age is encountered in the normal population. It could be suggested that the decrease in renal blood flow and glomerular filtration rate represents a response to the physiological decline in cardiac output. Indeed, the fraction of the cardiac output which perfuses the kidneys remains essentially unchanged in normotensives (Lee et al., 1966). However the reduction in cardiac output could also be related to diminished venous return and this, in turn, could reflect reduced capacity and requirement for flow in peripheral tissues (Hollenberg et al., 1974[a]). Although renal blood flow sometimes is normal in essential hypertension (Steinitz, 1941; Goldring and Chasis, 1944; Corcoran et al., 1948; Dutz, 1953; Heidland et al., 1962; Hollenberg, 1972; Pedersen and Kornerup, 1976; Pedersen, 1977), in the majority of patients renal perfusion appears to be diminished (Goldring et al., 1938, 1941; Friedman et al., 1941; Foà et al., 1942, 1943; Smith et al., 1943; Bradley et al., 1947; Corcoran et al., 1948; Hilden, 1948; Bolomy et al., 1949; Pfeiffer et al., 1950; Döring et al., 1954; Bello et al., 1960; Brod et al., 1962; Ladefoged, 1968; Hollenberg et al., 1969, Williams and Hollenberg, 1977). In most studies, where G.F.R. was measured, it was found to be within normal limits. Thus, an elevation of filtration fraction and renal vascular resistance is generally found in essential hypertension.

In this study, we observed a negative relationship of renal blood flow with respect to age. In view of the physiological decrease in renal blood flow and glomerular filtration rate due to senescence (which was already demonstrable in a very small sample of normotensives studied at our laboratory) the progressive changes in the course of hypertension should be offset against the former. We have compared our results, for the hypertensive patients, with those reported for normal men (Shock, 1945, 1946; Davies and Shock, 1950[b]; Klütsch et al., 1962; Smith, 1951; Lee et al., 1966; Wesson, 1969; Pedersen and Kornerup, 1976). It can be inferred that on the basis of age alone renal plasma flow decreases from the third to the eighth decade by about 50%.

It is interesting that in the small group of normotensives, presented in Chapter 3, renal plasma flow was reduced to a comparable degree in relation to age.

On the average, the reduction of renal plasma flow amounts 70 ml/min. per decade (Davies, 1950[b]). In our hypertensive population, this average per decade was 68 ml/min., which is, thus, similar to that of normotensives. When our results are compared to those of Wesson (1969), the decrease in renal plasma flow appears steeper for the hypertensives. Similarly, Safar et al. (1976[a]) found a negative relation between renal blood flow and age in hypertensives aged 20 to 40 years but not in age matched normotensives. In only one study, renal blood flow did not decrease with age in hypertensives, while it did in normotensives (Pedersen and Kornerup, 1976). This may have been due to an uncontrolled sodium intake. In the face of a rise in blood pressure, a reduced flow means an exaggerated increase of renal vascular

resistance with age. Moreover, extrapolated values, to early years, indicate that renal plasma flow, although in absolute terms still normal, is already diminished in the hypertensives. Therefore, an increase in renal vascular resistance is apparent even at a very early stage of the disease. With hypertension of longer duration, as reflected by age, there is a steep increase in renal vascular resistance.
It could be argued that the lower values for renal plasma flow in hypertensive patients are caused by depressed extraction of hippuran. Tubular function, as measured by the maximal capacity to excrete diodrast, tends to be decreased in hypertension (Goldring et al., 1941; Foà et al., 1942; Findley et al., 1942; Chasis et al., 1950), a phenomenon which could not be related to diminished perfusion per se (Goldring et al, 1941; Wesson, 1969). In normal man, it falls proportionally to the decline in G.F.R. (Davies and Shock, 1950b).
In contrast, extraction of P.A.H. is much less affected in hypertension (Bradley et al., 1947; Cargill, 1949; Bergström et al., 1959; Fukuda, 1964). Hippuran is cleared by the kidney through the same transport mechanism (Smith, 1951) as P.A.H. and diodrast; yet hippuran extraction at such low plasma levels as are required in isotope studies was not related to age or level of hippuran clearance (Kolsters, 1976). This argues, also, against extraction of hippuran as the cause of our finding that renal plasma flow decreases with age and hypertension.
In this study, a few patients were encountered with extremely high values for renal vascular resistance. No other characteristics were apparent in these patients, except for the fact that they were all women. The abnormality could, however, not be ascribed to the use of oral contraceptives.
In the original description of this subgroup of patients, there were also two men included. However, these two patients have died in the meantime; on postmortem examination both of them were found to have an aortic aneurysm with involvemement of the renal arteries. Although this was not readily apparent at the time of the haemodynamic investigations (physical examination, IVP and isotope renography were unremarkable), we cannot exclude the possibility that this already might have influenced the renal circulation and for this reason we have omitted them from this section.
With respect to the remaining patients, we are inclined to consider them as a separate group, an exception to the rule that renal vascular resistance increases with age in a linear fashion. It cannot be excluded, however, that just in these patients tubular extraction of hippuran was impaired.

Intrarenal haemodynamics

As described in the section on renal anatomy, the kidney is a structurally heterogeneous organ: a distinction can be made between superficial (outer cortical) and deep (juxtamedullary) glomeruli. They both seem to have a different function and blood supply. When blood enters the kidney, it is divided over these zones. Animal studies have revealed that cortical flow is much faster than medullary flow (Trueta et al., 1947; Kramer et al., 1960; Thurau et al., 1960). In 1963 Thorburn and co-corkers described a method for measuring the distribution of total renal blood flow. They identified four localized regions within the kidney, each of which could be associated with a specific

flow rate. These isotope studies were at the same time introduced in man (Ladefoged and Kemp, 1963); although the method is still under discussion (Kolsters, 1976), several studies have revealed that the intrarenal circulation in man is also subjected to regional distribution; about 80% of the renal blood flow perfuses the outer cortex (Kolsters, 1976), while the remaining part can be considered as subcortical and medullary flow. The normal cortex is perfused at a flow rate of about 300-500 ml/min/100 g (Rosen et al., 1968; Ladefoged and Pedersen, 1969; Hollenberg et al., 1968, 1969, 1970; Blaufox et al., 1970; Kew et al., 1971; Kilcoyne et al., 1973; Kolsters, 1976).
A relatively low blood flow exists in the deeper parts of the kidney; this is considered to be an important mechanism for the maintenance of the hypertonicity of the medulla (Berliner et al., 1958).
In 1947 Trueta and co-workers demonstrated that under certain experimental conditions (e.g. haemorrhage; limb injury; nerve stimulation) the blood stream was diverted away from the cortex. Since that time, many studies have been performed which revealed the significance of physiologic and non-physiologic stimuli for the intrarenal distribution of blood flow.
Several authors have reported a diminished cortical flow in hypertensive patients (Ladefoged and Pedersen, 1969; Hollenberg et al., 1968; Dell et al., 1973; Kilcoyne et al., 1973; Logan et al., 1973; Nomura et al., 1974; Kolsters, 1976).

Cortical flow rate declines with advancing age both in normals (Hollenberg et al., 1973, 1974[a]; Kolsters, 1976) and in hypertensives (Kolsters, 1976). Since this technique measures flow per unit mass of tissue, this again emphasizes a primary role of increased resistance.
This observation fits the anatomical features of the ageing cortex (Ljundquist, 1963).
The reduction of flow in the outer region of the kidney appears to be proportional to the decrease in total renal blood flow (Nomura et al., 1974; Kolsters, 1976). Although these data seem to indicate that cortical blood flow is already jeopardized at young age, this is far from proven. On the contrary, Kioschos et al. (1967) observed even higher flow rates in the outer cortex, this being related to a high cardiac output.
No consistent changes in flow rate in the other compartments have, thus far, been reported.
Fractional distribution of the blood stream towards the outer cortex is not significantly affected by age, nor by alterations in total renal blood flow or the presence of hypertension (Kolsters, 1976); it is, however, directly related to cardiac output.
It will be evident that absolute cortical flow declines with age; the absolute subcortical flow does not change markedly.
During actual follow-up this trend towards a reduction in cortical blood flow was also detectable.

Relations between renal and systemic haemodynamics

In a few early studies, renal haemodynamics were found to be more depressed at higher levels of blood pressure (Moyer et al., 1958; Möller, 1960;

Heidland et al., 1962). However, no regression analysis was carried out in these studies. Pedersen and Kornerup (1976) and Safar et al. (1976[a]) found significant inverse relations between renal blood flow and mean arterial pressure. This is confirmed by our study.
The relation is independent of age. Hypertension, therefore, has a considerable impact on the renal vasculature. Similar conclusions can be reached when the relation between renal blood flow and cardiac output is considered. In earlier studies from this laboratory, a direct relationship was found between renal blood flow and cardiac output (Birkenhäger et al. 1968, 1972). In this larger survey, this relation was still found but appeared to be explained by the effect of age alone. This is in contrast to the findings of Safar et al. (1976[a]) but in that study the direct relation of renal blood flow with cardiac output was based on only 48 hypertensive patients, aged 20 to 40 years. In 31 age-matched normotensive controls, no relation of renal blood flow with cardiac output existed either. These observations could support the concept that the kidney is able to keep its blood flow constant despite a fall in cardiac output, a phenomenon known as autoregulation. However, if this machanism really exists, one would expect the renal fraction which designates the ratio of total renal blood flow to cardiac output to increase. Yet, the opposite is found. In normotensives, Lee et al. (1966) observed only an insignificant tendency to decrease with age.
In our study, the renal fraction decreased significantly with age. At the age of 20 years, the expected renal fraction is about 20%, which is similar to what would be expected in normals (Lee et al., 1966).
With increasing age, however, renal fraction is reduced to about 16% at the age of 70. This implies that the physiological rise in renal vascular resistance is proportional to the rise in total vascular resistance, but in the presence of hypertension the rise in renal vascular resistance is in excess of that in total resistance. Other studies in hypertensive patients also revealed a lower renal fraction in comparison to normotensives, this being due to diminished renal blood flow rather than changes in cardiac output (Bolomey et al., 1949; Taquini et al., 1962; Brod, 1973; Kolsters, 1976).
These findings indicate that the kidney is preferentially affected by the hypertensive process. It is likely that, despite the raised resistance, the increased pressure is transmitted along the renal vessels, since renal venous wedge pressure is also elevated in hypertensive patients (Lowenstein et al, 1970). Moreover, morphological studies reveal striking abnormalities as described in 5.2.

Filtration processes

One of the intriguing features of essential hypertension is a steady increase in filtration fraction. This is due to the fact that glomerular filtration rate is less affected than renal plasma flow. In normotensives glomerular filtration rate is well preserved until about 40 years of age. Thereafter, it declines progressively, the average decrease, between 20 and 90 years, being 46% (Davies and Shock, 1950[b]). Regression analysis showed the reduction to be about 1.0 ml/min. per year.

Since renal plasma flow in these subjects was reduced only slightly more than that, the increase of filtration fraction with age was quite modest and usually occurred beyond the age of 60. The ratio of glomerular filtration rate to maximum transport capacity of diodrast remained unchanged throughout life, which indicates that loss of function with age affects nephrons as units. On the basis of these observations, it was concluded that formation of aglomerular tubules did not occur (Smith, 1951).
Although morphological studies have shown otherwise for the deeper cortical regions, this is less important since the age-related atrophy involves the renal cortex more than it does the medulla (Moore, 1931; Ljundquist, 1963).
As was described earlier in this chapter, the reduction in renal blood flow primarily affects the renal cortex and one would therefore, anticipate that glomerular filtration rate falls with age due to the disappearance of cortical nephrons with only little change in filtration fraction.
This indeed occurs in the first half of life; however, after the age of forty, the decrease in plasma flow exceeds that of filtration rate. In our hypertensive patients, the decline in filtration rate with age was even less in comparison to the normotensives. From 20 to 70 years of age filtration rate declined only 25% with an average reduction of 0.4 ml/min. per year. In a prospective study Reubi (1960) also showed that filtration rate does not decrease more rapidly with age in hypertensives than it does in normotensives.
So it is clear that whole kidney filtration rate cannot be considered as a simple function of total renal plasma flow. Although renal blood flow in hypertensives is reduced to a larger extent than in normotensives, the increase of filtration fraction in the former is related to a relative ,,increase" in filtration rate rather than to absolute changes in blood flow. The question is why filtration rate is less affected by age in hypertensives. A plausible explanation could be that the intrarenal blood stream is diverted from nephrons with a lower filtration fraction to those with a higher filtration fraction. This possibility was discarded by Kolsters (1976). Although he found an inverse relationship between filtration fraction and $\%C_I$, there was no relation of $\%C_I$ with age.
Since studies with cats had revealed higher filtration fractions in outer cortical glomeruli (Nissen, 1966, 1968), Kolsters argued that his observations based on 15 patients could not be explained by redistribution of blood flow. The relationship was explained by a relatively large reduction in absolute cortical flow without alterations in absolute juxtamedullary blood flow. It must be emphasized that this refers to hypertensive patients.
In contrast, Hollenberg et al. (1974[a]), in a study on 207 normal subjects, observed an inverse relationship between $\%C_I$ and age. In this study, filtration fraction was not measured but filtration rate, as assessed by creatinine clearance, decreased with age.
According to Hollenberg, the decrease in $\%C_I$ can account for preservation of glomerular filtration. In this respect, he refers to data obtained with rats, which indicate that it is the population of juxtamedullary nephrons, which has a higher filtration rate. Obviously, species differences exist with respect to single nephron glomerular filtration rate (S.N.G.F.R.).
Filtration fraction has been shown to be lower in the superficial nephrons of

the rat (Horster and Thurau, 1968; Jamison, 1973; Valtin, 1977), dog (Stein et al., 1972) and rabbit (Bankir et al., 1975) while it is higher in the cat (Nissen, 1966, 1968). So we can only speculate on the situation in the human kidney. It seems, however, that S.N.G.F.R. depends on the length of the proximal tubule (Valtin, 1977), of wich exact data for man are lacking.
Another explanation for the increase in filtration fraction could be that glomerular capillary permeability is increased. However, permeability for large molecules such as hemoglobin, is not affected by age nor do the upper molecular weight limits of dextrans excreted in the urine differ in separate age groups (Renkin and Gilmore, 1973). This naturally does not exclude the possibility that the glomerular unit becomes more porous for smaller substances.
It has been noted that structural, as well as haemodynamic, factors are involved in increased porosity of the glomerular basement membrane (Ryan and Karnovsky, 1976); at least, urinary excretion of albumin in essential hypertension is proportional to intra-arterial pressure (Parving, 1974[a]). At this point, we shall consider possible determinants of S.N.G.F.R.
Starling (1899) pointed out that the formation of an ultrafiltrate of plasma across the glomerular capillary wall is governed by the magnitude and direction of the imbalance of hydrostatic and oncotic pressures.
The net hydrostatic pressure, in turn, is the difference between glomerular capillary hydrostatic pressure and the pressure in Bowman's space. At any point along the glomerular capillary net filtration pressure is the resultant of the opposing forces. As protein free ultrafiltrate is formed in the single glomerular capillary, oncotic pressure progressively increases When, at the end of the glomerular capillary net, hydrostatic pressure equals oncotic pressure, a condition known as filtration equilibrium is reached. Such a condition has actually been found in the rat (Brenner et al., 1971, 1972; Andreucci et al., 1971; Andreucci, 1974; Robertson et al, 1972; Deen et al., 1973; Blantz, 1974) and in the primate (Maddox et al., 1974).

Filtration equilibrium is reached despite variations in arterial pressure or glomerular plasma flow. Single nephron filtration is determined by plasma flow, permeability coëfficient, transcapillary hydrostatic pressure difference and oncotic pressure. Brenner and coworkers recently reviewed the relative importance of each of these variables (Brenner et al., 1976; Brenner and Humes, 1977). The attainment of filtration pressure equilibrium requires that glomerular filtration rate depends to a high degree on renal plasma flow. An increase in plasma flow must be accompanied by an increase in capillary filtering area, in order to keep filtration rate constant.
Indeed, such a relationship was reported following vasodilatation in the rat (Brenner et al., 1972). The single nephron glomerular filtration rate then, depends entirely on glomerular plasma flow and the transcapillary pressure difference (effective filtration pressure). An increase in filtration fraction can now be explained either by an increase in effective filtration pressure or by alterations in the permeability of the glomerular capillaries (Robertson et al., 1972); changes in plasma flow alone do not affect filtration fraction (Brenner et al., 1971; Deen et al., 1973). In hypertensive rats, glomerular hydrostatic pressure is indeed raised (Azar et al., 1974, 1977) but it cannot be taken for

granted that the post-salt hypertension in these studies can serve as a model for essential hypertension.
According to Smith (1951), the rise of F.F. in hypertension is the result of an elevated postglomerular (efferent) vascular resistance due to active vasoconstriction. This would raise hydrostatic pressure within the glomerulus. However, anatomical studies in the rat (Barajas and Latta, 1963) as well as in man (Graham, 1956) failed to demonstrate many muscle cells, which would account for this vasoconstriction. Moreover, Gomez (1951), on the basis of a mathematical model, argued that the preglomerular (afferent) resistance was of much more importance than the efferent resistance. Nevertheless, in hypertensive subjects the elevated pressure can still be transmitted along the renal vessels, since the renal vein wedge pressure is also increased in these patients (Lowenstein et al., 1970). It is, therefore, reasonable to suggest that the intraglomerular hydrostatic pressure is also increased (Brown et al., 1974; Schalekamp et al., 1974). Changes in oncotic pressure, thus far, have not been found in hypertension. Although hypertensives tend to have slightly higher values for plasma proteins, the deviation from normal is not significant (Tibblin et al., 1966).
Despite changes in glomerular capillary pressure under various experimental conditions, approximately 60% of this pressure is dissipated by the efferent arteriole (Andreucci et al., 1976).
This, again, confirms the importance of preglomerular resistance and invalidates the hypothesis that efferent vessels are actively constricted.
Whether filtration equilibrium is also reached in man is, however, doubtful; several studies suggest that this is not the case in the dog (Stein et al., 1971; Baer and Navar, 1973; Strandhoy, 1974; Knox et al., 1975; Ott et al., 1976; Chenitz et al., 1976).
Although in some small primates filtration achieves equilibrium (Maddox et al., 1974), glomerular blood flow in man presumably resembles that in the dog more than in the rat or small primates (Chenitz et al., 1976).
If filtration equilibrium is not obtained, then variations in glomerular plasma flow would have only little effect on filtration rate (Knox et al., 1975). In this case, the increase in F.F. would not necessarily be pressure-dependent. It can not be ruled out, however, that alterations in permeability surface area are also responsible for the observed phenomena.

When we consider figure 33, a striking resemblance is noted between the flow-filtration relationship in our patients and that obtained for single nephrons (Brenner et al., 1976; Brenner and Humes, 1977). A reduction of renal plasma flow to approximately 300 ml/min/m^2 hardly affects glomerular filtration rate. When flow falls further, filtration rate declines proportionally. These data could indicate that at flow rates above 300 ml/min/m^2 filtration pressure disequilibrium exists in the human kidney. At lower flow rates, apparently, filtration equilibrium is reached within the glomerular capillary.
This hypothesis has several implications. First of all, it offers a reasonable explanation for the observations that under conditions of vasodilatation or volume loading glomerular filtration rate rises less than renal plasma flow. Conversely, vasoconstriction, in general, depresses filtration rate less than plasma flow (Smith, 1951). From a teleological point of view, Smith already

cast doubt on the assumption that filtration equilibrium is reached within the glomerular capillary.
He reasoned that, ideally, the point of equality between the opposing pressures should occur in the proximal end of the efferent arteriole. This would promote maximal filtration in the glomeruli and maximal reabsorption in the peritubular capillaries.
From our results, it further emerges that at a certain point, renal perfusion has declined so far that filtration pressure equilibrium will be reached. Although data, as presented above, are not available for normal man, it can be inferred from the data of Wesson (1969) and Smith (1951) that a similar mechanism must exist in normotensives.
Before the age of 40, filtration rate and plasma flow remain constant, with no change in filtration fraction.
Beyond the age of 40, filtration fraction rises in accordance with the disequilibrium hypothesis. On the basis of flow measurements, one would expect that filtration equilibrium will only be reached somehwere beyond the age of 60. In hypertensives, this "deflection point" is reached earlier due to the steep decrease of renal blood flow. In our series, this could be expected at about 40 years. If this is correct, the higher filtration fraction in hypertension is explained.
However, we must account for another difference between normotensives and hypertensives. As was pointed out above, glomerular filtration rate decreases more rapidly in normotensives than it does in hypertensives.
At a plasma flow rate of 300 ml/min/m^2, expected filtration fraction is 0.23. At the age of 40, expected filtration fraction is 0,24, which is in agreeement with the discussion above.
This implies that, above the age of 40 in a state of filtration pressure equilibrium, other factors tend to maintain filtration rate in hypertension. One would expect this factor to be the increased intraglomerular blood pressure. However, in our study, no relationship was found between mean arterial pressure and whole-kidney filtration rate. In other studies, negative relations between these two variables have been found (Pedersen and Kornerup, 1976; Berglund et al., 1976). This might indicate that in the presence of systemic hypertension afferent arteriolar constriction occurs as an autoregulatory phenomenon to prevent an excessive rise in intraglomerular pressure. In view of the increased wedge pressure, this mechanism obviously cannot fully prevent the transmission of the elevated pressure. On the other hand, the relative increase in S.N.G.F.R. is less when transcapillary pressure difference becomes higher due to a concurrent but smaller increase in oncotic pressure along the length of the capillary.
Therefore, the only possibility that remains to explain the elevated filtration fraction is an increased glomerular permeability. This could explain the increased transcapillary escape rate of albumin in essential hypertension (Parving et al., 1974[a]).
It is likely that distension of glomeruli, as seen in morphological studies (Ljundquist, 1963), leads to stretching and opening of fenestrations.

5.6 Conclusions

On the basis of the data presented in this chapter, the following conclusions can be drawn.

1. An increase in renal vascular resistance and filtration fraction is generally found in essential hypertension. Renal vascular resistance rises more steeply with age than it does in normotensives.

2. At an early stage of hypertension, renal vascular resistance is already elevated despite an almost normal renal blood flow. In the outer cortex, blood flow tends to be reduced in early hypertension.

3. The reduction in renal blood flow is not attributable to changes in cardiac output per se. An intrarenal site of elevated resistance contributes to the reduction in flow.

4. Glomerular filtration rate is biphasically related to renal plasma flow. At flow rates above 300 ml/min/m^2, filtration pressure disequilibrium appears to exist, while at lower flow rates equilibrium is achieved.

5. With hypertension of longer duration, and especially after 40 years of age, an increase in glomerular capillary porosity probably contributes to an elevation of single nephron glomerular filtration rate.

6. Although the possibility exists that redistribution of blood flow occurs to nephrons with other filtration characteristics, the available data do not permit the drawing of such conclusions.

CHAPTER 6

The kidney in essential hypertension
II Volume control

6.1 Introduction

Despite considerable variations in the daily intake of salt and water, extracellular fluid volume is kept remarkably constant by a number of regulatory processes which ultimately are effected through the kidney. By adjusting sodium and water excretion to body needs, the extracellular volume is expanded or contracted. Volume control is in a way dependent on the compliance of the interstitial and vascular space. Any degree of volume expansion reflects to some extent the ratio of actual volume to the capacity of the circulation (Dirks et al., 1976). In this way the volume factor could be important in "static" blood pressure control. On the other hand, the filling of the vascular system could modify venous return and thereby cardiac function. Along this line a "dynamic" function of blood volume would be possible. In this chapter an attempt will be made to interpret our volume measurements.

6.2 Results

6.2.1 Relations with age

Plasma volume was measured in 194 patients. The data are scattered over a wide range, but do not show a relationship with age (fig. 39) neither in absolute terms, nor when expressed per m^2. Plasma volume per m^2 was significantly lower in women than in men.

Calculated *blood volume* was not related to age either.

Extracellular volume was measured in 98 patients and appeared not to be related to age.

Interstitial fluid, as a result, was unrelated to age, nor was the quotient plasma volume/interstitial volume.

6.2.2 *Interrelations*

Systemic haemodynamics versus body fluid volumes

Plasma and blood volume show a weak but not significant tendency to increase with risting blood pressure. A similar direct relation is also observed between plasma and blood volume and total peripheral resistance ($r = 0.18$; $p<0.05$). However, these trends are predominantly caused by a few observations and even disappear when the effect of age is eliminated. Blood volume and cardiac output were not related to each other.

Renal haemodynamics versus volumes

For the whole group plasma volume is not related to renal plasma flow or glomerular filtration rate, but is is directly related to filtration fraction ($r = 0.25$; $p<0.005$).
It is interesting that in patients, in whom plasma volume was larger than 1700 ml/m^2, an inverse relationship was found between plasma volume and renal plasma flow ($n = 36$; $r = -0.39$; $p<0.02$) and between plasma volume and glomerular filtration rate ($n = 29$; $r = 0.39$; $p<0.05$). The intercepts were 300 ml/min/m^2 and 69 ml/min/m^2 respectively.
Plasma and blood volume were not related to renal vascular resistance. The quotient plasma volume/interstitial volume was not related to any haemodynamic variable.

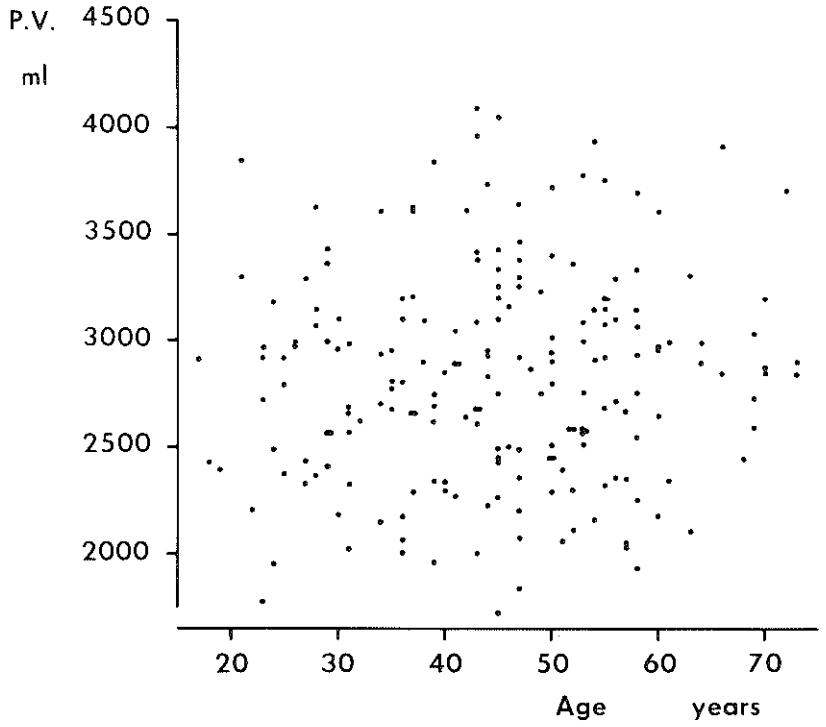

Fig. 39 Relationship between plasma volume and age.

6.3 Discussion

Several authors have emphasized the role of body fluid status in blood pressure control (Guyton 1963; Guyton and Coleman, 1969; Guyton et al., 1974; Coleman and Guyton, 1969, Tobian, 1972).
In this study, volumes were not related to age; this is in keeping with the observations of others (Tarazi et al., 1969; Schalekamp et al., 1971; Birkenhäger et al., 1972[a]). Even during actual follow-up no alterations with age were found in normotensives (Chien et al., 1966) and hypertensives (de Leeuw et al., 1978). In 51 normotensives studied at our laboratory (Chapter 3) the absence of an age relationship was also established. In hypertensive subjects, plasma volume or blood volume is said to be normal (Grollman and Shapiro, 1953; Teng et al., 1954; Walser et al., 1956; Cranston and Brown, 1963; Jones et al., 1964; Bello et al., 1965; Hansen, 1968; Ellis and Julius, 1973; Schalekamp et al., 1974; Distler et al., 1974; Weidmann et al., 1977; or reduced (Rochlin et al., 1960; Finkielman et al., 1965; Tibbin et al., 1966, Tarazi et al., 1968, 1969, 1970; Julius et al., 1971[c]; Molzahn et al., 1972; Ibsen and Leth, 1973; Parving et al., 1974[b]; Dustan et al., 1973; Safar et al., 1973, 1976; Ulrych, 1973). An inverse relationship between intravascular volume and blood pressure has been found in some studies (Tarazi et al., 1968; Kuramoto et al., 1968; Julius et al., 1971[c]; Ulrych, 1973; Safar et al., 1976) and denied in others (Tarazi et al., 1970; Ibsen and Leth, 1973; Birkenhäger and Schalekamp, 1976; Weidmann et al., 1977). On the other hand an inverse relation between plasma or blood volume and total peripheral resistance has been reported (Bello et al., 1965; Finkielman et al., 1965; Taylor et al., 1957; Birkenhäger et al., 1968; Julius et al., 1971[c]; Dustan et al., 1973; Ulrych, 1973; Safar et al., 1976, Chau et al., 1978.
Extracellular volume or total exchangeable sodium in hypertension have been found to be normal by some investigators (Walser et al., 1956; De Graeff, 1957; Hollander et al., 1961; Tarazi et al., 1969; Novak et al., 1972; Ibsen and Leth, 1973; Lebel et al., 1974; Schalekamp et al., 1974) and increased by others (Grollman and Shapiro, 1953; Teng et al., 1954; Ross, 1956; Levin and Goldberg, 1960; Hansen, 1968).
In one study exchangeable sodium was decreased (Woods et al., 1969). The differences between the various studies usually can be attributed to patient selection, time of measurement and body weight. The difference in plasma volume between males and females is generally recognized (Birkenhäger and Schalekamp, 1976). Values for plasma volume in hypertensives were not reduced when compared with 51 normotensive subjects, studied at our laboratory.
However, our values for extracellular volume are less than those observed by others (Tarazi et al., 1969; Ibsen and Leth, 1973). As a consequence, the ratio P.V./I.F. is higher in our series. Two explanations can be offered for this discrepancy. Firstly, the method of estimating E.C.V. differed in our laboratory. While we assessed E.C.V. as sulphate space, Tarazi and Ibsen measured bromide space, which is known to overestimate E.V.C. (Gamble et al., 1953; Staffurth and Birchall, 1960; Howe and Ekins, 1963). Secondly, sodium intake generally has not been controlled in other studies, while our patients

were subjected to mild sodium restriction, which should reduce extracellular volume. We have also studied 20 normotensives und similar conditions and their E.C.V. appeared not to differ from the hypertensives. This has been found before (Schalekamp et al., 1974[b]).

In our series, therefore, the P.V./I.F. ratio is not much different for both groups. On the basis of data from the literature this quotient would be either normal or slightly reduced. In case of the latter, fluid must have been extruded from the vascular space. In view of the normality of E.C.V. the kidneys do not contribute to this process. It has been suggested that in hypertensives capillary hydrostatic pressure is raised due to an increased venous tone (Ibsen and Leth, 1973). Although other studies seem to support the hypothesis of enhanced transcapillary leakage (Ulrych, 1973; Parving et al., 1974[b]), this could equally well be due to changes in arteriolar resistance (Birkenhäger and Schalekamp, 1976).
A plausible explanation for the differences in plasma volume measurements could be that there are differences in salt intake between studies. In those studies where sodium intake was controlled, no difference in plasma volume between hypertensives and normotensives emerged (Hansen, 1968; Schalekamp et al., 1974[b]). In the study of Safar et al. (1976) total blood volume was higher in normotensives who received the same amount of salt as the hypertensives, but in that study no data for plasma volume are given. Therefore, it cannot be excluded that the observed difference was due to differences in haematocrit.
In this study, no relations were found between volumes and haemodynamic variables. Although this is at variance with other studies, there is as yet no agreement whether volume is really related to systemic haemodynamics. Probably of more interest are the relations between plasma volume and renal haemodynamics as observed in this study. When the patients were divided according to their plasma volume, those with a volume higher than 1700 ml/m^2 exhibited an inverse relationship with renal plasma flow (the intercept being about 300 ml/min/m^2) and glomerular filtration rate. For the whole group P.V. is directly related to filtration fraction. An increase in filtration fraction shifts the balance between hydrostatic and oncotic pressure in such a way that tubular reabsorption of sodium is promoted at the level of the peritubular capillaries.
When renal blood flow is still relatively normal, the kidney is characterized by filtration disequilibrium. Presumably, the filtration null point is reached somewhere at the level of the efferent arterioles or peritubular capillaries. As long as filtration disequilibrium is maintained, absolute changes in renal blood flow or glomerular filtration rate per se do not contribute much to tubular reabsorption, since this is mainly determined by the drop of the hydrostatic pressure from the equilibrium point on, of which the filtration fraction is the clinical parameter. However, at flow rates below 300 ml/min/m^2, filtration equilibrium presumably is reached at the level of the glomerulus.
Under these circumstances filtration fraction only rises slightly when renal blood flow is diminished. It will be evident that the increase of plasma volume then depends primarily on the fall in renal plasma flow and glomerular filtra-

tion rate. The relationship between renal function and body fluid volumes under basal conditions has also been studied by Safar et al. (1976b). Based on the expectation that blood volume is decreased in hypertension, he demonstrated that the reduction in blood volume per unit rise in pressure was less at lower values for renal blood flow. This inverse relation still existed when the effect of blood pressure per se was eliminated. Although such mathematical derivations should be looked upon with scepticism, the results basically point in the same direction as our study.

6.4 Conclusions

On the basis of the results presented in this chapter, the following conclusions can be drawn.

1. Body fluid volumes are not altered by age or the presence of hypertension per se. Plasma volume in women is lower than in men even when corrected for body size.

2. Long-term regulation of plasma volume in hypertension appears to be related to renal filtration characteristics, filtration fraction being the main determinant.

3. From observations in established hypertension there is no evidence that the regulation of body fluid volumes is primarily involved in the pathogenesis of essential hypertension.

CHAPTER 7

Reflections on the basic haemodynamic mechanism in essential hypertension

As was demonstrated in chapter 4, hypertension appears to be related to an increase in total peripheral vascular resistance.
This is true even for subjects with a high cardiac output; in spite of the fact that calculated peripheral resistance may fall within the "normal range", it is not normal because it should have responded to the high output with vasodilatation in order to keep the blood pressure normal.
With increasing age, cardiac output falls in the face of an increased peripheral resistance. This increase is steeper than could be expected in terms of a response to the reduction of cardiac output per se. Although the results of cross-sectional studies like the present one appear to indicate that the haemodynamic pattern changes with time, only longitudinal studies can answer the question whether the average patient with essential hypertension passes through these stages. A few short-term follow-up studies (Eich et al., 1962, 1966; Birkenhäger et al, 1972b) and one long-term follow-up study are now available (Lund-Johansen, 1977). It appeared that the haemodynamic trends as described above could not be detected during a one-year period of follow-up, but they were clearly demonstrable after 10 years of follow-up. Although adequate control data (follow-up studies in normotensives) are lacking, the difference between the actual and the expected (on the basis of age) vascular resistance seems to increase with the duration of hypertension. This could be due to mechanical vascular damage or to enhanced pressor activity (vasoconstriction) or to impaired depressor activity (vasodilatation).
With respect to the variability studies, it was already suggested that impaired vasodilatation might play a role. The findings with respect to renal haemodynamics support the concept of an early increase in vascular resistance, as the basic hypertensive mechanism (chapter 5).
One could arbue that the increase in total peripheral resistance is due solely to the increased resistance in the renal vasculature. However, this is discarded by our observation that the renal fraction is still normal at an early stage of the disease. This is in agreement with Pickering (1968), who states that at the start of the disease the distribution of the cardiac output is still normal. With progression of the disorder a redistribution of blood flow occurs away from the kidneys. According to Brod et al. (1962), blood is diverted mainly to muscles, which show a near-normal resistance.

The nature of the increase in resistance appears to be complex. Both functional and structural components are recognized.
The haemodynamic situation at rest can be altered physiologically (exercise, change in posture, mental activity), experimentally (saline infusion) or pharmacologically (diuretics, anti-adrenergic agents). An overview of these provocative manoeuvres is given by Birkenhäger and Schalekamp (1976). It appears that peripheral resistance remains at a higher level in hypertensives than in normotensives even when differences in cardiac output are abolished. After ten years of follow-up, "minimal" peripheral resistance during exercise also increases (Lund-Johansen, 1977).
However, the ability of the peripheral vessels to dilate was still preserved and even exaggerated since the absolute difference in resistance between the two study periods was lower during exercise than under "basal" conditions. This points to a state of active vasoconstriction during rest. It must be emphasized, however, that basal values were obtained with the patients sitting and this could already have concealed the differences existing when the patients were supine.
Whatever the exact relations, it is apparent that vascular resistance during actual follow-up behaves as suggested by the results of our cross-sectional study.
The effect of saline loading in systemic haemodynamics is more difficult to interpret since this includes a number of adaptive mechanisms which are activated after expansion of the extracellular volume. Nevertheless, there is no indication that the changes in systemic haemodynamics after saline loading differ between normotensives and early hypertensives (Birkenhäger and Schalekamp, 1976). The abnormality of the haemodynamic setting persists after the infusion, since resistance values in the hypertensives only exceptionally decreased to the range found in normotensives.

At this point, it must be emphasized that total peripheral resistance is a quite virtual variable, which means that one cannot measure it directly. It always depends on calculation from cardiac output and (mean) arterial pressure. However, the intra-arterial pressure is not only determined by the resistance to blood flow, but also by the degree of filling and distensibility of the arterial system. The viscosity of the blood, which can also contribute to resistance, probably does not play an important role in essential hypertension (Pickering, 1968).
Although total blood volume can be easily measured in man, there are as yet no methods available to determine the fraction of blood volume wich is present in the arterial tree. This fraction could influence blood pressure in two ways. In the first place, changes in arterial blood volume could alter the volume-capacity ratio in this system; an expansion of blood volume thus increases blood pressure, provided arteriolar resistance is maintained. However, experimental volume expansion in hypertensive patients induces vasodilatation and this counteracts the expected rise in arterial pressure. The complex relationship between volume, pressure and flow in the arterial system is only poorly understood. Distensibility factors further complicate this problem.
Until the advent of more sophisticated techniques, it will be quite difficult to identify the various constituents of peripheral resistance. Its numerical value,

however, can be considered to reflect mainly the resistance, offered by the arteriolar vessels.

Structural changes have been thought to cause an increased vascular resistance (Sivertsson and Olander, 1968; Amery et al., 1969; Sivertsson, 1970; Folkow and Neil, 1971; Folkow et al., 1973). From the work of Folkow et al. (1973) it has become apparent that in established hypertension the architecture of the vascular bed is altered: the wall-to-lumen ratio is increased, presumably as a consequence of medial hypertrophy, although it cannot be ruled out that the total number of arterioles is reduced as occurs in spontaneous hypertensive rats (Hutchins and Darnell, 1974). For a great deal, these findings can account for the haemodynamic status in advanced hypertension, but do not entirely explain the situation in early (labile) hypertension. Although the resistance to blood flow in peripheral vascular beds at "maximal" vasodilation was raised in borderline hypertensives, thus suggesting structural changes already being present (Sannerstedt, et al., 1976), the changes in haemodynamics following physical exercise or volume expansion do not provide evidence for a decreased compliance of the vascular system (Birkenhäger and Schalekamp, 1976).
The elevation of renal vascular resistance has, at least partially, a functional character, since R.B.F. can be increased pharmacologically or experimentally by vasodilating agents (Reubi, 1950; Chrysant and Lavender, 1975; Chrysant et al., 1976; Wester et al., 1976), the noradrenaline precursor dopamine (Breckenridge et al., 1971; Hollenberg et al., 1973), alpha-adrenergic blockade with phentolamine (Hollenberg et al., 1975), acetylcholine (Hollenberg et al., 1975), pyrogens (Smith et al., 1938, 1943) and volume expansion (Buckalew et al., 1969; Ulrych et al., 1964; Lowenstein et al., 1970; Schalekamp et al., 1971; Kolsters, 1976). Hollenberg et al. (1975) in an attempt to discriminate between functional and structural changes infused vasodilating substances into the renal artery. His experiments revealed a quantitatively important functional vasoconstriction of the renal vessels in a number of patients with mild hypertension. On the contrary, flow reduction in elder normotensives appeared to be due to fixed organic lesions (Hollenberg et al., 1974[a]).
The results uniformly indicate that there is indeed increased tone in the renal vascular bed of patients with essential hypertension.
Moreover preliminary observations from our laboratory have shown that the increase in vascular resistance in the renal vessels is also demonstrable during actual follow-up (de Leeuw et al., 1978). Both the functional and the structural components of the increase in resistance may be the sequelae of vasoconstrictor stimuli, either originating from the tissue (auto-regulation) or from increased activity on the part of pressor systems.

A functional vasoconstriction has been thought to be the result of so-called autoregulation of tissue blood flow, in response to an increased cardiac output. There is no way to substantiate this view, mainly due to time relations. A firm autoregulatory control of tissue blood flow can be demonstrated rapidly in experimental conditions where the ability of the kidney to maintain extracellular fluid homeostasis is interfered with (Borst and Borst-de Geus, 1963; Ledingham and Cohen, 1963, 1964; Ledingham et al., 1967; Conway, 1966; Coleman and Guyton 1969; Guyton and Coleman, 1969; Guyton et al., 1970,

1971; Ferrario et al., 1970; Ferrario, 1974; Bianchi et al., 1972; Distler et al., 1973; Zaal et al., 1973). In essential hypertension no direct information on autoregulation is available, but the steady rise in vascular resistance over the years, in the face of progressive subnormality of cardiac output, would suggest that the mechanisms involved here are basically different from autoregulation. Enhanced systemic pressor activity could be based either on the renin-angiotensin system or on the adrenergic system or both.
In the next chapters we will consider to what extent the hormonal and neural factors contribute to blood pressure control in hypertension.

CHAPTER 8

Pressor mechanisms in essential hypertension

The renin-angiotensin-aldosterone system

8.1 Introduction

Renin is a proteolytic enzyme with a molecular weight of about 40.000; it has no direct physiological effect but acts only to cleave a leucine-leucine bond of its substrate, angiotensinogen. The latter substance is an alpha-2-globulin, synthesized in the liver. By the action of renin a decapeptide (angiotensin I) is liberated, which is relatively inacative. By a converting enzyme, which is present in blood and tissues, especially the lungs, angiotensin is cleaved to yield the octapeptide angiotension II, which to present knowledge is the most potent vasoconstrictor. Angiotensin II also stimulates the secretion of aldosterone by the adrenal cortex, either directly or by one of its metabolites.
Renin was first described in 1898 by Tigerstedt and Bergmann, but it lasted until 1940 before it was demonstrated that it was probably an enzyme acting upon another substance in the blood (Page 2 and Helmer, 1940; Braun-Menéndez et al., 1940). It is synthesized and stored in membrane-bound cytoplasmic granules by large, epitheloid-like cells which lie at the vascular pole of the glomerulus. These cells are part of the so-called „juxtaglomerular apparatus" which encompasses:

1. Those portions of the afferent and efferent arterioles, where the granular cells at the glomerular hilus first appear,

2. the macula densa and

3. the Goormaghtigh cells (Barajas and Latta, 1963).

The epitheloid cells of the afferent arterioles are located in the medial layer at the distal part close to the other elements of the juxtaglomerular apparatus. Ultrastructurally, these cells appear to contain myofibrils and they are sur-

rounded by a basement membrane, which is identical to that of the smooth muscle cells.
The macula densa consists of cells in the distal tubule; they are not mesenchymal in origin and contain only a small amount of renin (Mulrow, 1976). The role of the Goormaghtigh cells, which do not contain cytoplasmic granules is still obscure.

The autonomic nevous system may represent an important structural and functional part of the juxtaglomerular apparatus. Various authors described the existence of synapses between cells of the juxtaglomerular apparatus and nerve endings of the autonomic system (Barajas, 1964; Simpson and Devine, 1966; Rojo-Ortega et al., 1968; Wägermark, 1968).
Adrenergic fibers running along the arteries from the hilus of the kidney terminate in the walls of the arterioles; they come in contact with about one-third of the cells of the efferent arteriole and somewhat less than one-third of the cells of the afferent arterioles in the region of the juxtaglomerular apparatus (Barajas and Müller, 1973). Renin has been demonstrated within the juxtaglomerular apparatus, both by morphological (Chandra et al., 1965; Barajas and Latta, 1965; Barajas, 1966; Tisher et al., 1968) and immunofluorescence techniques (Cook and Pickering, 1959; Edelman and Hartroft, 1961; Bing and Kazimierczak, 1962), thus confirming the hypothesis of Goormaghtigh (1939).
Cook (1967) demonstrated by direct sampling that the cytoplasmic granules contain renin.
Except for the kidney, renin has also been found in the uterus, placenta, the adrenal glands, brain, submaxillary gland and in the wall of arteries and veins. The role of this extra-renal renin is not fully clear yet.

8.2 Release of renin

The factors which may influence renin secretion are:

1. renal perfusion pressure
2. sodium concentration at the macula densa
3. impulse traffic of the renal sympathetic nerves
4. alterations in extracellular volume and plasma concentration of sodium
5. potassium
6. angiotensin II and
7. anti-diuretic hormone.

Each of these will now be discussed briefly.

8.2.1. Renal perfusion pressure

One of the major theories concerning the regulation of renin release stresses the role of a renal vascular receptor in the afferent arteriole, which is sensitive to local changes in perfusion pressure (Tobian et al., 1959; Tobian, 1960, 1962; Skinner et al., 1964; Blaine et al., 1970, Blaine and Davis, 1971; Davis, 1971, 1973; Kaloyanides et al., 1973; Churchill et al., 1974). According to this theory, renin release varies inversely with local perfusion pressure, independently of changes in renal blood flow. It is suggested that the vascular receptor is a baroreceptor or stretch receptor (Tobian, 1960), which functions even without the involvement of the sympathetic system or other intrarenal mechanisms (Blaine et al., 1970; Blaine and Davis, 1971). Several authors have provided evidence that the intrarenal stretch receptor is a most important effector of renin release (Blaine and Davis, 1971; Witty et al., 1971, 1972; Davis, 1973; Gotshall et al., 1973, 1974; Kaloyanides et al., 1973). The nature of the stimulus and the haemodynamic alterations which influence the renin releasing cells are not fully clarified. Whereas the data of some investigators suggest that vasoconstriction is responsible (Romero et al., 1968; Tagawa and Vander, 1969; Blaine and Davis, 1971; Witty et al., 1971, 1972), other studies point in the direction of vasodilatation (Ayers et al., 1969; Harris and Ayers, 1972; Eide et al., 1973; Gutmann et al., 1973; Gotshall et al., 1974).
Thus, renin release is probably not merely dependent on the arteriolar diameter but rather on the wall tension of the afferent arteriole (Davis, 1973, 1974). On the basis of experiments in the isolated perfused rat kidney, Fray (1976) suggested that vasodilatation or higher perfusion pressure increases the stretch of the afferent arteriole, whereas vasoconstriction or low perfusion reduces the stretch on the wall. Renin release, then, would be most sensitive to changes in the ratio between inner and outer diameter of the afferent arteriole (Fray, 1976).

8.2.2. Sodium concentration at the macula densa.

The macula densa theory is the second major theory on renin release and postulates a receptor which is sensitive to distal tubular sodium (Goormaghtigh, 1945; Vander and Miller, 1964; Brown et al., 1964; Reeves and Sommers, 1965; Thurau et al, 1967; Vander and Luciano, 1967; Vander and Carlson, 1969). It has, however, two angles of incidence. While Vander and Miller suggest that a reduced sodium load at the macula densa stimulates renin release, Thurau and associates attribute enhanced renin release to an increased sodium load. The experiments of Freedman et al.,(1974) seem to support the first hypothesis, while other studies support the latter (Meyer et al., 1968; Cooke et al., 1970).
Barajas (1971) on the basis of morphological studies reported that the macula densa is frequently more in contact with the efferent than the afferent arteriole. In his view, renin release is stimulated by decreased contact of the macula densa with the afferent arteriole. Increased sodium load and tubular volume would restore the contact and suppress renin release. Thurau and associates

have proposed that an increase in sodium concentration at the macula densa activates preformed physiologically inactive renin molecules (rather than stimulating de novo synthesis). As a result angiotensin II is formed which is supposed to act locally on the afferent arterioles to produce constriction and decreased glomerular filtration rate thus closing a feed-back loop (Granger et al., 1972; Thurau et al., 1972). It should be emphasized that this feed-back hypothesis does not necessarily reflect integrated renin release. Nash et al. (1968) assumed that alterations in sodium transport across the macula densa would regulate renin release. The mechanism of the macula densa, however, seems to be overruled by the baroreceptor mechanism (Kaloyanides et al., 1973).

8.2.3. Sympathetic activity

There is now substantial evidence that the sympathetic nervous system and circulating catecholamines play an important role in the control of renin release (Davis, 1973). They seem to do so quite independently of the stretch and macula densa receptors (Johnson et al., 1971; Ganong, 1973; Johns et al., 1975; Zanchetti et al., 1976).

Electrical stimulation of the renal nerves (Vander, 1965; Johnson et al., 1971; Coote et al., 1972; Ganong. 1972; Loeffler et al., 1972; LaGrange et al., 1973) also promotes renin release.

The same effect can be brought about by stimulation of vasomotor centers in the medulla oblongata (Passo et al., 1971), mesencephalon (Ueda et al., 1967) and pons (Richardson et al., 1973b, 1974). It has been suggested that serotonin may play a role via central pathways in renin release (Epstein and Hamilton, 1977). On the contrary, stimulation of suprabulbar vasodepressor areas resulted in a decrease of plasma renin activity (Zehr and Feigl, 1973). The activity of this area, in turn, could be dependent on the firing rates of vagally innervated cardiopulmonary receptors (Mancia and Donald, 1975; Mancia et al., 1975; Zehr et al., 1976). Indeed, renin secretion rises after vagotomy (Yun et al., 1976), possibly by an increase in renal nerve activity after such a procedure (Clement et al., 1972; Mancia et al., 1973). Undoubtedly neural influences also contribute to the renin release during the first minutes after a sudden decrease in renal perfusion pressure (Stella et al., 1976), during tilting or upright posture (Gordon et al., 1967; Michelakis and McAllister, 1972; Stella et al., 1974), vasodilatation (Pettinger et al., 1973; Pettinger and Mitchell, 1975; Wester et al., 1976[b]) and after sodium depletion (Vander, 1967; Brubacher and Vander, 1968; Mogil et al., 1969; Stella et al., 1974) or hypoglycemia (Otsuka et al., 1970; Assaykeen et al., 1970; Lowder et al., 1975, 1976).

The physiological role of the renal sympathetic nerves in the experiments mentioned above, seems to be confirmed by in vitro studies on kidney slices (Aoi et al., 1976). Many studies have revealed that in the animal intravenous or intra-arterial infusion of catecholamines increases renin release (Vander, 1965; Wathen et al., 1965; Bunag et al., 1966; Ueda et al., 1970; Winer et al., 1971; Johnson et al., 1971; Tanigawa et al., 1972; Reid et al., 1972; Chokshi et al., 1972). In man the same effect occurs (De Champlain et al., 1966).

Adrenergic agents have also been shown to stimulate renin release in vitro

kidney preparations (Michelakis et al., 1969; Rosset and Veyrat, 1971; Veyrat and Rosset, 1972; Aoi et al., 1974; Nolly et al., 1974).
Controversy still exists about the type of receptor involved in these reactions. Although there is general agreement that beta-receptors can mediate renin secretion (Winer et al., 1969, 1971; Assaykeen et al., 1970, 1974; Otsuka et al., 1970; Passo et al., 1971; Ganong, 1972; Reid et al., 1972; VanDongen et al., 1973; Aoi et al., 1974; Nolly et al., 1974; Tanaka and Pettinger, 1974; VanDongen and Peart, 1974; Pettinger and Mitchell, 1975; Weinberger et al., 1975; Capponi and Valloton, 1976; Johnson et al., 1976), it is still unsettled whether extrarenal or intrarenal receptors are involved.
The studies of Reid et al. (1972) provided evidence for extrarenal beta-receptors mediating renin release, but on the other hand strong evidence for intrarenal beta-receptors is available from studies with kidney slices (Rosset and Veyrat, 1971; Aoi et al., 1974; Nolly et al., 1974), renal cell suspensions (Michelakis et al., 1969) and intrarenal infusions (VanDongen et al., 1973; VanDongen and Peart, 1974; Assaykeen et al., 1974; Johnson et al., 1976). It is not excluded that in the intact organism both receptors, if they really exist, come into play.
The opinions about the role of alpha-receptors are far more divergent. While some authors suggested a stimulatory effect of alpha-receptors (Winer et al., 1969, 1971; Coote et al., 1972), most other investigators support the concept that these receptors are inhibitory in origin (Nolly, et al., 1974; VanDongen and Peart, 1974; VanDongen and Greenwood, 1975; Pettinger et al., 1976). Studies with alpha-blocking agents have sometimes revealed the stimulatory role of alpha-receptors (Winer, et al., 1969, 1971; Coote, et al., 1972) but this could not be confirmed in other studies (Assaykeen et al., 1970; Michelakis and McAllister, 1972; Tanigawa et al., 1972; VanDongen et al., 1973; Nolly et al.,1974; Capponi and Valloton, 1976; Johnson et al., 1976). Recent data support the hypothesis that the alpha-adrenergic effect predominates and can effectively inhibit the action of the beta-receptor (Capponi and Valloton, 1976; Strang et al., 1977; Strang, 1978).

8.2.4. Humoral factors (electrolytes, angiotensin, antidiuretic hormone).

Alterations in plasma sodium concentration have been shown to influence renin secretion; an inverse relationship was found between plasma sodium concentration and plasma renin concentration (Brown et al., 1965[a]; Nielsen and Möller, 1967) or granulation of the juxtaglomerular cells (Pitcock and Hartroft, 1958). However, the effect of the sodium ion is overrided by changes in fluid balance and body fluid, since expansion of the extracellular volume decreases, plasma renin (Meyer et al., 1966[a]; Newsome and Bartter, 1968; Rosenthal et al., 1968; Gordon and Pawsey, 1971) even if this is accompanied by a decline in plasma sodium concentration. It is, however, quite probable that sodium plays a role in regulating renin release independently of its ability to expand intravascular volume (Nash et al., 1968; Yamamoto et al., 1969; Krakoff et al., 1970; Shade et al., 1972; Tuck et al., 1974). Salt loading which increases plasma volume (Lyons et al., 1944; Grant and Reischsman, 1946)

leads to a reduction in renin while salt depletion has the opposite effect (Brown et al., 1963; Gross et al., 1965; Peart, 1965; Genest et al.,1965; Laragh et al., 1966; De Champlain et al., 1966; Nielsen and Möller, 1967; Gunnels et al., 1967; Brubacher and Vander, 1968; Michelakis and Horton, 1970; Laragh et al., 1972[a]; Omvik et al., 1976). The relative contribution of pressure, sympathetic nerves and macula densa in this response is not fully known.
The potassium ion also has a suppressing effect on renin release (Veyrat et al., 1967; Brunner et al., 1970; Dluhy et al., 1970; Vander, 1970; Abbrecht and Vander, 1970; Sealey, et al., 1970) an effect which is independent of changes in aldosterone secretion (Brunner et al., 1970) or in sodium balance (Abbrecht and Vander, 1970). The action of potassium presumably is intrarenal at the level of the tubules (Vander 1970; Schneider et al., 1972; Shade et al., 1972).
A direct feed-back inhibition of renin release is exerted by angiotensin II (Vander and Geelhoed, 1965; Genest, et al., 1965; De Champlain et al., 1966; Bunag et al., 1967; Tanaka et al., 1969; Blair-West et al., 1971; Shade et al., 1973; Bing, et al., 1973; VanDongen et al., 1974; Oates et al., 1974; Sen et al., 1974; McDonald et al. 1975). The site of action is presumably intrarenal (Genest et al., 1965; Michelakis and Horton, 1970; Michelakis, 1971; Blair-west et al., 1971; Rosset and Veyrat, 1971; VanDongen et al., 1974) and independent of sodium metabolism (Shade et al., 1973).
An inhibitory effect on renin secretion is also shown by vasopressin (Bunag et al., 1967;Vander, 1968; Tagawa et al., 1971; Shade et al., 1973). This effect does not require alterations in sodium concentration at the macula densa (Shade, et al., 1973). Although the site of action can be intrarenal (VanDongen, 1975, Hesse and Nielsen, 1977) some investigators favor the view that expansion of plasma volume is prerequisite for the effect (Newsome and Bartter, 1968; Khokhär et al., 1976[a]).
Still other factors may be involved in renin release like calcium (Kotchen et al., 1974, 1977; Watkins et al., 1976) and hydrogen (Kisch et al., 1976), which suppress renin secretion. Whether this is a direct effect or mediated through changes in distal sodium delivery remains to be settled.

8.3 Aldosterone

Four determinants of aldosterone secretion are known: the renin-angiotensin system, adrenocorticotrophic hormone (A.C.T.H.), potassium and sodium. The renin-angiotensin system has been thought to be the most important modulator of aldosterone secretion.
Recently, evidence has been gathered that the above mentioned factors interact and that under certain circumstances A.C.T.H., sodium and potassium can even become the major regulating factor (Bayard et al., 1971; McCaa et al., 1972; Kem et al., 1973; Katz et al.,1975; Hata et al., 1976).

8.3.1. Renin-angiotensin system

This is still one of the major stimuli for aldosterone secretion and in many situations where renin and angiotensin are elevated, there is secondary increase in aldosterone production (Laragh et al., 1960; Gowenloch and Wrong, 1962; Barraclough et al., 1965; Ames et al., 1965; Laragh et al., 1966; Brown et al., 1972[a]). The factors regulating renin release have already been described.

8.3.2. A.C.T.H.

This pituitary peptide appears to have a permissive role in aldosterone secretion. At physiologic doses A.C.T.H. stimulates aldosterone release (Katz et al., 1975; Kem et al, 1975; Nicholls et al., 1976). This has even been demonstrated in patients with adrenal adenomas (Wenting et al., 1976). Higher doses initially increase aldosterone secretion but after a short time enhance its disappearance from the circulation (Liddle et al., 1956; Venning et al., 1962; Tucci et al., 1967; Newton and Laragh, 1968; Biglieri et al., 1969) by an effect on the metabolic clearance rate (Pratt et al., 1976; Messerli et al., 1976[a]).

8.3.3. Potassium

Hyperkalemia induces aldosterone secretion and hypokalemia suppresses it (Funder et al., 1969; Dluhy et al., 1972; Scholer et al., 1973; Himathongkam et al., 1975). Not only the potassium level in the serum, but also the intracellular potassium level in the zona glomerulosa appears to be responsible for this mechanism (Boyd and Mulrow, 1972).
In the salt depleted state potassium seems as important as the renin angiotensin system in regulating aldosterone release (Dluhy et al., 1974).

8.3.4. Sodium

The sodium ion per se seems to regulate aldosterone only at very low concentrations (Davis et al., 1963) where it stimulates, or at high concentrations during extreme dehydration (Schalekamp et al., 1976), where it inhibits.

Sodium balance appears to influence the response to angiotensin II; the systemic pressor response to A II is impaired by sodium depletion and enhanced by sodium loading (Davis et al., 1962; Blair-West et al.,1962; Kaplan and Silah, 1964; Reid and Laragh, 1965; Barraclough et al., 1967; Bianchi et al., 1968 Hollenberg et al., 1972, 1974[b]; Strewler et al., 1972; Oelkers et al., 1972; Samwer et al., 1974; Thurston and Laragh, 1975; Slack and Ledingham, 1976). Studies with isolated vascular preparations have made it reasonable that this phenomenon is not due to systemic effects (Strewler et al., 1972). The mechanism of this "desensitization" is not yet clear, but is probably related to saturation of A II receptors (Thurston, 1976).

While the receptors in the vascular wall and in the adrenal cortex differ from each other (Williams et al., 1974; Steele and Lowenstein, 1974; Bravo et al., 1975, 1976) several studies indicate that the adrenal cortex is sensitized by sodium depletion (Oelkers et al., 1974; Hollenberg et al., 1974[b]; Tuck et al., 1974).
A dissociation between the renin-angiotensin system and aldosterone under certain circumstances has also been observed by others (Chinn et al., 1970; Best et al., 1971; Epstein and Satura, 1971; Boyd et al., 1972[a]; Mendelsohn et al., 1972). It has been suggested that during volume changes factors, other than the renin-angiotensin system modulate aldosterone release (Birkhäuser et al., 1973; Muller and Valloton, 1974). Except for A.C.T.H. and potassium this has been attributed to alterations in metabolic clearance rate (Gaillard et al., 1976) and to an as yet still hypothetical factor (Blair-West et al., 1973; McCaa et al., 1974).

8.4 Results

8.4.1. Introduction

In this chapter we shall investigate the possible role of the renin-angiotensin-aldosterone system in our patients with essential hypertension.
Originally, in our laboratory total plasma renin concentration was assayed (as described in Chapter 2) after an acidification step to pH 3.3. This procedure has been followed for the group of 226 patients which have been described in the preceding chapters. As already mentioned in Chapter 2.1, we have selected a second group of 59 patients (mean age 43 years) in whom specifically active renin was measured. Furthermore, in most of these patients the same haemodynamic investigations were carried out as in the original group. Both groups will be referred to as group I and II for the larger (original) and smaller group, respectively.

8.4.2. Relations with age

Plasma renin concentration

In a mere 11 patients of group I no values for T.P.R.C. were obtained; in most cases, this was due to incorrect handling of material at the time of sampling or during the technical procedure. Data from the remaining 205 patients are plotted against age in figure 40. There is a tendency for T.P.R.C. to decline with age ($r = -0.15$; $p<0.05$). Low renin values are most often encountered between 40 and 60 years of age. When the patients are divided according to their glomerular filtration rate the following pattern is observed. When glomerular filtration rate remains above 55 ml/min/m^2, the relation of T.P.R.C. versus age is more pronounced ($r= -0.25$; $p <0.001$), while in those patients where G.F.R. has fallen below that limit, renin levels tend to increase with age

although this is only of borderline significance ($n = 30$; $r = 0.32$; $0.05 < p < 0.10$). Arbitrarily we considered a G.F.R. of less than 55 ml/min/m^2 as an index of depressed renal function.

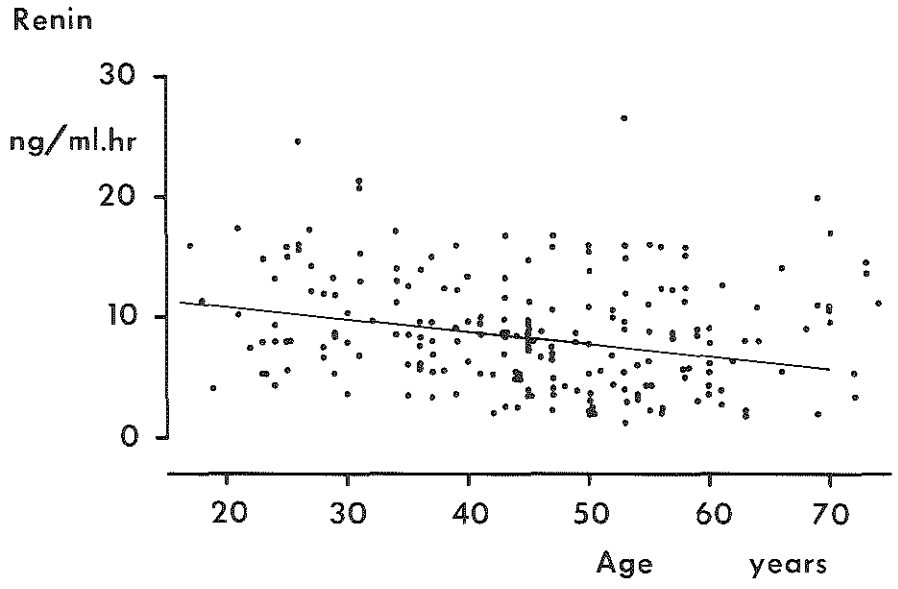

Fig. 40 Relationship between total renin concentration and age. The regression line indicates this relation in patients with normal GFR.

In group II total renin concentration also declined with age ($r = -0.39$; $p < 0.01$). In this group active renin was also measured and this again exhibited an inverse relation with age ($n = 39$; $r = -0.37$; $p < 0.025$).
The ratio active/total renin was not related to age. In none of the patients were renin levels abnormally high.

Plasma aldosterone

From the total of 100 observations in group I there is no obvious relation with age (fig. 41). The values for aldosterone are within normal limits in 89 patients. In the remainder, we observed no development of clinical hyperaldosteronism during follow-up in the hypertension clinic. The parients in group II also did not exhibit a relation of aldosterone with age.

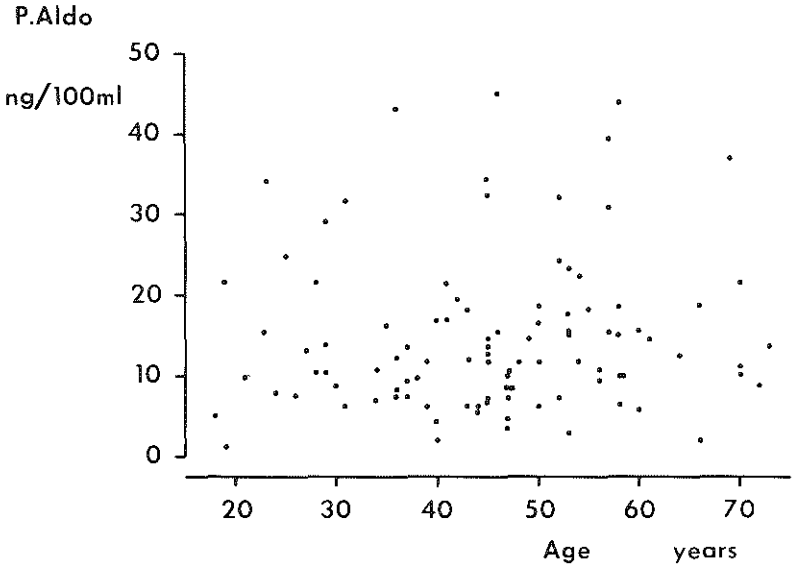

Fig. 41 Relationship between plasma aldosterone and age.

8.4.3. Interrelations

Renin and aldosterone

A significant direct relationship was observed between total and active renin ($r = 0.74$; $p < 0.001$; fig 42). On the average active renin made up 33% of total renin; this value was not affected by the absolute level of total renin. From figure 43, it is apparent that there is no relation between, total or active renin concentration and aldosterone. In group II, the same phenomenon was observed. Moreover, no relationship was found between active or inactive renin and aldosterone.

Renin versus systematic haemodynamics

The relationship between total renin concentration and mean arterial pressure is presented in figure 44. For the entire group no significant relationship could be detected.
However, this pattern seems to be disturbed, in a way, by only a few patients. In one of them, G.F.R. was lower than 55 ml/min/m^2, while in another renal haemodynamics had not been measured. If these patients are omitted from the analysis an inverse relationship between renin and mean arterial pressure is apparent.
In group II, active renin tended to decrease at higher levels of blood pressure but this relation was not significant.
Total and active renin are unrelated to cardiac output and peripheral resistance, although there was a tendency for plasma renin concentration to decline with higher levels of peripheral resistance, provided that G.F.R. had not fallen below 55 ml/min/m^2.

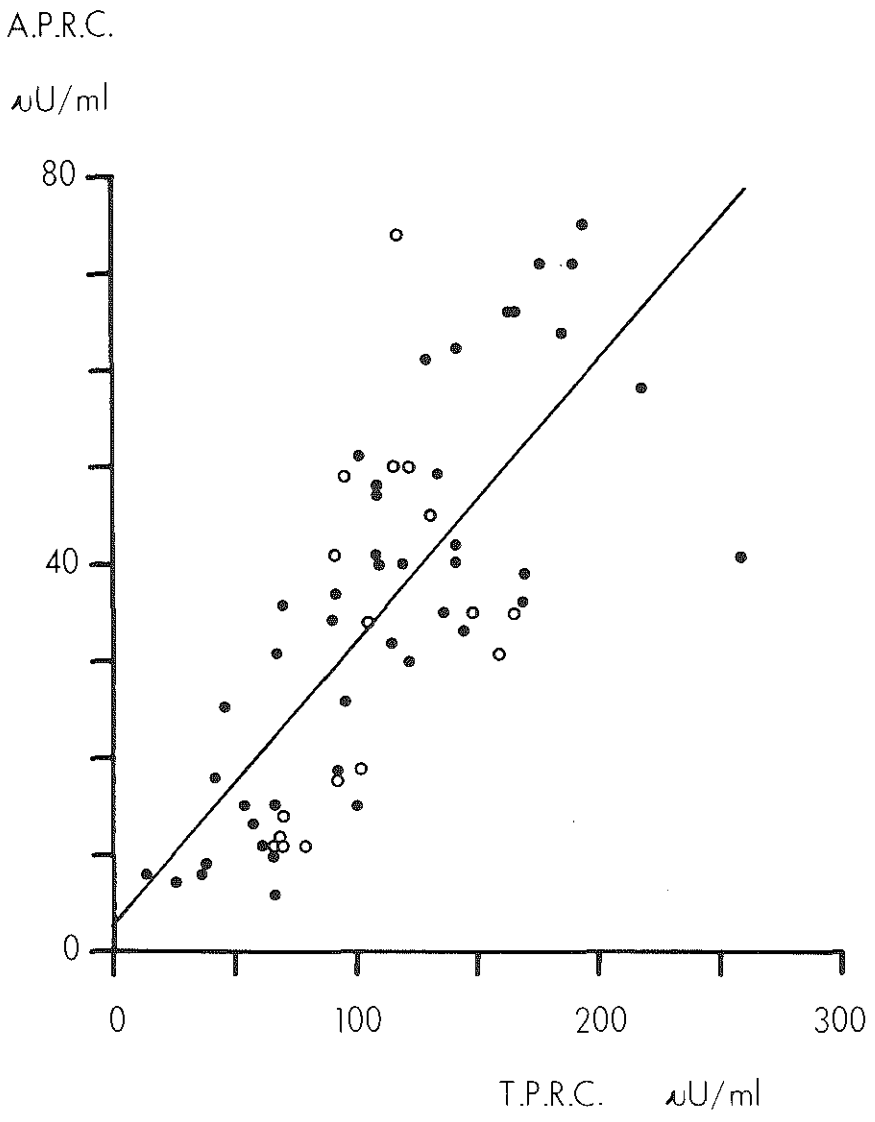

Fig. 42 Relationship between total and active renin concentration in peripheral venous blood (closed circles) and in arterial samples (open circles).

Renin versus renal haemodynamics

Total renin concentration is inversely related to G.F.R. ($r = -0.22$; $p<0.005$), as shown in figure 45. On the other hand, renin levels are not related to renal blood flow or filtration fraction, even when corrected for the effect of glomerular filtration rate. In figure 46, the relation between renin and renal vascular resistance is given, which appears to be a complex one. Again a

distinction is made between patients with normal and those with subnormal G.F.R. While the former group exhibits an inverse relation between renin and R.V.R. ($r = -0.28$; $p<0.001$), a positive though not significant relation is found in the latter group ($r = 0.24$; n.s.).

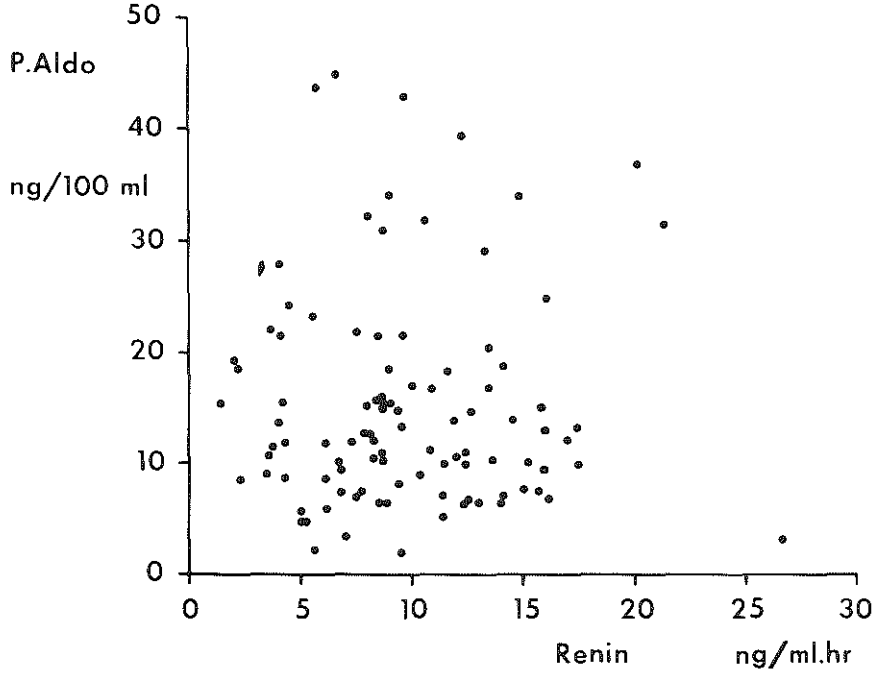

Fig. 43 Relationship between total renin concentration and plasma aldosterone.

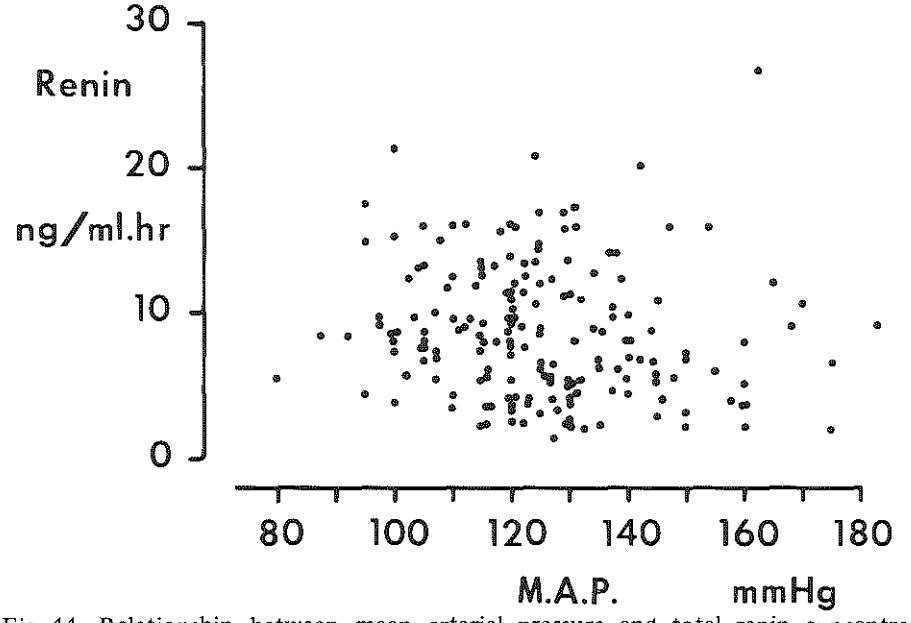

Fig. 44 Relationship between mean arterial pressure and total renin concentration.

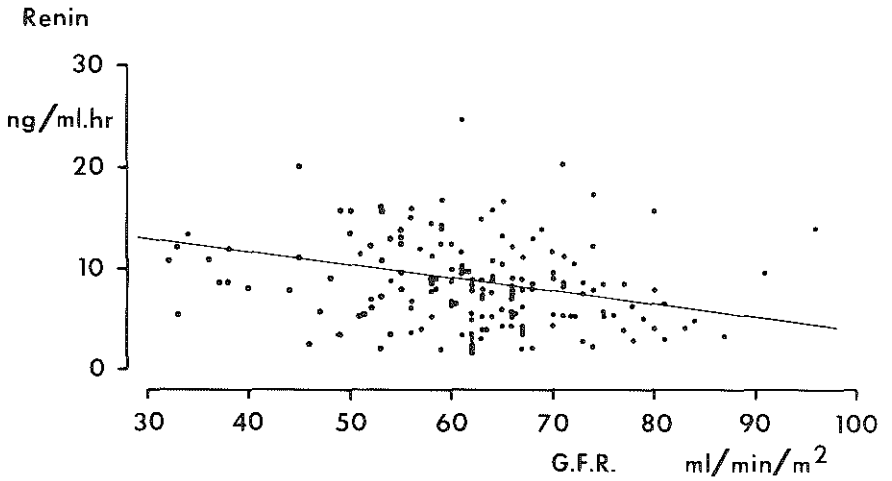

Fig. 45 Relationship between glomerular filtration rate and total renin concentration.

Partial regression analysis

Since renin is inversely related to age and G.F.R., we have two opposing factors, for G.F.R. is also inversely related to age. Moreover, the relations with blood pressure should be corrected for these trends.

The inverse relation between renin and age remains even when we eliminate either the effect of blood pressure or the effect of G.F.R. When both these factors are eliminated the regression coëfficient is -0.20 ($p<0.005$). The relation between renin and G.F.R. still exists when the effects of both age and blood pressure are eliminated ($r = -0.24$; $p<0.005$).

The relationship between renin and blood pressure becomes stronger when we correct for the effect of G.F.R. Although eliminating the effect of age alone abolishes this relation, simultaneous elimination of age and G.F.R. yield a still significant inverse relation.

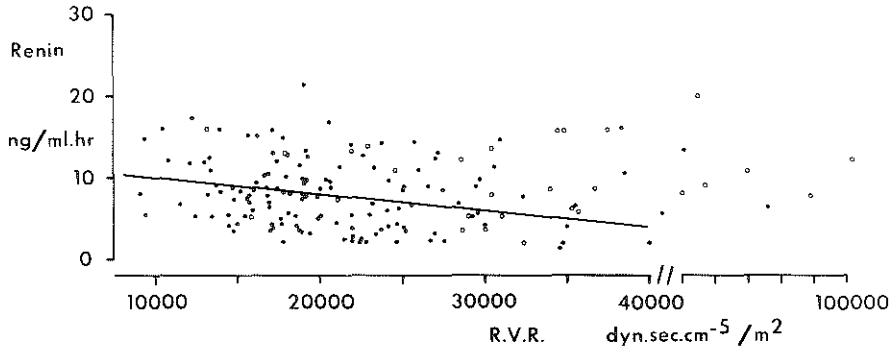

Fig. 46 Relationship between renal vascular resistance and total renin concentration in patients with normal (closed circles) and reduced (open circles) GFR.

Renin and aldosterone versus body fluid volumes

Renin and aldosterone are not related to plasma (or blood) volume; however, in the subgroup of patients with a reduced G.F.R., renin is positively related to plasma volume ($r = 0.37$; $p<0.05$), but not to interstitial or total extracellular volume. Aldosterone is not related to mean arterial pressure and shows a direct relationship of borderline significance with extracellular and interstitial fluid. It is not related to the quotient P.V./I.F.

8.4.4. Renin secretion rate

In 10 patients (age range 29 - 68, average 47 years) the secretion of total and active renin by the kidney was determined. Concentration of total renin averaged 111 ± 18 μU/ml in renal arterial and 123 ± 18 μU/ml in renal venous blood. Values for active renin were 30 ± 4.7 μU/ml and 36 μU/ml respectively. Secretion of total renin ranged from 0 to 13.920 μU/min (average 6189 μU/min) and of active renin from 0 to 10.270 μU/min (average 3407 μU/min). Per 100 grams of tissue mass these values were 0 to 5046 (average 2495) μU/min and 0 to 3744 (average 1395) μU/min. The relative amount of active renin was 28 ± 3.2% in arterial and 29 ± 3.2% in venous blood. This did not differ from the percentage of active renin in peripheral venous blood (24 ± 2.5%), the latter samples being drawn on a sepearate day.
In view of the wide range of data in this series, it is not possible to obtain any significant difference in absolute concentrations of renin in arterial and venous blood. Therefore, another approach was chosen. The total amount of renin in renal venous blood was expressed as a percentage of that in arterial blood. When the levels in arterial blood are taken as 100% then the amount of total renin increased to 112 ± 2.5% in renal venous blood ($p<0.005$) and that of active renin to 121 ±5.1% ($p<0.005$). Inactive renin rose by 9 ± 4.1%, this not being significant. Secretion patterns appeared not to be related to age, level of blood pressure or haemodynamic parameters.

8.5 Discussion

Several different methods are available to estimate plasma renin. The measurement of plasma renin concentration according to the method of Skinner (1967) involves an acidification step to pH 3.3. However, it has been shown by Lumbers (1971) that acidification increases the assayed concentration of renin. The increase apparently is due to activation of an inactive prorenin (Lumbers, 1971; Skinner et al., 1975; Day et al., 1975; Boyd, 1977) and occurs only when the pH falls below 4. This result was shown not to be caused by inactivation of angiotensinases. It has been suggested that acidification destroys an inhibitor of active renin. This would account for the higher molecular weight renin found by several investigators (Boyd, 1972; Leckie, 1973; Day and Luetscher, 1974, 1975; Leckie and McConnell, 1975; Day et al., 1976). Although inactive renin

has been found in several species, including man (Boyd, 1974, 1977; Leckie and McConnell, 1975; Morris and Johnston, 1976; Day et al., 1976; Derkx et al., 1976; VanDongen et al., 1977) the origin of this compound is still obscure. The presence of inactive renin in anephric man suggests an extrarenal source (Weinberger et al., 1976; Deheneffe et al., 1976).

Similarly, VanDongen et al., (1977) could not detect inactive renin in the venous effluent of the isolated perfused rat kidney, whilst this was demonstrable in peripheral plasma samples. Apparently, our study in 10 subjects with essential hypertension is too small to draw firm conclusions about secretion patterns of active and inactive renin by the kidney. However, it could be demonstrated that the amount of total and active renin was significantly higher in blood leaving the kidney than that entering it. In contrast, the differences were not significant for inactive renin.

This may indicate that renin is predominantly secreted in the active form, at least under basal conditions. This is at variance with the observations of Derkx et al. (1976), who suggested that both active and inactive renin were secreted by the kidney. However, in that study no direct arterial-venous concentration gradients across the kidney were measured.

Still we are inclined to believe that the kidney is able to secrete inactive renin, since in some cases the actual A-V difference for this substance was too large to be explained by experimental error. In one other patient secretion of total renin was zero, while there was secretion of active renin.

These observations suggest that in vivo there is a continuum between inactive and active renin, both forms probably being in dynamic equilibrium. It seems reasonable to suggest that the inactive part of renin serves as a buffer for situations such as tilting or acute vasodilatation where an prompt increase in active renin is required (Derkx et al., 1976). This would also fit the observation of Thurau et al. (1972).

Under steady state conditions about one-third of the total amount of renin circulates in the active form. This relation in our patients was not disturbed by age or the height of blood pressure. Therefore, the estimation of total renin quite accurately reflects the amount of active renin present. This is in agreement with the observation of others (Skinner et al., 1975; Leckie et al., 1976; Fagard et al., 1977). At high concentrations of plasma renin, however, the equilibrium may shift to the active form (Derkx et al., 1976), although our study failed to reveal such a mechanism.

Much interest has been focussed on the possible role of the renin-angiotensin system in the development and maintainance of essential hypertension. However, only a limited number of patients have elevated plasma renin levels (Frohlich et al., 1970; Molzahn et al., 1972; Brunner et al., 1972; Esler and Nestel, 1973[a]).

Values for renin, angiotensin and aldosterone are within normal limits in most patients with essential hypertension, although rather wide ranges are found (Laragh et al., 1960[a]; Cope et al., 1962; Genest et al., 1964; Helmer, 1964; Brown et al., 1965, 1966[a]; Meyer et al., 1966[b]; Creditor and Lotschky, 1967; Gunnells et al., 1967; Ledingham et al., 1967; George et al., 1968; Fishman et al., 1968; Streeten et al., 1969; Doyle and Jerums, 1970; Nielsen and Jacobsen,

1970; Catt et al., 1971; Düsterdieck and McElwee, 1971; Kotchen et al., 1971; Boyd et al., 1972[b]; Khokhär et al., 1976[b]). In about one-third of the hypertensive population plasma renin is abnormally low (for references see Dunn and Tannen, 1974), this not being due to decreased substrate concentration. Such a distribution in itself already argues against a primary role for the renin-angiotensin system in essential hypertension. Nevertheless, hyper tensive patients have been classified according to their renin levels (Brunner et al., 1972). It was suggested that in high-renin hypertension (HRH) arteriolar vasoconstriction was responsible for the hypertension, the circulating volume being contracted. Arteriolar dilatation and volume expansion were thought to exist in low-renin hypertension (Laragh, 1973). Laragh and associates have argued that cardiovascular complications from hypertension mainly occur when renin is high (Brunner et al., 1972, 1973; Laragh, 1973). This view has, however, been severely critisized (Schalekamp and Birkenhäger, 1972; Doyle et al., 1973; Genest et al., 1973; Mroczek et al., 1973; Stroobandt et al., 1973; Birkenhäger, et al., 1977[a]). Moreover, a follow-up study conducted at our hospital revealed that patients in whom hypertension was complicated by myocardial infarction had even slightly lower renin levels prior to the event than those without such a complication (Birkenhäger, et al., 1977[a]; de Leeuw et al., 1978).

Of special interest is the group with low renin levels; in these patients renin is suppressed and unresponsive to stimuli such as sodium restriction and tilting (Helmer, 1964, 1965; Ledingham et al., 1967; Channick et al., 1969; Jose and Kaplan, 1969; Jose et al., 1970; Williams et al., 1970; Espiner et al., 1971; Spark and Melby, 1971; Crane et al., 1972; Gavras et al., 1976). Stronger and prolonged stimuli, however, do raise the renin level (Helmer and Judson, 1968; Lowder and Liddle, 1974; Spark et al., 1974; Gavras et al., 1976).

Different stimuli have been used to identify low renin hypertension (LRH). Unfortunately, these different methods do not precisely divide the same patients into the same subgroups (Crane et al., 1972; Drayer et al., 1975; Woods et al., 1976).

Although angiotensin II levels in the hypertensive population show a similar distribution as renin levels (Padfield et al., 1975[a]; Beevers et al., 1977), it is not certain whether the close relation between renin and angiotensin under different clinical conditions Swales and Thurston, 1977) also applies to low-renin hypertension (Walker et al., 1976).

The mechanisms causing the low renin state, have not been unequivocally elucidated.Defective sympathetic stimulation has been proposed as an explanation for LRH (Collins et al., 1970[a]; Esler and Nestel, 1973[a]; Esler et al., 1976; Lowder et al., 1976; Noth and Mulrow, 1976) but Mitchell et al. (1977) did not find evidence for such a mechanism.

Weidmann et al. (1977) found a decreased urinary adrenaline excretion rate in LRH, but this does not necessarily reflect a causal relationship.

A plausible explanation for the low-renin state would be mineralocorticoid excess as is observed in primary hyperaldosteronism (Conn et al., 1964). Aldosterone secretion and excretion are, however, normal in LRH (Channick et al., 1969; Woods et al., 1969; Collins et al., 1970[b]; Jose et al., 1970; Kotchen

et al., 1971; Laragh et al., 1972[b]; Schalekamp et al., 1974; Padfield et al., 1975[b,c]).

In some patients aldosterone is unresponsive to alterations in sodium intake (Weinberger et al., 1968; Collins et al., 1970[b]; Williams et al., 1972; Kloppenborg et al., 1974; Helber et al., 1974), but this abnormality sometimes also occurs with normal renin levels. Moreover, the fixed aldosterone levels rather seem to be the result of unresponsive renin. Nowaczynski et al. (1971) reported on a decreased metabolic clearance rate (M.C.R.) of aldosterone in patients with essential hypertension (not categorized according to renin levels). However, others found that aldosterone M.C.R. was normal in L.R.H. (Lommer et al., 1972; Brown 1976). The concept of aldosterone excess in essential hypertension is further invalidated by the demonstration of suppressed aldosterone at higher levels of blood pressure (Walker et al., 1976).

Other steroids have also been claimed to produce hypertension (Woods et al., 1969; Brown et al., 1972[b]; Genest et al., 1972; Melby et al., 1972; Liddle and Sennett, 1974) but the evidence is not conclusive and even not credible, since one would expect aldosterone suppression as well in these cases (Shade and Grim, 1975; Khokhär et al., 1976[b]). Neither is there support for a role of the potassium ion in low-renin hypertension (Carey et al., 1972; Distler et al., 1974; Kloppenborg et al., 1974; Schalekamp et al., 1974[b]).

Volume expansion or a higher exchangeable sodium in L.R.H. was suggested in earlier reports (Woods et al., 1969; Jose et al., 1970) but more defined studies have rejected this view (Helmer and Judson, 1968; Jose and Kaplan, 1969; Lebel et al., 1974; Schalekamp et al., 1974; Distler et al., 1974; Weidmann et al., 1975, 1977).

So far all attempts to characterize low-renin hypertension as a distinct nosological entity have failed to provide conclusive evidence for such a condition.

Renin concentration (or activity) has been found to vary inversely with age in hypertensive patients (Schalekamp et al., 1971, 1974; Birkenhäger et al., 1972[a], Sambhi et al., 1973; Tuck et al., 1973; Abe et al., 1975; Padfield et al., 1975; Guthrie et al., 1976; Woods et al., 1976). In a few studies, on the contrary, this pattern has not been found (Jose et al., 1970; Wisenbaugh et al., 1972; Pedersen and Kornerup, 1976; Fagard et al., 1977; Weidmann et al., 1977). It must be emphasized that any age-related trend could, as well, represent the result of a physiological ageing process. Indeed, an inverse relation between renin and age has also been described for normotensives (Hayduk et al., 1973; Sambhi et al., 1973; Noth et al., 1975; Abe et al., 1975; Weidmann et al., 1975, 1977; Crane and Harris, 1976; Mitchell et al., 1977), although this also is not found by all investigators (Schalekamp et al., 1971, 1974; Tuck et al., 1973; Padfield et al., 1975; Woods et al., 1976), probably because the main reduction occurs in early life.

Low renin levels with a diminished response to stimulation have been found in normotensive subjects (Noth et al., 1975), but it seems that renin is suppressed in hypertension more markedly. In our study renin levels were also inversely related to age and even more so when glomerular filtration is within the normal range. On the basis of these observations it can be postulated that the low renin state is a stage in the development of essential hypertension; in support of this idea is the negative relationship between renin and blood pressure observed in

a number of studies (Bloomfield et al., 1970; Schalekamp et al., 1971; Stroobandt et al., 1973; Tuck et al., 1973; Klaus et al., 1974; Kolsters et al., 1975; Fagard et al., 1977; Walker et al., 1976).
In other studies, however, this relationship was not found (Dustan et al., 1970; Brunner et al., 1972; Wisenbaugh et al., 1972; Lucas et al., 1974; Pedersen and Kornerup, 1976; Weidmann et al., 1977). In our study renin was also not clearly related to blood pressure, when all patients were considered together. However, such a relationship was revealed when the effect of glomerular filtration rate was taken into account.
This suggests some feed-back suppression of renin at higher levels of blood pressure, as long as glomerular filtration is not compromised. In view of the inverse relationship between renin and G.F.R., it is probable that blood pressure per se is not the only determinant of renin secretion. Since G.F.R. declines with age one would expect an increase in renin with age. Yet, the opposite is found. This indicates that there is a suppressing factor which overrules the effect of G.F.R. This suppressing factor could be ageing alone. In support of this idea is the observation that the inverse relationship between renin and blood pressure is abolished by eliminating the effect of age, while the inverse relationship between renin and age is independent of blood pressure. However, such an interpretation implies that renin levels are bound to decrease with age, irrespective of the presence of hypertension. If we assume, on the other hand, that the effect of age actually is the effect of hypertension, then the absence of an apparent relationship between renin and blood pressure indicates that the stimulating effect of a reduction in G.F.R. counteracts and effectively balances the influence of the elevated pressure. It will be apparent that the problem cannot be solved simply in terms of statistical relations, since the juxtaglomerular cells only respond to the net influence of various different stimuli acting simultaneously.

It has been reported that renin levels correlate positively with renal blood flow and inversely with filtration fraction and renal vascular resistance (Schalekamp et al., 1970, 1971, 1977; Molzahn et al., 1972; Pedersen and Kornerup, 1976).
These findings have been interpreted in favour of the baroreceptor theory on renin release. In this large study we failed to observe a relationship between renin and renal blood flow or filtration fraction. However, a significant inverse relation was found between renin and glomerular filtration rate. This may indicate that renin secretion is governed by the combined effect of intravascular pressure and the sensing of the macula densa.
A reduction in glomerular filtration rate decreases the filtered load of sodium and therefore, presumably sodium load to the distal tubule. In accordance with the concept of Vander and Miller (1964) this could stimulate renin release. A diminution of G.F.R. at the same time coincides with an elevated intravascular pressure as shown in Chapter 5. This in turn suppresses renin secretion by the baroreceptor mechanism and this can happen because the pressure is transmitted along the renal vessels (Lowenstein et al., 1970).
Apparently, the effect of the baroreceptor dominates. However, the drop in arterial pressure along the vascular tree in the kidney is dependent on the

resistance of the intrarenal vessels. Therefore, the height of the blood pressure at the level of the juxtaglomerular apparatus does not necessarily reflect the pressure as measured in a peripheral artery.
As long as G.F.R. is intact, blood pressure seems to be transmitted quite well, as can be concluded from the inverse relation between renin and renal vascular resistance in these patients. Apparently, beyond a certain age and, consequently beyond a certain level of renal vascular resistance, blood pressure is less easily transmitted along the renal vessels which coincides with more impaired glomerular filtration and consequent stimulation of renin secretion. At this stage, renin could well be involved in a further increase in renal vascular resistance, as may be the case in those patients who exhibited extremely high values for the R.V.R. One could argue that sodium intake could disturb the other relations by influencing renin secretion. However, all our patients were in sodium balance during the studies. They received 60 mmol of sodium a day. From the original description of Laragh's group (Brunner et al., 1972), where plasma renin activity is related to urinary excretion of sodium, it is apparent that at an excretory level of about 60 mmol of sodium, a good differentiation can be made between low, normal and high renin levels. It should be borne in mind, however, that sodium restriction could affect plasma volume more readily in those subjects who exhibit a low renin state. Our low sodium intake regime can, therefore, have disturbed a negative relationship between plasma volume and plasma renin concentration.
Another objection to the results could be that over the years the results of the P.R.C. determination may have been fluctuating. We have therefore, frequently tested our samples and even checked the relationships for three periods of three years. These tests did not cause any differences in the relationships observed.
It has been stated that aldosterone levels and aldosterone secretion rate are lower in older (normotensive) age groups (Flood et al., 1967; Weidmann et al., 1975; Crane and Harris, 1976; Mitchell et al., 1977) and at higher diastolic pressures (Walker et al., 1976). The effect of age on aldosterone in patients with essential hypertension is not yet clear. While Mitchell et al. (1977) reported a decrease with age, this was not apparent in the study of Guthrie et al. (1976). This discrepancy may be due to differences in sodium intake. Since aldosterone secretion is dependent on several factors, including the renin-angiotensin system, most studies on this hormone have a dynamic, rather than a static character. In hypertensive subjects, the role of aldosterone production has mainly been investigated in the low-renin state. In these patients aldosterone secretion and excretion have been reported to be normal and sometimes less responsive than renin (Woods et al., 1969; Channick et al., 1969; Collins et al., 1970[b]; Jose et al., 1970; Kotchen et al., 1971; Williams et al., 1972; Laragh et al., 1972[b]; Luetscher et al., 1972; Helber et al., 1974; Kloppenborg et al., 1974; Schalekamp et al., 1974; Padfield et al., 1975[b,c]). On the other hand, Walker et al. (1976) demonstrated suppression of aldosterone at higher levels of blood pressure, thus simulating the renin pattern. This finding argues against the concept of aldosterone excess in low-renin hypertension. In our study, aldosterone was not related to age, blood pressure or plasma renin concentration. The latter is in keeping with the finding of Guhrie et al. (1976).

Considering all these observations, it is unlikely that the renin-angiotensin-aldosterone system is of primary importance in the elaboration of essential hypertension. Moreover, no relationship could be detected between circulating renin levels and peripheral vascular resistance. As soon as substantial vascular alterations occur, the system apparently becomes geared into action, even before the onset of malignant hypertension.

8.6 Conclusions

From the data presented in this chapter, the following conclusions can be drawn.

1. Under basal conditions approximately 30% of the circulating renin is found to be in the active form. The kidney mainly secretes active renin, although sometimes secretion of inactive renin is found.

2. Renin levels in patients with essential hypertension usually are normal or low. There is no convincing evidence that the renin-angiotensin system is primarily involved in the pathogenesis of essential hypertension.

3. Renin secretion seems to be dependent on intravascular pressure (baroreceptor mechanism) and glomerular filtration rate (macula densa mechanism). The actual renin level is the result of the interaction between these mechanisms which oppose each other during the progression of hypertension.

4. The functional importance of the baroreceptor exceeds that of the macula densa as evidenced by the inverse relationship between renin and renal vascular resistance in patients with normal glomerular filtration.

5. The discrepancy between age, blood pressure and renin may in part be due to the fact that insufficient account has been given to glomerular filtration rate.

CHAPTER 9

The adrenergic system in essential hypertension

I Biochemical evaluation

9.1 Introduction

At various levels, the autonomic nervous system is involved in blood pressure control. Although interest has mainly been focused on the sympathetic part, several experiments indicate that the possibility of parasympathetic inhibition cannot be ignored (Julius et al., 1971[b], 1975; Korner et al., 1973). An exaggerated activity of the sympathetic nervous system could easily explain some of the features of essential hypertension, especially in its early phase. Even if cardiac output is not swept up, the elevated vascular resistance could be the result of increased alpha-adrenergic tone. To further our insight into the role of the sympathetic system in the development and maintainance of essential hypertension, two kinds of approach are possible: biochemical and functional. Since reliable methods for determination of circulating catecholamines have become available only recently, much knowledge of the sympathetic nervous system stems from functional studies. We will first discuss the biochemical part and the receptors of the system.

9.2 Catecholamines

9.2.1. Biosynthesis of catecholamines (fig. 47)

L-noradrenaline is synthesized from phenylalanine in the axoplasm of postganglionic sympathetic neurones. Oxidation of tyrosine to dopa is catalyzed by tyrosine hydroxylase, this reaction being the rate-limiting step in the biogenesis of the catecholamines; subsequent decarboxylation to dopamine occurs under the catalytic influence of an aromatic L- amino acid decarboxylase, which action is dependent on the presence of pyridoxal phosphate. Finally, 3.4-dihydroxyphenylethylamine-beta-hydroxylase (or dopamine-beta hydroxlase, D.B.H.) converts dopamine to noradrenaline (NA).
Methylation of NA to adrenaline is catalyzed by phenylethanolamine-N-methyl-transferase, utilising S-adenosylmethionine as methyldonor.

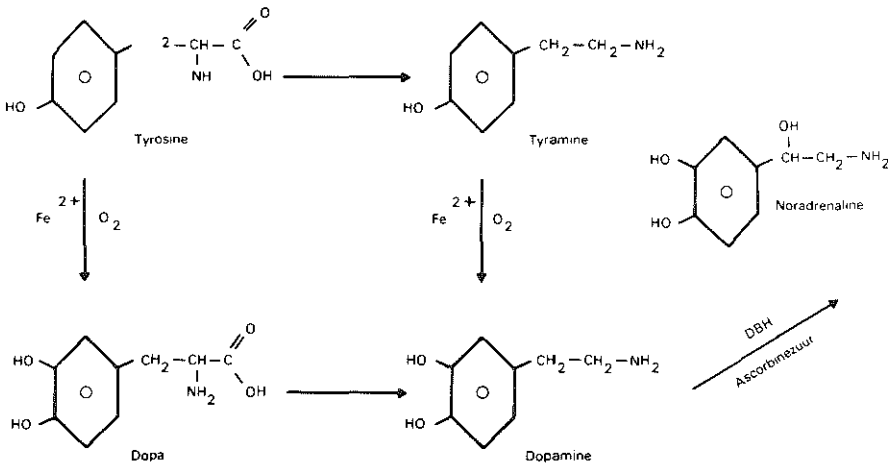

Fig. 47 Biosynthesis of noradrenaline.

Adrenaline is mainly found in the adrenal medulla, which contains three to ten times as much adrenaline as noradrenaline. In the sympathetic nerve endings noradrenaline is stored in small vesicles. Adrenaline is found in nervous tissue, in the adrenal medulla and in chromaffin cells throughout the body.

9.2.2 Factors governing release of neurotransmitter substance (fig. 48)

The principle transmitter substance released from sympathetic nerve endings is noradrenaline. When an electrical impulse reaches the presynaptic nervous membrane, noradrenaline stores release their contents. This is thought to occur via exocytosis (Viveros et al., 1968; Weinshilboum er al., 1971).
The neurally released noradrenaline passes into the synaptic cleft, where it is now known to act on at least two sides. Firstly, it combines with the post-synaptic receptor sites, where it triggers a response (alpha or beta depending on the type of receptor) and secondly, it reacts with presynaptic alpha-adrenoreceptors which then exert an inhibiting effect on noradrenaline release. This second reaction, therefore, can be considered as a negative feed-back mechanism, depressing the release of NA when its concentration in the synaptic cleft rises too much (Kirpekar and Puig, 1971; Enero et al., 1972; Farnebo and Hamberger, 1973; Häggendal, 1973; Kirpekar et al., 1973; Langer, 1973, 1974; Starke, 1973; Stjärne, 1973; Starke and Montel,1974).
Recently, evidence has been presented which favors the existence of a presynaptic beta-receptor mediating a positive feed-back mechanism (Adler-Graschinsky and Langer, 1975; Yamaguchi et al., 1977). The transmitter-receptor interaction represents a dynamic situation: continuous bombardment of the receptor surface by noradrenaline results in another equilibrium between occupied place and nonoccupied places.

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with respect to fig. 47 and 48.

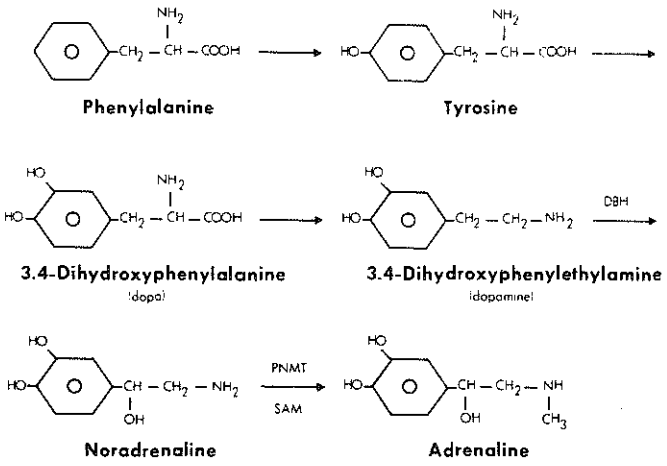


Fig. 47 Biosynthesis of noradrenaline

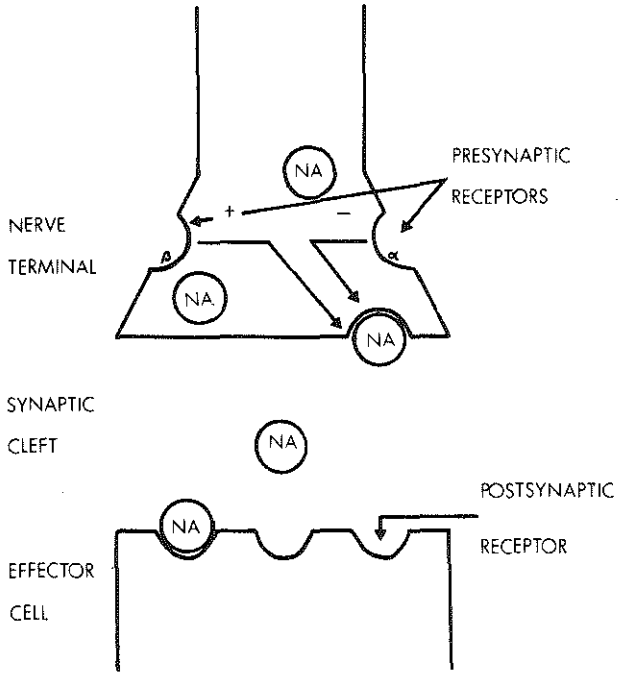


Fig. 48 Schematic representation of neural transmitter release

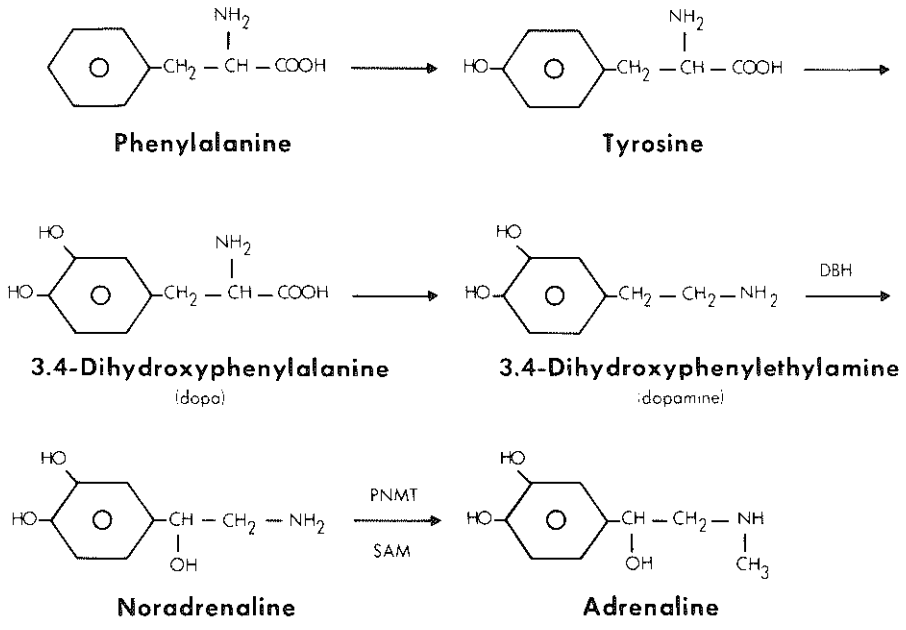


Fig. 48 Schematic representation of neutral transmitter release.

Pharmacologically, NA can be released from its stores by tyramine, amphetamine and ephedrine (Bevan, 1969; Trendelenburg, 1972).
Although not uniformly accepted, it has been hypothesized that the liberation of NA by sympathetic firing is mediated by acetylcholine, which would be released first (Burn et al., 1959; Ferry, 1966).

9.2.3 Metabolism of catecholamines

NA can be eliminated from the synaptic cleft by several processes, including:

- re-uptake
- diffusion into the circulation
- metabolisation

The re-uptake of NA into the nerve therminal (uptake I) which is an active process, is by far the most important mechanism in the inactivation of this substance. Only by re-uptake the local excitatory action of released NA is terminated (Iversen, 1973).
Although, the catecholamines are mainly metabolized in the liver, some enzymatic destruction occurs locally (Wurtman, 1965). Besides this "direct" elimination part of the amount of NA is removed by diffusion into the circulation (Iversen, 1967) and subsequent extraction by the liver. Finally, NA can be

taken up into extraneuronal peripheral tissues, such as muscle (uptake II; Iversen, 1967), a process blocked by steroids (Kalsner, 1964).
Cholesterol blocks a similar process in heart muscle (Salt and Iversen, 1972). While uptake I is followed by retention of NA, uptake II is followed by metabolism (Iversen, 1973). Inhibition of one of these processes leads to a compensatory increase in the other (Gillespie, 1973). Three mechanisms are involved in the break-down of the neuronal hormones, namely: o-methylation, oxidative deamination and conjugation. The different metabolic pathways are shown in figure 49. O-methylation by S-adenosylmethionine (catalyzed by catechol O-methyltransferase, C.O.M.T.), is the major pathway for adrenaline and oxidative deamination (enzyme: Mono-amine oxidase, M.A.O.) for noradrenaline. The metabolites are excreted either as free compounds or conjugated via the bile and via the urine.

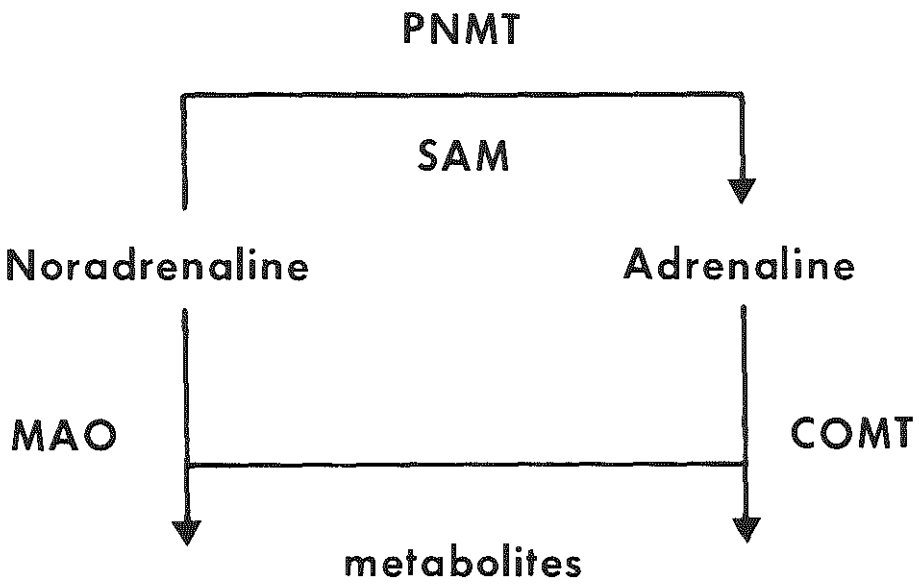


Fig. 49 Metabolism of noradrenaline.

Noradrenaline makes up about 80% of the total plasma catecholamine level (Engelman et al., 1970); the major sources of plasma noradrenaline seem to be the sympathetic nerves of the heart (De Quattro and Sjoerdsma, 1968). The plasma level of NA is dependent on the following parameters:rate of diffusion into the circulation and rate of removal from the circulation. The former is further influenced by release by nerve terminals, post-synaptic binding, reuptake and local enzymatic break-down.
The rate of removal depends on the integrity of the metabolic processes, especially in the liver. Although it can be seen that the plasma level can change when any of the above mentioned variables alters, it is still thought that NA

levels are, at least qualitatively, a reliable index of sympathetic nervous activity (Yamaguchi et al., 1975).
Whether urinary excretion of catecholamines runs parallel with changes in plasma concentration, remains a subject of controversy. The amount of noradrenaline and adrenaline, excreted in the urine, is affected by changes in glomerular filtration rate and perhaps also by tubular processes (Rennick and Pryor 1965; Overy et al., 1967). In addition, it is still unknown to what extent the kidney participates in the metabolism of catecholamines and therefore by its function per se determines the excretion of metabolites (Ikoma, 1965).
Despite these theoretical objections, there is ample evidence that urinary excretion of noradrenaline is proportional to its plasma level under various clinical conditions (Engelman et al., 1970; Fluck, 1972; De Quattro and Chan, 1972; Videback et al., 1972; Esler et al., 1973[c]; Louis et al., 1973; Cuche et al., 1974).

9.3 Adrenergic receptors

9.3.1 General remarks

Dale (1906) first conceived the adrenergic receptor to explain his experiments with an ergot alkaloid. Although, in the following years, many physiological responses to catecholamines became known, it was not until 1948 that the amount of data was put together and organized within a conceptual framework (Ahlquist, 1948). On the basis of pharamacological studies, namely the relative potency of different catecholamines to evoke physiologic processes, the adrenergic effects were divided into two main groups, mediated by two different receptors, which were called alpha and beta.
The alpha-receptors appeared to be stimulated by adrenaline and noradrenaline, but not by isoproterenol (isoprenaline); adrenaline was the most potent of these drugs. On the contrary, beta-receptors were most sensitive to isoprenaline, while showing relatively few responses to adrenaline and noradrenaline. The naturally occurring catecholamines (adrenaline and noradrenaline) are able to stimulate both receptors; for this reason the physiologic response of each of these receptors has been studied mainly by administration of pharmacological agents, which possess either alpha- or beta agonistic, c.q. antagonistic effect. The beta-adrenergic responses have been further subdivided into beta-1 and beta-2 (Lands et al., 1967). Beta-1 receptors are almost equally stimulated by adrenaline and noradrenaline, while beta-2 receptors are far more sensitive to the action of adrenaline.
Isoprenaline acts on both beta-receptors; its relative potency over noradrenaline is greater for beta-2 than for beta-1 receptors.
Recently, a third type of adrenergic has been added to the list; this one has been called dopaminergic, since it is stimulated by dopamine, the direct precurser of noradrenaline (Iversen, 1975; Reid, 1977).
Although molecular characteristics are unknown the adrenergic receptors could be considered as specific structures within or at the surface of certain cells. These structures are able to bind natural catecholamines and synthetic

(agonistic or antagonistic) agents with an appropriate complementary structure. The drug-receptor interaction is a dynamic process, based on forces between molecules which probably lead to conformational (stereo-isometric) changes; these, in turn, are thought to induce a sequence of intracellular biochemical reactions, ultimately leading to a specific effect (Ariens and Simonis, 1976).
The chain of interacellular events, evoked by stimulation, is best known for beta-receptors, where activation enhances the activity of the enzyme adenylate cyclase. This results in an elevation of the intracellular level of cyclic A.M.P., the "second messenger" (Sutherland and Rall, 1960). By this substance a number of enzymes are activated, which are involved in the metabolism of substrates mediating the responses to many hormones and drugs (Langan, 1975). Responses of dopaminergic receptors seem to follow the same pathway (Iversen, 1975; Reid, 1977), but alpha-adrenergic receptors differ somewhat in that they probably accumulate cyclic G.M.P. upon stimulation (Goldberg et al., 1975).

9.3.2. Distribution and effects of adrenergic receptors

Adrenergic receptors are still hypothetical entities, which means that we do not know anything about their chemical or structural characteristics. Even histological studies cannot yet unequivocally demonstrate the existence of such specialised elements. The lack of exact knowledge about them is furthermore reflected by the fact that the precise location and the number of receptors is unknown. All that is known about receptors mainly depends on the interpretation of drug interactions with physiological processes.
Recently studies with radioactively labeled beta-adrenergic antagonists have indicated that the number of beta-receptors in the human leucocyte approximates 2000 (Williams et al., 1975). Sympathetic innervation is not a prerequisite for tissues to contain adrenergic receptors, since their presence has been demonstrated not only in circulating cells like leukocytes (Williams et al., 1975), but also in uterine smooth muscle (Tsai and Fleming, 1964), which is devoid of sympathetic innervation (van Driel et al., 1973).
Although the adrenergic receptors are widely distributed throughout the body, we will deal in this section only with those involed in circulatory control.

Peripheral alpha-receptors

These are located in blood vessels and smooth muscle; they are stimulatory in nature, thus leading to vasoconstriction and arteriolar muscle contraction.

The vasoconstriction is most pronounced in the vascular bed of the kidney and the skin; the effect is least in skeletal muscle and totally absent in the cerebral circulation (Ahlquist, 1976). The effect on the coronary circulation has been the subject of debate; although it has been stated that neurogenic control of coronary arterial tone is of relatively little importance (Berne, 1964; Berne et al., 1965; Gellai et al., 1973), it has been established quite firmly that the

coronary arteries are supplied with both alpha- and beta-receptors (Pitt et al., 1967; Feigl, 1967; Vatner et al., 1970; McRaven et al., 1971; Mark et al., 1972), the former being predominant in the larger vascular segments (Zuberbuhler and Bohr, 1965; Bohr, 1967). Coronary alpha-receptors indeed are sensitive to catecholamines (Gaal et al., 1966) and recently they were attributed pathophysiological significane in the syndrome of variant angina pectoris (Yasue et al., 1974, 1976).
Administration of alpha-agonists causes systemic hypertension by an increase in peripheral vascular resistance. Heart rate slows due to baroreceptor reflexes. Alpha-receptors are stimulated both by noradrenaline and adrenaline, the latter being the most potent. There are several pharmacological agents with either stimulate (e.g. phenylephrine) or block (e.g. phenoxybenzamine) the alpha-receptors. Practically no chemical relation exists between endogenous catecolamines and alpha-blocking drugs (Ariens, 1967; Ariens and Simonis, 1967) which are chemically more close to cholinergic or histaminergic receptors.
It is thought that noradrenaline, as the neurotransmitter substance, activates the receptors in response to stimulation of sympathetic nerves, whereas adrenaline is likely to activate those which are not in connection with sympathetic nerve fibers (Ariens and Simonis, 1976). On the basis of these differences, one could postulate two types of alpha-receptors, which are sensitive either to the transmitter or the circulating hormone.

Peripheral beta-receptors

These are located in the heart, blood vessels and smooth muscle; the cardiac receptors are stimulatory and are called beta-1; the smooth muscle receptors are called beta-2; they have a relaxant action. Thus beta-1 stimulation augments cardiac contractility, and increases heart rate and cardiac output; stimulation of beta-2 receptors results in a fall in peripheral resistance due to vasodilation.
Noradrenaline also acts as neurotransmitter substance for beta-receptors; it is as potent as adrenaline in stimulating betha-1 receptors, but considerably less potent in stimulating beta-2 receptors. As for the alpha-receptors the possibility exists that the relative sensitivity of beta-receptors for endogenous catecholamines depends on the degree of sympathetic innervation.
A large number of pharmacological agents has been synthesized with an effect on beta-receptors. Isoprenaline, for instance, stimulates both beta-receptors; beta-adrenergic blocking agents appeared to be relatively selective for beta-1 (atenolol, practolol) or beta-2 (butoxamine) receptors, whereas others were not selective at all (e.g. propranolol). Agents which block or stimulate beta-receptors do show a chemical relationship, with a hydroxy-ethylamino-group as a common constituent.

Peripheral dopaminergic receptors
These newly discoverd receptors are encountered mainly in the renal vasculature. They are most potently stimulated by the noradrenaline precursor dopamine, while haloperidol inhibits this effect. Catecholamines, alpha- and

beta-antagonist, have little effect on these receptors. Dopamine administration augments myocardial contractile state with relatively little effect on heart rate (Rosenblum et al., 1972; Goldberg, 1972). It also increases renal blood flow (Talley et al., 1969; Breckenridge et al., 1971; Goldberg, 1972; Hollenberg et al., 1973) and sodium execretion while systemic vascular resistance is further reduced through coeliac and mesenteric vasodilation (Rosenblum et al., 1972).

It must be emphasized that above mentioned characteristics are related to peripheral adrenoceptors. Similar receptors are found in the brain and these contribute to neuroendocrine control of the circulation and other vital functions. This matter will not be pursued in this thesis.

9.4 Dopamine beta hydroxylase (D.B.H.)

This enzyme is responsible for the conversion of dopamine into noradrenaline (Levin et al., 1960). It is firmly bound to the catecholamine storage vesicle membrane (Kirshner, 1957), but there is also a soluble form of this protein (Duch et al., 1968; Viveros et al., 1968; Hortnagl et al., 1972; Wooten and Cardon, 1973). It is released together with the catecholamines in equal amounts by exocytosis (Viveros et al., 1968). Presynaptic innervation of chromaffin cells in the adrenal medulla not only controls secretion of catecholamines and D.B.H., but also its rate of synthesis (Viveros et al., 1969; Kvetnansky et al., 1971).

In the sympathetic nerve fibers the storage vesicles are formed in the perikaryon; at this moment they do not contain catecholamines, but they do have D.B.H. (Kopin et al., 1976). The catecholamines are formed as the vesicles travel down to the nerve terminal. When the latter is depolarized, the soluble contents of the vesicle are secreted into the synaptic cleft; the same exocytotic process is operative in the nerve terminal and in the adrenal medulla (Smith and Winkler, 1972; Weinshilboum et al., 1971). Unlike noradrenaline, D.B.H. by its protein structure, is not able to diffuse rapidly into the circulation. Except for some organs with large endothelial gaps (such as in the adrenal medulla and in the spleen), through which D.B.H. can leak away, most of it enters the circulation by way of the lymphatics (Ngai et al., 1974). Animal studies have shown that plasma D.B.H. is derived mainly from the sympathetic nerves (Weinshilboum and Axelrod, 1971[a]). In man, this is also probable (Noth and Mulrow, 1976).

Studies on the turnover rate of this enzyme (Rush and Geffen, 1972; Reid and Kopin, 1974,1975) thus far, did not yield conclusive data. However, since only soluble D.B.H. is implicated in these studies and since the behaviour of the membrane bound fraction is still unknown, it cannot be excluded that this latter fraction maintains plasma D.B.H. levels by some mechanism, unrelated to the secretory process.
In fact, this has been proposed (Kopin et al., 1976) to explain the observation that alterations of plasma D.B.H. do not always run parallel with greater or

lesser release of catecholamines (De Quattro et al., 1975). Whether D.B.H. levels in plasma reflect sympathetic activity remains unclear. Although a rise in D.B.H. during exercise (Plantz et al., 1975) or after assumption of the upright posture (Okada et al., 1974) was noted, these observations have not generally been confirmed (Ogihara and Nugent, 1974; Leon et al., 1974; Noth and Mulrow, 1976) and changes in D.B.H. are not always related to changes in noradrenaline (Lake et al., 1977[a]).
Moreover, the amount of D.B.H., determined by radio-immunoassay, does not correlate with its enzymatic activity (Geffen, 1974). Despite these criticisms, D.B.H. is still considered by several authors to be an index of the activity or the sympathetic nervous system (Weinshilboum and Axelrod, 1971[b]; Geffen et al., 1973; Wooten and Cardon, 1973; Planz et al., 1975; Schanberg and Kirshner, 1976; Mathias et al., 1976).

It is extremely difficult to assess the possible role of serum D.B.H. in essential hypertension, since in normal man there is already a wide variety in serum levels. There is strong evidence that this is highly influenced by genetic determinants (Lamprecht et al., 1973; Ross et al., 1973; Weinshilboum et al., 1973; Ogihara et al., 1975). D.B.H. levels tend to increase with age in early life (Weinshilboum et al., 1971, 1973; Wetterberg et al., 1972; Ross et al., 1973) till about the 15th year, whereafter, it decreases (Ogihara et al., 1975), to rise again in the sixth decade (Freedman et al., 1972). In individual studies over a relatively short period, D.B.H. levels remain remarkably constant; furthermore, it tends to decrease when hypertension develops (Lamprecht et al., 1975).

The above mentioned variables have, in general, not been taken into account in studies on D.B.H. in hypertension and this could be an explanation for the rather conflicting results. Schanberg and coworkers (1974) found a positive correlation between elevated D.B.H. levels and the lability of blood pressure; a positive relation between D.B.H. and blood pressure has been reported by Geffen et al. (1973). Such a relationship could not be confirmed in another study (Horwitz et al., 1973). Although the mean D.B.H. level is sometimes reported to be elevated in essential hypertension (Wetterberg et al., 1972; De Quattro and Miura, 1973;) In other series there was no significant difference (Nagatsu et al., 1970; Horwitz et al., 1973; Aberg et al., 1974; Ogihara et al., 1975; Alexandre et al., 1975; Lake et al., 1977[a]) Or even a decrease (De Quattro et al., 1975) as compared with a normotensive control group.
In borderline hypertension the situation is also unclear, D.B.H. being found elevated (Stone et al., 1974) and normal (Horwitz et al., 1973; Geffen et al., 1973).

9.5 Results

9.5.1 Introduction

In this chapter we will investigate the role of the sympathetic system in essential hypertension, as assessed by measurements of noradrenaline in plasma under basal conditions. This was done in the group of 59 patients, which was described in chapter 8. In view of the drawbacks mentioned above for the determination and interpretation of D.B.H. levels we have confined ourselves to the measurement of noradrenaline.
In addition, we were interested in the kidney as a potential source of noradrenaline secretion. Such a mechanism would be quite possible in view of the dense connections between the sympathetic system and the kidney. Moreover, it has been suggested recently that in a number of patients with mild blood pressure elevation the urinary excretion of free catecholamines, supposed to be of renal origin, is increased (Kuchel et al., 1976). Finally, it has been demonstrated that the kidney contains appreciable amounts of dopadecarboxylase and M.A.O. (Sandler and Ruthven 1969), which points to active metabolism. These observations prompted us to study the renal release of noradrenaline in blood.

9.5.2 Relation with age

The average noradrenaline level was 0.28 ± 0.02 ng/ml. In two patients (one man and one woman) rather high values for plasma noradrenaline were found but without an apparent cause. No relationship was found between noradrenaline concentration and age (fig. 50).

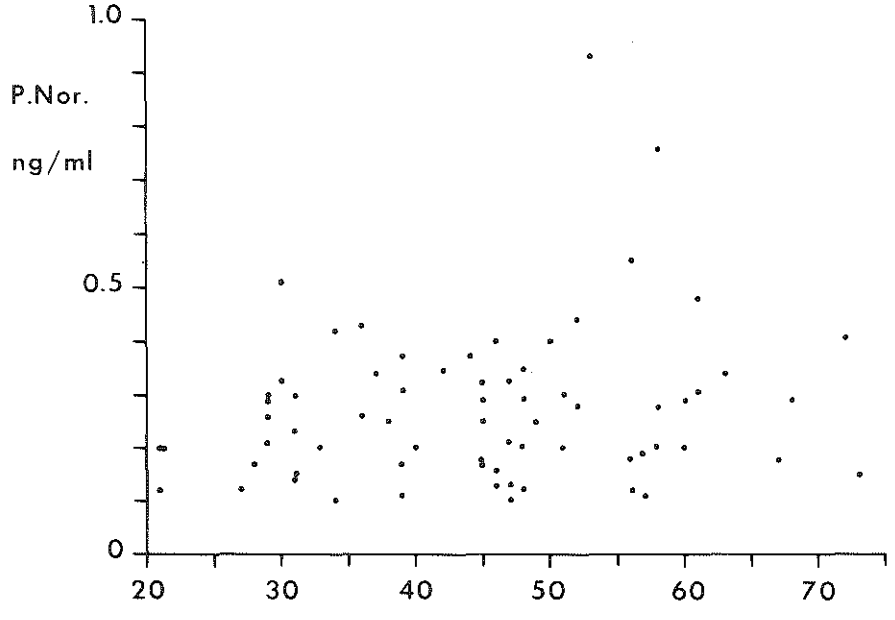


Fig. 50 Relationship between noradrenaline levels and age.

9.5.3 Interrelations

Noradrenaline versus systemic haemodynamics

Noradrenaline levels were not related to 10 am blood pressure. In 45 patients the relationship of noradrenaline and diurnal variation of blood pressure (cf. Chapter 4) was assessed.
Noradrenaline was not relate to basal blood pressure. Although there was a tendency towards an inverse relationship between absolute or relative diastolic variability and noradrenaline, these relations were not significant. However, despite a wide scatter, significant inverse relations were obtained between noradrenaline and absolute ($r = -0.35$; $p<0.02$) or relative ($r = -0.37$; $p<0.02$) systolic variability. A similar pattern was found for the relation between noradrenaline and variability of mean arterial pressure either expressed in mm Hg ($r = -0.37$; $p<0.02$) or as a percentage ($r = -0.35$; $p<0.02$).
Moreover, noradrenaline exhibited an inverse relationship with pressor range (fig. 51), irrespective of its expression in mm Hg ($r = -0.34$; $p<0.025$) or as a percentage ($r = -0.31$; $p<0.05$). No relations were found between NA and depressor range.

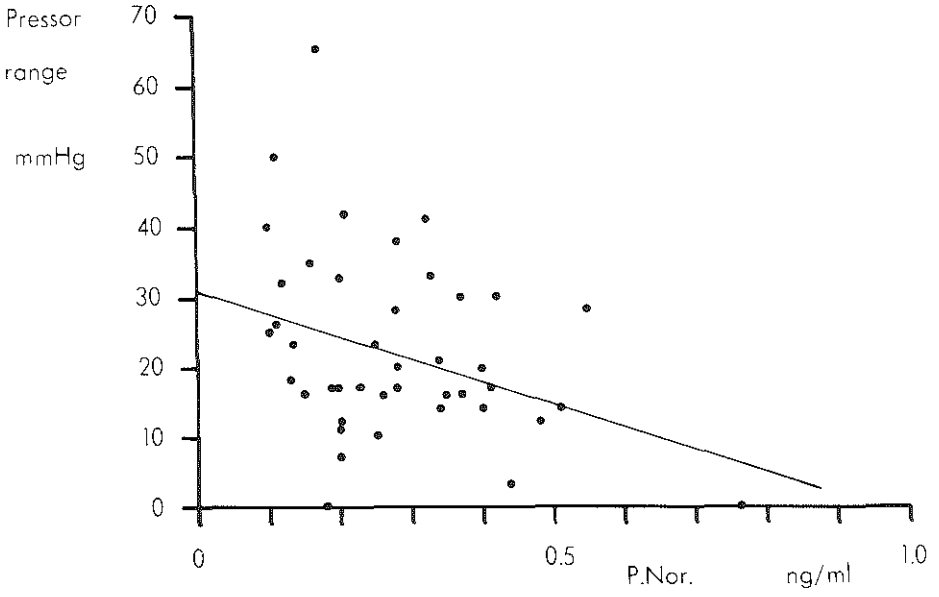


Fig. 51 Relationship between pressor range and noradrenaline.

Noradrenaline levels were not related to heart rate, stroke volume, cardiac output and total peripheral vascular resistance.

Noradrenaline versus the renin-angiotensin-aldosterone system

No relationships were found between noradrenaline levels and total, active or inactive renin (fig. 52). Neither is there a relation between noradrenaline and aldosterone.

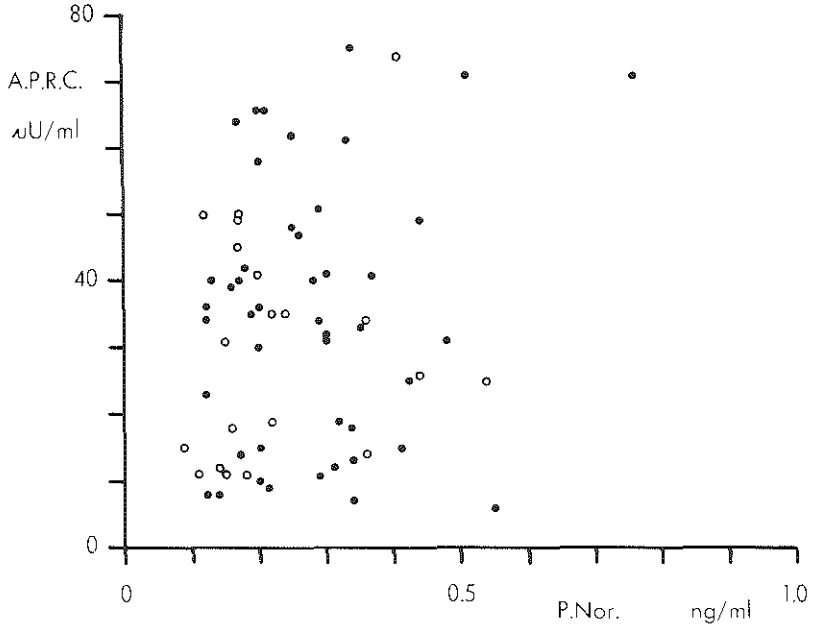


Fig. 52[a] Relationship between noradrenaline levels and active renin concentration.

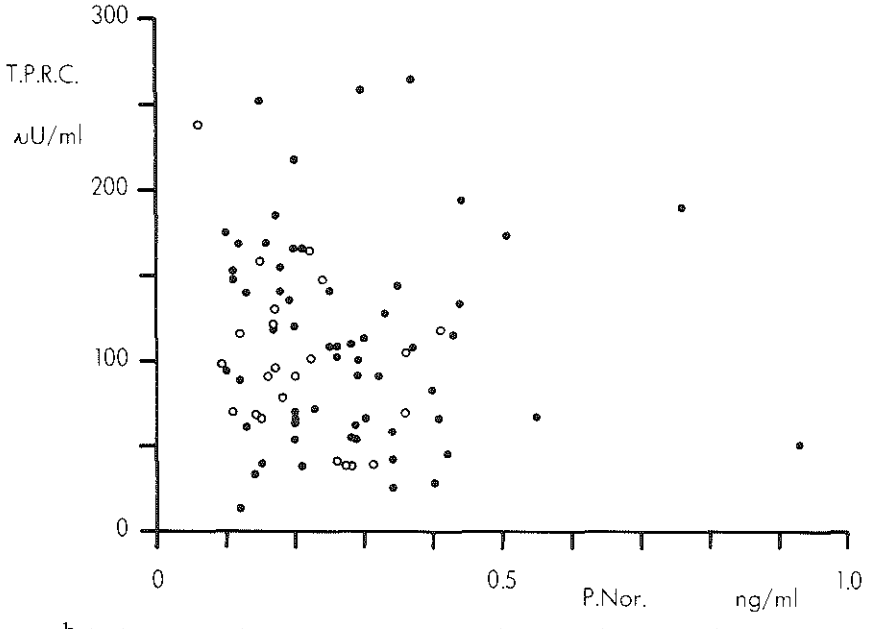


Fig. 52[b] Relationship between noradrenaline levels and total renin concentration.

Noradrenaline versus renal haemodynamics and plasma volume

No relationships were found between noradrenaline levels and either renal plasma flow, glomerular filtration rate, renal vascular resistance, filtration fraction, renal fraction and plasma volume.

Noradrenaline versus intrarenal haemodynamics and noradrenaline secretion by the kidney

In 10 patients the relation of noradrenaline to intrarenal haemodynamics could be assessed. When the arterial levels of noradrenaline were plotted against renal plasma flow and total renal blood flow no significant relations were found. In contrast, arterial noradrenaline levels exhibited an inverse relationship with C_1 ($r = -0.72$; $p<0.05$) and M.B.F. ($r = -0.65$; $0.05<p<0.10$) but not with C_2 or C_3. Noradrenaline levels in renal arterial blood also showed an inverse relationship of borderline significance with % C_1 ($r = -0.65$; $0.05<p<0.10$).
No significant relationship was found between arterial noradrenaline and absolute cortical blood flow ($r = -0.58$; n.s.). However, when the peripheral venous level of noradrenaline (the sample being drawn on a separate day) was substituted in these relations, it appeared that similar patterns were found with the exeption that the relation between C_1 and noradrenaline became weaker ($r = -0.65$; $0.05<p<0.10$), while the relation between absolute cortical flow and noradrenaline became stronger ($r = -0.76$; $p<0.05$). (fig. 53).

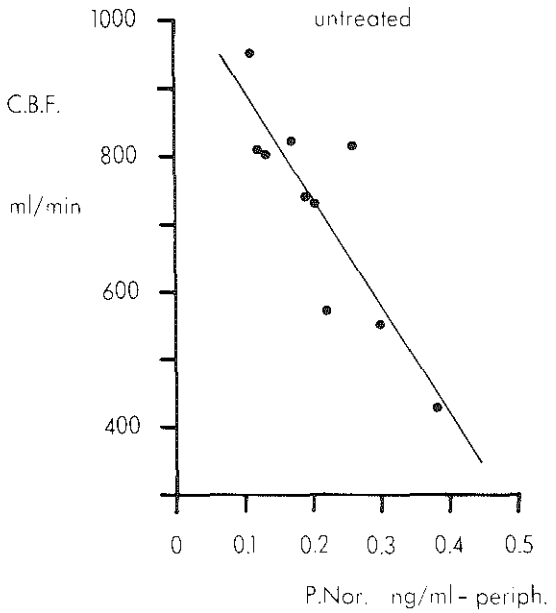


Fig. 53[a] Relationship between renal cortical blood flow and peripheral noradrenaline levels, the sample being drawn on a separate day.

The average concentration of noradrenaline in arterial blood was 0.25 ± 0.02 ng/ml; in renal venous blood this amounted 0.27 ± 0.02 ng/ml. Due to the scatter of data this difference was not significant. When the venous level was expressed as a percentage of the arterial concentration this level was 118 ± 2% (or 115 ± 2% depending on which the "negative secreters" were considered to have 100% or below.) In both cases the increase was significant. Noradrenaline secretion rate on the average was 18.6 ± 1.9 ng.min.
Noradrenaline secretion rate was not related to age, blood pressure or any haemodynamic parameter. Moreover, no relationship was found between secretion of noradrenaline and active or inactive (or total) renin.

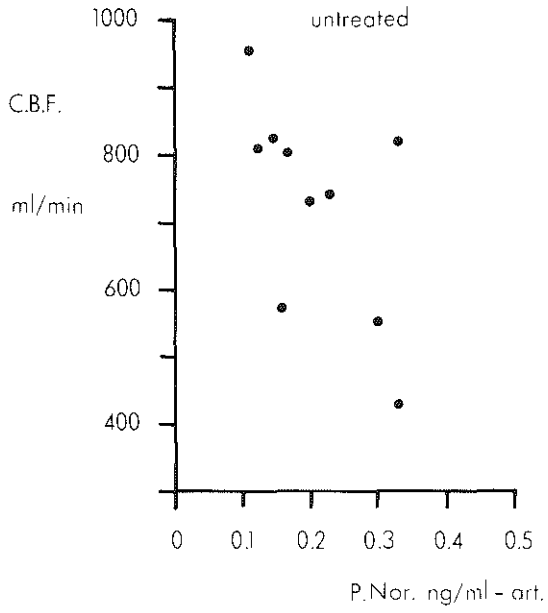


Fig. 53[b] Relationship between renal cortical blood flow and arterial noradrenaline levels.

9.6 Discussion

When labeled noradrenaline is infused, the plasma disappearance rate appears to be higher in essential hypertensives than in normotensive subjects (Gitlow et al., 1964). Urinary excretion, on the other hand, is increased in the hypertensive group (Gitlow et al., 1969), when noradrenaline is administered in low doses. From these observations it has been concluded that hypertensive subjects exhibit a diminished uptake or retention of (exogenous) noradrenaline. When apparent "NA secretion rate" is calculated in such experiments, it appears to be decreased (Wolf et al., 1967).

However, there are several methodological objections to these kinds of experiments, as has recently been reviewed by Mendlowitz and Lachakis (1976). The only fact, which remains valid, is the enhanced disappearance of NA from the circulation in essential hypertension. Whether this is due to increased turnover or mainly to diminished retention has still to be settled.

Early studies on the excretion of catecholamines and their metabolites in patients with essential hypertension frequently gave results which are within (Von Euler et al., 1954; Griffiths and Collinson, 1957; Sato et al., 1961; Sjoerdsma, 1961; Brunjes et al., 1963; Brunjes, 1964; Stott and Robinson, 1967) or slightly above (Von Studnitz, 1960) the normal range. On the other hand, elevated urinary catecholamine excretion was described (Nestel and Doyle, 1968; Kuschke, 1961) in patients with "borderline" hypertension. Initially plasma levels were also reported to be normal (Hoobler et al., 1954; Manger, 1962). However, recently more sensitive methods have become available to determine plasma and urinary catecholamines.

Urinary excretion of catecholamines usually is normal in essential hypertension (Lorimer et al., 1971; Bing et al., 1977), only a small portion of the patients showing an increase in catecholamine excretion (Kuchel, 1977). In view of the tubular reabsorption of NA (Overy et al., 1967) and the relationship between noradrenaline excretion and urine flow (Kuchel, 1977) serious doubt raises against the usefullness of such an assessment. It seems preferable, therefore, to measure plasma catecholamines.

Several authors using different new techniques demonstrated an increased level of noradrenaline in hypertensive patients (Engelman et al., 1970; De Quattro and Chan, 1972; De Quattro and Miura, 1973; De Quattro et al., 1975; Jiang er al., 1973; Louis et al., 1973, 1974; Esler and Nestel, 1973[c]; Cuche et al., 1974; De Champlain et al., 1976), although this could not always be confirmed (Christensen and Christensen, 1972; Pedersen and Christensen, 1975).

Moreover, Louis et al. (1973, 1974) found a significant direct relationship between resting plasma NA and systolic and diastolic blood pressure. A correlation between NA and diasolic blood pressure has also been reported by De Quattro et al. (1975). It appeared from several of the above mentioned studies that noradrenaline was more often raised in patients with "established" hypertension than in those with "labile" hypertension.

This suggests the possibility of a physiological increase of sympathetic activity with age. Indeed such trends have been observed both in normotensives and in hypertensives (Pedersen and Christensen, 1975; Lake et al., 1977[b]; Weidmann

et al., 1977). In contrast, Sever et al. (1977) found such a trend only in normotensives.

In our study no relations were found between noradrenaline and either age or blood pressure. This may in part be explained by selection of patients. Moreover, some of these differences may be due to sodium intake. In most studies cited, sodium intake was not controlled; yet sodium restriction is known to raise noradrenaline levels (Bennett et al., 1976; Bühler and Lutold, 1976). In the study of Cuche et al. (1974) patients received a fixed amount of 135 meq. sodium. Although urinary excretion of catecholamines was not affected by age, those patients considered to have "labile" hypertension showed an enhanced excretion of noradrenaline, while plasma noradrenaline was lower than in the patients with "stable" hypertension. In the same study, however, it was shown that the latter group also excreted less sodium. Finally, the time of sampling may have played a role.

Our study also indicates that the pattern of blood pressure variability may have influenced various studies. The relations between blood pressure variability and noradrenaline levels were rather weak, but this could be caused by the fact that noradrenaline samples were drawn only once on the day of study. Nevertheless, we found an inverse relationship between plasma noradrenaline and variability of mean blood pressure. Moreover, a similar relationship existed between noradrenaline levels and pressor range. If it is assumed that pressor reactions are due to an increase in vascular resistance, this precludes a role of the sympathetic system in this aspect of blood pressure variability. On the other hand, one could argue that the results indicate that alterations in pressor range are accompanied by parallel changes in urinary excretion of noradrenaline. This would then account for the fact that in older age groups plasma noradrenaline is more often found to be raised while urinary excretion of this substance is normal and also support the direct relationship between variability of blood pressure and enhanced excretion of adrenaline (DeGuia et al., 1973). However, such a mechanism seems unlikely since one would expect more pronounced variations in the urinary excretion of noradrenaline. Moreover such an assumption is contradictory to the reported direct relationship between plasma and urinary catecholamines. Finally, Aronov et al. (1973) did not find a consistent diurnal variation in levels of plasma and urinary noradrenaline.

Another possibility would be that noradrenaline secretion is stimulated or inhibited (by feed-back) to compensate for alterations in vessel wall tone induced by another mechanism which has yet to be defined. Such a mechanism could be evoked by presynaptic stimulation of alpha-receptors leading to a decrease in noradrenaline release. Alternatively, re-uptake of noradrenaline could be affected by local changes in vascular tone. Except for these local regulations one could think of reduced sympathetic outflow from the central nervous system, caused by baroreceptor reflexes. In this respect the study of Lew (1976) is of interest. In genetically hypertensive rats this investigator found noradrenaline levels in the hypothalamus to vary inversely with diurnal blood pressure variations.

Whatever the exact mechanism, the sympathetic nervous system in essential hypertension seems to be related more to daily pressor reactions rather than to

the "absolute" level of blood pressure. So no firm evidence is found that the system is pathogenetically involved in this disorder. This is also confirmed by the lack of a relationship between noradrenaline and vascular resistance. The arguments cited by Bing et al. (1977) fit this view.

On the other hand, from a view point of methodology any conclusions at this time are bound to be premature. Firstly, the absence of a relation between NA and vascular resistance does not prove that such a relation indeed does not exist, since NA can affect cardiac output simultaneously. Secondly, it is still possible that NA levels do not reflect sympathetic activity. It must be borne in mind that plasma NA only mirrors the overflow from synaptic clefts, which is only manifest "after the action".

In respect to renal function we found a tendency for the cortical circulation to be reduced at higher levels of noradrenaline. Intrarenal infusion of NA also causes a progressive decrease in mean renal blood flow and C_1 flow rate (Hollenberg et al., 1972). Whereas no relations were found between noradrenaline and total renal blood flow or renal vascular resistance, the highly significant inverse relationship between endogenous NA and cortical flow point to an extreme sensitivity of the renal cortical vessels. Since it can be reasoned that it will be rather difficult to demonstrate such a relationship in the intact human being, the actual finding suggests a direct causality. So a high degree of fuctionalvasoconstiction in this area seems to be at least in part dependent on sympathetic activity. This agrees with the assumption of Hollenberg and Dams (1976) on cortical vascular tone.

It further demonstrates that studies on the intrarenal circulation can no longer be interpreted without paying attention to sympathetic involvement. This has to be emphasized in appreciating the results of our Xe-washout studies. Of further interest is the observation that the kidney is able to release NA, a fact which has not been reported hitherto. Lake et al. (1976) found that NA levels were higher in blood samples drawn from the superior vena cava than in arterial blood, which was explained by removal of NA through the lungs. However, no attempt was made to find a source for the venous catecholamines. Although it is not excluded that other organs contribute to the higher venous level of noradrenaline, at least the kidney is one of its origins. Since NA production was quite independent of several factors, including age, level of blood pressure and arterial or peripheral venous level of noradrenaline, we seem to be faced here with an independently acting mechanism. If NA production would merely reflect sympathetic tone and overflow of transmitter, one would expect more directional relations between noradrenaline production and flow patterns. No relationship was found between NA secretion and renin secretion. Peripheral samples did not correlate either. This is in contrast with the observations of others. The relationship between NA and plasma renin levels varies in the literature from positive (De Quattro and Miura, 1973) to negative (Louis et al., 1974), thus suggesting that there is no relation at all.

When patients were stratified according to their renin levels, average noradrenaline levels have more often been found to correlate with the average renin level (Esler et al., 1976, 1977; De Quattro et al., 1976) although again the data are conflicting (Mitchell et al., 1977). At present there is insufficient evidence for a role of the sympathetic system in regulating basal levels of renin in hypertension.

9.7 Conclusions

From the data presented this chapter the following conclusions can be drawn.

1. Plasma noradrenaline levels are not increased in patients with essential hypertension when compared to normotensive controls.
2. Noradrenaline levels are not related to age or blood pressure, but vary inversely with variability of mean (and systolic) blood pressure and pressor range.
3. Whereas haemodynamic parameters, in general, do not correlate with noradrenaline levels, outer cortical blood flow through the kidney appears to be highly dependent on sympathetic tone.
4. At least in patients with essential hypertension, the kidney is able to release noradrenaline regardless of other factors like blood pressure of sympathetic activity.
5. There is no firm evidence that renin levels under basal conditions are related to sympathetic activity.

CHAPTER 10

The adrenergic system in essential hypertension

II Functional approach

10.1 Introduction

In the previous chapter it was shown that there is still insufficient evidence for a causative role of the sympathetic nervous system in essential hypertension. Catecholamines are only raised in a minority of patients with essential hypertension and sometimes normotensive persons also appear to have increased amounts of catecholamines. This raises the possibility that there is an increased sensitivity or reactivity to sympathetic stimuli in hypertension.
One problem is that plasma levels of NA or D.B.H. may fail to reflect sympathetic activity. In view of the complex mechanisms involved in release and in activation of NA, it could be argued that only an excessive sympathetic drive will lead to an increase in plasma NA. Indeed, the studies of Louis et al. lend some support to this hypothesis. On the other hand, a normal sympathetic impulse could be related to an abnormal release or defective re-uptake of neurotransmitter. The first possibility is unlikely, since tilting produces similar increases in NA in normotensive and hypertensive subjects (De Quattro and Chan, 1972). A defective re-uptake of NA cannot be completely ruled out, but if this were the case, D.B.H. levels, whatever their significance, would be in the normal range, since this enzyme is not affected by the re-uptake mechanism.
The data of Geffen et al. (1973) contradict this re-uptake defect. On the other hand, the wide variation in D.B.H. levels could possibly mean that there is a more or less defective re-uptake in some patients with essential hypertension.
An increase in sensitivity to sympathetic stimuli implicate either alpha-receptors or beta-receptors. While the former are involved in vasoconstriction, the latter may account for a hyperdynamic circulation. Under normal circumstances the interplay between both divisions of the sympathetic system is thought to be balanced carefully by baroreceptor reflexes and other feedback mechanisms. This balance could be disturbed in essential hypertension.

10.2 Adrenergic reactivity

10.2.1. Vascular reactivity

Experimental studies on isolated vascular segments have revealed that the vasoconstrictor response to noradrenaline can be potentiated by low density lipoproteins (Bloom et al., 1976) and by angiotensin II (A II) (McGregor, 1965; Panisset and Bourdois, 1968; Zimmerman et al., 1972; Malik and Nasjletti, 1976). The facilitation of adrenergic transmission by A II follows enhanced synthesis (Roth, 1972) and release (Zimmerman and Gisslen, 1968; Starke et al., 1969; Hughes and Roth, 1971) of NA, while inhibition of the re-uptake process (Khairlallah, 1972) could also participate. This phenomenon probably reflects a local A II mechanism (Malik and Nasjletti, 1976). When NA is released by tyramine, the pressor response is still increased by A II (McCubbin and Page, 1963; Page, et al., 1966; Kaneko, et al., 1966).
Another possible cause for the increased vascular sensitivity is an alteration in muscle cell properties and this, in fact, has been found by Jones (1973, 1974) in spontaneously hypertensive rats. These rats, originally bred by Okamoto and Aohi (1963), show features which are very similar to those of human essential hypertension (Grollman, 1972). It appeared that the turnover of K and CL was increased, while intracellular NA was accumulated in excess in spontaneously hypertensive rats, as compared to a normotensive strain of rats. These observation have been extended by Hermsmeyer (1976) who discovered an alteration in membrane potential in arterial vascular muscle cells of spontaneously hypertensive rats, presumably due to increased membrane permeability of NA, K and CL ions. Experiments with noradrenaline revealed a greater depolarization in spontaneously hypertensive rats as a result of the altered membrane potential electrogenesis.
These observations link together current insights in molecular physiology and the old concepts about the finding of sodium accumulation in vascular walls (Tobian and Binion, 1952, 1954; Tobian and Redleaf, 1958; Tobian et al., 1961). It has been suggested that the ratio between intracellular and extracellular sodium would either narrow mechanically the vessel lumen or increase the sensitivity to pressor substances (Raab, 1952; Friedman et al., 1959; Tobian, 1960). The present evidence, relating membrane polarisation to vascular tone seems to confirm an old hypothesis (Bacq and Monnier 1935). In addition, anatomical changes alter the normal reactivity to pressor agents (Folkow, 1971; Tobian, 1972).
There is some evidence that in a number of hypertensives the vascular response to exogenous catecholamines is increased (Goldenberg et al., 1948; Greisman, 1952; Doyle and Smirk, 1955; Duff, 1957; Mendlowitz and Naftchi, 1958; Doyle et al., 1959; Mendlowitz et al., 1965; Sivertsson and Olander, 1968; Suck et al., 1971). Release of endogenous NA by tyramine produces the same results (Mendlowitz et al., 1967). This reaction pattern, however, is not always present (Gombos et al., 1962) and also occurs in normotensive off-spring of hypertensive patients (Doyle and Fraser, 1961). This phenomenon, therefore, may be related rather to genetic determination than to the hypertension as such. In addition, the hyperresponsiveness probably is not cofined to the

action, of noradrenaline, since adrenaline (Vlachakis et al., 1974; De Guia et al., 1973) and angiotensin (Mendlowitz et al., 1961) are capable of inducing an exaggerated response as well. The influence of stress on blood pressure and catecholamines is also more pronounced in hypertensive subjects (Nestel, 1969; Lorimer et al., 1971).
Although initially hyperresponsiveness was not demonstrated in renal vessels (Gombos et al., 1962), more recent investigations seem to contradict this finding (Hollenberg and Adams, 1976; Collis and Vanhoutte, 1977). In "borderline" hypertension, tilting (Esler an Nestel, 1973; Frohlich et al., 1967), mental arithmetic (Nestel, 1969) and a negative pressure in the lower part of the body (Mark et al., 1975) all reveal hyperresponsiveness of the peripheral resistance vessels. As indicated before, it is still unclear whether the sensitivity to NA is determined by genetic factors, hypertension per se or by smooth muscle hypertrophy (Sivertsson and Olander, 1968).

10.2.2 Beta-adrenergic hyperreactivity

Besides the vascular (alpha-receptor) hypersensitivity, an hyperresponsiveness of beta-receptors has been described in young patients with "labile" hypertension. It must be admitted that some clinical features, in particular, a rise in heart rate and/or stroke volume, indeed, suggest adrenergic overactivity. Safar et al. (1975), however, found the "chronotropic" dose of isoproterenol to be normal in patients with "labile" hypertension in comparison with normotesives. In contrast, the dose appeared to be increased in patients with more sustained hypertension.
Frohlich et al. (1966, 1969, 1970) described a hyperresponsiveness of cardiac beta-receptors in hypertensive patients, after infusion of isoproterenol. However, in the studies of Frohlich only a minority of the patients had "hyperkinetic borderline hypertension". Moreover, in a number of patients with "borderline" hypertension and an elevated cardiac output, no exaggerated rise in heart rate and cardiac output was found after infusion of isoproterenol.
Isoproterenol has also been shown to produce exaggerated rises in cyclic A.M.P. and renin (Messerli er al., 1976b; Kuchel, 1977) in a number of patients with "borderline" hypertension. This may implicate a generalized hyperresponsiveness of beta-receptors. At present, however, there is little evidence to assimilate a beta-adrenergic hyperresponsiveness with hypertension.

10.3 Baroreceptor reflexes

The adrenergic system is involved in several reflex arches and feed-back mechanisms regulating vasomotor control, blood flow distribution, renin release and possibly renal excretion of water and electrolytes.
The most extensively studied division has been the baroreceptor reflex arch. The baroreceptors, located in the aortic arch and carotid sinus, serve to maintain blood pressure within fairly constant limits. If blood pressure falls, the altered rate of discharge tends to diminish the inhibitory action on

sympathetic nerve fibers. The resultant features are increased vasoconstriction and tachycardia.
Conversely, a rise in blood pressure will lead to less active vasoconstriction and cardiac slowing. Although in man the discharge from the baroreceptor cannot be determined directly, the sensitivity of the system to acute alterations in blood pressure either by postural changes or by injecting pressor substances can be established quite well. Baroreceptor sensitivity is undoubtedly reduced by age and also by high blood pressure itself (Gribbin et al., 1971). Bristow et al (1969) clearly demonstrated that baroreceptor function is diminished in established hypertension; whether this is also true for the early phase is still controversial. Studies from different laboratories have yielded conflicting results, both in favour of this theory (Gribbin et al., 1971; Takeshita et al., 1975) and against (Julius et al., 1975).
A high variability of blood pressure which is especially encountered in younger patients with essential hypertension is also compatible with diminished baroreceptor functioning, as has been suggested by the results of animal studies (Cowley et al., 1973). According to some investigators the baroreceptor can be "reset" to allow a higher level of blood pressure (McCubbin et al., 1956; Korner et al., 1974).

In the experimental animal this resetting can occur by stimulation or destruction of certain brain areas (Reis and Cuénod, 1965; Folkow and Rubinstein, 1966; Gebber and Snyder, 1970; Doba and Reis, 1973). There is, however, also evidence that the baroreceptor in itself is malfunctioning (Aars, 1968; Angell-James, 1973; Sleight et al., 1975).

Whether in man this mechanism is of primary importance for the development of essential hypertension or merely is the result of the elevated pressure is still unsettled.

In spontaneously hypertensive rats baroreceptor resetting has also been demonstrated (Nosaka and Okamoto, 1970; Nosaka and Wang, 1972; Coote and Sato, 1977; Brown et al., 1976). However, this phenomenon probably is secondary to the elevated blood pressure and related to aortic hypertrophy (Sapru and Wang, 1976).

10.4 Propranolol, an anti-adrenergic agent

10.4.1 Introduction

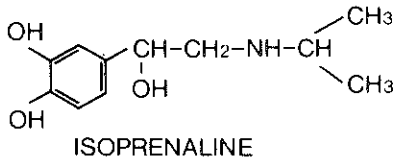
In the treatment of hypertension a large number of pharmaca have been used. Their mode of action has sometimes provided new insight in pathophysiological processes. Of particular interest is the group of beta-blocking agents. The development of this class of drugs started in the fifties with the discovery of dichloroisoprenaline, which inhibited the relaxation of tracheal smooth muscle and the fall in arterial pressure, produced by isoprenaline (Powell and Slater, 1958). It also inhibited the effect of adrenergic agents on the heart (Moran and

Perkins, 1958). These drugs, however, also had a marked sympathomimetic action (Moran and Perkins, 1958; Glover et al., 1962). Shortly after pronethalol was synthesized, which counteracted the effect of sympathetic stimulation and, in addition, did not exhibit stimulant activity (Black and Stephenson, 1962). Its clinical significance, however, was curtailed by its ability to produce thymic tumours (Alcock and Bond, 1964). The next stage was the development of propranolol, which, while being more active than its predecessors, did not exhibit carcinogenic properties (Black et al., 1965). Propranolol has become the standard beta-adrenergic blocking agent and has withstood the test of time despite the introduction of many related compounds. For several reasons, the main one being the experience with this drug in-our department, propranolol has been selected as the drug of choice in our study.

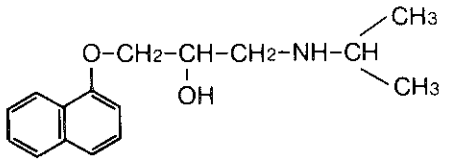
10.4.2 Properties of propranolol

Chemical structure

From the structural formulas given in figure 54 it can be inferred that propranolol shows similarities with the beta-stimulating agent isoprenaline. The side chain determines interaction with beta-adrenoceptors. Owing to the asymmetric carbonatom two optically active enantiomers occur and, as is the case with catecholamines, the L-isomer of propranolol has considerably more activity than the D-isomer (Howe and Shanks, 1966; Patil, 1968; Buckner and Patil, 1971).



ISOPRENALINE



PROPRANOLOL (Inderal)

Fig. 54 Structural formulas of isoprenaline and propranolol.

The two hydroxyl groups in the 3-4-positions in the aromatic ring of isoprenaline are optimal for stimulating activity (Innes and Nickerson, 1970). The fused aromatic ring in the place of these hydroxyl groups and the insertion of the methylenoxy bridge ($O\text{-}CH_2$) between the aromatic ring and the asymmetric carbon atom greatly reduces the stimulating activity (Clark, 1976).

Effect on beta-adrenoceptors

Propranolol binds with beta-1 as well as beta-2 receptors. It does not react with alpha-receptors. Since it acts by competitive antagonism, complete blockade can never be reached for increasing the dose of a simultaneously administered agonist (like isoprenaline) can overcome the blockade. The dose-response curve for the agonist is shifted to the right by propranolol (Cleaveland and Shand, 1972; George et al., 1972; Clark, 1976). The potency of this drug can be assessed both in vitro and in vivo but since this is only meaningful when compared to another drug, we will leave this from the discussion.

Pharmacokinetics of propranolol

When propranolol is administered orally, it is completely absorbed from the gut (Paterson et al., 1970) and transported to the liver by the portal vein. Complete bioavailability, however, does not occur owing to a high hepatic extraction, known as presystemic (or "first pass") elimination (Rowland, 1972). In man, a single dose higher than 30 mg, saturates the hepatic removal process, resulting in a larger fraction reaching the systemic circulation (Shand and Rangno, 1972). Nevertheless, even under chronic treatment the systemic availability of propranolol is not higher than 20-50% (Nies and Shand, 1975). Since the hepatic uptake remains saturated for several hours, repeated administration results in accumulation of the drug in the blood (Evans and Shand, 1973[a]). In the steady state during continuous oral administration, drug concentrations are proportional to dosage (Chidsey et al., 1975; Nies and Shand, 1975; Shand, 1976). In the blood, propranolol is bound to albumin for about 90% (Evans and Shand 1973[b]; Evans et al., 1973). Still, its distribution volume approximates about 250 liter (Evans et al., 1973; Shand and Rangno, 1972).
It is obvious therefore that there must be a significant accumulation of the drug in extravascular tissues. This occurs predominantly in liver and lung (Hayes and Cooper, 1971). In this chapter we will describe the results of two types of investigations with respect to sympathetic activity. In the first, we have stimulated the system by tilting, while in the other, we studied the haemodynamic and endocrinological responses to beta-adrenergic blockade with propranolol.

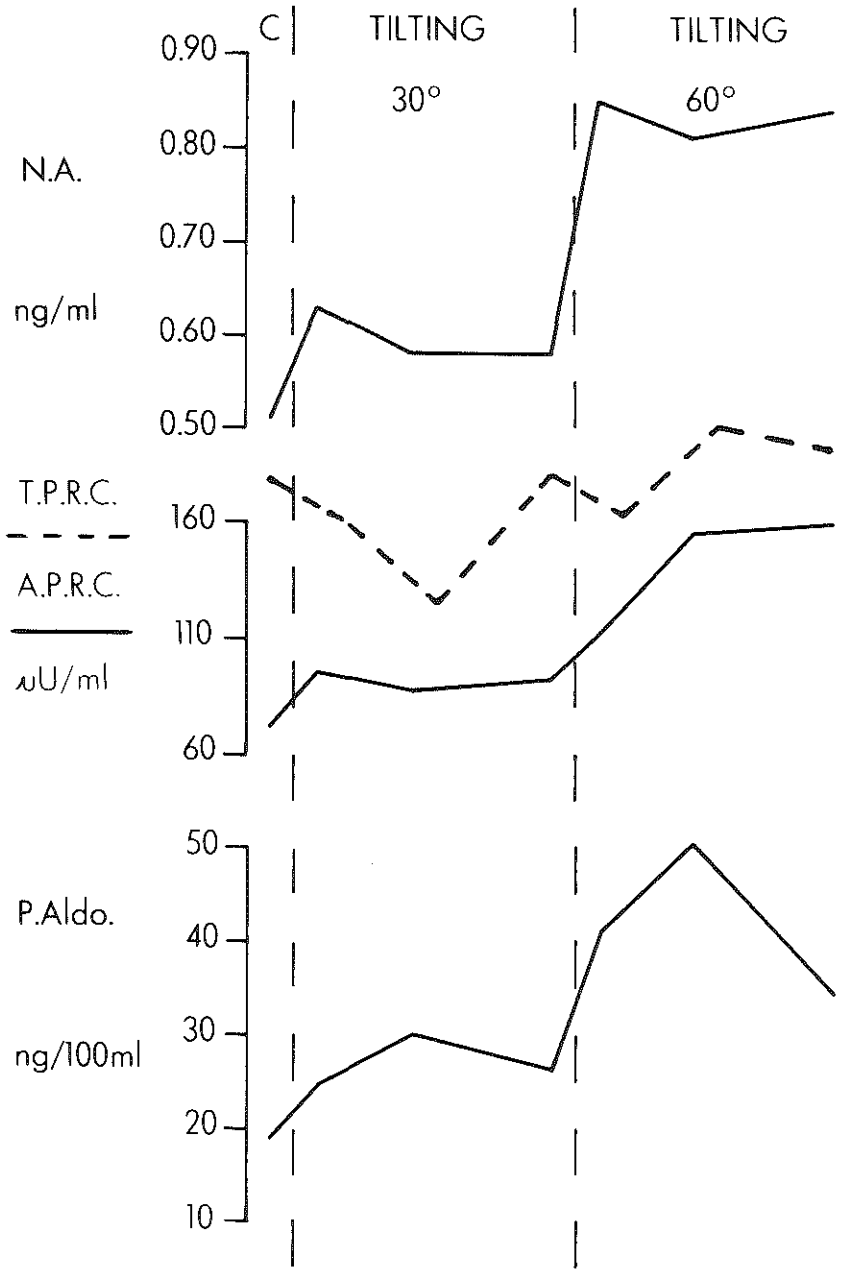


Fig. 55 Example of hormonal changes during tilting.

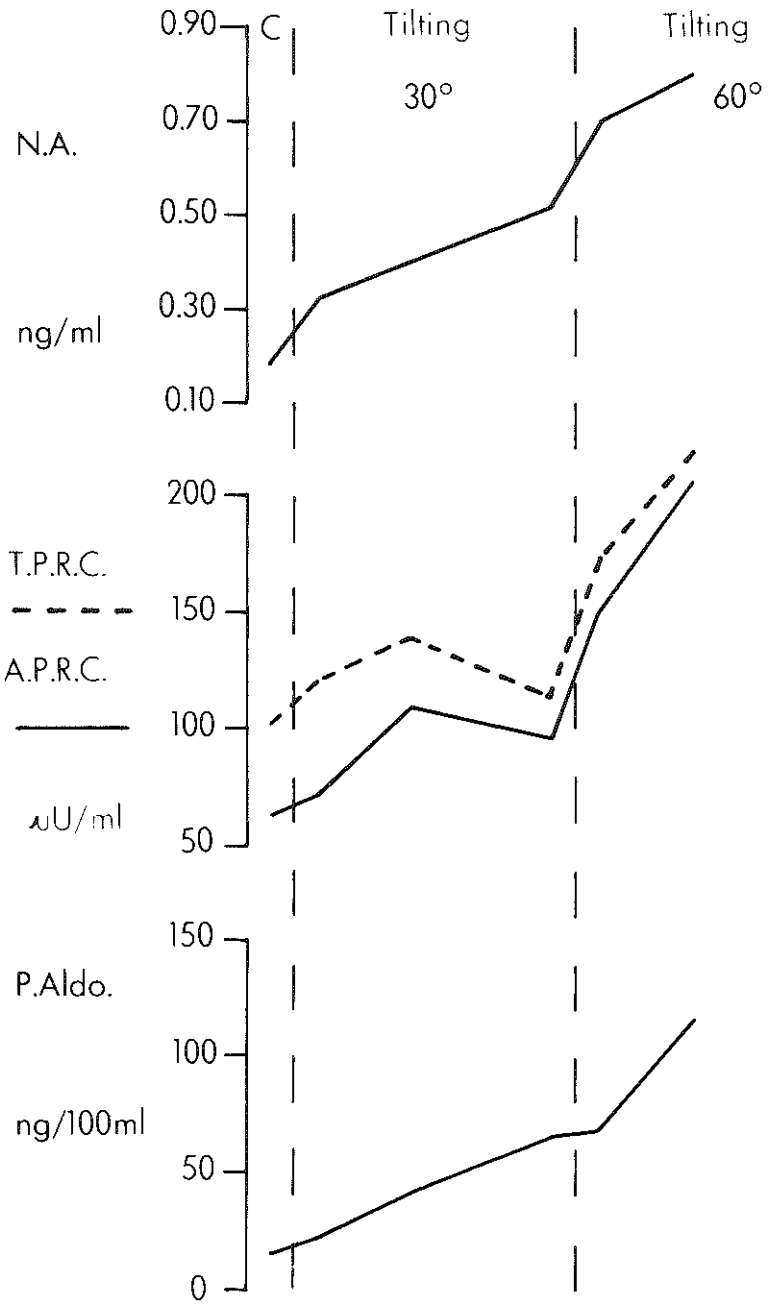


Fig. 56 Example of hormonal changes during tilting in an other patient.

10.5 Tilt studies

10.5.1 Study protocol

Studies were carried out in six subjects (aged 26 to 63 years) with blood pressures between 120 and 200 mm Hg systolic and between 70 and 120 mm Hg diastolic. After an overnight fast subjects were transported in a recumbant position to the investigation room. At 09.00 a.m. indwelling catheters were inserted for haemodynamic investigations. After 2½ hours subjects were tilted to 30° for 30 minutes and subsequently to 60° for another 30 minutes. Samples for renin, aldosterone and noradrenaline were drawn before tilting, twice during the first ten minutes and at the end of each tilting period. In two patients we could not complete the protocol because of syncope shortly after tilting to 60°. Before and after tilting blood samples were drawn for determination of hippuran to estimate renal plasma flow.

10.5.2 Results

During tilting blood pressure did not show marked variations. In all patients renal blood declined and renal vascular resistance increased. Although not significant in a statistical way, the increase in renal vascular resistance was more closely associated with the rise in noradrenaline ($r = 0.73$) than with the rise in active renin ($r = -0.01$). Examples of the hormonal changes are presented in figures 55 and 56. Tilting to 30° proved to be a rather weak stimulus. During this manoeuver levels of noradrenaline, renin and aldosterone remained either unchanged or showed a moderate increase. In contrast, tilting to 60° usually was accompanied by a substantial rise in hormone levels. Noradrenaline levels reached their peak values within the first five minutes of tilting, while both total and active renin concentration arrived at a zenith between five and fifteen minutes. Total and active renin followed a similar course and their respective changes were related to each other ($r = 0.79$; $p<0.001$).

Aldosterone closely followed the pattern of renin and peak values coincided with those of renin. There was no relationship between changes in noradrenaline and in total plasma renin concentration. However, a highly significant relation was observed between alterations in noradrenaline and in active plasma renin concentration ($r = 0.90$; $p<0.002$) as shown in fig. 57.

Changes in plasma aldosterone were significantly related both to alterations in total ($r = 0.64$; $p<0.02$) and active ($r = 0.88$; $p<0.001$; fig. 58) renin concentration and to those in noradrenaline ($r = 0.81$; $p<0.001$).

Changes in inactive renin were not related to any of the above mentioned variables.

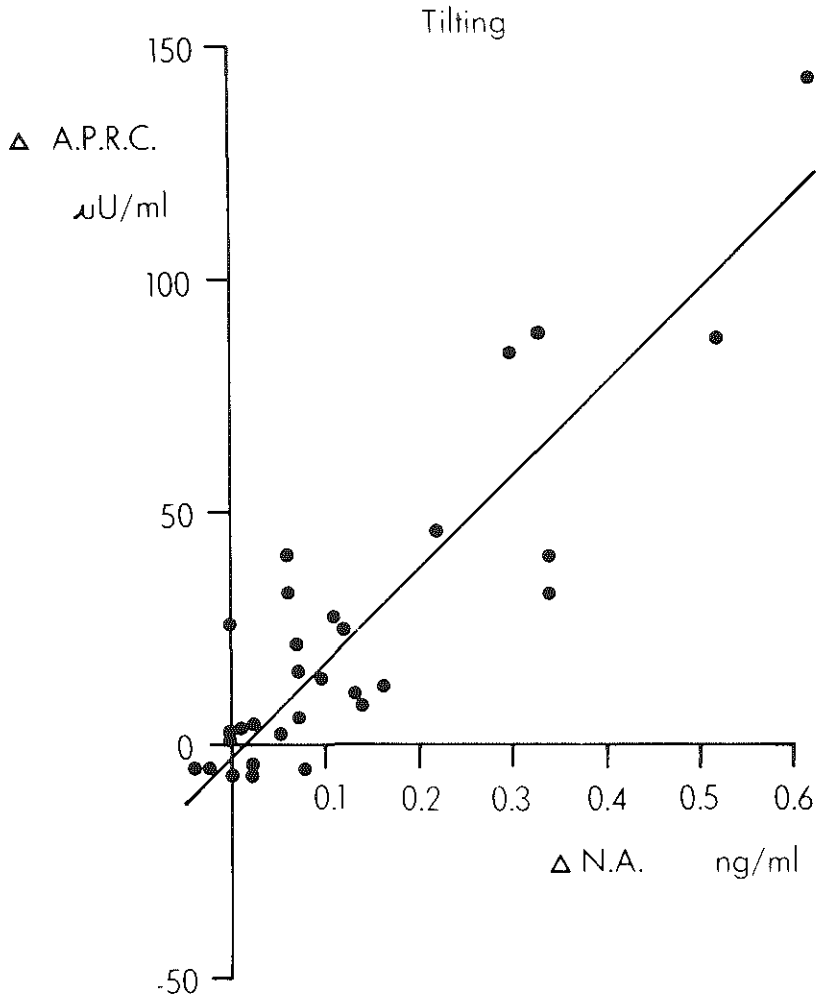


Fig. 57 Relationship between changes in noradrenaline levels and those of active renin during tilting.

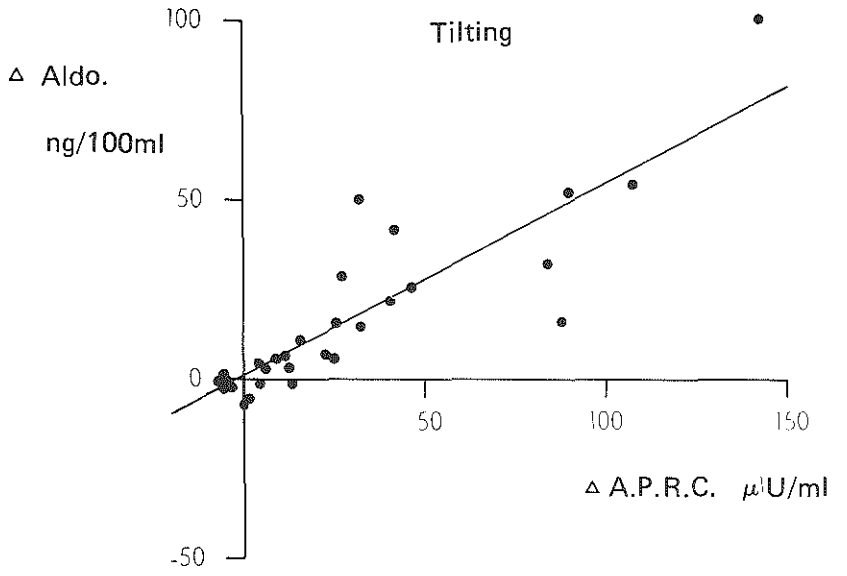


Fig. 58 Relationship between changes in active renin concentration and aldosterone during tilting.

10.6 Beta-blockade

10.6.1 Study protocol

From the group of patients described in the first part of this thesis, 45 subjects were treated with the beta-adrenergic agent propranolol. The average daily dose was 240 mg and the duration of the treatment 17 days. Before and after two weeks of treatment a number of the determinations as referred to in chapter 2 were carried out. Active renin and noradrenaline were measured in a minority of these patients, after the methods had become available.

10.6.2 Results

Effect on systemic haemodynamics

Individual data are presented in table A-19. Systolic, diastolic and mean blood pressure decreased significantly during propranolol treatment. However, the individual response was quite variable. When responders are defined as those patients showing a decrease in mean blood pressure of 10 mm Hg or more, it is

apparent that at the start of the treatment the responders tended to have a higher blood pressure than the non-responders. No significant changes were observed in the parameters of blood pressure variability before and during treatment, with the exception of a decrease in systolic pressure variability.
Pulse pressure was slightly lower during treatment, but the difference with pre-treatment values was not significant. Heart rate declined in all but two patients. Although the reduction in heart rate exhibited a wide scatter, the difference between pre- and post-treatment level was highly significant.
Although in the entire group average cardiac output decreased by slightly more than 0.5 l/min.; this reduction was not significant. However, when the data are scrutinized more closely, it appears that the response of cardiac output varied between a decrease and an increase. In view of the variability of test results (Ch. 3), we would consider only changes of more than 10 percent as substantial. When the patients who responded with a fall in cardiac output are compared with those who exhibited an increase in cardiac output during treatment,the first groups had a significantly higher cardiac output at the start of the study. In this group the fall in cardiac output was statistically significant.
Stroke volume increased moderately, but again the response was variable.
Total peripheral resistance on the average remained essentially unchanged, half of the patients showing a reduction and the other half an increase.

Effect on renal haemodynamics and plasma volume

Glomerular filtration rate, renal plasma flow and filtration fraction did not exhibit significant changes during treatment. By contrast, renal blood flow decreased from 895 ± 248 ml/min to 803 ±248 ml/min ($p<0.05$, as assessed by Student's one-paired t test). Renal vascular resistance as a consequence rose slightly, but the increase was not significant. The renal fraction was, on the average, not affected by beta-blockade. It must be emphasized that for all these variables, marked variations (both upwards and downwards) were found. The same pattern was found with respect to plasma volume.

Effect on renin, aldosterone and noradrenaline

Total renin concentration decreased in some patients, while it increased in others; for the total of observations there was no significant difference in pre- and post-treatment values. For active renin there was a more marked tendency to decrease although the difference between pre- and posttreatment values was not statistically significant. The relative amount of active renin, however, decreased from 32% to 23% ($p<0.0025$). Aldosterone levels were markedly reduced during propranolol treatment ($p<0.0025$), but noradrenaline levels remained practically unchanged.

Predictability of response (fig. 59-66).

For all variables there was a significant direct relationship between pre-and post-treatment values, with the exception of the so-called depressor range. The response of mean blood pressure was not related to such factors as age and control values of heart rate, cardiac output, peripheral vascular resistance,

renin or variability of blood pressure. Even noradrenaline levels failed to predict the observed fall in blood pressure.

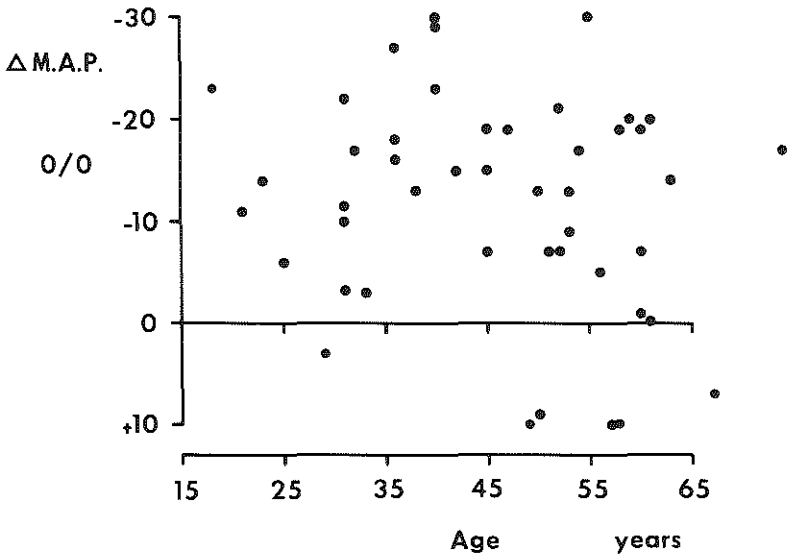


Fig. 59 "Predictive" value of age with respect to the decrease in blood pressure during treatment with propranolol.

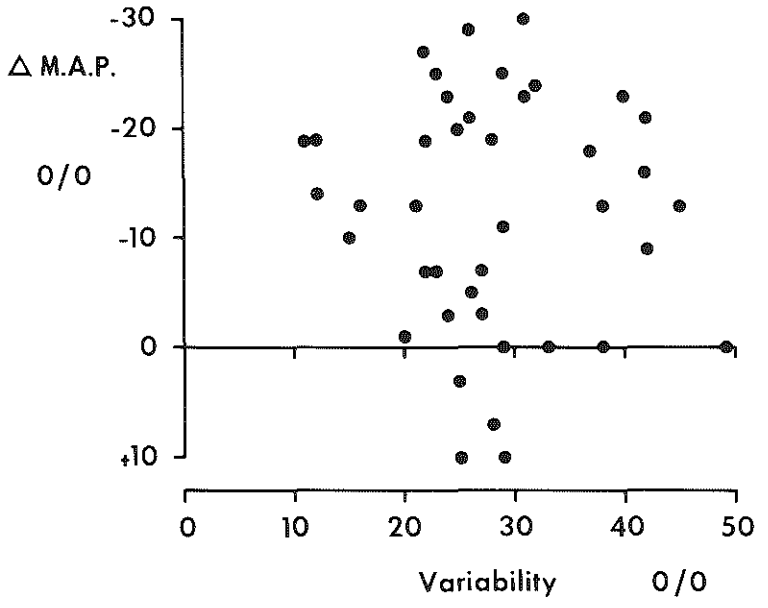


Fig. 60 "Predictive" value of variability of blood pressure with respect to the decrease in blood pressure during treatment with propranolol.

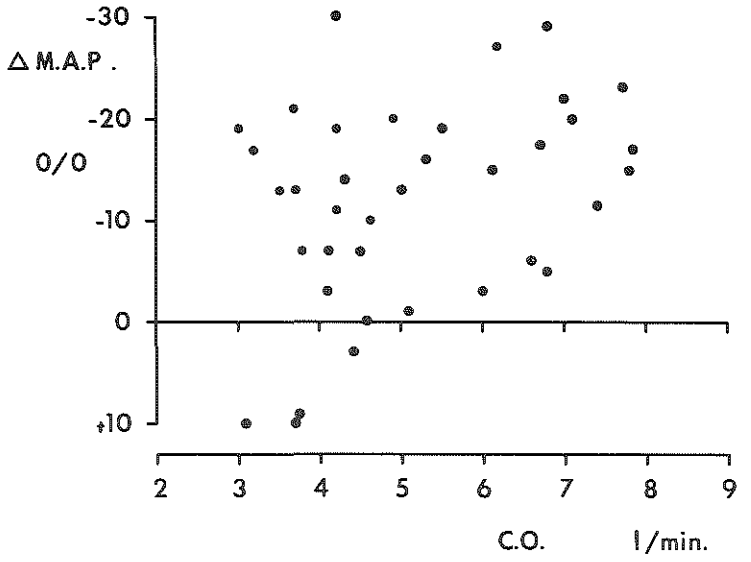


Fig. 61 Reduction in blood pressure during propranolol treatment and initial cardiac output.

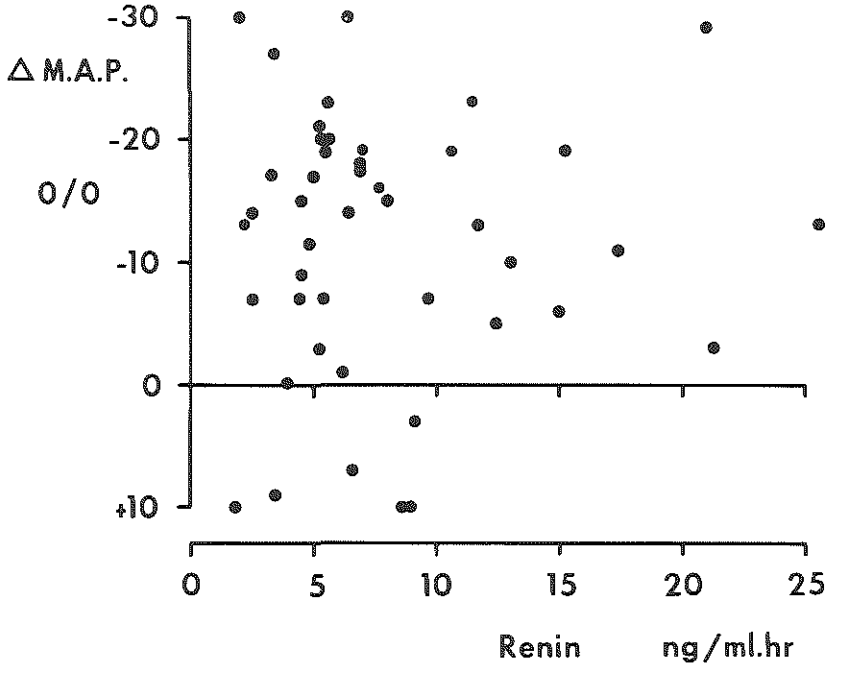


Fig. 62 Reduction in blood pressure during propranolol treatment and initial total renin concentration.

However, the change in mean arterial pressure was inversely related to its initial value ($r = -0.46$; $p<0.005$). The decrease in heart rate was also inversely related to its pre-treatment level ($r = -0.79$; $p<0.001$). Similar relationships were found for stroke volume ($r = -0.52$; $p<0.005$), renal plasma flow ($r= -0.33$; $p<0.05$), renal fraction ($r = -0.61$; $p<0.001$), total renin concentration ($r = -0.39$; $p<0.005$), active renin concentration ($r = -0.61$; $p<0.001$), percentage amount of active renin ($r = -0.85$; $p<0.001$), inactive renin concentration ($r = -0.44$; $p<0.025$), plasma aldosterone ($r = -0.72$; $p<0.001$) and plasma noradrenaline ($r = -0.61$; $p<0.001$). For total peripheral and renal vascular resistance the relations did not reach statistical significance.

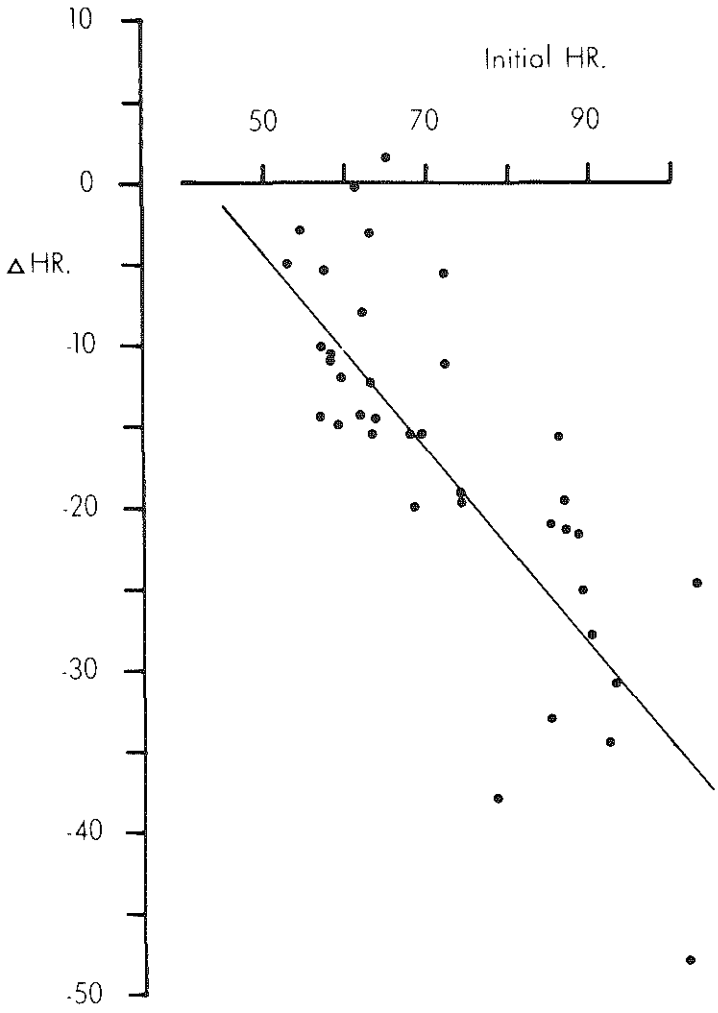


Fig. 63 Relationship between decrease in heart rate and initial value during propranolol treatment.

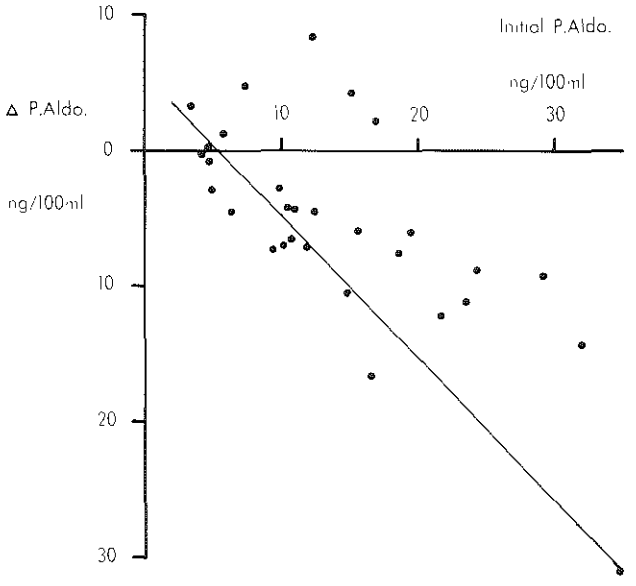


Fig.64 Changes in aldosterone levels and initial value during propranolol treatment.

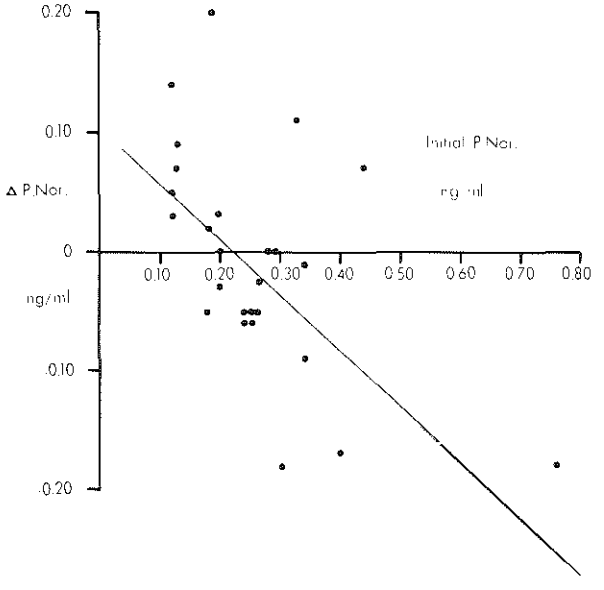


Fig. 65 Relationship between changes in noradrenaline levels and initial value during propranolol treatment.

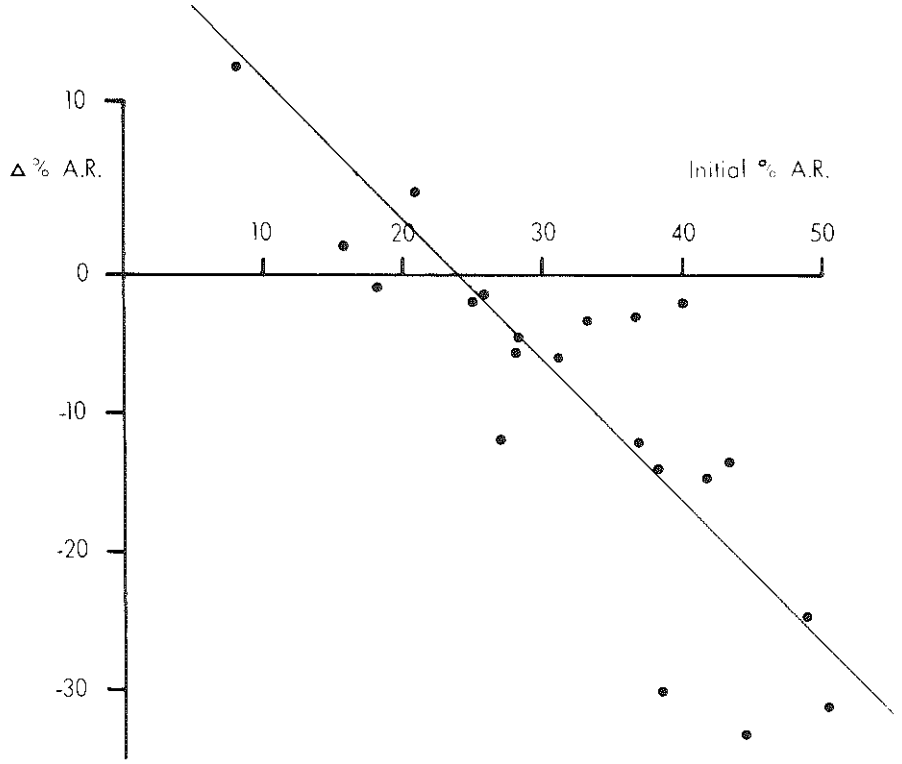


Fig. 66 Relationship between changes and initial value for the percentual amount of active renin during propranolol treatment.

One could hypothesize that these relations correspond to the statistical-epidemiological phenomenon of "regression towards the mean" and would therefore be devoid of physiological significance. This possibility can be ruled out, however, by taking into account the lack of such patterns in sequential analyses in untreated subjects. (Ch.3)

Interrelations

The fall (or rise) in blood pressure was not related to changes in heart rate, stroke volume or cardiac output. Neither was there a relation between blood pressure changes and alterations in renin or noradrenaline concentration. No relationship was observed between changes in cardiac output and in renal blood flow.

Changes in glomerular filtration rate were not related to changes in renal plasma flow. Alterations in filtration fraction and in plasma volume exhibited a direct relationship ($r = 0.52$; $p<0.02$). Changes in hormonal levels were not related to each other nor to the other variables. Shifts in pressor range (cf Ch.4)

were inversely related to changes in noradrenaline concentration (fig. 67), ($r = -0.61$; $p<0.001$). Although less significant, a direct relationship was observed between changes in depressor range and in noradrenaline concentration ($r = 0.42$; $p<0.05$). No relationship was observed between alterations in noradrenaline and basal blood pressure.

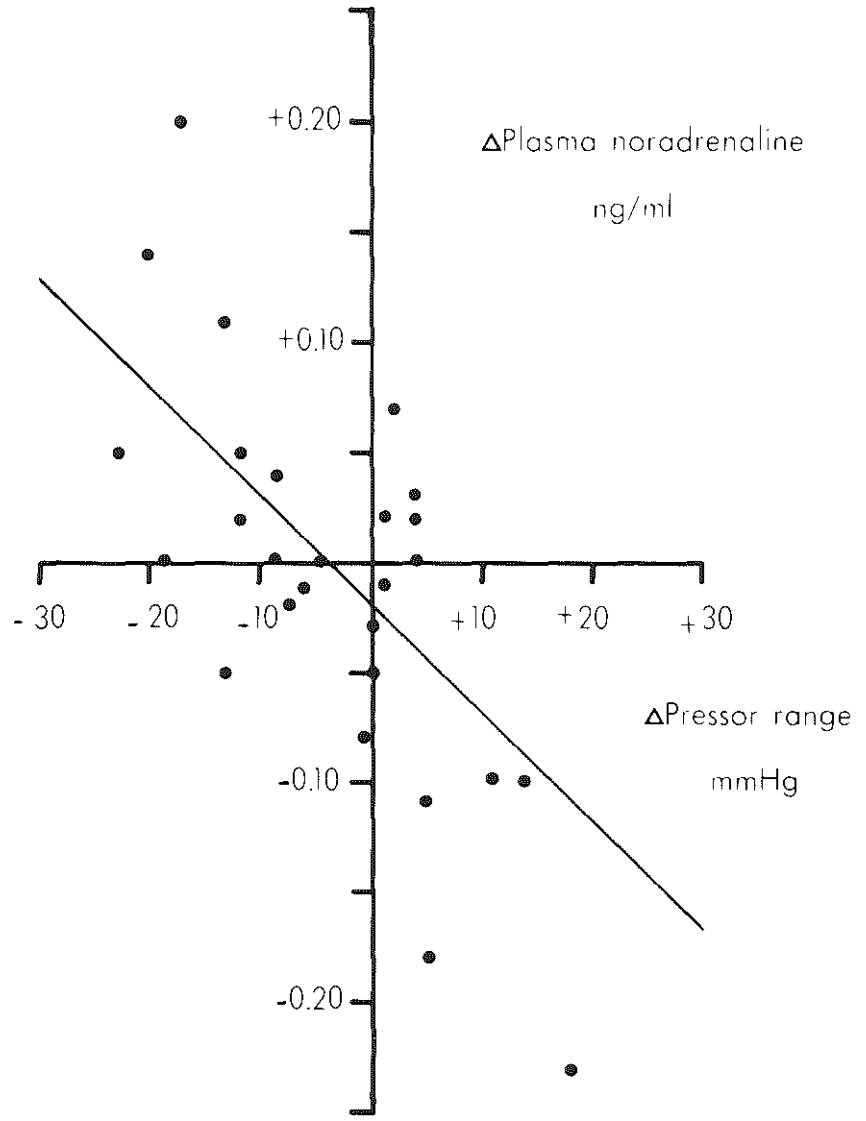


Fig. 67 Relationship between changes in pressor range and in noradrenaline levels during propranolol treatment.

Effect on intrarenal haemodynamics

In 23 Patients with essential hypertension (mean age 46 years) who were on propranolol therapy for at least two weeks, intrarenal haemodynamics were measured by the Xe-washout technique.

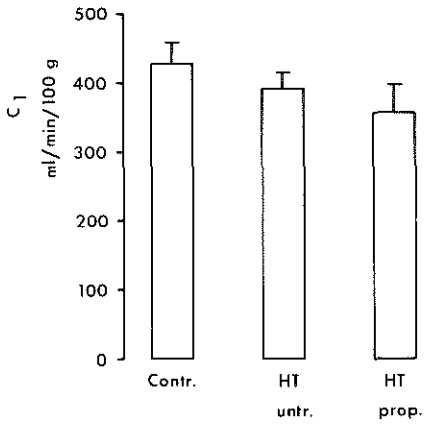


Fig. 68 C_1 flow rate in control subjects, untreated hypertensives and patients on propranolol treatment.

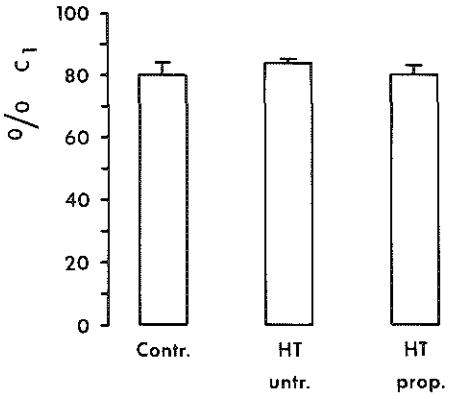


Fig. 69 Percentage C_1 flow rate in control subjects, untreated hypertensives and patients on propranolol treatment.

Mean values for C_1 and $\%C_1$ were 377 ± 109 ml/min/100 gr and 83 ± 9% respectively (Fig. 68 and 69). Mean blood flow averaged 322 ± 95 ml/min/100 gr. In this group of patients C_1 decreased with age ($r = -0.48$; $p<0.0025$) and with increasing blood pressure. The latter relation, however, was only of borderline significance when the effect of age was eliminated. C_1 did not correlate with the arterial noradrenaline levels, but absolute cortical blood flow did show a relationship with noradrenaline ($r = -0.74$; $p<0.02$) (Fig. 70).

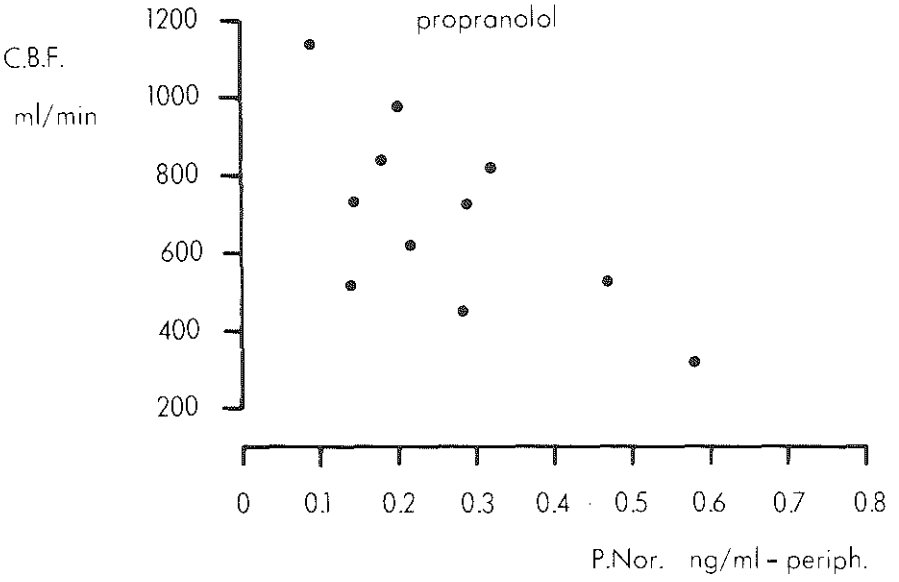


Fig. 70[a] Relationship between cortical blood flow and peripheral noradrenaline levels in patients on propranolol.

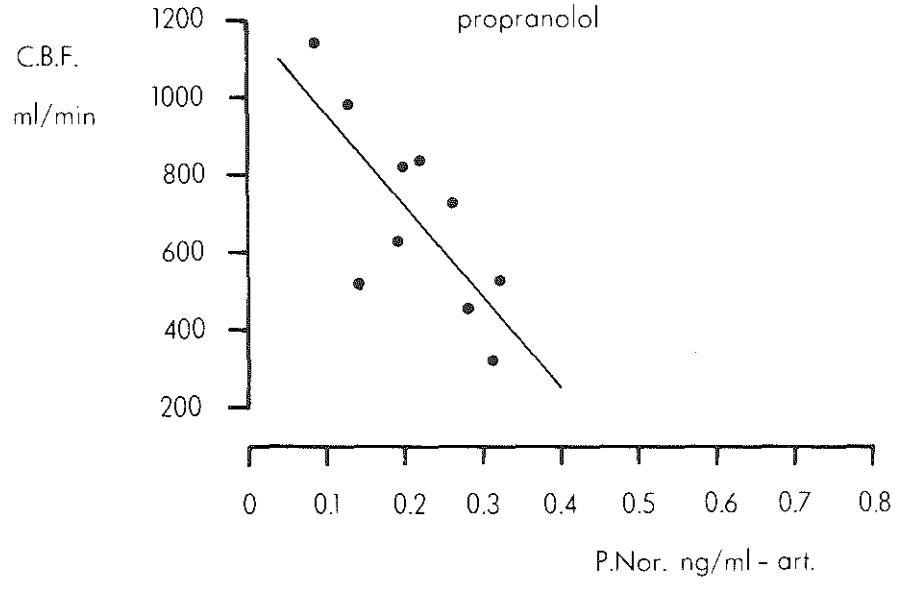


Fig. 70[b] Relationship between cortical blood flow and arterial noradrenaline levels in patients on propranolol.

When the data for intrarenal haemodynamics are comparend with those of normotensives and untreated hypertensives studied in our laboratory (Kolsters, 1976) no significant differences appear to exist in these three groups with respect to C_I, MBF and $\% C_I$.

Effect on renal secretion of pressor hormones

In 16 of the patients in whom intrarenal haemodynamics were measured, total renin secretion was measured. The arterial level of this substance was 106 ± 61 μU/ml and the renal venous level 110 ± 65 μU/ml. In terms of percentage this level increased from 100% to 106 ± 5% ($p<0.0005$).
Active renin concentration also increased significantly from 100% to 112 ±15%. Inactive renin was essentially of the same order in renal arterial and venous blood (86 ± 38 μU/ml vs. 85 ±35 μU/ml). Percentage amounts of active renin were 20 ± 12% and 21 ± 15% respectively. When these values for renin secretion are compared with the values in untreated hypertensives (Ch.8), the only significant difference which is found is a reduced secretion of total renin in the propranolol group (fig. 71). Although active renin, both as a percentage of total renin and in terms of secretion appeared to be reduced in the propranolol group, the difference with the untreated group was not significant.
It must be emphasized, however, that in five of the nine patients on propranolol active renin secretion was actually zero. As for release of nordrenaline, a more consistent pattern of secretion was found. The average arterial level was 0.26 ± 0.15 ng/ml and the venous level 0.32 ± 0.020 ng/ml. This represents an average increase of 131 ± 52% ($p<0.025$). Total secretion of noradrenaline was 26 ±44 ng/min. Although this was higher than in the untreated group (19 ± 6 ng/min), the difference was not significant.

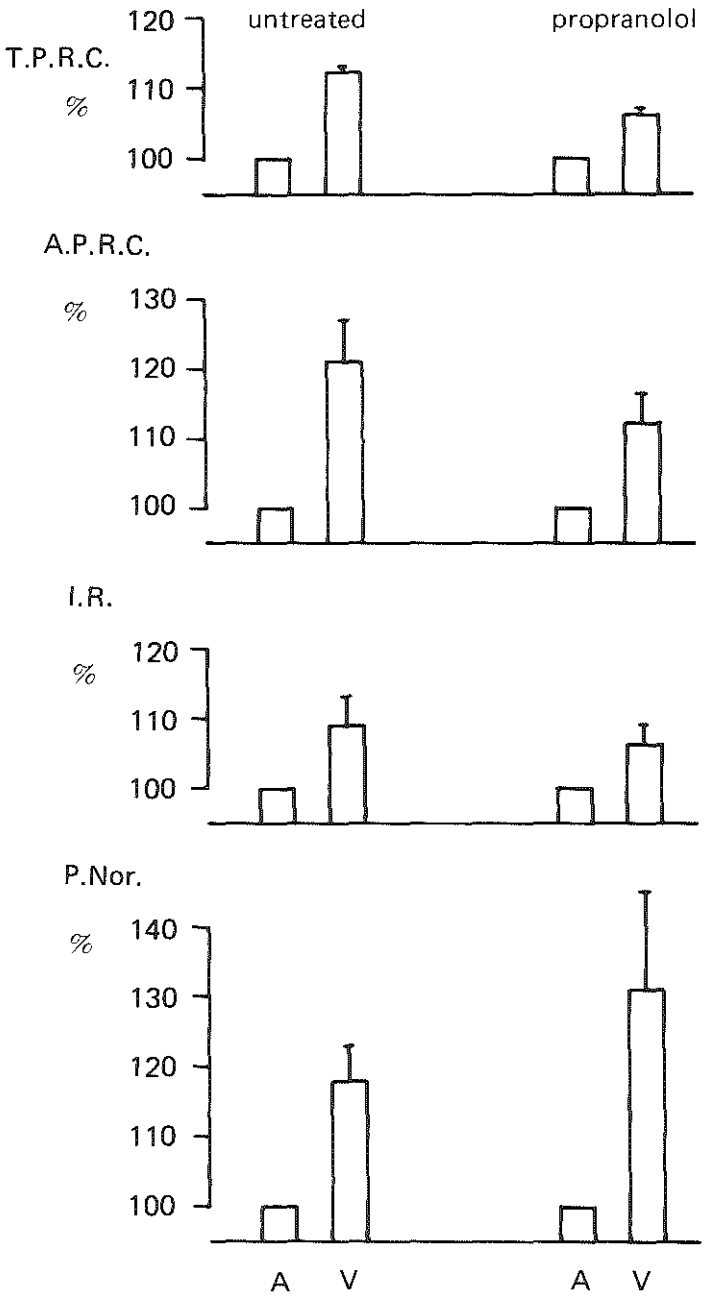


Fig. 71 Secretion patterns of renin and noradrenaline by the kidney in untreated hypertensive patients and those on propranolol.

10.7 Discussion

In chapters 8 and 9 some relations between the sympathetic system and the renin-angiotensin system have been outlined. Obviously, such neuro-humoral mechanisms could act in concert during the short-term regulation of blood pressure, although it is difficult to demonstrate such interrelations in the intact organism.
During tilting several factors could contribute to the rise in renin levels. Among these, a fall in renal perfusion pressure could be a major factor. Since systemic arterial pressure does not change much, one has to assume that renal vascular resistance rises to such a degree that blood pressure falls at the level of the juxtaglomerular apparatus. Indeed, renal blood flow was found to decrease during tilting, which in the face of an unaltered blood pressure indicates renal vasoconstriction (Molzahn et al., 1972). In our study renal vascular resistance also increased. However, assuming a pressure drop at the level of the juxtaglomerular apparatus would not be compatible with the discussion in Chapter 8. For we have reasoned that blood pressure can be transmitted along the renal vessels, and such a marked vasoconstriction which would impede further transmission of blood pressure did not occur during tilting. Moreover, the rise in renin levels is far in excess of that which would be explained by changes in renal haemodynamics per se. There might be several other explanations. A relationship between changes in plasma renin and changes in effective blood volume during tilting was considered by Brown et al. (1966[b]), but denied by Nielsen and Möller (1968). The latter authors explained the rise in renin by a concomitant increase in colloid-osmotic pressure. Although we did not measure colloid-osmotic pressure, it would be very unlikely that this factor is responsible for renin secretion, since it remains quite stable after assuming the upright posture (Nielsen and Möller, 1968), while in our study renin levels exhibited a much more variable pattern.

Serum electrolytes do not change consistently and therefore are unrelated to the renin response. Plasma A.D.H. rises rather than decreases (Davies et al., 1976[a]) and can therefore not have mediated the renin response. In constrast, a neural stimulus would be a most likely mechanism. It is common experience that tilting by reducing venous return increases sympathetic activity. In some cases the alpha-adrenergic response was found to be accompanied by an increase in plasma noradrenaline levels (Molzahn et al., 1972) or urinary excretion of catecholamines (Esler and Nestel, 1973). Although it is believed that orthostasis in the intact human being stimulates renin release through increased adrenergic activity (Brown et al., 1966[b]; Kuchel et al., 1967; Gordon et al., 1967; Cohen et al., 1967; Oparil et al., 1970; Salvetti et al., 1971; Molzahn et al., 1972; Esler and Nestel, 1973) definite evidence is still lacking. In favour of this theory is the observation that the increase of plasma renin with posture can be blunted by means of adrenergic blocking agents (Winer et al., 1969; Michelakis and McAllister, 1972; Tobert et al., 1973; Leonetti et al., 1975; Davies and Slater, 1976; Davies et al., 1976[b]).
Molzahn et al., (1972) reported a positive relationship between changes in plasma noradrenaline and plasma renin concentration during a 45° head-up tilt.

However, this observation was based on only 8 paired data and the relationship was of borderline significance. In the present study we failed to observe a relation between changes in levels of noradrenaline and those in plasma renin concentration. On the other hand, the alterations in noradrenaline were significantly related to changes in active plasma renin concentration. Although there was a rise in total and in active renin, the absolute increase in active renin exceeded that of the total amount of renin.
As a consequence inactive renin decreased, which is in keeping with the findings of Derkx et al. (1976). It is apparent that under conditions of tilt the adrenergic system is mainly concerned with the active part of renin. Although a causal relationship is not proven, the results are in favor of such a mechanism, since other known factors are unlikely to have caused the relation. Diminished hepatic clearance is unlikely since the clearance of noradrenaline and active renin is affected in exactly the same way but differently from inactive renin. Moreover, it should be pointed out that hepatic blood flow during tilting does not alter sufficiently to explain the amplitude of the changes we observed. We therefore are inclined to favour the interpretation that the available data indicate a direct effect of enhanced adrenergic activity on the regulation of active renin concentration during tilting. It is too early to exclude the possibility that the reverse causal sequence may also be true. A mutual amplification of the response would guarantee an optimal flexability of both systems in the face of sudden variations in gravitational factors. From this study it can also be concluded that the release of aldosterone by angiotensin is mediated through active rather than inactive renin.

A different way to assess sympathetic system involvement in cardiovascular homeostasis is to monitor the effect of beta-blockade which we also did in this study. It is well known that propranolol lowers blood pressure, cardiac output and renin. A causal relationship between these actions has frequently been suggested but never been proven.
The anti-hypertensive mechanism of propranolol is still unclear. It would be incorrect to discuss all theoretical and empirical aspects of current theories since this has been the subject of several recent reviews (Birkenhäger et al., 1976[b], 1977; Gross, 1977; Prichard, 1976; Lorimer et al., 1976; Lewis, 1976). Nevertheless, it is quite relevant to present some thoughts on the predictability and nature of the response.
It is well known that propranolol lowers blood pressure mainly after some delay (Ulrych et al., 1968; Hansson et al., 1974) and that hypotension due to overdosage does not occur (Wermut and Wojcicki, 1973). Morover, the blood pressure lowering effect in normotensives is only small. On the other hand, individual doses needed to achieve a certain level of blood pressure reduction may vary greatly (Zacharias et al., 1972), yet the decrease in diastolic blood pressure is proportional to plasma concentrations (Leonetti et al., 1975). These considerations suggest that, except for differences in bio-availability of the drug, the response is mainly dependent on the strength of the feedback mechanisms responsible for the maintenance of blood pressure or, more specifically, the balance between alpha- and beta-receptors. The haemodynamic basis for an adequate fall in blood pressure cannot be related to a reduction of

cardiac output per se. First of all, cardiac output is reduced to the same extent in responders and non-responders (Tarazi and Dusten, 1972) and secondly, pre-treatment values of cardiac output do not predict the hypotensive response to propranolol (Birkenhäger et al., 1971; Tarazi and Dustan, 1972; Hansson et al., 1974; Ibrahim et al., 1975). All these observations actually confirm our proposal that cardiac output is not of major importance in the pathogenesis of essential hypertension. In our study the effect of propranolol could also not be predicted on the basis of age, heart rate, (cardiac output), or variability of blood pressure. However, our results indicate a more pronounced effect when the initial blood pressure is higher. The relationship is rather weak for the blood pressure decrements, but for heart rate and cardiac output such relations are much stronger. This again raises the possibility of predicting the response. Whereas all investigators have judged the predictive value of several parameters with respect to the reduction in blood pressure, it is now evident that it is unjustified to follow this standard approach. The effect on heart rate and cardiac output is predicted to some extent by its pre-treatment value, and this regression appeared to be independent of drug dosage. Moreover patients responding with an increase in cardiac output had significantly lower pre-treatment values for cardiac output than the others. The relation between absolute change and initial value suggests that we are dealing with a true physiological phenomenon. It is interesting that similar reaction patterns were found with respect to a number of other variables, including renin and noradrenaline. For each parameter the regression line for the relations response-initial value can be calculated and this line will cross the X-axis at some point. It is tempting to speculate that this point of intersection represents the "intrinsic tuning" of the receptors, a point above which sympathetic input becomes important. For instance, the point of intersect was found to be 43 beats minute for heart rate, which agrees reasonably with the frequency of the "sympathectomized" heart.
If the above reasoning is correct, it follows that for a beta-adrenergic function the effect of propranolol represents sympathetic input to that particular receptor. Conversely, below the "intrinsic tuning" no alterations or even changes in opposite direction would occur. Indeed, in a number of patients renin concentration increased after beta-blockade. Also, Drayer et al. (1976) found unsuspected pressor responses to propranolol in patients in whom the initial renin levels were low and insufficiently in suppressed by the drug.

Along this line of reasoning it is not surprising that the beta-blocking drugs have been propagated for patients with a high cardiac output (Frohlich et al., 1968) or with high renin levels (Bühler et al., 1972). The disagreement of the observations of Frohlich and Bühler with the extensive experience of other authors probably is due to the fact that the several beta-receptors function independently of each other. For example, a patient can respond to propranolol with a substantial decrease in cardiac output but with an increase in renin levels. The predictive response was most pronounced for the ratio active/total renin concentration. This suggests that this ratio is under neurogenic control, a conclusion which was already reached on the basis of the tilt studies. Sympathetic control was also evident for heart rate. An interesting

observation was that the response of plasma aldosterone was also highly dependent on its pretreatment value. This raises the possibility of a neural mechanism regulating aldosterone secretion, since changes in aldosterone levels were not related to changes in active, inactive or total renin and not to changes in plasma volume or electrolytes.

The sympathetic influence on renin levels was most pronounced for active renin and less for inactive and total renin. This again supports the concept that the adrenergic system is mainly operative in regulating the active part of renin. From the catheterization studies it is also evident that propranolol exerts its effect predominantly on active renin. Although secretion of active renin was not different in the untreated and treated group, there was a strong indication that such a mechanism does exist. Apparently the size of the population is still too small to substantiate such a difference in statistical terms. Whereas peripheral noradrenaline levels show a beta-receptor sensitivity effect in their response (in relation to pre-treatment values), the kidney shows a tendency to produce more noradrenaline during propranolol treatment. Again the difference with the untreated group was not significant and further studies are needed to confirm this impression.
Beta-blockade did not have adverse effects on kidney function. Both total and cortical flow were well preserved. In addition, it was apparent that even under conditions of beta-blockade the cortical blood flow depends largely on the level of circulating (arterial) noradrenaline. Figure 53 and 70 depict this relation both for untreated and treated subjects. The response of renal blood flow and renal fraction is also dependent on initial values but to a lesser degree than the "direct" beta-adrenergic functions. These changes presumably reflect the effect of therapy on cardiac output (Sannerstedt and Conway, 1970). An effect on glomerular filtration rate was not apparent in our study, but has been reported by Ibsen and Sederberg-Olsen (1973). These authors found a reduction in glomerular filtration, which they ascribed to a decrease in renal blood flow, although they did not measure the latter variable. In the same study, however, no effect on plasma volume was observed. No change or a reduction in plasma volume has been observed by Tarazi et al. (1971). In our study plasma volume increased by approximately ± 100 ml and this was not significant.

With respect to blood pressure variability it can be concluded that beta-blockade does not affect this aspect of blood pressure control. This is in keeping with the findings of others (Clement et al., 1976; West et al., 1976; de Leeuw et al., 1977). In view of the result from Chapter 9 it seems that propranolol has shifted the equilibrium between noradrenaline and pressor range. Whether this effect is exerted primarily through reduction of central sympathetic activity or to a direct influence on vessel wall tone cannot be determined at this stage.

10.8 Conclusions

From the data presented in this chapter the following conclusions can be drawn:

1. During activation or inhibition of the sympathetic system some relations with other components of cardiovascular control are revealed which are not evident in the basal state.

2. The combined results of beta-blockade and tilting suggest that the sympathetic nervous systeem is involved in the regulation of active renin secretion, possibly by an effect on intrarenal beta-receptors.

3. It is hypothesized that the release of aldosterone is partly under neural control.

4. The effect of propranolol on blood pressure variability and sympathetic function suggests a shift in the physiological equilibrium.

5. Although the effect of beta-blockade cannot be predicted in terms of blood pressure, the responses of separate parameters of beta-adrenergic functions can be predicted on the basis of their initial values.

SUMMARY

The natural history of essential hypertension is known from its end-points but this does not provide information on possible changes in the functions of blood pressure control mechanisms. Although many studies have been carried out with respect to haemodynamic and endocrine variables in hypertension, most of them deal with limited areas.
In this thesis an attempt is made to study an extensive set of variables concerned with circulatory control. For this purpose more than 250 patients with uncomplicated essential hypertension were investigated.
Prior to the investigation itself we have assessed the validity of our methods which have been described in Chapter 2.
The reproducibility of the methods used has been described in Chapter 3. Day-to-day variability was 10% for cardiac output (as assessed by the impedance method), 8.8% for glomerular filtration rate, 6.8% for renal plasma flow, increasing to 8.8% when the measurements after angiography were considered, 10% for renal cortical blood flow per 100 g, 9% for mean renal blood flow per 100 g. (measured by the Xe-washout) and 7% for the percentual distribution of renal blood flow towards the outer cortex.
Variability was 4.2% for determinations of plasma volume, 16% for total and 14% for active renin concentration, 28% for aldosterone and 12% for noradrenaline. It is evident that reproducibility is good for all methods used with the exception of plasma aldosterone, which shows considerable intra-individual variation.
This might be explained by the multiplicity of factors which control its release.
In the next chapters the results of the haemodynamic and endocrinological determinations in a population of hypertensive patients are described.
In the first part 226 patients (group I) with essential hypertension are studied. We studied 138 men (age range 17 – 74 years) and 88 women (aged 19 – 73 years). All subjects were selected on an out-patient basis, their diastolic blood pressure being repeatedly 100 mmHg or more.
All patients were admitted to a metabolic ward where they were studied under standardized conditions. Sodium intake was fixed at 60 mmol daily ad no medication was given.
The following parameters were determined: blood pressure (either intra-arterially or indirectly with the Arteriosonde), 24 hour variability of blood -

pressure, cardiac output, renal plasma flow, glomerular filtration rate, plasma volume and plasma levels of total renin concentration and aldosterone.
In Chapter 4 the results of the measurements of systemic haemodynamics are studied in order to define the 24 hour variability of blood pressure and the haemodynamic abnormality underlying essential hypertension. When the 10 am blood pressure was plotted against age, a direct relationship was found ($r = 0.44$; $p < 0.001$), there being no difference between direct and indirect estimations.
Blood pressure shows marked diurnal variations which in absolute terms do not show a relation with age. No justification was found in separating entities of ,,labile'' and ,,fixed'' hypertension. The 24 hour blood pressure pattern was further analyzed and a distinction was made between basal blood pressure (taken immediately after waking) and the maximum and minimum levels of blood pressure.
Maximum values usually occurred during daytime while minimal values always occurred during sleep. When basal blood pressure is taken as a reference point, the maximal upward variations during daytime (called pressor range) appeared to decline with age ($r = -0.35$; $p < 0.01$) while depressor range (maximum nocturnal fall in blood pressure) increased with age ($r = 0.31$; $p < 0.025$).
These trends are caused by the fact that basal blood pressure rose steeper with age than maximal blood pressure.
Although cardiac output was higher in the younger hypertensives we could not find evidence for a cardiac factor in the pathogenesis of essential hypertension. When the inverse relation between cardiac output and age as found in this study ($r = -0.31$; $p < 0.001$) is compared with such data in normotensives (adapted from the literature) similar regressions are found.
Total peripheral vascular resistance rises with age ($r = 0.41$; $p < 0.001$) but even at an early stage, when cardiac output is still normal or even sometimes elevated the increase in vascular resistance is already apparent. An increase in total peripheral vascular resistance seems, therefore, the basic hypertensive mechanism.
To see whether the general haemodynamic pattern was reflected in a single organ, namely the kidney, we also studied renal haemodynamics (Chapter 5).
Renal plasma flow decreased with age ($r= -0.53$; $p < 0.001$) and so did glomerular filtration rate ($r -0.21$; $p < 0.01$). Renal vascular resistance rose with age ($r = 0.43$; $p < 0.001$) and filtration fraction also ($r = 0.51$; $p < 0.001$). Thus with respect to renal function it was also found that an increase in vascular resistance is demonstrable as an early expression of the hypertensive process. This refers particularly to the resistance offered by the vessels in the outer cortex of the kidney.
Despite the decrease in renal blood flow, glomerular filtration rate remains well preserved in patients with uncomplicated hypertension and even better than in normotensives. Consequently, filtration fraction rises with age in hypertensives. This is primarily explained by filtration disequilibrium in the human kidney. With hypertension of longer duration and especially after 40 years of age, an increase in glomerular capillary porosity contributes to an elevation of glomerular filtration rate.

As is described in Chapter 6, plasma volume does not exhibit a relationship with age or systemic haemodynamics. There is, however, a direct relation between plasma volume and filtration fraction ($r = 0.25$; $p < 0.005$). The long-term regulation of plasma volume is therefore possibly dependent on filtration characteristics.
In association with the rise in filtration fraction plasma volume increases, but this increase is only small and effectively counterbalanced by other factors since there is no indication that body fluid volumes increase with age in hypertensive subjects.
It is thus concluded in Chapter 7 that essential hypertension basically is a vascular disease. Although structural changes may play a role in the increased resistance, there is ample evidence that functional factors are also involved. Since it is unlikely that the vasoconstrictor stimuli originate from autoregulation, the next step was to look for enhanced activity of pressor systems.
In Chapter 8 the renin-angiotensin-aldosterone system has been studied. There is, at present, little support for implicating this system as an important factor in the pathogenesis of essential hypertension. On the contrary, renin levels decrease with age ($r = 0.15$; $p < 0.05$).
Renin levels do not correlate with the height of blood pressure, but there appears to be an inverse relationship between glomerular filtration rate and renin ($r = -0.22$; $p < 0.005$).
In patients with a filtration rate above 55 ml/min/m^2, renin levels vary inversely with renal vascular resistance ($r = -0.28$; $p < 0.001$).
When the effects of both age and glomerular filtration rate are eliminated, renin concentrations are inversely related to blood pressure.
It seems, therefore, that there is feed-back suppression (baroreceptor mechanism) of renin levels in older age groups, who show more advanced hypertension. More-over, there is no relation between renin and total peripheral vascular resistance.
A fall in glomerular filtration rate again stimulates renin release (ma cula densa mechanism).
Since methods for measurement of active renin and noradrenaline became available only recently, a second group of 59 patients (40 men and 19 women) was selected (group II) in whom specifically these hormones were measured together with most other parameters. It was found that, under basal conditions, about 30% of renin circulates in an active form. Active and total renin concentration are closely correlated ($r = 0.74$; $p < 0.001$).
In a separate study the secretion of renin by the kidney was measured in 10 patients. From the results it was concluded that renin is secreted mainly in the active form, this not being related to age or any haemodynamic variable.
Aldosterone levels were normal in the majority of patients from group I and II and there was no indication that this hormone was involved pathogenetically in hypertension.
The role of the sympathetic nervous system has been studied in Chapters 9 and 10.
In Chapter 9 the results of the noradrenaline assays are presented. Noradrenaline levels did not correlate with blood pressure, systemic vascular resistance or cardiac output.

Although noradrenaline levels were not related to total renal blood flow or renal vascular resistance, a highly significant inverse relationship was found between absolute blood flow through the outer cortex of the kidney and the peripheral noradrenaline level ($r = -0.76$; $p < 0.05$). A similar relationship existed with the arterial noradrenaline concentration.
In addition, it was found that the kidney is able to release noradrenaline, although the significance of this finding is not yet clear.
Since the adrenergic and the renin-angiotensin-aldosterone system show complex interrelations, it might be that under steady state conditions no conclusions can be drawn about the part of each system in maintaining vascular tone.
To study some of these interrelations we challenged the system by stimulation (tilt studies) as well as by inhibition (beta-blockade). The results of these studies are described in Chapter 10.
Both studies revealed a high degree of interrelation between the adrenergic and the renin-angiotensin-aldosterone system. This is not necessarily reflected in the level of blood pressure.
It was found for example that during tilting both total and active renin increase while inactive renin decreases.
It is suggested that active and inactive renin are in dynamic equilibrium which shifts as a function of beta-adrenergic activity.
When beta-receptors are blocked by propranolol, the relative amount of active renin changes, like some other beta-adrenergic parameters, in a predictable way. It seems as if the different beta-receptors are intrinsically tuned to a certain level on which sympathetic activity is superimposed.

Taking all results together, it is not yet possible to assess the quantitative role of both pressor systems in the elaboration of vascular tone.

SAMENVATTING

Essentiële hypertensie kan worden beschouwd als een haemodynamische ontsporing die in zijn vroege (ongecompliceerde) stadium geen noemenswaardige klinische verschijnselen geeft.
Het natuurlijk beloop van essentiële hypertensie is bekend wat betreft zijn complicaties; hieruit kunnen echter geen conclusies getrokken worden ten aanzien van de veranderingen in de regulatie-mechanismen die daaraan vooraf gaan.
Hoewel in veel studies de haemodynamische en endocriene aspecten van essentiële hypertensie ter sprake komen, beperkt men zich veelal tot een klein onderdeel hiervan.
In dit proefschrift wordt een poging gedaan om een groot aantal variabelen welke betrokken lijken te zijn bij de regulatie van de bloeddruk te bestuderen en in onderling verband te plaatsen. Daartoe werden ruim 250 patiënten met ongecompliceerde essentiële hypertensie onderzocht.
Voorafgaande aan dit eigenlijke onderzoek hebben wij de reproduceerbaarheid van onze meettechnieken welke beschreven worden in hoofdstuk 2 nagegaan.
De resultaten hiervan zijn beschreven in hoofdstuk 3. Uitgedrukt als percentage is de reproduceerbaarheid van de metingen als volgt: 10% voor het hartminutenvolume (gemeten met de impedantie techniek), 8,8% voor de glomerulaire filtratiesnelheid, 6,8% voor de plasmastroom door de nier (8,8% wanneer de bepalingen na angiografie worden beschouwd), 10% voor de corticale doorstromingssnelheid van de nier, 9% voor de gemiddelde nierdoorbloeding per 100 gram en 7% voor de procentuele verdeling van de bloedstroom naar de buitenste schorslaag. De variabiliteit bedroeg 4,2% voor de bepaling van het plasma-volume, 16% respectievelijk 14% voor de bepaling van totale en actieve renine concentratie, 28% voor aldosteron en 12% voor noradrenaline.
Het blijkt derhalve dat de uitkomsten binnen een periode van enkele dagen niet in belangrijke mate variëren. Een uitzondering hierop vormt de aldosteronspiegel in het bloed, die aanzienlijke schommelingen kan tonen. Dit zou verklaard kunnen worden door het feit dat bij de regulatie van de aldosteronsecretie vele factoren tegelijk betrokken zijn.
In de volgende hoofdstukken worden de resultaten van het haemodynamische en endocrinologische onderzoek beschreven. In het eerste deel wordt het onderzoek bij 226 patiënten met essentiële hypertensie bestudeerd. Deze

groep (groep I) bestond uit 138 mannen (leeftijd 17 tot 74 jaar) en 88 vrouwen (leeftijd 19 tot 73 jaar).
Alle patiënten werden geselecteerd op poliklinische basis wanneer hun diastolische bloeddruk bij herhaling 100 mm kwik of meer bedroeg. Alle geselecteerde patiënten werden opgenomen op de ,,Metabolic Ward'', waar zij onder gestandaardiseerde condities werden bestudeerd. De zoutinname werd beperkt tot 60 mmol per dag en geen van de patiënten kreeg medicamenten.
De volgende parameters werden bepaald: bloeddruk (hetzij intra-arterieel, hetzij indirect met de Arteriosonde gemeten), 24 uurs variabiliteit van de bloeddruk, hartminutenvolume renale plasma doorstroming, glomerulaire filtratiesnelheid, plasma volume, en plasma spiegels van totale renine concentratie en aldosteron.
In hoofdstuk 4 worden de resultaten van het algemene haemodynamisch onderzoek bestudeerd. Daarbij wordt getracht de variabiliteit van de bloeddruk vast te leggen. Tevens wordt gezocht naar de haemodynamische afwijking welke ten grondslag ligt aan de bloeddruk verhoging. Wanneer de bloeddruk, genomen rond 10 uur 's morgens wordt uitgezet tegen de leeftijd wordt een directe relatie gevonden ($r = 0.44$; $p < 0.001$). Er is geen duidelijk verschil tussen directe en indirecte metingen.
De bloeddrukschommelingen gedurende de dag blijken zeer aanzienlijk te zijn en in absolute zin niet afhankelijk van leeftijd of hoogte van de bloeddruk. Het blijkt derhalve niet mogelijk een onderscheid te maken tussen ,,labiele'' of ,,gefixeerde'' hypertensie. De basale bloeddruk, opgenomen direkt na het ontwaken, stijgt met de leeftijd en wel sterker dan de maximale bloeddruk. Als gevolg hiervan werd een negatieve relatie gevonden ($r = -0.35$; $p < 0.01$) tussen de opwaartse schommelingen gedurende de dag (,,pressor range'') en de leeftijd. Daarentegen neemt de ,,depressor range'' (maximale daling van de bloeddruk gedurende de nacht) toe met de leeftijd ($r = 0.31$; $p < 0.025$). Deze trendmatige veranderingen zijn een gevolg van het feit dat de basale bloeddruk welke als referentiepunt gold sterker stijgt met de leeftijd dan de maximale bloeddruk.
Hoewel het hartminuutvolume hoger was in jonge patiënten met essentiële hypertensie konden wij er geen aanwijzingen voor vinden dat dit van pathofysiologische betekenis is bij het ontstaan van de aandoening. Wanneer de negatieve relatie tussen hartminuutvolume en de leeftijd ($r = -0.31$; $p < 0.001$) zoals deze door ons vastgesteld is, vergeleken wordt met soortgelijke relaties bij groepen personen met normale bloeddruk (gegevens verkregen uit de literatuur), dan blijken deze praktisch samen te vallen.
De totale perifere vaatweerstand stijgt met de leeftijd ($r = 0.41$; $p < 0.001$), maar zelfs in een vroeg stadium wanneer het hartminuutvolume nog normaal of zelfs iets verhoogd is, is deze toename in vaatweerstand al aantoonbaar. Een toeneming in totale perifere vaatweerstand lijkt derhalve van wezenlijke betekenis voor het ontstaan van bloeddrukverhoging te zijn.
In hoofdstuk 5 wordt nagegaan in hoeverre zich haemodynamische veranderingen in de nier manifesteren.
De renale plasmadoorstroming neemt af met de leeftijd ($r = -0.53$; $p < 0.001$) terwijl de niervaatweerstand met de leeftijd stijgt ($r = 0.43$; $p < 0.001$). De glomerulaire filtratiesnelheid neemt af met de leeftijd ($r = -0.21$; $p < 0.01$),

doch de filtratiefractie stijgt met de leeftijd ($r = 0.51$; $p < 0.001$). Ook met betrekking tot de nierfunctie kan gesteld worden dat een toename in de vaatweerstand al vroeg merkbaar is. Dit betreft met name ook de weerstand in de buitenste nierschors.
Ondanks de daling in nierdoorbloeding blijft de glomerulus filtratie redelijk gehandhaafd en bij ongecompliceerde hypertensie zelfs nog iets beter dan bij normotensieve personen. Dit leidt tot een toeneming van de filtratie-fractie bij hypertensiepatiënten. Dit kan verklaard worden door de veronderstelling dat in de menselijke nier geen filtratie-evenwicht wordt bereikt zolang de nierdoorbloeding niet beneden een kritische waarde komt. Naarmate de hypertensie langer bestaat en met name na het veertigste levensjaar, draagt een toeneming in de doorlaatbaarheid van de glomeruluscapillairen waarschijnlijk bij aan de relatief hoge filtratiesnelheid.
Zoals beschreven wordt in hoofdstuk 6 is er geen relatie tussen het plasmavolume en de leeftijd; noch is er een relatie tussen plasma-volume en systeem haemodynamica. Er bestaat echter een directe relatie tussen het plasma-volume en de filtratie fractie ($r = 0.25$; $p < 0.005$).
In hoofdstuk 7 wordt aandacht besteed aan de interpretatie van haemodynamische gegevens.
Hoewel structurele veranderingen in de vaatwand zeker verantwoordelijk kunnen zijn voor een toegenomen weerstand zijn er toch duidelijke aanwijzingen dat functionele factoren hier ook bij betrokken zijn. Het is onwaarschijnlijk dat de prikkel tot vaatvernauwing het gevolg is van autoregulatie. De volgende stap bestond derhalve uit het vastleggen van de activiteit van pressor hormonen.
Hoofdstuk 8 handelt over het renine-angiotensine-aldosteron systeem. Wij hebben geen aanwijzingen gevonden voor de veronderstelling dat dit systeem rechtstreeks betrokken is bij de pathogenese van essentiële hypertensie. Renine spiegels correleren namelijk negatief met de leeftijd ($r = -0.15$; $p < 0.05$) en positief met de glomerulaire filtratiesnelheid ($r = 0.22$; $p < 0.005$).
Bij patiënten met een filtratiesnelheid boven 55 ml/min/m^2, bestaat een negatieve relatie tussen renine spiegel en vaatweerstand ($r = -0.28$; $p < 0.001$).
Wanneer de effecten van zowel leeftijd als glomerulaire filtratiesnelheid worden geëlimineerd blijkt er een negatieve correlatie te bestaan tussen renine concentratie en bloeddruk. Het lijkt daarom aannemelijk dat de renine secretie gesupprimeerd wordt door de hoge druk (baroreceptor mechanisme). Een daling in de glomerulaire filtratiesnelheid stimuleert vervolgens wederom de renine secretie. Er bestaat geen relatie tussen reninespiegels en de vaatweerstand. Aangezien wij slechts kortgeleden zijn overgegaan tot het bepalen van actief renine en noradrenaline werd een tweede groep van 59 patiënten (40 mannen en 19 vrouwen) samengesteld (groep II) bij wie specifiek deze hormonen werden bepaald. Het blijkt dat onder basale omstandigheden ongeveer 30% van het renine in een actieve vorm circuleert. De concentratie van actief en totaal renine zijn nauw gerelateerd ($r = 0.74$; $p < 0.001$). In een afzonderlijke studie werd de secretie van renine door de nier bij 10 patiënten bepaald. Het blijkt dat onafhankelijk van leeftijd of haemodynamische status het renine voornamelijk in de actieve vorm wordt gesecerneerd.
De aldosteron spiegel was normaal in het merendeel van de patiënten uit groep

I en II en er waren geen aanwijzingen dat dit hormoon betrokken is bij de pathogenese van essentiële hypertensie.
De rol van het sympathisch zenuwstelsel werd bestudeerd in hoofdstuk 9 en 10. Hoofdstuk 9 handelt over de resultaten van de noradrenaline bepaling. Noradrenaline spiegels bleken niet te correleren met de bloeddruk, vaatweerstand en hartminuutvolume.
Hoewel er geen relatie bestond tussen nierdoorbloeding of niervaatweerstand met de noradrenalinespiegel, bleek er een hoog significante negatieve relatie te zijn tussen het noradrenaline gehalte en de absolute doorstroming door de buitenste nierschors. Er werd bovendien gevonden dat de nier in staat is noradrenaline af te geven, hoewel de betekenis van dit fenomeen nog niet geheel duidelijk is.
Aangezien er vele interrelaties bestaan tussen het adrenergische en het renine-angiotensine-aldosteron systeem, is het zeer goed mogelijk dat men onder basale omstandigheden nimmer een uitspraak zal kunnen doen over het aandeel van beide systemen in de vaattonus. Om dan ook meer inzicht te krijgen in de onderlinge afhankelijkheid van beide werd het sympathisch zenuwstelsel geactiveerd tijdens kiepproeven en geremd door middel van de beta-blokkerende stof propranolol. De resultaten van deze proefnemingen die beschreven worden in hoofdstuk 10, tonen aan dat inderdaad onder sommige omstandigheden een opmerkelijke samenhang aantoonbaar is tussen beide genoemde systemen. Dit is niet altijd af te lezen aan de hoogte van de bloeddruk.
Zo werd b.v. tijdens kiepen gevonden dat zowel het totale als het actieve renine toenemen, terwijl het inactieve renine afneemt. Verondersteld wordt dat het actieve en inactieve renine in dynamisch evenwicht zijn waarbij het evenwicht onderhevig is aan variaties in beta-adrenerge activiteit.
Daarnaast suggereren de uitkomsten tijdens beta-blokkade dat de diverse beta-receptoren in het organisme ieder een intrinsieke gevoeligheid hebben; waarschijnlijk is de z.g. sympathische activiteit hierop gesuperponeerd.

Wanneer men de in dit proefschrift beschreven uitkomsten onder een noemer tracht te brengen dan blijkt het vooralsnog niet mogelijk om het aandeel van beide genoemde pressor-systemen in de vaattonus in maat en getal uit te drukken. Er zal naar nieuwe invalshoeken moeten worden gezocht om de relatieve betekenis van deze en andere systemen voor de vasoregulatie vast te leggen.

NAWOORD.

Toen Prof. Birkenhäger mij in september 1974 benaderde met het verzoek om het eertijds door Dr. G. Kolsters opgezette onderzoek naar intrarenale circulatie-patronen voort te zetten, maakte de bereidwilligheid daartoe al snel plaats voor twijfel over de juistheid van deze beslissing. Slechts dankzij de plezierige samenwerking met de collegae Cremer, Kho, Wester en Zaal en de continue inspiratie van Prof. Birkenhäger lukte het uiteindelijk om enig inzicht te krijgen in de problematiek van het hypertensie-onderzoek.
Dr. B. Speyer ben ik zeer erkentelijk voor de wijze waarop hij mij geleerd heeft katheterisaties volgens Seldinger uit te voeren.
Het beheersen van deze techniek bleek, ook buiten het eigenlijke onderzoeksproject, van nut te zijn.
Dr. G. Kolsters maakte wij wegwijs in de theorie en de praktijk van de Xenon-uitwas studies.
Tijdens de katheterisaties was de hulp van An Maas, Jeanine Ornée en later ook van Elma van der Giessen en Joke v. Vliet onmisbaar.
Ook de technische bijstand van Herman Kammeraat en Theo Emens bleek onontbeerlijk.
In dit proefschrift worden ook de resultaten beschreven van diverse andere experimenten. Hoewel alle gegevens, welke hier vermeld zijn, door mijzelf werden opgespoord en herberekend, is het toch de verdienste van vele anderen geweest dat dit verzamelwerk mogelijk was. Zonder alle artsen en verpleegsters die, met name onder auspiciën van Prof. Birkenhäger en Dr. Schalekamp, hieraan hebben meegewerkt, tekort te willen doen, moeten met name toch de "dames" van de onderzoekcentrale genoemd worden: Tony Edixhoven, Anneke Quaak, Ada Willemstein, Lidwien Baar, Engelien Sparnaay en Jenny Moor.
Het vele bloed dat zij de patiënten ontnamen werd ten dele door henzelf "bewerkt", ten dele belandde dit bij het tweede echelon : het assistentenlaboratorium.
Aldaar vonden de hormoonbepalingen plaats, verricht door: René

Punt, Julia Vaarties, Truus van Soest, Joan van der Wey, Bert Kleinjan, Aleid Muller en Dory Fawzi.
Het laatste jaar geschiedde zulks onder het toeziend oog van de biochemicus Dr. H. E. Falke.
Nadat alle resultaten vergaard en bewerkt waren wist dan de heer R. O. Hatt zijn kwaliteiten als tekenaar volledig uit te buiten, waarbij materiaal noch nachtrust werden gespaard.
Dat hij daarbij ook nog optreedt als fotograaf wordt eigenlijk te vaak als vanzelfsprekend ervaren.
Ans van Poelvoorde stond voor de schier onmogelijke taak een groot gedeelte van het manuscript te ontcijferen. Haar tiksel vormde de basis van waaruit het verdere proefschrift werd opgebouwd.
Nadat het concept kritisch was beoordeeld door Prof. Birkenhäger, werd de definitieve tekst snel en goed aan het papier toevertrouwd door Bonny Steenhuis.
Tevens kreeg ik van haar, alsmede van Ann Lustig, beiden uit Amerika afkomstig, nuttige stilistische adviezen.
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Aan de (nachtelijke) uren die ik met hen doorbracht houd ik niet alleen plezierige herinneringen, doch ook de Appendix uit dit proefschrift over.
De co-referenten, Prof. Dr. J. Gerbrandy en Prof. Dr. A. Amery ben ik zeer erkentelijk voor de bereidwilligheid waarmee zij het uiteindelijke werk hebben beoordeeld.
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CURRICULUM VITAE.

De auteur van dit proefschrift werd in 1948 te Velp (Gld.) geboren. Na een kortstondig verblijf in het land Gelre bracht hij zijn verdere jeugd door in Zeeland, waar het Luctor et Emergo resulteerde in het behalen van het einddiploma gymnasium te Middelburg. Deze gebeurtenis, welke in 1967 plaatsvond, werd gevolgd door inschrijving aan de Medische Faculteit Rotterdam.
De periode van de medische studie werd opgeluisterd door student-assistentschappen bij de afdelingen Anatomie (hoofd Prof. Dr. J. Moll) en Huisartsgeneeskunde (hoofd destijds Dr. M. J. van Trommel).
In 1973 werd het artsdiploma behaald.
Vanaf februari 1974 is de promovendus als assistent werkzaam op de afdeling Inwendige Geneeskunde van het Zuiderziekenhuis te Rotterdam, waar hij bij Prof. Dr. W. H. Birkenhäger opgeleid wordt tot internist.

REFERENCES.

AARS, H. Aortic baroceptor activity in normal and hypertensive rabbits. Acta Physiol. Scand. 72: 298, 1968[a].

AARS, H. Static load-length characteristics of aortic strips from hypertensive rabbits. Acta Physiol. Scand. 73: 101, 1968[b].

ABBRECHT, P. H. and VANDER, A. J. Effects of chronic potassium deficiency on plasma renin activity. J. Clin. Invest. 49: 1510–1970.

ABE, K. IROKAWA, N. AOYAGI, H. MEMEZAWA, H. YASUJIMA, M. OTSUKA, Y., SAIKO, T. and YOSHINAGA, K. Circulating renin in essential hypertension: an evaluation of its significance in the Japanese population. Amer. Heart J. 89: 723, 1975.

ABERG, H. WETTERBERG, L., ROSS, S. B. and FRODEN, O. Dopamine-beta-hydroxylase in hypertension. Acta Med. Scand. 196: 17, 1974.

ADDIS, T. Blood pressure and pulse rate levels. Arch. Int. Med. 29: 539, 1922.

ADLER-GRASCHINSKY, E. and LANGER, S. Z. Possible role of a beta-adrenoceptor in the regulation of noradrenaline release by nerve stimulation. Brit. J. Pharmacol. 53: 43, 1975.

AHLQUIST, R. P. A study of the adrenotropic receptors. Amer. J. Physiol. 153: 586, 1948.

AHLQUIST, R. P. Adrenergic receptors in the cardiovascular system. In: Beta-adreneceptor blocking agents. Ed. by Saxena, P. R. and Forsyth, R. P. North-Holland Publishing Company, Amsterdam, The Netherlands, 1976.

ALAM, G. M. ans SMIRK, F. H. Casual and basal blood pressures. I. In british and egyptian men. Brit. Heart J. 5: 152, 1943.

ALCOCK, S. J. and BOND, P. A. Observations on the toxity of Alderin (pronethalol) in laboratory animals. Proc. Eur. Soc. Stud. Drug Tox. 4: 30, 1964.

ALEXANDRE, J. M., LONDON, G. M. CHEVILLARD, C. LEMAIRE, P., SAFAR, M. E. and WEISS, Y. The meaning of dopamine-beta-hydroxylase in essential hypertension. Clin. Sci. Mol. Med. 49: 573, 1975.

AMERY, A., JULIUS, S., WHITLOCK, L. S. and CONWAY, J. Influence of hypertension on the haemodynamic response to exercise. Circulation 36: 231, 1967.

AMERY, A. BOSSAERT, H. and VERSTRAETE, M. Muscle blood flow in normal and hypertensive subjects. Amer. Heart J. 78: 211, 1969.

AMES, R. P., BORKOWSKY, A. J., SICINSKI, A. M. and LARAGH, J. H. Prolonged infusions of angiotensin II and norepinephrine and blood pressure, electrolyte balance and aldosterone and cortisol secretion in normal man and in cirrhosis with ascites. J. Clin. Invest 44: 1171, 1965.

ANDERSEN, A. M. and LADEFOGED, J. Relationship between hematocrit and solubility of Xenon-133 in blood. J. Pharmac. Sci. 54: 1685, 1965.

ANDREUCCI, V. E., HERRERA-ACOSTA, J., RECTOR, F. C. Jr., and SELDIN, D. W. Effective glomerular filtration pressure and single nephron filtration rate during hydropenia, elevated ureteral pressure and acute volume expansion with isotonic saline. J. Clin. Invest. 50: 2230, 1971[a].

ANDREUCCI, V. E., BLANTZ, R. C., HERRERA-ACOSTA, J. RECTOR, F. C. Jr., and SELDIN, D. W. Effect of parial ureteral obstruction and acute volume expansion on glomerular pressure, effective filtration pressure and single nephron glomerular filtration rate in the rat. Clin. Res. 14: 524, 1971[b].

ANDREUCCI, V. E. Glomerular haemodynamics and autoregulation. Proc. Eur. Dial. Transpl. Assoc. 11: 77, 1974.
ANDREUCCI, V. E., DAL CANTON, A., CORRADI, A., STANZIALE, R. and MIGONE, L. Role of the efferent arteriole in glomerular hemodynamics of superficial nephrons. Kidney Intern. 9: 475–480, 1976.
ANGELL-JAMES, J. E. Characteristics of single aortic and right subclavian baroreceptor fibre activity in rabbits with chronic renal hypertension. Circ. Res. 32: 149, 1973.
AOI, W., WADE, M. B., ROSNER, D. R. and WEINBERGER, M. H. Renin release by rat kidney slices in vitro: effects of cations and catecholamines. Amer.J. Physiol. 227: 630, 1974.
AOI, W., HENRY, D. P. and WEINBERGER, M. H. Evidence for a physiological role of renal sympathetic nerves in adrenergic stimulation of renin release in the rat. Circ. Res. 38: 123, 1976.
ARCILLA, R. A. and ROWE, M. I. Modefied dye dilution technique for cardiac output studies in tiny subjects. Amer. Heart J. 77: 798, 1969.
ARIENS, E. J. Wirkung und Wirkungsmechanismus von Katecholaminen und ihre Derivaten. Naunyn-Schmied. Arch. Pharmak. Exp. Path. 257: 118, 1967.
ARIËNS, E. J. and SIMONES, A. M. Cholinergic and anti-cholinergic drugs, do they act on common receptors? Ann. N. Y. Acad. Sci. 144: 842, 1967.
ARIËNS, E. J. and SIMONIS, A. M. Receptors and receptor mechanisms. In: Beta-adrenoceptor blocking agents. Ed. by Saxena, P. R. and Forsyth, R. P. North-Holland Publishing Company, Amsterdam, The Netherlands, 1976.
ARONOW, W. S., HARDING, P. R., DE QUATTRO, V. and ISBELL, M. Diurnal variation of plasma catecholamines and systolic time intervals. Chest 63: 722,, 1973.
ASSAYKEEN, T. A., CLAYTON, P. L., GOLDFEIN, A. and GANONG, W. F. Effect of alpha- and beta-adrenergic blocking agents on the renin response to hypoglycemia and epinephrine in dogs. Endocrin. 87: 1318, 1970.
ASSAYKEEN, T. A. TANIGAWA, H. and ALLISON, D. J. Effect of adrenoceptor-blocking agents on the renin response to isoproterenol in dogs. Eur. J. Pharmacol. 26: 185, 1974.
AYERS, C. R., HARRIS, R. H. and LEFER, L. G. Control of renin release in experimental hypertension. Circ. Res., 24 and 25, Suppl. 1: 103, 1969.
AZAR, S., TOBIAN, L., and JOHNSON, M. A. Pressures, flows and resistances in single nephrons of the hypertensive kidney. Clin. Res. 22: 259A, 1974.
AZAR, S., JOHNSON, M. A., HERTEL, B. and TOBIAN, L. Single-nephron pressures, flows and resistances in hypertensive kidneys with nephrosclerosis, Kidney Intern. Vol. 12: 28, 1977.
BACQ, Z. M. AND MONNIER, A. M. Recherches sur la physiologie et la pharmacologie du système nerveux autonome. XV. Variations de la polarisation des muscles lisses sous l'influence du système nerveux autonome et de ses mimetiques. Arch. Int. Physiol. 40: 467, 1935.
BAER, P. G. and NAVAR, L. G. Renal vasodilation and uncoupling of blood flow and filtration rate auto-regulation. Kidney Intern. 4: 14, 1973.
BAKER, L. E. and GEDDES, L. A. The measurement of respiratory volumes in animals and man with use of impedance. Ann. N.Y. Acad. Sci. 170: 667, 1971.
BANGHAM, D. R., ROBERTSON, I., ROBERTSON, J. I. S., ROBINSON, C. J. and TREE, M. An international collaborative study of renin assay: establishment of the international reference preparation of human renin. Clin. Sci. Mol. Med. 48 (Suppl. 2): 135s, 1975.
BANKIR, L. DE ROUFFIGNAC, C., GRÜNFELD, J. P., SABTO, J. and FUNCK-BRENTANO, J. L. In: Radionuclides in Nephrology. Proceedings of the IIIrd International Symposium, Berlin, April, 1974. Edited by: Winkel, zum K., Blaufox, M. D. and Funck-Brentano, J. L., Georg Thieme Publishers, Stuttgart, 1975.
BARAJAS, L. and LATTA, H. A three-dimensional study of the juxtaglomerular apparatus in the rat. Light and electron microscopic observations. Lab. Invest. 12: 257, 1963.
BARAJAS, L. The innervation of the juxtaglomerular apparatus. An electron microscopic study of the innervation of the glomerular arterioles. Lab. Invest. 13: 916, 1964.
BARAJAS, L. and LATTA, H. The development of the juxta-glomerular cell granule. Anat. Rec. 151: 321, 1965.
BARAJAS, L. The development and ultrastructure of the juxta-glomerular cell granule. J. Ultrastruct. Res. 15: 400, 1966.

BARAJAS, L. Renin secretion: an anatomical basis for tubular control. Science 172: 485, 1971.
BARAJAS, L. and MÜLLER, J. The innervation of the juxta-glomerular apparatus and surrounding tubules: a quantitative analysis by serial section electron microscopy. J. Ultrastruct. Res. 43: 107, 1973.
BARRACLOUGH, M. A., BACCHUS, B., BROWN, J. J., DAVIES, D. L., LEVER, A. F. and ROBERTSON, J. I. S. Plasma-renin and aldosterone secretion in hypertensive patients with renal or renal artery lesions. Lancet 2: 1310, 1965.
BARRACLOUGH, M. A., JONES, N. F., MARSDEN, C. D. and BRADFORD, B. C. Renal and pressor effects of angiotensin in salt loaded and depleted rabbits. Experientia (Basel) 23:553, 1967.
BAYARD, F., COOKE, C. R., TILLER, D. J., BEITINS, I. Z., KOWARSKI, A., WALKER, W. G. and MIGEON, C. J. The regulation of aldosterone secretion in anephric man. J. Clin. Invest. 50: 1585, 1971.
BEEVERS, D. G., MORTON, J. J., NELSON, C. S., PADFIELD, P. L., TITTERINGTON, M., and TREE, M. Angiotensin II in essential hypertension. Brit. Med. J. II: 415, 1977
BELL, E. T. Renal diseases. 2d ed. Philadelphia, Lea & Febiger, 1950.
BELLMAN, S., FRANK, H. A., LAMBERT, P. B. and ROY, A. J. Studies of collateral vascular responses. I. Effects of selective occlusions of major trunks within an extensively anastomosing arterial system. Angiology 10: 214, 1959.
BELLO, C. T., SEVY, R. W., OKKER, E. A., PAPACOSTAS, C. A. and BUCHER, R. M. Renal hemodynamic responses to stress in normotensive and hypertensive subjects. Circulation 22: 573, 1960.
BELLO, C. T., SEVY, R. W. and HARAKAL, C. Varying hemodynamic patterns in essential hypertension. Amer. J. Med. Sci. 250: 24, 1965.
BELLO, C. T., SEVY, R. W., HARAKAL, C. and HILLYER, P. N. Relationship between clinical severity of disease and hemodynamic patterns in essential hypertension. Amer. J. Med. Sci. 253: 194, 1967.
BELLO-REUSS, E. COLINDRES, R. E., PASTORIZA-MUNOZ, E., MÜLLER, R. A. and GOTTSCHALK, C. W. Effects of acute unilateral renal denervation in the rat. J. Clin. Invest. 56: 208, 1975.
BELLO-REUSS, E., TREVINO, D. L. and GOTTSCHALK, C. W. Effect of renal sympathetic nerve stimulation on proximal water and sodium reabsorption. J. Clin. Invest. 57: 1104, 1976.
BENNETT, C. M., FARNSWORTH, L. and JOHNSON, G. A. Plasma norepinephrine and sodium balance. Kidney Intern. 10: 529, 1976.
BERGLUND, G., AURELL, M. and WILHELMSEN, L. Renal function in normo- and hypertensive 50-year-old males. Acta Med. Scand. 199: 25, 1976.
BERGSTRÖM, J., BUCHT, H., EK, J., JOSEPHSON, B., SUNDELL, H. and WERKÖ, L. The renal extraction of para-aminohippurate (PAH) in normal persons and in patients with diseased kidneys. Scand. J. Clin. Lab. Invest. 11: 361, 1959.
BERLINER, R. W., LEVINSKY, N. G., DAVIDSON, D. G. and EDEN, M. Dilution and concentration of the urine and the action of antidiurectic hormone. Amer. J. Med. 24: 730, 1958.
BERNE, R. Regulation of coronary blood flow. Physiol. Rev. 44: 1, 1964.
BERNE, R. M., DEGUST, H. and LEVY, M. N. Influence of the cardiac nerves on coronary resistance. Amer. J. Physiol. 208: 763, 1975.
BEST, J. B., BETT, J. H. N., COGHLAN, J. P., CRAN, E. J. and SCOGGINS, B. A. Circulating angiotensin II and aldosterone levels during dietary sodium restriction. Lancet 2: 1353, 1971.
BEVAN, J. A. Essentials of pharmacology. Hoeber Medical Division, Harper and Row, New York – Evanston – London. 1969.
BIANCHI, G., BROWN, J. J., LEVER, A. F., ROBERTSON, J. I. S. and ROTH, N. Changes of plasma renin concentration during pressor infusions of renin in the conscious dog: the influence of dietary sodium intake. Clin. Sci. 34: 303, 1968.
BIANCHI, G., BALDOLI, E., LUCCA, R. and BARBIN, P. Pathogenesis in arterial hypertension after the constriction of the renal artery leaving the opposite kidney intact both in the anaesthetized and in the conscious dog. Clin. Sci. 42: 651, 1972.
BIGLIERI, E. G., SHAMBELAN, M. and SLATON, P. E. Jr. Effect of adrenocorticotropin in deoxycorticosterone, corticosterone and aldosterone excretion. J. Clin. Endocrinol. Metab. 29: 1090, 1969.

BING, J. and KAZIMIERCZAK, J. Renin content of different parts of the juxtaglomerular apparatus. Acta Pathol. Microbiol. Scand. 54: 80, 1962.
BING, J. Rapid marked increase in plasma renin in rats treated wits inhibitors of the renin system. Effects of 1-Sar-8-Ala-angiotensin II and of a synthetic converting enzyme inhibitor on normal and adrenalectomized rats. Acta Pathol. Microbiol. Scand. (A) 81: 376, 1973.
BING, R. F., HARLOW, J., SMITH, A. J. and TOWNSHEND, M. H. The urinary excretion of catecholamines and their derivatives in primary hypertension in man. Clin. Sci. Mol. Metab. 29: 1090, 1969.
BIRKENHÄGER, W. H., VAN ES, L. A. HOUWING, A., LAMERS, H. J. and MULDER, A. H. Studies on the lability of hypertension in man. Clin. Sci. 35: 445, 1968.
BIRKENHÄGER, W. H. KRAUSS, X. H., SCHALEKAMP, M. A. D. H., KOLSTERS, G. and KROON, B. J. M. Antihypertensive effects of propranolol. Folia Med. Neerl. 14: 67, 1971.
BIRKENHÄGER, W. H., SCHALEKAMP, M. A. D. H., KRAUSS, X. H., KOLSTERS, G., SCHALEKAMP-KUYKEN, M. P. A., KROON, B. J. M. and TEULINGS, F. A. G. Systemic and renal haemodynamics, body fluids and renin in benign essential hypertension with special reference to natural history. Europ. J. Clin. Invest. 2: 115, 1972[a].
BIRKENHÄGER, W. H., SCHALEKAMP, M. A. D. H., KRAUSS, X. H., KOLSTERS, G. and ZAAL, G. A. Consecutive haemodynamic patterns in essential hypertension. Lancet I: 560, 1972[b].
BIRKENHÄGER, W. H. and SCHALEKAMP, M. A. D. H. Control mechanisms in essential hypertension. Elsevier/North-Holland Biomedical Press, Amsterdam, 1976.
BIRKENHÄGER, W. H., WESTER, A., KHO, T. L., SCHALEKAMP, M. A. D. H., ZAAL, G. A. and DE LEEUW, P. W. Hypotensive mechanisms in beta-adrenergic blockade. In: Beta-adrenergic blockers and hypertension. International symposium Rottach-Egern/ Tegernsee, West-Germany, Georg Thieme, Stuttgart, 1976.
BIRKENHAGER, W. H., KHO, T. L., SCHALEKAMP, M. A. D. H., KOLSTERS, G., WESTER, A. and DE LEEUW, P. W. Renin levels and cardiovascular morbidity in essential hypertension. Acta Clin. Belg., 32: 168, 1977[a].
BIRKENHÄGER, W. H., DE LEEUW, P. W., WESTER, A., KHO, T. L., VANDONGEN, R. and FALKE, H. E. Therapeutic effects of beta-adrenoceptor blocking agents in hypertension. Ergebnisse der Inneren Medizin und Kinderheilkunde 39: 117, 1977b.
BIRKHÄUSER, M., GAILLARD, R., RIONDEL, A. M., SCHOULER, D., VALLOTON, M. B. and MULLER, A. F. Effect of volume expansion by hyperosmolar and hyperoncotic solutions under constant infusion of angiotensin II on plasma aldosterone in man and its counterbalance by potassium administration. Europ. J. Clin. Invest. 3: 307, 1973.
BLACK, J. W. and STEPHENSON, J. S. Pharmacology of a new adrenergic beta-receptor blocking compound (Nethalide). Lancet II: 311, 1962.
BLACK, J. W., DUNCAN, W. A. M. and SHANKS, R. G. Comparison of some properties of pronethalol and propranolol. Brit. J. Pharmacol. 25: 577, 1965.
BLAINE, E. H., DAVIS, J. O. and WITTY, R. T. Renin release after hemorrhage and after suprarenal aortic constriction in dogs without sodium delivery to the macula densa. Circ. Res. 27: 1081, 1970.
BLAINE, E. H., DAVIS, J. O. and PREWITT, R. L. Evidence for a renal vascular receptor in control of renin secretion. Amer. J. Physiol. 220: 1593, 1971[a].
BLAINE, E. H. and DAVIS, J. O. Evidence for a renal vascular mechanism in renin release: new observations with graded stimulation by aortic constriction. Circ. Res. 28: 29, (suppl. II): 118, 1971[b].
BLAIR-WEST, J. R., COGHLAN, J. P., DENTON, D. A., GODING, J. R., MUNRO, J. A., PETERSON, R. E. and WINTOUR, M. Humoral stimulation of adrenal cortical secretion. J. Clin. Invest. 41: 1606, 1962.
BLAIR-WEST, J. R., COGHLAN, J. P., DENTON, D. A., FUNDER, J. W., SCOGGINS, B. A. and WRIGHT, R. D. Inhibition of renin secretion by systemic and intrarenal angiotensin infusion. Amer. J. Physiol. 220: 1309, 1971.
BLAIR-WEST, J. R., COGHLAN, J. P., CRAN, E., DENTON, D. A., FUNDER, J. W. and SCOGGINS, B. A. Increased aldosterone secretion during sodium depletion with inhibition of renin release. Amer. J. Physiol. 224: 1409, 1973.
BLANTZ, R. C. Effect of mannitol on glomerular ultrafiltration in the hydropenic rat. J. Clin. Invest. 54: 1135, 1974.

BLAUFOX, M. D., FROMOWITZ, A., GRUSKIN, A., MENG CHIEN-HSING and ELKIN, M. Validation of use of Xenon-133 to measure intra-renal distribution of blood flow. Amer. J. Physiol. 219: 440, 1970.

BLOOM, D. S., STEIN, M. G. and ROSENDORFF, C. Effects of hypertensive plasma on the responses of an isolated artery preparation to noradrenaline. Cardiovasc. Res. 10: 268, 1976.

BLOOMFIELD, D. K., GOULD, A. B., CAMGIANO, J. L. and VERTES, V. The relationship of blood pressure tot hospitalization, dietary sodium and serum renin in essential hypertension. Angiology 21: 75, 1970.

BLUMGART, H. L. and WEISS, S. Studies on the velocity of blood flow. IV The velocity of blood flow and its relation to other aspects of the circulation in patients with arteriosclerosis and in patients with arterial hypertension. J. Clin. Invest. 4: 173, 1927.

BOHR, D. F. Adrenergic receptors in coronary arteries. Ann. N. Y. Acad. Sci. 139: 799, 1967.

BOLOMEY, A. A., MICHIE, A. J., MICHIE, C., BREED, E. S., SCHREINER, G. E. and LAUSON, H. D. Simultaneous measurements of effective renal blood flow and cardiac output in resting normal subjects and patients with essential hypertension. J. Clin. Invest. 28: 10, 1949.

BORST, J. G. G. and BORST-DE GEUS, A. Hypertension explained by Starling's theory of circulatory homeostasis. Lancet I: 677, 1963.

BOYD, G. W. The nature of renal renin. In Hypertension, ed. Genest, J. and Koid, E. Berlin, Springer-Verlag, 1972.

BOYD, G. W., ADAMSON, A. R., ARNOLD, M., JAMES, V. H. T. and PEART, W. S. The role of angiotensin II in the control of aldosterone in man. Clin. Sci. 42: 91, 1972[a].

BOYD, G. W., JONES, M. B. S. and PEART, W. S. The radio-immunoassay of angiotensin II and plasma renin activity in human hypertension. In : Hypertension, ed. Genest, J. and Koiw, E.; Springer, Berlin, 1972[b].

BOYD, J. E., and MULROW, P. J. Intracellular potassium: the regulator of aldosterone production (Abstract). J. Clin. Invest. 51: 13a, 1972.

BOYD, G. W. A protein bound form of porcine renal renin. Circ. Res. 35: 426, 1974.

BOYD, G. W. An inactive higher molecular weight renin in normal subjects and hyptertensive patients. Lancet I: 215, 1977.

BRADLEY, S. C., CURRY, J. J. and BRADLEY, G. P. Renal extraction of p-amino-hippurate in normal subjects and in essential hypertension and chronic diffuse glomerulonephritis. Fed. Proc. 6: 79, 1947.

BRANDFONBRENER, M., LANDOWNE, M. and SHOCK, N. W. Changes in cardiac output with age. Circulation 12: 557, 1955.

BRAUN-MENENDEZ, E., FACIOLO, J. C., LELOIR, L. F. and MUNOZ, J. M. The substance causing renal hypertension. J. Physiol 98: 283, 1940.

BRAVO, E. L., KHOSLA, M. C. and BUMPUS, F. M. Action of (I.des-(aspartic acid), 8-isoleucine) angiotensin II. J. Clin. Endocr. Metab. 40: 530, 1975.

BRAVO, E. L. KHOSLA, M. C. and BUMPUS, F. M. Differential effects of Asp ^{1}-angiotensin II and Sar ^{1}-angiotensin II on vascular and adrenal receptors in the dog. Clin. Sci. Mol. Med. 51: 41, 1976.

BRECKENRIDGE, A., ORME, M. and DOLLERY, C. T. The effect of dopamine on renal blood flow in man. Europ. J. Clin. Pharmacol. 3: 131, 1971.

BRENNER, B. M., TROY, J. L. and DAUGHERTY, T. M. The dynamics of glomerular ultrafiltration in the rat. J. Clin. Invest. 50: 1776, 1971.

BRENNER, B. M., TROY, J. L., DAUGHARTY, T. M., DEEN, W. M. and ROBERTSON, C. R. Dynamics of glomerular ultrafiltration in the rat. II. Plasma-flow dependence of G.F.R. Amer. J. Physiol. 223: 1184, 1972.

BRENNER, B. M., DEEN, W. M. and ROBERTSON, C. R. Glomerular Filtration. In: The Kidney. Eds.: Brenner, B. M. and Rector, F. C. Jr.; W. B. Saunders Company, Philadelphia, London, Toronto, 1976.

BRENNER, B. M. and HUMES, H. D. Mechanics of glomerular ultrafiltration. New Eng. J. Med. 297: 148, 1977.

BRISTOW, J. D., HONOUR, A. J., PICKERING, G. W., SLEIGHT, P. and SMYTH, H. S. Diminished baroreflex sensitivity in high blood pressure. Circulation 39: 48, 1969.

BROD, J. Essential hypertension: haemodynamic observations with a bearing on its pathogenesis. Lancet I: 773, 1960.

BROD, J., FENCL, V., HEJL, Z., JIRKA, J. and ULRYCH, M. General and regional haemodynamic pattern underlying essential hypertension. Clin. Sci. 23: 339, 1962.
BROD, J. The Kidney, Butterworth & Co. Ltd. London, 1973.
BROWN, A. M., SAUM, W. R. and TULEY, F. H. A comparison of aortic baroreceptor discharge in normotensive and spontaneously hypertensive rats. Circ. Res. 39: 448, 1976.
BROWN, J. J., DAVIES, K. L., LEVER, A. F. and ROBERTSON, J. I. S. Influence of sodium loading and sodium depletion on plasma renin in man. Lancet II: 278, 1963.
BROWN, J. J., DAVIES, D. L., LEVER, A. F. and ROBERTSON, J. I. S. Influence of sodium deprivation and loading on the plasma renin in man. I. Physiol. 173: 408, 1964.
BROWN, J. J., DAVIES, D. L., LEVER, A. F. and ROBERTSON, J. I. S. Plasma renin concentration in human hypertension. I. Relationship between renin, sodium and potassium. Brit. Med. J. II: 144, 1965[a].
BROWN, J. J., DAVIES, D. L., LEVER, A. F. and ROBERTSON, J. I. S. Plasma renin concentration in human hypertension. II. Renin in relation to aetiology. Brit. Med. J. II: 1215, 1965[b].
BROWN, J. J., DAVIES, D. L., LEVER, A. F. and ROBERTSON, J. I. S. Plasma renin concentration in human hypertension. III. Renin in relation to complications of hypertension. Brit. Med. J. I: 505, 1966[a].
BROWN, J. J., DAVIES, D. L., LEVER, A. F., McPHERSON, D. and ROBERTSON, J. I. S. Plasma renin concentration in relation to changes in posture. Clin. Sci. 30: 279, 1966[b].
BROWN, J. J., FRASER, R., LEVER, A. F. and ROBERTSON, J. I. S. Aldosterone: physiological variations in man. In: Clinics in endocrinology and metabolism, vol. 1, Saunders, London, 1972[a].
BROWN, J. J., FERRISS, J. B., FRASER, R., LEVER, A. F., LOVER, D. R. and ROBERTSON, J. I. S. Apparently isolated excess deoxycorticosterone in hypertension. Lancet II: 243, 1972[b].
BROWN, J. J., LEVER, A. F., ROBERTSON J. I. S. and SCHALEKAMP, M. A. D. H. Renal abnormality of essential hypertension. Lancet II: 320, 1974.
BROWN, R. D. Aldosterone metabolic clearance rate is normal in low-renin hypertension. J. Clin. Endocrinol. Metab. 42: 661, 1976.
BRUBACHER, E. S. and VANDER, A. J. Sodium deprivation and renin secretion in unanesthetized dogs. Amer. J. Physiol. 214: 15, 1968.
BRUNJES, S., HAYWOOD, L. J. and MARONDE, R. E. Controlled study of antihypertensive response to MAO inhibitor. B. Urinary excretion of catecholamines and their metabolites. Ann. N. Y. Acad. Sci. 107: 982, 1963.
BRUNJES, S. Catecholamine metabolism in essential hypertension. New Engl. J. Med. 271: 120, 1964.
BRUNNER, H. R., BAER, L., SEALEY, J. E., LEDINGHAM, J. G. G. and LARAGH, J. H. The influence of potassium loading and potassium deprivation on plasma renin in normal and hypertensive subjects. J. Clin. Invest. 49: 2128, 1970.
BRUNNER, H. R., LARAGH, J. H., BAER, L., NEWTON, M. A., GOODWIN, F. T., KRAKOFF, L. R., BARD, R. H. and BÜHLER, F. R. Essential hypertension: renin and aldosterone, heart attack and strokes. New Engl. J. Med. 286: 441, 1972.
BRUNNER, H. R., SEALEY, J. E. and LARAGH, J. H. Renin as a risk factor in essential hypertension: more evidence. Amer. J. Med. 55: 295, 1973.
BUCHALI, K. ZIMMERMANN, H. B., STRANGFELD, D. and SCHNEIDER, G. Vergleich der Bestimmung der Nierendurchblutung mit Radioxenon mit anderen klinischen Parametern. Rad. Biol. Ther. 11: 295, 1971.
BUCK, C. W. The persistance of elevated blood pressure first observed at age five. J. Chronic Dis. 26: 101, 1973.
BUCKALEW, V. M. Jr., PUSCHETT, J. B., KINTZEL, J. E. and GOLDBERG, M. Mechanism of exaggerated natriuresis in hypertensive man: impaired sodium transport in the loop of Henle. J. Clin. Invest. 48: 1007, 1969.
BUCKNER, C. K. and PATIL, P. N. Steric aspects of adrenergic drugs. XVI. Beta-adrenergic receptors of guinea-pig atria and trachea. J. Pharmacol. Exp. Ther. 176: 634, 1971.
BÜHLER, F. R., LARAGH, J. H., BAER, L., VAUGHN, E. D. Jr. aand BRUNNER, H. R. Propranolol inhibition of renin secretion. New. Engl. J. Med. 287: 1209, 1972.
BUHLER, F. R. and LÜTOLD, B. E. Plasmakatecholaminstimulation unter Salzentzug und unterschiedliche Anpassung der Adrenozeptoremfindlichkeit. Therapiewoche 26: 7538, 1976.

BUNAG, R. D., PAGE, I. H. and McCUBBIN, J. W. Neural stimulation of renin release. Circ. Res. 21: 851, 1966.
BUNAG, R. D., PAGE, I. H. and McCUBBIN, J. W. Inhibition of renin release by vasopressin and angiotensin. Cardiovas. Res. 1: 67, 1967.
BURN, J. H., LEACH, E. H., RAND, M. J. and THOMPSON, J. W. Peripheral effects of nicotine and acetylcholine resembling those of sympathetic stimulation. J. Physiol. 148: 332, 1959.
BURWELL, C. S. and SMITH, W. C. The output of the heart in patients with abnormal blood pressures. J. Clin. Invest. 7: 1, 1929.
CAPPONI, A. M. and VALLOTTON, M. B. Renin release by rat kidney slices incubated in vitro. Circ. Res. 39: 200, 1976.
CAREY, R. M., DOUGLAS, J. G., SCHWEIKERT, J. R. and LIDDLE, G. W. The syndrome of essential hypertension and suppressed plama renin activity. Arch. Int. Med. 130: 849, 1972.
CARGILL, W. H. The measurement of glomerular and tubular plasma flow in the normal and diseased human kidney. J. Clin. Invest. 28: 533, 1949.
CASTLEMAN, B. and SMITHWICK, R. H. The relation of vascular disease to the hypertensive state. II. The adequacy of the renal biopsy as determined from a study of 500 patients. New. Engl. J. Med. 239: 729, 1948.
CATT, K. J., LAN, E., ZIMMET, P. Z., BEST, J. B., CAIN, M. D. and COGHLAN, J. P. Angiotensin II blood levels in human hypertension. Lancet I: 459, 1971.
DE CHAMPLAIN, J., GENEST, J., VEYRAT, R. and BOUCHER, R. Factors controlling renin in man. Arch. Int. Med. 117: 355, 1966.
DE CHAMPLAIN, J., FARLEY, L., COUSINEAU, D. and VAN AMERINGEN, M. R. Circulating catecholamine levels in human and experimental hypertension. Circ. Res. 38: 109, 1976.
CHANDRA, S., HUBBARD, J. C., SKELTON, F. R., BERNARDIS, L. L. and KAMURA, S. Genesis of juxta glomerular cell granules. Lab. Invest. 14: 1834, 1965.
CHANNICK, B. J., ADLIN, E. V. and MARKS, A. D. Suppressed plasma renin activity in hypertension. Arch. Int. Med. 123: 131, 1969.
CHASIS, H., GOLDRING, W., BREED, E. S., SCHREINER, G. E. and BOLOMEY, A. A. Salt and protein restriction: Effects on blood pressure and renal hemodynamics in hypertensive patients. J.A.M.A. 142: 711, 1950.
CHAU, N. P., SAFAR, M. E., WEISS, Y. A., LONDON, G. M., SIMON, A. Ch. and MILLIEZ, P. L. Relationships between cardiac output, heart rate and blood volume in essential hypertension. Clin. Sci. Mol. Med. 54: 175, 1978.
CHENITZ, W. R., NEVINS, B. A. and HOLLENBERG, N. K. Preglomerular resistance and glomerular perfusion in the rat and dog. Amer. J. of Physiol. 231: 961, 1976.
CHIDSEY, C. A., MORSELLI, P., BIANCHETTI, G., MORGANTI, A., LEONETTI, G. and ZANCHETTI, A. Studies of the absorption and removal of propranolol in hypertensive patients during therapy. Circulation 52: 313, 1975.
CHIEN, S., USAMI, S., McALLISTER, R. L. S. F. F. and GREGERSEM, M. I. Blood volume and age: repeated measurements of normal men after 17 years. J. Appl. Physiol. 21: 583, 1966.
CHINN, R. H., BROWN, J. J., FRASER, R., HERON, S. M., LEVER, A. F., MURCHISON, L. and ROBERTSON, J. I. S. The natriuresis of fasting: relationship to changes in plasma renin and plasma aldosterone concentrations. Clin. Sci. 39: 437, 1970.
CHOKSHI, D. S., YEH, B. K. and SAMET, P. Effects of dopamime and isoproterenol on renin secretion in the dog. Proc. Soc. Exp. Biol. Med. 140: 54, 1972.
CHRISTENSEN, M. S. and CHRISTENSEN, N. J. Plasma catecholamines in hypertension. Scand. J. Clin. Lab. Invest. 30: 169, 1972.
CHRYSANT, S. G. and LAVENDER, A. R. Direct renal hemodynamic effects of two vasodilators: Diazoxide and acetylcholine. Arch. Int. Pharmacodyn. Ther. 217: 44, 1975.
CHRYSANT, S. G., ADAMOPOULOS, P., TSUCHIYA, M. and FROHLICH, E. D. Systemic and renal hemodynamic effects of bupicomide: A new vasodilator. Amer Heart J. 92: 335, 1976.
CHURCHILL, P. C., MALVIN, R. L. and OPAVA, S. C. Evidence for baroreceptor control of renin release. Nephron 13: 382, 1974.

CLARK, B. J. Pharmacology of beta-adrenoceptor blocking agents. In: Beta-adrenoceptor blocking agents. Ed. by Saxena, P. R. and Forsyth, R. P. North-Holland Publishing Company, Amsterdam, The Netherlands, 1976.

CLEAVELAND, C. R. and SHAND, D. G. Effect of route of administration of the relationship between beta-adrenergic blockade and plasma propranolol levels. Clin. Pharmacol. Ther. 13: 181, 1972.

CLEMENT, D. L., PELLETIER, C. L. and SHEPHERD, J. T. Role of vagal afferents in the control of renal sympathetic nerve activity in the rabbit. Circ. Res. 31: 824, 1972.

CLEMENT, D. L., BOGAERT, M. G. and PANNIER, R. Role of beta-adrenergic activity in blood pressure variability of hypertensive patients. In: Abstract book II of the seventh European Congress of Cardiology. Amsterdam, 1976.

COHEN, E. L., CONN, J. W. and ROVNER, D. R. Postural augmentation of plasma renin activity and aldosterone excretion in normal people. J. Clin. Invest. 46: 418, 1967.

COLEMAN, T. G. and GUYTON, A. C. Hypertension caused by salt loading in the dog. III Onset transients of cardiac output and other circulatory variables. Circ. Res. 15: 153, 1969.

COLLINS, R. D., WEINBERGER, M. H., GONZALES, C., NOKES, G. W. and LUETSCHER, J. A. Catecholamine excretion in lowrenin hypertension. Clin. Res. 18: 167, 1970[b].

COLLINS, D. R., WEINBERGER, M. H., DOWDY, A. J., NOLUS, G. W. GONZALES, G. M. and LUETSCHER, J. A. Abnormally sustained aldosterone secretion during salt loading in patients with various forms of benign hypertension: relation to plasma renin. J. Clin. Invest. 49: 1415, 1970[b].

COLLIS, M. G. and VANHOUTTE, P. M. Vascular reactivity of isolated perfused kidneys from male and female spontaneously hypertensive rats. Circ. Res. 41: 759, 1977.

CONN, J. W., COHEN, E. L. and ROVNER, D. R. Suppression of plasma renin activity in primary aldosteronism. J. Amer. Med. Ass. 190: 213, 1964.

COMWAY, J. Hemodynamic concequences of induced changes in blood volume. Circ. Res. 18: 190, 1966.

COOK, W. F. The detection of renin in juxtaglomerular cells. J. Physiol. (London) 194: 73p, 1967.

COOK, W. F. and PICKERING, G. W. The location of renin in the rabbit kidney. J. Physiol. (London), 149: 526, 1959.

COOKE, C. R., BROWN, T. C., ZACHERIE, B. J. and WALKER, G. W. Effect of altered sodium concentration in the distal nephron segments on renin release. J. Clin. Invest. 49: 1630, 1970.

COOTE, J. H., JOHNS, E. L., MacLEOD, V. H. and SINGER, B. Effect of renal nerve stimulation, renal blood flow and adrenergic blockade on plasma activity renin in the cat. J. Physiol. (London) 226: 15, 1972.

COOTE, J. H. and SATO, Y. Reflex regulation of sympathetic activity in the spontaneously hypertensive rat. Circ. Res. 40: 571, 1977.

COPE, C. L., HARWOOD, M. and PEARSON, J. Aldosterone secretion in hypertensive diseases. Brit. Med. J. 1: 659, 1962.

CORCORAN, A. C., TAYLOR, R. D. and PAGE, I. H. Circulatory responses to spinal and caudal anesthesia in hypertension: relation to the effect of sympathectomy. II Effect on renal function. Amer. Heart J. 36: 226, 1948[a].

CORCORAN, A. C., TAYLOR, R. D. and PAGE, I. H. Functional patterns in renal disease. Ann. Int. Med. 28: 560, 1948[b].

COWLEY, A. W. Jr., LIARD, J. F. and GUYTON, A. C. Role of the baroreceptor reflex in daily control of arterial blood pressure and other variables in dogs. Circ. Res. 32: 564, 1973.

CRANE, M. G., HARRIS, J. J. and JOHNS, V. J. Hyporeninemic hypertension. Amer. J. Med. 52: 457, 1972.

CRANE, M. G., and HARRIS, J. J. Effect of ageing on renin activity and aldosterone excretion. J. Lab. Clin. Med. 87: 947, 1976.

CRANSTON, W. I. and BROWN, W. Diurnal variation in plasma volume in normal and hypertensive subjects. Clin. Sci. 25: 107, 1963.

CREDITOR, M. C. and LOTSCHKY, U. K. Plasma renin activity in hypertension. Amer. J. Med. 43: 371, 1967.

CUCHE, J. L., KUCHEL, C., BARBEAU, A., LANGLOIS,, Y., BOUCHER, R. and GENEST, J. Autonomic nervous system and benign essential hypertension in man. Circ. Res. 35: 281, 1974.

DABAJ, E., MENGES, H. Jr. and PRITCHARD, W. H. Determination of renal blood flow by single injection of Hippuran-I^{131} in man. Amer. Heart J. 71: 79, 1966.

DALE, H. H. On some physiological actions of ergot. J. Physiol. (London) 34: 163, 1906.
DAVIES, D. F. and SHOCK, N. W. The variability of measurement of inulin and diodrast tests of kidney function. J. Clin. Invest. 29: 491, 1950[a].
DAVIES, D. F. and SHOCK, N. W. Age changes in glomerular filtration rate, effective renal plasma flow and tubular excretory capacity in adult males. J. Clin. Invest. 29: 496, 1950[b].
DAVIES, R. and SLATER, J. D. H. Is the adrenergic control of renin release dominant in man? Lancet II: 594, 1976.
DAVIES, R., SLATER, J. D. H., FORSLING, M. L. and PAYNE, N. The response of arginine vasopressin and plasma renin to postural change in normal man, with observations on syncope. Clin. Sci. Mol. Med. 51: 267, 1976[a].
DAVIES, R., PAYNE, N. N. and SLATER, J. D. H. Beta-adrenergic blockade and diuretic therapy in benign essential hypertension: a dynamic assessment. Amer. J. Cardiol. 37: 637, 1976[b].
DAVIS, J. O., HARTROFT, P. M., TITUS, E. O., CARPENTER, C. J., AYERS, C. R. and SPIEGEL, H. E. The role of the renin-angiotensin system in the control of aldosterone secretion. J. Clin. Invest. 41: 378, 1962.
DAVIS, J. O., URQUHART, J. and HIGGINS, J. T. Jr. The effects of alterations of plasma sodium and potassium concentration on aldosterone secretion. J. Clin. Invest. 42: 597, 1963.
DAVIS, J. O. What signals the kidney to release renin? Circ. Res. 28: 301, 1971.
DAVIS, J. O. The control of renin release. Amer. J. Med. 55: 333, 1973.
DAVIS, J. O. The control of renin release. In Hypertension Manual, Vol. 163, J. H. Laragh (Ed.), Yorke Medical Books, Dun-Donnelley publ. Corp., New York, 1974.
DAY, R. P. and LUETSCHER, J. A. Big renin: a possible prohormone in kidney and plasma of a patient with Wilms' tumor. J. Clin. Endocr. 38: 923, 1974.
DAY, R. P. and LUETSCHER, J. A. Biochemical properties of big renin extracted from human plasma. J. Clin. Endocr. 40: 1085, 1975.
DAY, R. P., LUETSCHER, J. A. and GONZALES, C. M. Occurence of big renin in human plasma, amniotic fluid and kidney extracts. J. Clin. Endocr. Metab. 40: 1078, 1975.
DAY, R. P., LUETSCHER, J. A. and ZAGER, P. G. Big renin: identification, chemical properties and clinical implications. Amer. J. Card. 37: 667, 1976.
DEEN, W. M., TROY, J. L., ROBERTSON, C. R. and BRENNER, B. M. Dynamics of glomerular ultrafiltration in the rat. IV. Determination of the ultrafiltration coefficient. J. Clin. Invest. 52: 1500, 1973.
DEHENEFFE, J., CUESTA, V., BRIGGS, J. D., BROWN, J. J., LECKIE, B. J., LEVER, A. F., MORTON, J. J., SEMPLE, P. F., ROBERTSON, J. I. S. and TREE, M. The renin-angiotensin system in anephric man. Proc. Europ. Dialysis and Transpl. Ass. 13: 495, 1976.
DELL, R. G., SCIACCA, R., LIEBERMAN, K., CASE, D. B. and CANNON, P. J. A weighted least-squares technique for analysis of kinetic data and its application to the study of renal ^{133} Xenon washout in dogs and man. Circ. Res. 32: 71, 1973.
DEMANGE, J., PERNOD, J., HAGUENEUER, G. and COLIN, J. Mesure de débit cardiaque par pléthysmographie électrique thoracique localiste. Nouv. Presse Med. 1: 3067: 1972.
DENNISTON, J. C., MAHER, J. T., REEVES, J. T., CRUZ, J. C., CYMERMAN, A. and GROVER, R. F. Measurement of cardiac output by electrical impedance at rest and during exercise. J. Appl. Physiol. 40: 91, 1976.
DERKX, F. H. M., WENTING, G. J., MAN IN 't VELD, A. J., VAN GOOL, J. M. G., VERHOEVEN, R. P. and SCHALEKAMP, M. A. D. H. Inactive renin in human plasma. Lancet II: 496, 1976.
DIRKS, J., SEALY, J. AND LEVY, M. Control of extracellular fluid volume and the pathophysiology of edema formation. In: The kidney, ed. Brenner, B. M. and Rector,F. C. Jr. W. B. Saunders Company, Philadelphia, London, Toronto, 1976.
DISTLER, A., JUST, H. J. and PHILIPP, Th. Studies on the mechanism of aldosterone induced hypertension in man. Clin. Sci. Mol. Med. 45: 743, 1973.
DISTLER, A., KEIM, H. J., PHILIPP, Th., PHILIPPI, A., WALTER, U., WERNER, E. and WOLFF, H. P. Low renin hypertension. Evidence for mineral-corticoid excess? Hypertension – Current Problems. Ed. by Distler, A. and Wolff, H. P., Georg Thieme, Stuttgart, 1974.

DLUHY, R. G., UNDERWOOD, R. H. and WILLIAMS, G. H. Influence of dietary potassium on plasma renin activity in normal man. J. Appl. Physiol. 28: 299, 1970.
DLUHY, R. G., AXELROD, L., UNDERWOOD, R. H. and WILLIAMS, G. H. Studies of the control of plasma aldosterone concentration in normal man. II. Effect of dietary potassium and acute potassium infusion. J. Clin. Invest. 51: 1950, 1972.
DLUHY, R. G., CAIN, J. P. and WILLIAMS, G. H. The influence of dietary potassium on the renin and aldosterone response to diuretic-induced volume depletion. J. Lab. Clin. Med. 83: 249, 1974.
DOBA, N. and REIS, D. J. Acute fulminating neurogenic hypertension produced by brainstem lesions in the rat. Circ. Res. 32: 594, 1973.
DOBSON, E. L. and WARNER, G. F. Measurement of regional sodium turnover rates and their application to the estimation of regional blood flow. Amer. J. Physiol. 189: 269, 1957.
DONKER, A. J. M., VAN DER HEM G. K., SLUITER, W. J. and BEEKHUIS, H. A radioisotope method for simultaneous determination of the glomerular filtration rate and the effective renal plasma flow. Neth. J. Med. 20: 97, 1977.
DÖRING, P., KOCH, R., SANCKEN, H. and SCHWAB, M. Die intrarenale Hämodynamik bei essentieller Hypertonie. Klin. Wschr. 32: 71, 1954.
DOYLE, A. E. and SMIRK, F. J. Neurogenic component in hypertension. Circulation 12: 543, 1955.
DOYLE, A. E., FRASER, J. R. E. and MARSHALL, R. J. Reactivity of forearm vessels to vasoconstrictive substances in hypertensive and normotensive subjects. Clin. Sci. 18: 441, 1959.
DOYLE, A. E. and FRASER, J. R. E. Vascular reactivity in hypertension. Circ. Res. 9: 755, 1961[a].
DOYLE, A. E. and FRASER, J. R. E. Essential hypertension and inheritance of vascular reactivity. Lancet 2: 509, 1961[b].
DOYLE, A. and JERUMS, G. Sodium balance, plasma renin and aldosterone in hypertension. Circ. Res. 26/27 (suppl. 2): 267, 1970.
DOYLE, A. E., JERUMS, G., JOHNSTON, C. J. and LOUIS, W. J. Plasma renin levels and vascular complications in hypertension. Brit. Med. J. 2: 206, 1973.
DRAYER, J. I. M., KLOPPENBORG, P. W. C. and BENRAAD, T. J. Detection of low-renin hypertension: evaluation of outpatient department renin-stimulating methods. Clin. Sci. Mol. Med. 48: 91, 1975.
DRAYER, J. I. M., KEIM, H. J., WEBER, M. A., CASE, D. B. and LARAGH, J. H. Unexpected pressor responses to propranolol in essential hypertension. Amer. J. Med. 60: 897, 1976.
DRIEL C. VAN, HOUTHOFF, H. J. and BALJET, B. The innervation of the myometrium, some histochemical observations in man and rat. Eur. J. Obstet. Gynec. Biol. 3: 11, 1973.
DUCH, D. S., VIVEROS, O. H. and KIRSHNER, N. Endogenous inhibitor(s) in adrenal medulla of dopamine-beta-hydroxylase. Biochem. Pharmacol. 17: 255, 1968.
DUFF, R. S. Adrenaline sensitivity of peripheral blood vessels in human hypertension. Brit. Heart J. 19: 45, 1957.
DUNN, M. J. and TANNEN, R. L. Low-renin hypertension. Kidney Intern. 5: 317, 1974.
DUNN, F. G., CHANDRARATNA, P., DE CARVALHO, J., BASTA, L. L. and FROHLICH, E. D. Pathophysiologic assessment of hypertensive heart disease with echocardiography. Amer. J. Card. 39: 789, 1977.
DUSTAN, H. P., TARAZI, R. C. and FROHLICH, E. D. Functional correlates of plasma renin activity in hypertensive patients. Circulation 41: 555, 1970.
DUSTAN, H. P., TARAZI, R. C., BRAVO, E. L. and DART, R. A. Plasma and extracellular fluid volumes in hypertension. Circ. Res. 32/33 (suppl. 1): 73, 1973.
DÜSTERDIECK, G. and McELWEE, G. M. Estimation of angiotensin II concentrations in human plasma by radioimmunoassay. Some applications to physiological and clinical states. Eur. J. Clin. Invest. 2: 32, 1971.
DUTZ, H. Die Bedeutung der Clearance-Methodik zur Prüfung der Nierenfunktion für die Klinik unter besonderer Berücksichtigung differentialdiagnostischer Fragestellungen. II Nierenerkrankungen. Z. Ges. Inn. Med. 8: 436, 1953.
EDELMAN, R. and HARTCROFT, P. M. Localization of renin in juxtaglomerular cells of rabbit and dog through the use of the fluorescent- and antibody technique. Circ. Res. 9: 1069, 1961.

EICH, R. H., PETERSON, R. J., CUDDY, R. P., SMULYAN, H. and LYONS, R. H. The hemodynamics in labile hypertension. Amer. Heart J. 63: 188, 1962.
EICH, R. H., CUDDY, R. P., SMULYAN, H. and LYONS, R. H. Hemodynamics in labile hypertension. Circulation 34: 299, 1966.
EIDE, I., LOYNING, E. and KIIL, F. Evidence for hemodynamic autoregulation of renin release. Circ. Res. 32: 237, 1973.
ELLIS, C. H. and JULIUS, S. Role of central blood volume in hyperkinetic borderline hypertension Brit. heart J. 35: 450, 1973.
ENERO, M. A., LANGER, S. Z., ROTHLIN, R. P. and STEFANO, F. J. E. Role of the alpha-adrenoceptor in regulating noradrenaline overflow by nerve stimulation. Brit. J. Pharmacol. 44: 672, 1972.
ENGELMAN, K., PARTNOY, B. and SJOERDSMA,A. Plasma catecholamine concentrations in patients with hypertension. Circ. Res. 26/27 (suppl. 1): 141, 1970.
EPSTEIN, M. and SATUR, A. T. J. Effect of water immersion on renin aldosterone and renal handling in normal man. J. Appl. Physiol. 31: 368, 1971
EPSTEIN, S. and HAMILTON, S. Cyproheptadine inhibition of stimulated plasma renin activity. J. Clin. Endocrin. Metab. 45: 1235, 1977.
ESLER, M. D. and NESTEL, P. J. Renin and sympathetic nervous system responsiveness to adrenergic stimuli in essential hypertension. Amer. J. Cardiol. 32: 643- 1973[a].
ESLER, M. D., and NESTEL, P. J. Symphathetic responsiveness to head-up tilt in essential hypertension. Clin. Sci. 44: 213, 1973[b].
ESLER, M. D. and NESTEL, P. J. High catecholamine essential hypertension: clinical and physiological characteristics. Aust. N.-Z. J. Med. 3: 117, 1973.[c].
ESLER, M., RANDALL, O., BENNETT, J., ZWEIFLER, A., JULIUS, S. RYDELEK, P., COHEN, E. and DE QUATTRRO, V. Suppression of sympathetic nervous function in low-renin hypertension. Lancet 2: 115, 1976.
ESLER, M., JULIUS, S., ZWEIFLER, A., RANDALL, O., HARBURG, E. GARDINER, H., and DE QUATTRO, V. Mild high-renin essential hypertension. New Engl. J. Med. 296: 405, 1977.
ESPINER, E. A. CHRISTLIEB, A. R., AMSTERDAM, E. A. JAGGER, P. I., DOBRINZINSKI, S. J., LAULER, D. P. and HICKLER, R. B. The pattern of plasma renin activity and aldosterone secretion in normal and hypertensive subjects before and after saline infusions. Amer. J. Cardiol. 27: 585, 1971.
EULER, U. S. VON, HELLNER, S. and PURKHOLD, A. Excretion of noradrenaline in urine in hypertension. Scand. J. Clin. Lab. Invest. 6: 54, 1954.
EVANS, G. H. and SHAND, D. G. Disposition of propanolol. V. Drug accumulation and steady-state concentrations during chronic oral administration in man. Clin. Pharmacol. Ther. 14: 487, 1973[a].
EVANS, G. H. and SHAND, D. G. Disposition of propanolol. VI Independent variation in steady state circulating drug concentration and half-life as a result of plasma drug binding in man. Clin. Pharmacol. Ther. 14: 494, 1973[b].
EVANS, G. H., NIES, A. S. and SHAND, D. G. Thedisposition of propranolol. III. Decreased half-life and volume of distribution as a result of plasma binding in man, monkey, dog and rat. J. Pharmacol. Ther. 186: 114, 1973.
EWIG, W. and HINSBERG, K. Über die Bestimmung des Minutenvolumens. Klin. Wschr. 9: 647, 1930.
FAGARD, R., AMERY, A., REYBROUCK, T., LIJNEN, P., BILLIET, L. and JOOSSENS, J. V. Plasma renin levels and systemic haemodynamics in essential hypertension. Clin. Sci. Mol. Med. 52: 591, 1977.
FALKE, H. E., PUNT, R. and BIRKENHÄGER, W. H. Radioenzymatic estimation of noradrenaline in small plasma samples without previous extraction.
FARNEBO, L. O. and HAMBERGER, B. Catecholamine release and receptors in brain slices. In: Frontiers in catecholamine research, ed. by Usdin, E. and Snyder, S. H. Pergamon Press, N Y. – Toronto, Oxford, Sydney
FEIGL, E. O. Sympathetic control of coronary circulation. Circ. Res. 21: 262, 1967.
FEJFAR, Z. and WIDIMSKI, J. Juvenile hypertension. In: Proceedings of the Joint W.H.O., Czechoslovak Cardiological Society Symposium on the pathogenesis of essential hypertension. Ed. by Cort, J. H., Fencl, V. and Hejl, Z. State Medical Publishing House, Prague, 1961.

FERRARIO, C. M., PAGE, I. H. and McCUBBIN, J. W. Increased cardiac output as a contributory factor in experimental renal hypertension in dogs. Circ. Res. 27: 799, 1970.
FERRARIO, C. M. Contribution of cardiac output and peripheral resistance to experimental renal hypertension. Amer. J. Physiol. 226: 711, 1974.
FERRY, C. B. Cholinergic link hypothesis in adrenergic neuroëffector transmission. Physiol. Rev. 46: 420, 1966.
FINDLEY, T., EDWARDS, J. C., CLINTON, E. and WHITE, H. L. Clearance of diodrast, phenolsulphthalein and inulin in hypertension and nephritis. Arch. Int. Med. 70: 935, 1942.
FINKIELMAN, S., WORCEL, M. and AGREST, A. Hemodynamic patterns in essential hypertension. Circulation 31: 356, 1965.
FISHMAN, L. M., KUCHEL, D., LIDDLE, G. W., MICHELAKIS, A. M., GORDON, R. D. and CHICK, W. T. Incidence of primary aldosteronism in uncomplicated „essential" hypertension. J.A.M.A. 205: 497, 1968.
FLOOD, C., GHERONDACHE, C., PINCUS, G., TAIT, J. F., TAIT, S. A. S. and WILLOUGHBY, S. The metabolism and secretion of aldosterone in elderly subjects. J. Clin. Invest. 46: 960, 1967.
FLUCK, D. C. Catecholamines. Brit. Heart J. 34: 869, 1972.
FOA, P. P., WOODS, W. W., PEET, M. M. and FOA, N. L. Effective renal blood flow, glomerular filtration rate and tubular excretory mass in arterial hypertension. Arch. Int. Med. 69: 822, 1942.
FOA, P. P., WOODS, W. W., PEET, M. M. and FOA, N. L. Effective renal blood flow, glomerular filtration rate and tubular excretory mass in arterial hypertension. Arch. Int. Med. 71: 357, 1943.
FOLKOW, B. and RUBINSTEIN, E. H. Cardiovascular effects of acute and chronic stimulation of the hypothalamus defence area in the rat. Acta Physiol. Scand. 68: 48, 1966.
FOLKOW, B. and NEIL, E. Circulation, chapter 31, Oxford University Press. 1971.
FOLKOW, B. Haemodynamic consequences of adaptive structural changes of the resistance vessels in hypertension. Clin. Sci. 41: 1, 1971.
FOLKOW, B., HALLBÄCK, M., LUNDGREN, Y., SIVERTSSON, R. and WEISS, L. Importance of adaptive changes in vascular design for establishment of primary hypertension, studied in man and in spontaneously hypertensive rats. Circ. Res. 32/33 (suppl. 1): 2, 1973.
FOURMAN, J. and MOFFAT, D. B. Observations on the fine blood vessels of the kidney. Symp. Zool. Soc. London, 11, 57, 1964.
FRASER, R., GUEST, S. and YOUNG, J. A comparison of double-isotope derivative and radioimmunological estimation of plasma aldosterone concentration in man. Clin. Sci. Mol. Med. 45: 411, 1973.
FRAY, J. C. S. Stretch receptor model for renin release with evidence from perfused rat kidney. Amer. J. Physiol. 231: 936, 1976.
FREEDMAN, L. S., OHUCHI, T., GOLDSTEIN, M., AXELROD, F., FISH, I. and DANCIS, I. Changes in serum dopamine-beta-hydroxylase with age. Nature 236: 310, 1972.
FREEDMAN, R. H., DAVIS, J. O., GOTSHALL, R. W., JOHNSON, J. A. and SPEILMAN, W. S. The signal perceived by the macula densa during changes in renin release. Circ. Res. 35: 307, 1974.
FREIS, E. D. Hemodynamics of hypertension. Physiol. Rev. 40: 27, 1960.
FRIEDMAN, M., SELZER, A. and ROSENBLUM, H. The renal blood flow in hypertension as determined in patients with early and with longstanding hypertension. J.A.M.A. 117: 92, 1941.
FRIEDMAN, S. M., FRIEDMAN, C. L. and NAKASHIMA, M. Sodium gradient, smooth muscle tone and blood pressure regulation. Circ. Res. 7, 44, 1959.
FROHLICH, E. D., DUSTAN, H. P. and PAGE, I. H. Hyperdynamic beta-adrenergic circulatory states. Arch. Int. Med. 117: 614, 1966.
FROHLICH, E. D. TARAZI, R. C. and ULRYCH, M. Tilt test for investigating a neural component in hypertension. Circulation: 36: 387, 1967.
FROHLICH, E. D., ULRYCH, M. and TARAZI, R. C. A hemodynamic comparison of essential hypertension. Cardiac output and total peripheral resistance supine and tilted. Circulation 35: 289, 1967.
FROHLICH, E. D., TARAZI, R. C., DUSTAN, H. P. and PAGE, I. H. The paradox of beta-adrenergic blockade in hypertension. Circulation 37: 417, 1968.

FROHLICH, E. D., TARAZI, R. C. and DUSTAN, H. P. Hyperdynamic beta-adrenergic responsiveness. Arch. Int. Med. 123: 1, 1969a
FROHLICH, E. D., TARAZI, R. C. and DUSTAN, H. P. Re-examination of the hemodynamics of hypertension. Amer. J. Med. Sci. 257: 9, 1969b.
FROHLICH, E. D., KOZUL, V., TARAZI, R. C. and DUSTAN, H. P. Physiological comparison of labile and essential hypertension. Circ. Res. 26–27, Suppl. 1: 55, 1970.
FUKADA, I. Clinical patho-physiological investigation on renal haemodynamics of normal individuals and patients with pulmonary tuberculosis, hypertension and nephrosclerosis in acute induced hypoxemia. Jap. Circ. J. 28: 266, 1964.
FUNDER, J. W., BLAIR-WEST, J. R., COGHLAN, J. P., DENTON, D. A., SCOGGINS, B. A. and WRIGHT, R. D. Effect of plasma (K^+) on the secretion of aldosterone. Endocrinology 85: 381, 1969.
GAAL, P. G., KATTUS, A. A., KOLIN, A. and ROSS, G. Effects of adrenaline and noradrenaline on coronary blood flow before and after beta-adrenergic blockade. Brit. J. 1782, 1973.
GAILLARD, R. C., MERKELBACH, U., RIONDEL, A. M., VALLOTON, M. B. and MULLER, A. F. Effect on plasma aldosterone, renin activity and cortisol of acute volume depletion induced by ethacrynic acid under constant infusion of angiotensin II and dexamethasone in man. Europ. J. Clin. Invest. 6: 51, 1976.
GAMBLE, J. L., ROBERTSON, J. S., HANNIGAN, C. A., FOSTER, C. B. and FARR, L. E. Chloride, bromide, sodium and sucrose space in man. J. Clin. Invest. 32: 483, 1953.
GANONG, W. F. Sympathetic effects on renin secretion: mechanism and physiological role. In: Control of renin secretion. T. A. Assaykeen, editor. Plenum Press New York, 1972.
GANONG, W. F. Biogenic amines, sympathetic nerves, and renin secretion. Fed. Proc. 32: 1782, 1973.
GAVRAS, H., RIBEIRO, A. B., GAVRAS, I. and BRUNNER, H. R. Reciprocal relation between renin dependency and sodium deficiency in essential hypertension. New Engl. J. Med. 295: 1278, 1976.
GEBBER, G. L. and SNYDER, D. W. Hypothalamic control of bara receptor reflexes. Amer. J Physiol. 218: 124, 1970.
GEFFEN, R. L. B., RUSH, R. A., LOUIS, W. J. and DOYLE, A. E. Plasma dopamine-beta-hydroxylase and noradrenaline amounts in essential hypertension. Clin. Sci. 44: 617, 1973.
GEFFEN, L. Serum dopamine beta-hydroxylase as a index of sympathetic function. Life Sci. 14: 1593, 1974.
GELLAI, M., NORTON, J. M. and DETAR, R. Evidence for direct control of coronary vascular tone by oxygen. Circ. Res. 32: 279, 1973.
GENEST, J., BOUCHER, R., DE CHAMPLAIN, J., VEYRAT, R., CHRETIEN, M., BIRON, P., TREMBLAY, G., ROY, P. and CARTIER, P. Studies on the renin-angiotensin system in hypertensive patients. Canad. Med. Ass. J. 90: 263, 1964.
GENEST, J., DE CHAMPLAIN, J., VEYRAT, R., BOUCHER, R., TREMBLAY, G. Y., STRONG, C. G., KOIW, E. and MARC-AURELE, J. Role of the renin-angiotensin system in various physiological and pathological states. Hypertension 13: 97, 1965.
GENEST, J., NOWACYNSKI, W., KUCHEL, O. and SASAKI, C. Plasma progresterone levels and 18-hydroxy-deoxycorticosterone secretion rate in benign essential hypertension in humans. In Hypertension. J. Genest and E. Koiw (Eds.). Springer, Berlin, 1972.
GENEST, J., BOUCHER, R., KUCHEL, O. and NOWACZYNSKI, W. Renin in hypertension: how important as a risk factor? Canad. Med. Ass. J. 109: 475, 1973.
GEORGE, C. F., CONOLLY, M. E., FENYVESI, T., BRIANT, R. and DOLLERY, C. T. Intravenously administered isoproterenol sulphate dose-response in man. Arch. Int. Med. 130: 361, 1972.
GEORGE, J., GILLESPIE, L. and BARTTER, F. C. Aldosterone secretion in hypertension. Ann. Int. Med. 69: 693, 1968.
GILLESPIE, J. S. Uptake of noradrenaline by smooth muscle. Brit. Med. Bull. 9: 136, 1973.
GITLOW, S. E., MENDLOWITZ, M., WILK, E. K., WILK, S., WOLF, R. L. and NAFTCHI, N. E. Plasma clearance of dl-beta-3-H norepinephrine in normal human subjects and patients with essential hypertension. J. Clin. Invest. 43: 2009, 1964.
GITLOW, S. E., MENDLOWITZ, M., BERTANI, L. M., WILK, E. K. and LABMAN, S. G. Tritium excretion of normotensive and hypertensive subjects after administration of triated norepinephrine. J. Lab. Clin. Med. 73: 129, 1969.

GLAZER, G. A. A study of some haemodynamic parameters in essential hypertension. Cor Vasa 5: 165, 1963.
GLOVER, W. E., GREENFIELD, A. D. M. and SHANKS, R. G. Effects of dichloroisoprenaline on the peripheral vascular responses to adrenaline in man. Brit. J. Pharmacol. 19: 235, 1962.
GOLDBERG, L. I. Cardiovascular and renal actions of dopamine: potential clinical applications. Pharmacol. Rev. 24: 1, 1972.
GOLDBERG, N., O'DEA, R. F. and HADDOX, M. K. Cyclic GMP. In: Advances in cyclic nucleotide research. Ed. by Drummond, G. I., Greengard, P. and Robison, G. A. New York, Raven Press, 1975.
GOLDBLATT, H., LYNCH, J., HANZAL, R. F. and SUMMERVILLE, W. W. Studies on experimental hypertension: I. Production of persistent elevation of systolic blood pressure by means of renal ischemia. J. Exp. Med. 59: 347, 1934.
GOLDENBERG, M., PINES, K. L., BALDWIN, E., de F., GREENE, D. G. and ROH, C. H. E. The hemodynamic response of man to norepinephrine and epinephrine and its relation to the problem of hypertension. Amer. J. Med. 5: 792, 1948.
GOLDRING, W., CHASIS, H. A. and SMITH, H. W. Effective renal blood flow and functional excretory mass in essential hypertension. J. Clin. Invest. 17: 505, 1938.
GOLDRING, W., CHASIS, H., RANGES, H. A. and SMITH, H. W. Effective renal blood flow in subjects with essential hypertension. J. Clin. Invest. 20: 637, 1941.
GOLDRING, W. and CHASIS, H. Hypertension and Hypertensive Disease. The Common Wealth Fund, New York, 1944.
COLUBOFF, B., BOGASH, M., COPE, A., WOLGIN, W. and ISARD, H. J. Renal blood flow measured by radio-Xenon 133: evaluation of a technique in dogs. J. Appl. Physiol. 26: 208, 1969.
GOMBOS, E. A., HULET, W. H., BOPP, P., GOLDRING, W., BALDWIN, D. S. and CHASIS, H. Reactivity of renal and systemic circulation to vasoconstrictor agents in normotensive and hypertensive subjects. J. Clin. Invest. 41: 203, 1962.
GOMEZ, D. M. Evaluation of renal resistances with special reference to changes in essential hypertension. J. Clin. Invest. 30: 1143, 1951.
GOORMAGHTIGH, N. Existence of an endocrine gland in the media of the renal arterioles. Proc. Soc. Exp. Biol. Med. 42: 688, 1939.
GOORMAGHTIGH, N. Facts in favor of an endocrine function of the renal arterioles. J. Pathol. Microbiol. 57: 392, 1945.
GORDON, R. D., KUCHEL, O., LIDDLE, G. W. and ISLAND, D. P. Role of the sympathetic nervous system in regulating renin and aldosterone production in man. J. Clin. Invest. 46: 599, 1967.
GORDON, R. D. and PAWSEY, C. G. K. Relative effects of serum sodium concentration and the state of body fluid balance on renin secretion. J. Clin. Endocrinol. 32: 117, 1971.
GOTSHALL, R. W., DAVIS, J. O., SHADE, R. E., SPIELMAN, W., JOHNSON, J. A. and BRAVERMAN, B. Effects of renal denervation on renin release in sodium-depleted dogs. Amer. J. Physiol. 225: 344, 1973.
GOTSHALL, R. W., DAVIS, J. O., BLAINE, E. H., MUSACCHIA, X. J., BRAVERMAN, B., FREEMAN, R. and JOHNSON, J. A. Increased renin release during renal arteriolar dilation in dogs. Amer. J. Physiol, 227: 251, 1974.
GOWENLOCH, A. H. and WRONG, O. Hyperaldosteronism secondary to renal inschaemia. Quart. J. Med. 31: 323, 1962.
GRAEFF, J. DE. Inulin space and total exchangeable sodium in patients with essential hypertension. Acta med. Scand. 156: 337, 1957.
GRAHAM, J. E. Efferent arterioles of glomeruli in the juxtamedullary zone of the human kidney. Anat. Rec. 125: 521, 1956.
GRANGER, P., ROJO-ORTEGA, J. M., GRUNER, A., DAHLHEIM, H., THURAU, K., BOUCHER, R. and GENEST, J. On the intrarenal role of the renin-angiotensin system. In: Control of renin secretion, ed. by Assaykeen, T. A., Plenum Press, New York, 1972.
GRANT, H. and REISCHMAN, F. The effects on the ingestion of large amounts of sodium chloride on the arterial and venous pressures of normal subjects. Amer. Heart J. 32: 704, 1946.
GREISMAN, S. E. The reactivity of the capillary bed of the nailfold to circulating epinephrine and norepinephrine in patients with normal blood pressure and with essential hypertension. J. Clin. Invest. 31: 782, 1952.

GRIBBIN, B., PICKERING, T. G., SLEIGHT, P. and PETO, R. Effect of age and high blood pressure on baroreflex sensitivity in man. Circ. Res. 29: 424, 1971.
GRIFFITHS, W. J. and COLLINSON, S. Estimation of noradrenaline in urnine in normal and hypertensive subjects. J. Clin. Pathol. 10: 120, 1957.
GROLLMAN, A. and SHAPIRO, A. D. The volume of the extracellular fluid in experimental and human hypertension. J. Clin. Invest. 32: 312, 1953.
GROLLMAN, A. The spontaneous hypertensive rat: an experimental analogue of essential hypertension in the human being. In: Spontaneous hypertension, ed. by Okamoto, K., Igaku Shoin, Tokyo, 1972.
GROSS, F., BRUNNER, H. and ZIEGLER, M. Renin-angiotensin system, aldosterone, and sodium balance. Recent Prog. Horm. Res. 21: 119, 1965.
GROSS, F. Beta-adrenergic blockade, blood pressure and the renin-angiotensin system. Eur. J. Clin. Invest. 7: 321, 1977.
deGUIA, D., MENDLOWITZ, M., VLACHAKIS, N. D. and GITLOW, S. E. Urinary tritium excretion after administration of tritium-labeled epinephrine (HE) to normotensive and essential hypertensive subjects. Clin. Res. 21: 947, 1973.
GUNNELS, J. S., GRIM, C. E., ROBINSON, R. R. and WILDERMAN, N. M. Plasma renin activity in healthy subjects and patients with hypertension. Arch. Int. Med. 119: 232, 1967.
GUTHRIE, G. P. Jr., GENEST, J., NOWACZYNSKI, W., BOUCHER, R. and KUCHEL, O. Dissociation of plasma renin activity and aldosterone in essential hypertension. J. Clin. Endocrinol. Metab. 43: 446, 1976.
GUTMAN, F. D., TAGAWA, H., HABER, E. and BARGER, A. C. Renal arterial pressure, renin secretion and blood pressure control in trained dogs. Amer. J. Physiol. 224: 66, 1973.
GUYTON, A. C. Circulatory physiology: cardiac output and its regulation. W. B. Saunders, Philadelphia, 1963.
GUYTON, A. C. and COLEMAN, T. G. Quantitative analysis of the pathophysiology of hypertension. Circ. Res. 24/25 (suppl. 1): 1, 1969.
GUYTON, A. C., COLEMAN, T. G., BOWER, J. D. and GRANGER, H. J. Criculatory control in hypertension. Circ. Res. 26/27 (suppl. 2): 135, 1970.
GUYTON, A. C., GRANGER, H. J. and COLEMAN, T. G. Autoregulation of the total systemic circulation and its relation to control of cardiac output and arterial pressure. Circ. Res. 28/29 (suppl. 1): 93, 1971.
GUYTON, A. C., COLEMAN, T. G., COWLEY, A. W., SCHEEL, K. W., MANNING, R. D. and NORMAN, R. A. Arterial pressure regulation. Overriding dominance of the kidneys in long-term regulation and in hypertension. In: Hypertension Manual, ed. by Laragh, J. H., Yorke Med. Books, Dun-Donnelley Publ. Corp., New York, 1974[a].
GUYTON, A. C., COLEMAN, T. G., COWLEY, A. W., MANNING, R. D., NORMAN, R. A. and FERGUSON, J. D. A systems analysis approach to understanding long-range arterial blood pressure control and hypertension. Circ. Res. 35: 159, 1974[b].
HÄGGENDAL, J. Regulation of catecholamine release. In: Frontiers in catecholamine research, ed. by Usdin, E. and Snyder, S. H., Pergamon Press, New York, 1973.
HAMILTON, M., PICKERING, G. W., ROBERTS, J. A. F. and SOWRY, G. S. C. The aetiology of essential hypertension. I The arterial pressure in the general population. Clin. Sci. 13: 11, 1954.
HAMILTON, W. F., MOORE, J. W., KINSMAN, J. M. and SPURLING, R. G. Studies on the circulation. IV. Further analysis of the injection method and of changes in hemodynamics under physiological and pathological conditions. Amer. J. Physiol. 99: 534, 1932.
HANSEN, J. Blood volume and exchangeable sodium in essential hypertension. Acta Med. Scand. 184: 517, 1968.
HANSSON, L., ZWEIFLER, A. J., JULIUS, S. and ELLIS, C. N. Propranolol therapy in essential hypertension. Observations on predictability of therapeutic response. Int. J. Clin. Pharmacol. 10: 79, 1974.
HARRIS, R. C. and AYERS, C. R. Renal hemodynamics and plasma renin activity after renal artery constriction in conscious dogs. Circ. Res. 31: 520, 1972.
HATA, S., KUNITA, H. and OKAMOTO, M., Aldosterone response to hypoglycemia: evidence of ACTH mediation. J. Clin. Endocrinol. Metab. 43: 173, 1976.
HAYASAKA, E. On the minute volume of the heart in hypertension. Tohoku J. exp. Med. 9: 401, 1927.

HAYDUK, K., KRAUSE, D. K., KAUFMANN, W., HUENGES, R., SCHILLMÖLLER, U. and UNBEHAUN, V. Age-dependent changes of plasma renin concentration in humans. Clin. Sci. Mol. Med. 45 (suppl. 1): 273s, 1973.

HAYES, A. and COOPER, R. G. Studies on the absorption distribution and excretion of propranolol in rat, dog and monkey. J. Pharmacol. Exp. Ther. 176: 302, 1971.

HEIDLAND, A., KLÜTSCH, K., SCHNEIDER, K. W. and PIPPIG, L. Nierenhämodynamik bei kompensierten und plusdekompensierten essentieller Hypertonie. Klin. Wschr. 40: 1003, 1962.

HEJL, Z. Changes in cardiac output and peripheral resistance during simple stimuli influencing blood pressure. Cardiologia 31: 375, 1957.

HELBER, A., MEURER, K. A., WAMBACH, G. and KAUFMANN, W. Aldosterone exkretion von Patienten mit essentieller Hypertonie unter Natrium-Entzug und Natrium-Belastung. In: Hypertension-Current Problems, ed. by Distler, A. and Wolff, H. P., Georg Thieme, Stuttgart, 1974.

HELMER, O. M. Renin activity in blood from patients with hypertension. Canad. Med. Ass. J. 90: 221, 1964.

HELMER, O. M. Renin-angiotensin system and its relation to hypertension. Prog. Cardiovasc. Dis. 8: 117, 1965.

HELMER, O. M. and JUDSON, W. E. Metabolic studies on hypertensive patients with suppressed plasma renin activity not due to hyperaldosteronism. Circulation 38: 965, 1968.

HENRY, D. P., STARMAN, B. J., JOHNSON, D. G. and WILLIAMS, R. H. A sensitive radioenzymatic assay for norepinephrine in tissues and plasma. Life Sci. 16: 375, 1975.

HERMSMEYER, K. Electrogenesis of increased norepinephrine sensitivity of arterial vascular muscle in hypertension, Circ. Res. 38: 362, 1976.

HESSE, B. and NIELSEN, I. Suppression of plasma renin activity by intravenous infusion of antidiuretic hormone in man. Clin. Sci. Mol. Med. 52: 357, 1977.

HILDEN, T. Diodrast clearance in essential hypertension. Acta Med. Scand. Suppl. 206: 242, 1948.

HIMATHONGKAM, T., DLUHY, R. G. and WILLIAMS, G. H. Potassium-aldosterone-renin interrelationships. J. Clin. Endocrinol. Metab. 41: 153, 1975.

HOLLANDER, P., CHOBANIAN, A. V. and BURROWS, B. A. Body fluid and electrolyte composition in arterial hypertension: I. Studies in essential, renal and malignant hypertension. J. Clin. Invest. 40: 408, 1961.

HOLLENBERG, N. K., ROSEN, S. M. O'CONNOR, J. F., POTCHEN, E. J., BASCH, R., DEALY, J. B. and MERRILL, J. P. Effect of aortography on renal hemodynamics in normal man. Invest. Radiol. 3: 92, 1968.

HOLLENBERG, N. K., EPSTEIN, M., BASCH, R. I. and MERRILL, J. P. "No man's land" of the renal vasculature. An arteriographic and hemodynamic assessment of the interlobar and arcuate arteries in essential and accelerated hypertension. Amer. J. Med. 47: 845, 1969[a].

HOLLENBERG, N. K., EPSTEIN, M., BASCH, R. I., COUGH, N. P., HICKLER, R. B. and MERRILL, J. P. Renin secretion in essential and accelerated hypertension. Amer. J. Med. 47: 855, 1969[b].

HOLLENBERG, N. K., EPSTEIN, M., BASCH, R. I., MERRILL, J. P. and HICKLER, R. B. Renin secretion in the patient with hypertension. Relationship to intrarenal blood flow distribution. Circ. Res. 24/25 (suppl. 1): 113, 1969[c].

HOLLENBERG, N. K., EPSTEIN, M., CUTTMAN, R. D., BASCH, R. I. and MERRILL, J. P. Effect of sodium balance on intrarenal distribution of blood flow in normal man. J. Appl. Physiol. 28: 312, 1970.

HOLLENBERG, N. K. In: Progress in Nuclear Medicine, vol. 2; ed. by Blaufox, M. D., Karger Basel and University Press, Baltimore, 1972.

HOLLENBERG, N. K., SOLOMON, H. S., ADAMS, D. F., ABRAMS, H. L. and MERRILL, J. P. Renal vascular responses to angiotensin and norepinephrine in normal man: effect of sodium intake. Circ. Res. 31: 750, 1972.

HOLLENBERG, N. K., ADAMS, D. F., MENDELL, P., ABRAMS, H. L. and MERRILL, J. P. Renal vascular responses to dopamine: haemodynamic and angiographic observations in normal man. Clin. Sci. Mol. Med. 45: 733, 1973.

HOLLENBERG, N. K., ADAMS, D. F., SOLOMON, H. S., RASHID, A., ABRAMS, H. L. and MERRILL, J. P. Senescence and the renal vasculature in normal man. Circ. Res. 34: 309, 1974[a].

HOLLENBERG, N. K., CHENITZ, W. R., ADAMS, D. F. and WILLIAMS, G. H. Salt intake exerts a reciprocal influence on adrenal glomerulosa and renal vascular responses to angiotensin II in normal man. J. Clin. Invest. 54: 34, 1974[b].

HOLLENBERG, N. K., ADAMS, D. F., SOLOMON, H., CHENITZ, W. R., BURGER, B. M., ABRAMS, H. L. and MERRILL, J. P. Renal vascular tone in essential and secondary hypertension. Medicine 54: 29, 1975.

HOLLENBERG, N. K. and ADAMS, D. F. The renal circulation in hypertensive disease. Amer. J. Med. 60: 773, 1976.

HOLLENBERG, N. K., MANGEL, R. and FUNG, H. Y. M. Assessment of intrerenal perfusion with radioxenon: a critical review of analytical factors and their implications in man. Sem. Nucl. Med. 6: 193, 1976.

HOOBLER, S. W., AGREST, A. and WARZYNSKI, R. J. Biochemical determination of blood and urine catecholamines as a measure of sympathoadrenal activity in hypertension. J. Clin. Invest. 33: 943, 1954.

HORSTER, M. and THURAU, K. Micropuncture studies on the filtration rate of single superficial and juxtamedullary glomeruli in the rat kidney. Pflügers Arch. 301: 162, 1968.

HORTNAGL, H., WINKLER, H. and LOCHS, H. Membrane proteins of chromaffin granules. Dopamine-beta-hydroxylase, a major constituent. Biochem. J. 129: 187, 1972.

HORWITZ, D., ALEXANDRE, R. W., LOVENBERG, W. and KEISER, H. R. Human serum dopamine-beta-hydroxylase: relationship to hypertension and sympathetic activity. Circ. Res. 32: 594, 1973.

HOSAIN, F. and WAGNER, H. N. Jr. Measurement of extracellular fluid volume with ^{169}Yb-diethylenetriaminepentaacetate. J. Lab. Clin. Med. 77: 699, 1971.

HOUWEN, B., DONKER, A. M. J., WOLDING, M. G., BEEKHUIS, H., VAN ZANTEN, A. K., LOOYE, A. and VAN DER HEM, G. K. Simultaneous determination of glomerular filtration rate with ^{125}I-iothalamate and effective renal plasma flow with ^{131}I-hippuran. Symposium on dynamic studies with radioisotopes in clinical medicine and research. Rotterdam, 1970.

HOWE, C. T. and EKINS, R. P. The bromide space after the intravenous administration of ^{82}Brit. J. Nucl. Med. 4: 469, 1963.

HOWE, R. and SHANKS, R. G. Optical isomers of propranolol. Nature 210: 1336, 1966.

HUGGINS, R. A., SMITH, E. L. and DEAVERS, S. Volume distribution of Evans blue dye and iodinated albumin in the dog. Amer. J. Physiol. 205: 351, 1963.

HUGHES, J. and ROTH, R. H. Evidence that angiotensin enhances transmitter release during sympathetic nerve stimulation. Brit. J. Pharmacol. 41: 239, 1971.

HUTCHINS, P. A. and DARNELL, A. E. Observation of a decreased number of small arterioles in spontaneously hypertensive rats. Circulation 34/35 (suppl. 1): 161, 1974.

IBRAHIM, M. M, TARAZI, R. C., DUSTAN, H. P., BRAVO, E. L. and GIFFORD, R. W., Hyperkinetic heart in severe hypertension: a separate clinical hemodynamic entity. Amer. J. Card. 35: 667, 1975.

IBSEN, H. and LETH, A. Plasma volume and extracellular fluid volume in essential hypertension. Acta med. Scand. 194: 93, 1973.

IBSEN, H. and SEDERBERG-OLSEN, P. Changes in glomerular filtration rate during long term treatment with propranolol in patients with arterial hypertension. Clin. Sci. 44: 129, 1973.

INNES, I. R. and NICKERSON, M. Drugs acting on postganglionic adrenergic nerve endings and structures innervated by them (sympathomimetic drugs). In: The pharmacological basis of therapeutics. Ed. by Goodman, L. S. and Gilman, A., McMillan Company, London, 1970.

INTERNATIONAL COMMISSION ON RADIOLOGY PROTECTION (ICRP). Protection of the patient in radionuclide investigations. Radiation protection ICRP publication 17, Pergamon Press, Oxford, 1971.

ICSH: Standard techniques for the measurement of red-cell and plasma volume. Brit. J. Haematol. 25: 801, 1973.

IKOMA, T. Studies on catechols with reference to hypertension. Jap. Clin. J. 29: 1269, 1965.

IVERSEN, L. L. The uptake and storage of noradrenaline in sympathetic nerves. Cambridge University Press, London, 1967.

IVERSEN, L. L. Catecholamine uptake processes. Brit. Med. Bull. 29: 130, 1973.

IVERSEN, L. L. Dopamine receptors in the brain: a dopamine-sensitive adenylate cyclase models synaptic receptors, illuminating antipsychotic drug action. Science 188: 1084, 1975.
JAGO, R. H. Inconstancy of renal extraction of Hippuran with changing plasma concentration. Amer. J. Physiol. 224: 1180, 1973.
JAMISON, R. L. Intrarenal heterogeneity. The case for two functionally dissimilar populations of nephrons in the mammalian kidney. Amer. J. Med. 54: 281, 1973.
JIANG, N. S., STOFFER, S. S. and PIKLER, G. M. Laboratory and clinical observations with a two-column plasma catecholamine assay. Mayo Clinic Proc. 48: 47, 1973.
JOHNS, E. J., RICHARDS, H. K. and SINGER, B. Effects of adrenaline, noradrenaline, isoprenaline and salbutamol on the production and release of renin by isolated renal cortical cells of the cat. Brit. J. Pharmacol. 53: 67, 1975.
JOHNSON, J. A., DAVIS, J. O. and WITTY, R. T. Effects of catecholamines and renal nerve stimulation on renin release in the nonfiltering kidney. Circ. Res. 29: 646, 1971.
JOHNSON, J. A., DAVIS, J. O., GOTSHALL, R. W., LOHMEIER, T. E., DAVIS, J. L., BRAVERMAN, B. and TEMPEL, G. E. Evidence for an intrarenal beta-receptor in control of renin release. Amer. J. Physiol. 230: 410, 1076.
JONES, A. W. Altered ion transport in vascular smooth muscle from spontaneously hypertensive rats; influences of aldosterone, norepinephrine and angiotensin. Circ. Res. 33: 563, 1973.
JONES, A. W. Reactivity of ion fluxes in rat aorta during hypertension and circulatory control. Fed. Proc. 33: 133, 1974.
JONES, N. F., CLAPHAM, W. F., BARRACLOUGH, M. A. and MILLS, I. H. Blood volume total body water and aldosterone excretion in essential hypertension. Clin. Sci. 26: 307, 1964.
JOSE, A. and KAPLAN, N. M. Plasma renin activity in the diagnosis of primary hyperaldosteronism. Arch. Int. Med. 123: 141, 1969.
JOSE, A., CROUT, J. R. and KAPLAN, N. M. Suppressed plasma renin activity in essential hypertension. Ann. Int. Med. 72: 9, 1970.
JUDY, W. V., LANGLEY, F. M, McCOWEN, K. D., STINNETT, D. M., BAKER, L. E. and JOHNSON, P. C. Comparative evaluation of the thoracic impedance and isotope dilution methods for measuring cardiac output. Aerospace Med. 40: 532, 1969.
JULIUS, S. and SCHORK, M. A. Borderline hypertension – a critical review. J. Chron. Dis. 23: 723, 1971.
JULIUS, S., PASCUAL, A. V., SANNERSTEDT, R. and MITCHELL, C. Relationship between cardiac output and peripheral resistance in borderline hypertension. Circulation 43: 382, 1971[a].
JULIUS, S., PASCUAL, A. V. and LONDON, R. Role of parasympathetic inhibition in the hyperkinetic type of borderline hypertension. Circulation 44: 413, 1971[b].
JULIUS, S., PASCUAL, A. V., REILLY, K. and LONDON, R. Abnormalities of plasma volume in borderline hypertension. Arch. Int. Med. 127: 116, 1971[c].
JULIUS, S., RANDALL, O. S., ESLER, M. D., KAHIMA, T., ELLIS, C. N. and BENNETT, J. Altered cardiac responsiveness and regulation in the normal cardiac output type of borderline hypertension. Circ. Res. 36/37 (suppl. 1): 199, 1975[a].
JULIUS, S., ESLER, M. D. and RANDALL, O. S. Role of the autonomic nervous system in mild human hypertension. Clin. Sci. Mol. Med. 48 (suppl. 2): 243s, 1975[b].
KAHN, H. A., MEDALIE, J. H., NEUFELD, H. N., RISS, E. and GOLDBOURT, U. The incidence of hypertension and associated factors: the Israel ischemic heart disease study. Amer. Heart J. 84: 171, 1972.
KALOYANIDES, G. J., BASTRON, R. D. and diBONA, G. F. Effect of ureteral clamping and increased renal arterial pressure on renin release. Amer. J. Physiol. 225: 95, 1973.
KALSNER, S. Steroid potentation of responses to sympathomimetic amines in aortic strips. Brit. J. Pharmacol. 36: 582, 1964.
KANEKO, Y., TAKEDA, T., NAKIJAMA, K. and UEDA, H. Effect of angiotensin on the pressor response to tyramine in normotensive subjects and hypertensive patients. Circ. Res. 19: 673, 1966.
KAPLAN, N. M and SILAH, J. G. The effects of angiotensin II on the blood pressure in humans with hypertensive disease. J. Clin. Invest. 43: 659, 1964.
KASS, E. H. and ZINNER, S. H. How early can the tendency towards hypertension be detected? Milbank Mem. Fund Q. 47: 143, 1969.

KATZ, F. H., ROMFH, P. and SMITH, J. A. Diurnal variations of plasma aldosterone, cortisol and renin activity in supine man. J. Clin. Endocrinol. Metab. 40: 125, 1975.
KAZAMIAS, T. M., GANDER, M. P., FRANKLIN, D. L. and ROSS, J. Jr. Blood pressure measurement with Doppler ultrasonic flowmeter. J. Appl. Physiol. 30: 585, 1971.
KEIM, H. J., WALLACE, J. M., THURSTON, H., CASE, D. B., DRAYER, J. I. M. and LARAGH, J. H. Impedence cardiography for determination of stroke index. J. Appl. Physiol. 41: 797, 1976.
KEM, D. C., WEINBERGER, C. G., SANCHEZ, N. J., LERMAN, R., FURUYAMA, S. and NUGENT, C. A. Circadian rhythm of plasma aldosterone concentration in patients with primary aldosteronism. J. Clin. Invest. 52: 2272, 1973.
KEM, D. C., GOMEZ-SANCHEZ, C., KRAMER, N. J., HOLLAND, O. B. and HIGGINS, J. R. Plasma aldosterone and renin activity response to ACTH infusion in dexamethasone-suppressed normal and sodium-depleted man. J. Clin. Endocrinol. Metab. 40: 116, 1975.
KETY, S. S. The theory and applications of the exchange of inert gas at the lungs and tissues. Pharmacol. Rev. 3: 1, 1951.
KEW, M. C., BRUNT, P. W., VARMA, R. R., HOURIGAN, K. J., WILLIAMS, M. S. and SHERLOCK, S. Renal and intrarenal blood flow in cirrhosis of the liver. Lancet II: 504, 1971.
KHAIRLALLAH, P. A. Action of angiotensin on adrenergic nerve endings: inhibition of norepinephrine uptake. Fed. Proc. 31: 1351, 1972.
KHOKHAR, A. M., SLATER, J. D. H., FORSLING, M. L. and PAYNE, N. N. Effect of vasopressin on plasma volume and renin release in man. Clin. Sci. Mol. Med. 50: 415, 1976[a].
KOHKHAR, A. M., SLATER, J. D. H., JOWETT, T. P. and PAYNE, N. N. Suppression of the renin-aldosterone system in mild essential hypertension. Clin. Sci. Mol. Med. 50: 269, 1976[b].
KILCOYNE, M. M., SCHMIDT, D. H. and CANNON, P. J. Intrarenal blood flow in congestive heart failure. Circulation 47: 786, 1973.
KIMURA, T. An epidemiological study of hypertension. Clin. Sci. Mol. Med. 45 (suppl. 1): 103, 1973.
KINOSHITA, M., HOLMAN, B. L., ZIMMERMAN, R. E., ADAMS, D. F., ADELSTEIN, S. J. and HOLLENBERG, N. K. Regional intrarenal perfusion in man an assessment with the scintillation camera. J. Nucl. Med. 15: 775, 1974.
KIOSCHOS, J. M., KIRKENDALL, W. M., VALENCA, M. R. and FITZ, A. E. Unilateral renal hemodynamics and characteristics of dye-dilution curves in patients with essential hypertension and renal disease. Circulation 35: 229, 1967.
KIRPEKAR, S. M. and PUIG, M. Effect of flow-stop on noradrenaline release from normal spleens and spleens treated with cocaine, phentolamine of phenoxybenzamin. Brit. J. Pharmacol 43: 359, 1971.
KIRPEKAR, M., FURCHGOTT, R. F., WAKADE, A. R. and PRAT, J. C. Inhibition by sympathomimetic amines of the release of norepinephrine evoked by nerve stimultation in the cat spleen. J. Pharmacol. Exp. Ther. 187: 529, 1973.
KIRSHNER, N. Pathway of noradrenaline formation from dopa. J. Biol. Chem. 226: 821, 1957.
KISCH, E. A., DLUHY, R. G. and WILLIAMS, G. H. Regulation of renin release by calcium and ammonium ions in normal man. J. Clin. Endocrinol. Metab. 43: 1343, 1976.
KLAUS, D., KLUMPP, F. and ZEHNER, J. Suppressed plasma renin in advanced primary hypertension. In: Hypertension Current Problems.Ed. by Distler, A. and Wolff, H. P. Georg Thieme, Stuttgart 1974.
KLOPPENBORG, P. W. C., DRAYER, J. I. M., BENRAAD, H. B. and BENRAAD, Th. J. Normal aldosterone versus supra-normal aldosterone hypertension: an alternative to normal versus low-renin hypertension. In: Hypertension current Problems. Ed. by Distler, A. and Wolff, H. P. Georg Thieme, Stuttgart, 1974.
KLÜTSCH, K., HEIDLAND, A. und ÖBEK, A. Altersabhängigkeit der Nierenhämodynamik. Klin. Wschr. 40: 1002, 1962.
KNOX, F. G., CUCHE, Ph. D., OTT, C. E., DIAZ-BUXO, J. A. and MARCHAND, G. Regulation of glomerular filtration and proximal tubule reabsorption. Circ. Res.: 36, 37 (suppl. 1): 107, 1975.

KOLSTERS, G., SCHALEKAMP, M. A. D. H., BIRKENHÄGER, W. H. and LEVER, A. F. Renin and renal function in benign essential hypertension: evidence for a renal abnormality. In: Pathophysiology and management of arterial hypertension. Ed. by Berglund, G., Hansson, L. and Werkö, L., Lindgren and Söner AB, Möhndal, 1975.

KOLSTERS, G. De bloedsomloop door de nieren bij essentiële hypertensie. Thesis, Rotterdam, 1976.

KOPIN, I. J., KAUFMAN, S., VIVEROS, H., JACOBOWITZ, D., LAKE, R., ZIEGLER, M. G., LOVENBERG, W. and GOODWIN, F. K. Dopamine-beta-hydroxylase. Ann. Int. Med. 85: 211, 1976.

KORNER, P. I., SHAW, J., UTHER, J. B., WEST, J. J., McRITCHIE, R. J. and RICHARDS, J. G. Autonomic and non-automatic circulatory components in essential hypertension in man. Circulation 48: 107, 1973.

KORNER, P. I., WEST, M. J., SHAW, J. and UTHER, J. B. "Steadystate" properties of the baroreceptor-heart rate reflex in essential hypertension in man. Clin. Exp. Pharmacol. Physiol. 1: 65, 1974.

KOTCHEN, T. A., MULROW, P. J., MORROW, L. B., SHUTKIN, P. M. and MARIEB, N. Renin and aldosterone in essential hypertension. Clin. Sci. 41: 321, 1971.

KOTCHEN, T. A., MAULL, K. I., LUKE, R., REES, D. and FLAMENBAUM, W. Effect of acute and chronic calcium administration on plasma renin. J. Clin. Invest. 54: 1279, 1974.

KOTCHEN, T. A., GALLA, J. H. and LUKE, R. G. Effects of calcium on renin and aldosterone in the rat. Amer. J. Physiol. 232 (4): E 388, 1977.

KRAKOFF, L. R., GOODWIN, F. J., BAER, L., TORRES, M. and LARAGH, J. H. The role of renin in the exaggerated natriuresis of hypertension. Circulation 42: 335, 1970.

KRAMER, K., THURAU, K. and DEETJEN, P. Hämodynamik des Nierenmarks. I. Mitteilung, Capilläre Passagezeit, Blutvolumen, Durchblutung, Gewebshämatokrit und O_2-Verbrauch des Nierenmarks in situ. Pfluegers Arch. Ges. Physiol. 270: 251, 1960.

KUBICHEK, W. G., KARNEGIS, J. N., PATTERSON, R. P., WITSOE, D. A. and MATSON, R. H. Development and evaluation of an impedance cardiac output system. Aerospace Med. 37: 1208, 1966.

KUCHEL, O., FISHMAN, L. M., LIDDLE, G. W. and MICHELAKIS, A. Effect of diazoxide on plasma renin activity in hypertensive patients. Ann. Int. Med. 76: 791, 1967.

KUCHEL, O., CUCHE, J. L., BUU, N. T. and GENEST, J. An increase in urinary catecholamines of renal origin in patients with "borderline" hypertension. Amer. J. Med. Sci. 272: 263, 1976.

KUCHEL, O. Autonomic nervous system in hypertension: clinical aspects. In: Hypertension – physiopathology and treatment. Ed. by Genest, J., Koiw, E. and Kuchel, O. McGraw-Hill Book Company, New York. 1977.

KURAMOTO, K., MURATA, K., YAZAKI, Y., IKEDA, M. and NAKAO, K. Hemodynamics in the juvenile hypertension with special reference to the response to propranolol. Jap. Circ. J. 32: 981, 1968.

KUSCHKE, H. J. Research on the excitation status of the sympathetic nervous system and adrenal medulla in cardiovascular diseases. Arch. Kreislaufforschr. 36: 104, 1961.

KUSCHKE, H. J.

KVETNANSKY, R., GEWIRTZ, G. P., WEISE, V. K. Enhanced synthesis of adrenal dopamine-beta-hydroxylase induced by repeated immobilization in rats. Mol. Pharmacol. 7: 81, 1971.

LABABIDI, A., EHMKE, D. A., DURNIN, R. E., LEAVERTON, P. E. and LAVER, R. M. Evaluation of impedance cardiac output in children. Pediatrics 47: 870, 1971.

LADEFOGED, J. and KEMP, E. A new method for measurement of divided renal blood flow in man by use of radio-active inert gas. Proc. Intern. Congr. of Nephrol., 1963.

LADEFOGED, J. Measurement of the renal blood flow in man with the ^{133}Xenon washout-technique; a description of the method. Scand. J. Clin. Lab. Invest. 18: 299, 1966.

LADEFOGED, J. Renal circulation in Hypertension. Munskgaard, Copenhagen, 1968.

LADEFOGED, J. and PEDERSEN, F. Renal blood flow in patients with hypertension. Clin. Sci. 37: 253, 1969.

LADEGAARD-PEDERSEN, J. J. Measurement of extracellular volume and renal clearance by a single injection of inulin. Scand. J. Clin. Lab. Invest. 29: 145, 1972.

LaGRANGE, R. G., SLOOP, C. H. and SCHMID, H. E. Selective stimulation of renal nerves in the anesthetized dog. Effect on renin release during controlled changes in renal hemodynamics. Circ. Res. 33: 704, 1973.

LAKE, C. R., ZIEGLER, M. G. and KOPIN, I. J. Use of plasma norepinephrine for evaluation of sympathetic neuronal function in man. Life Sci. 18: 1315, 1976.

LAKE, C. R., ZIEGLER, M. G., COLEMAN, M. and KOPIN, I. J. Lack of correlation of plasma norepinephrine and dopamine-beta-hydroxylase in hypertensive and normotensive subjects. Circ. Res. 41: 865, 1977[a].

LAKE, C. R., ZIEGLER, M. G., COLEMAN, M. D. and KOPIN, I. J. Age-adjusted plasma norepinephrine levels are similar in normotensive and hypertensive subjects. New Engl. J. Med. 296: 208, 1977[b].

LAMPRECHT, F., WYATT, R. J., BELMAKER, R. Plasma dopamine-beta-hydroxylase in indentical twins discordant for schizophrenia. In: Frontiers in Catecholamine Research. Ed. by Usdin, E. and Snyder, S. H. New York, Pergamon Press, 1973.

LAMPRECHT, F., ANDRES, R. and KOPIN, I. J. Plasma dopamine-beta-hydroxylase: constance of levels in normotensive adults and decreases with development of blood pressure elevation. Life Sci. 17: 749, 1975.

LANDS, A. M., ARNOLD, A., McAULIFF, J. P., LUDUENA, F. P. and BROWN, T. G. Differentiation of receptor systems activated by sympathomimetic amines. Nature 214: 597, 1967.

LANGAN, T. A. Proteinkinases and protein kinase subtrates. In: Advances in cyclic nucleotide research. Ed. by Drummond, G. I., Greengard, P. and Robinson, G. A. New York, Raven Press, 1975.

LANGER, S. Z. The regulation of transmitter release elicited by nerve stimulation through a presynaptic feed-back mechanism. In: Frontiers in catecholamine research. Ed. by Usdin, E. and Snyder, S. H. Pergamon Press, New York, Toronto, Oxford, Sydney, Braunschweig, 1973.

LANGER, S. Z. Presynaptic regulation of catecholamine release. Biochem. Pharmacol. 23: 1793, 1974.

LARAGH, J. G., ULICK, S., JANUSZEWICZ, V., DEMING, Q. B., KELLY, W. G. and LIEBERMAN, S. Aldosterone secretion in primary and malignant hypertension. J. Clin. Invest. 39: 1091, 1960[a].

LARAGH, J. H., ANGERS, M., KELLEY, W. G. and LIEBERMAN, S. Hypotensive agents and pressor substances. The effect of epinephrine, norepinephrine, angiotensin II and others on the secretory rate of aldosterone in man. J.A.M.A. 174: 234, 1960[b].

LARAGH, J. H., SEALEY, J. E. and SOMMERS, S. C. Patterns of adrenal secretion and urinary excretion of aldosterone and plasma renin activity in normal and hypertensive subjects. Circ. Res. 19, Suppl. 1:158, 1966.

LARAGH, J. H., BAER, L. H., BRUNNER, H. R., BÜHLER, F. R., SEALEY, J. E. and VAUGHAN, E. D. Jr. Renin, angiotensin and aldosteron in pathogenesis and management of hypertensive vascular disease. Amer. J. Med. 52, 631, 1972[a].

LARAGH, J. H., SEALEY, J. E. and BRUNNER, H. R. The control of aldosterone secretion in normal and hypertensive man: abnormal renin-aldosterone patterns in low-renin hypertension. Amer. J. Med. 53: 649, 1972[b].

LARAGH, J. H. Vasoconstriction – volume analysis for understanding and treating hypertension: the use of renin and aldosterone profiles. Amer. J. Med. 55: 261, 1973.

LAUTER, S. und BAUMANN, H. Über den Kreislauf bei Hochdruck, Arteriosklerose und Apoplexie. Z. Klin. Med. 109: 415, 1928.

LEBEL, M., SCHALEKAMP, M. A. D. H., BEEVERS, D. C., BROWN, J. J., DAVIES, D. L., FRASER, R., KREMER, D., LEVER, A. F., MORTON, J. J., ROBERTSON, J. I. S., TREE, M. and WILSON, A. Sodium and the renin-angiotensin system in essential hypertension and mineralocorticoid excess. Lancet II: 308, 1974.

LECKIE, B. The activation of a possible zymogen of renin in rabbit kidney. Clin. Sci. 44: 301, 1973.

LECKIE, B. J. and McCONNELL, A. A renin inhibitor from rabbit kidney. Circ. Res. 36: 513, 1975.

LECKIE, B., LEVER, A. F., MORTON, J. J., BROWN, J. J., McCONNELL, A., ROBERTSON, J. I. S. and TREE, M. Inactive renin in human plasma. Lancet II: 748, 1976.

LEDINGHAM, J. M. and COHEN, R. D. The role of the heart in the pathogenesis of renal hypertension. Lancet II: 979, 1973.

LEDINGHAM, J. M. and COHEN, R. D. Changes in extracellular fluid volume and cardiac output during the development of experimental renal hypertension. Canad. Med. Ass. J. 90: 292, 1964.

LEDINGHAM, J. G. G., BULL, M. G. and LARAGH, J. H. The meaning of aldosteronism in hypertensive disease. Circ. Res. 20 and 21, suppl. 2: 177, 1967.

LEE, T. D., LINDEMAN, R. D., YIENGST, M. J. and SHOCK, N. W. Influence of age on the cardiovascular and renal response to tilting. J. Appl. Physiol. 21: 55, 1966.

DE LEEUW, P. W., FALKE, H. E., KHO, T. L., VANDONGEN, R., WESTER, A., and BIRKENHÄGER, W. H. Effects of beta-adrenergic blockade on diurnal variability of blood pressure and plasma noradrenaline levels. Acta Med. Scand. 202: 389, 1977.

DE LEEUW, P. W., KHO, T. L., FALKE, H. E. and BIRKENHÄGER, W. H. Haemodynamic and endocrinological profile of essential hypertension. Acta Med. Scand. Suppl. 1978. In press.

LEON, A. S., THOMAS, P. E., SERNATINGER, E. and CANIAS, A. Serum dopamine-beta-hydroxylase activity as an index of sympathetic activity. J. Clin. Pharmacol. 14: 354, 1974.

LEONETTI, G., MAYER, G., MORGANTI, A.,TERZOLI, L., ZANCHETTI, A., BIANCHETTI, G., SALLE, E. D., MORSELLI, P. and CHIDSEY, C. Hypotensive and renin suppressing activities of propranolol in hypertensive patients. Clin. Sci. Mol. Med. 48: 491, 1975.

LEVIN, N. W. and GOLDBERG, B. Studies in hypertension: I. Extracellular fluid volume (inulin space) in hypertension. S. Afr. J. Med. Sci. 25: 1, 1960.

LEVIN, E. Y., LEVENBERG, B., and KAUFMANS, S. The enzymatic conversion of 3,4-dihydroxyphenylethylamine to norepinephrine. J. Biol. Chem. 235, 1960.

LEVY, R. L., HILLMAN, C. C., STROUD, W. D. and WHITE, P. D. Transient hypertension. J.A.M.A. 126: 829, 1944.

LEVY, R. L., WHITE, P. D., STROUD, W. D. and HILLMAN, C. C. Transient tachycardia. Prognostic significance alone and in association with transient hypertension. J.A.M.A. 129: 585.

Transient hypertension. The relative prognostic importance of various systolic and diastolic levels. J.A.M.A. 128: 1059, 1945.

LEW, G. M. Circadian rhythms in blood pressure and norepinephrine in genetically hypertensive and normotensive rats. Gen. Pharm. 7: 35, 1976.

LEWIS, P. The essential action of propranolol in hypertension. Amer. J. Med. 60: 837, 1976.

LIDDLE, G. W., DUNCAN, L. E. Jr. and BARTTER, F. C. Dual mechanism regulating arenocortical function in man. Amer. J. Med. 21: 380, 1956.

LIDDLE, G. W. and SENNETT, J. A. Steriods and the syndrome of low-renin hypertension. Proceedings of the 4th International Congress on Hormonal Steriods, Mexico City, Abstract S 23,1974.

LILJESTRAND, G. and STENSTRÖM, M. Clinical studies on the work of the heart during rest. III. Blood flow in cases of increased arterial blood pressure with observations on the influence of pregnancy on the blood flow. Acta Med. Scand. 63: 142, 1925.

LJUNDQUIST, A. The intrarenal arterial pattern in essential hypertension. J. Path. Bact. 84: 313, 1962.

LJUNDQUIST, A. The intrarenal arterial pattern in the normal and diseased human kidney; a micro-angiographic and histologic study. Acta Med. Scand., Suppl., 401, 1963.

LOEFFLER, J. R., STOCKIGT, J. R. and GANONG, W. F. Effect of alpha- and beta-adrenergic blocking agents on the increase in renin secretion produced by stimulation of the renal nerves. Neuroendocrinology 10: 129, 1972.

LOGAN, A. G., VELASQUEZ, M. T. and COHN, N. N. Renal cortical blood flow, cortical fraction and cortical blood volume in hypertensive subjects. Ciculation 47: 1306, 1973.

LOMMER, D., DISTLER, A., PHILIPP, T. and WOLFF, H. P. Secretion, distribution and turnover of aldosterone in essential hypertension, primary aldosteronism and hypertension associated with renal artery stenosis. In: Hypertension '72. Ed. by Genest, J. Springer-Verlag, New York 1972.

LORIMER, A. R., McFARLANE, P. W., PROVAN, G., DUFFY, T. and LOWRIE, T. D. Blood pressure and catecholamine responses to "stress" in normotensive and hypertensive subjects. Cardiovasc. Res. 5: 169, 1971.

LORIMER, A. R., BUNN, F. G., JONES, J. V. and LOWRIE, T. D. V. Beta-adrenoceptor blockade in hypertension. Amer. J. Med. 60: 877, 1976.
LOUIS, W. J., DOYLE, A. E. and ANAVEKAR, S. Plasma norepinephrine levels in essential hypertension. New Eng. J. Med. 228: 599, 1973.
LOUIS, W. J., DOYLE, A. E., ANAVEKAR, S. N. and JOHNSTON, C. I. Plasma catecholamine, dopamine beta-hydroxylase and renin levels in hypertension. In: Hypertension – Current Problems. Ed. by A. Distler and H. P. Wolff, Georg Thieme, Stuttgart, 1974[a].
LOUIS, W. J., DOYLE, A. E., ANEVEKAR, S. N., JOHNSTON, C. I., GEFFEN, L. B. and RUSH, R. Plasma catecholamine, dopamine-beta-hydroxylase, and renin levels in essential hypertension. Circ. Res. 34/35 suppl. I:1, 1974[b].
LOWDER, S. C. and LIDDLE, G. W. Prolonged alteration of renin responsiveness after spironolactone therapy. New Eng. J. Med. 291: 1243, 1974.
LOWDER, S. C., FRAZER, M. G. and LIDDLE, G. W. Effect of insulin-induced hypoglycemia upon plasma renin activity in man. J. Clin. Endocrinol. Metab. 41: 97, 1975.
LOWDER, S. C., HAMET, P. and LIDDLE, G. W. Contrasting effects of hypoglycemia on plasma renin activity and cyclic adenosine 3', 5'-monophosphate (cyclic AMP) in low renin and normal renin essential hypertension. Circ. Res. 38: 105, 1976.
LOWENSTEIN, J., BERANBAUM, E. R., CHASIS, H. and BALDWIN, D. S. Intrarenal pressure and exaggerate natriuresis in essential hypertension. Clin. Sci. 38: 359, 1970.
LUCAS, C. P., HOLZWARTH, G. J., OCOBOCK, R. W., SOZEN, T., STERN, M. P., WOOD, P. D. S., HASKELL, W. L. and FARQUHAR, J. W. Disturbed relationship of plasma renin to blood pressure in hypertension. Lancet II: 1337, 1974.
LUETSCHER, J. A., BECKERHOFF, R., DOWDY, A. J. and WILKINSON, R. Incomplete suppression of aldosterone secretion and plasma concentration in hypertensive patients on high sodium intake. In: Hypertension, ed. by Genest, J. and Koiw, E. Springer, Berlin, 1972.
LUMBERS, E. R. Activation of renin in human amniotic fluid by low pH. Enzymologia 40: 329, 1971.
LUND-JOHANSEN, P. Hemodynamics in early essential hypertension. Acta Med. Scand. 181, Suppl. 482, 1967.
LUND-JOHANSEN, P. Hemodynamic alterations in essential hypertension. In: Hypertension: Mechanisms and Management. Proceedings of the 26th Hahnemann Symposium. Ed. by Onesti, G., Kim, K. E. and Moyer, J. H. Grune and Stratton, New York – London, 1973.
LUND-JOHANSEN, P. Hemodynamic trends in untreated essential hypertension. Preliminary report on a 10 year follow-up study. Acta Med. Scand. Suppl. 602, 1976.
LUND-JOHANSEN, P. Central haemodynamics in essential hypertension. Acta Med. Scand. Suppl. 606, 1977.
LYONS, R. H., JACOBSON, S. D. and AVERY, N. L. Increases in the plasma volume following the administration of sodium salts. Amer. J. Med. Sci. 208: 148, 1944.
MADDOX, D. A., DEEN, W. A. and BRENNER, B. M. Dynamics of glomerular ultrafiltration; IV. Studies in the primate. Kidney Intern. 5: 271, 1974.
MALIK, K. U. and NASJLETTI, A. Facilitation of adrenergic transmission by locally generated angiotensin II in rat mesenteric arteries. Circ. Res. 38: 26, 1976.
MALVANO, R., GANDOLFI, C., GIANNESSI, D., GIANOTTI, P. and GROSSO, P. Radioimmunoassay of aldosterone in crude plasma extracts. J. Nucl. Biol. Med. 20: 37, 1976.
MANCIA, G., DONALD, D. E. and SHEPHERD, J. T. Inhibition of adrenergic outflow to peripheral blood vessels by vagal afferents from the cardiopulmonary region in the dog. Circ. Res. 33: 713, 1973.
MANCIA, G. and DONALD, D. E. Demonstration that the atria, ventricles and lungs each are responsible for a tonic inhibition of the vasomotor center in the dog. Circ. Res. 36: 310, 1975.
MANCIA, G., ROMERO, J. C. and SHEPHERD, J. T. Continuous inhibition of renin release in dogs by vagally innervated receptors in the cardiopulmonary region. Circ. Res. 36: 529, 1975.
MANGER, W. M. Observations on plasma catecholamines in patients with diastolic hypertension. Amer. J. Cardiol. 9: 731, 1962.

MARKL A. L., ABBOUD, F. M., SCHMID, P. G., HEISTAD, D. D. and MAYER, H. E. Differences in direct effects of adrenergic stimuli on coronary, cutaneous and muscular vessels. J. Clin. Invest. 51: 279, 1972.

MARK, A. L., LAWTON, W. J., ABBOUD, F. M., FITZ, A. E., CONNOR, W. E. and HEISTAD, D. D. Effects of high and low sodium intake on arterial pressure and forearm vascular resistance in borderline hypertension. A preliminary report. Circ. Res. 36 (suppl. 1): 194, 1975.

MASTER, A. M., DUBLIN, L. I. and MARKS, H. H. The normal blood pressure range and its clinical implications. J.A.M.A. 143: 1464, 1950.

MATHIAS, C. J., SMITH, A. D., FRANKEL, H. L. and SPALDING, J. M. K. Dopamine-beta-hydroxyglase release during hypertension from sympathetic nervous overactivity in man. Cardiovasc. Res. 10: 176, 1976.

McCAA, R. E., McCAA, C. S., READ, D. G., BOWER, J. D. and GUYTON, A. C. Increased plasma aldosterone concentration in response to hemodialysis in nephrectomized man. Circ. Res. 31: 473, 1972.

McCAA, R. E., YOUNG, D. B., GUYTON, A. C. and McCAA, C. S. Evidence for a role of an unidentified pituitary factor in regulating aldosterone secretion during altered sodium balance. Circ. Res. Suppl. 1: 34, 15, 1974.

McCUBBIN, J. W., GREEN, J. H. and PAGE, I. H. Baroreceptor function in chronic renal hypertension. Circ. Res. 4: 205, 1956.

McCUBBIN, J. W. and PAGE, I. H. Renal pressor system and neurogenic control of arterial pressure. Circ. Res. 12: 553, 1963.

MacDONALD, K. M., TAHER, S. and AISENBREY, G. Effect of angiotensin II and an angiotensin II inhibitor on renin secretion in the dog. Amer. J. Physiol. 228: 1562, 1975.

McGREGOR, D. D. Effect of sympathetic nerve stimulation on the vasoconstrictor responses in perfused blood vessels of the rat. J. Physiol. (London) 177: 21, 1965.

McINTOSH, H. D., BURNUM, J. F., HICKAM, J. B. and WARREN, J. V. Circulatory changes produced by the Valsalva maneuver in normal subjects, patients with mitral stenosis and autonomic nervous system alterations. Circulation 9: 511, 1954.

McKENNA, O. C. and ANGELAKOS, E. T. Adrenergic innervaton of the canine kidney. Circ. Res. 22: 345, 1968[a].

McKENNA, O. C. and ANGELAKOS, E. T. Acetylcholinesterase-containing fibers in the canine kidney. Circ. Res. 23: 645, 1968[b].

McRAVEN, D. R., MARK, A. L., ABBOUD, F. M. and MAYER, H. E. Responses of coronary vessels to adrenergic stimuli. J. Clin. Invest. 50: 773, 1971.

MELBY, J. C., DALE, S. L., GREKIN, R. J., GAUNT, R. and WILSON, T. E. 18-hydroxy-11-deoxycorticorterone (18-OH-DOC) secretion in experimental and human hypertension. Recent Progr. Hormone Res., 28, 287, 1972.

MENDELSOHN, F. A. O., JOHNSTON, C. I., DOYLE, A. E., SCOGGINGS, B. A., DENTON, D. A. and COGHLAN, J. P. Renin, angiotensin II and adrenal corticosteriod relationships during sodium deprivation and angiotensin infusion in normotensive and hypertensive man. Circ. Res. 31: 728, 1972.

MENDLOWITZ, M., and NAFTCHI, N. Work of digital vasoconstriction produced by infused norepinephrine in primary hypertension. J. Appl. Physiol. 13: 247, 1958.

MENDLOWITZ, M., WOLF, R. L., GITLOW, S. E. and NAFTCHI, N. Digital vascular reactivity to angiotensin II. Amer. Heart J. 62: 221, 1961.

MENDLOWITZ, M., NAFTCHI, N. E., GITLOW, S. E. and WOLFF, R. E. Vascular responsiveness in hypotensive and hypertensive states. Geriatrics 20: 797, 1965.

MENDLOWITZ, M., NAFTCHI, N. E., TUCKMAN, J., GITLOW, S. E. and WOLF, R. L. The effect of tyramine on the digital circulation in normotensive and hypertensive subjects. Dis. Chest 52: 709, 1967.

MENDLOWITZ, M. and VLACHAKIS, N. D. The catecholamines in essential hypertension. Amer. Heart J. 91: 378, 1976.

MESCHAN, J., SCHMIDT, H. E., WATTS, F. C. and WITCOFSKI, R. The utilization of radioactive iodinated hippuran for determination of renal clearance rates. Radiology 81: 437, 1963.

MESSERLI, F. H., NOWACZYNSKI, W., HONDA, M., GENEST, J. and KUCHEL, O. Effects of ACTH on steroid metabiolism. J. Clin. Endocrinol. Metab. 42: 1074, 1976[a].

MESSERLI, F. H., KUCHEL, O., TOLIS, G., HAMET, P., FRAYSSE, J. and GENEST, J. Plasma cyclic AMP and response to isoproterenol and glucagon in labile (borderline) hypertension. Clin. Res. 23: 197, A, 1975. In extenso: Circ. Res. 38 (suppl. 2) 42, 1976[b].

METCALF, W. The intrinsic method for serial plasma volume determination. J. Lab. Clin. Med. 58: 704, 1961.

MEYER, P., MENARD, J., ALEXANDRE, M. and WEIL, B. Correlations between plasma renin, hematocrit and natriuresis. Rev. Canad. Biol. 25: 111, 1966[a].

MEYER, P., ALEXANDRE, J. M., DEVAUX, C., LEROUX-ROBERT, C. et MILLIEZ, P. Détermination de l'activité rénine plasmatique chez 261 hypertendus. Presse Méd. 40: 2025, 1966[b].

MEYER, P., MENARD, J., PAPANICOLAOU, N., ALEXANDRE, J. M., DEVAUX, C. and MILLIEZ, P. Mechanism of renin release following furosemide diuresis in rabbit. Amer. J. Physiol. 215: 908, 1968.

MIALL, W. E. and CHIN, S. Blood pressure and ageing: results of a fifteen to seventeen year follow-up study in South Wales. Clin. Sci. Mol. Med. 45 (Suppl. I): 23, 1973.

MICHELAKIS, A. M., CAUDLE, J. and LIDDLE, G. W. In vitro stimulation of renin production by epinephrine, norepinephrine, and cyclic AMP. Proc. Soc. Exp. Biol. Med. 130: 748, 1969.

MICHELAKIS, A. M. and HORTON, R. The relationship between plasma renin and aldosterone in normal man. Circ. Res. (Suppl.) 26-27: 1, 1970.

MICHELAKIS, A. M. Effect of angiotensin on renin production and release in vitro. Proc. Soc. Exp. Biol. Med. 138: 1106, 1971.

MICHELAKIS, A. M. and McALLISTER, R. G. The effect of chronic adrenergic receptor blockade on plasma renin activity in man. J. Clin. Endocr. 34: 386, 1972.

MITCHELL, J. R., TAYLOR, A. A., POOL, J. L., LAKE, C. R., ROLLINS, D. E. and BARTTER, C. Renin-aldosterone profiling in hypertension. Ann. Int. Med. 87: 596, 1977.

MOFFAT, S. M. and FOURMAN, J. The vascular pattern of the rat kidney. J. Anat. 97: 543, 1963.

MOGIL, R. A., ITSKOVITZ, H. D., RUSSELL, J. H. and MURPHY, J. J. Renal innervation and renin activity in salt metabolism and hypertension. Am. J. Physiol. 216: 693, 1969.

MÖLLER, J. Die Nierenfunktion beim essentiellen Hochdruk. Die Med. Welt, 12: 609, 1960.

MOLZAHN, M., DISSMAN, T., HALIM, S., LOHMANN, F. W. and OELKERS, W. Orthostatic changes of haemodyhamics, renal function, plasma catecholamines and plasma renin concentration in normal and hypertensive man. Clin. Sci. 42: 209, 1972.

MOORE, R. A. Total number of glomeruli in the normal human kidney. Anat. Rec. 48: 153, 1931.

MORAN, N. C. and PERKINS, M. E. Adrenergic blockade of the mammalian heart by a dichloro analog of isoproterenol. J. Pharmacol. Exp. Ther. 124: 223, 1958.

MORRIS, B. J. and JOHNSTON, C. I. Isolation of renin granules from rat kidney cortex and evidence for an inactive form of renin (pro-renin) in granules and plasma. Endocrinology 98: 1466, 1976.

MOYER, J. H., HEIDER, C., PEVEY, K. and FORD, R. V. The effect of treatment on the vascular deterioration, associated with hypertension, with particular emphasis in renal function. Amer. J. Med. 24: 177, 1958.

MROCZEK, W. J., FINNERTY, F. A. and CATT, K. J. Lack of association between plasma renin and history of heart attack of stroke in patients with essential hypertension. Lancet II: 464, 1973.

MULDER, A. H. Haemodynamische gevolgen van de Valsalva-proef. Een experimenteel onderzoek van intra-arteriële bloeddruk en stroomsterkte bij patiënten met normale en gestoorde bloedsomloop. Thesis, Rotterdam 1972.

MÜLLER, J. and BARAJAS, L. Electron microscopic and histo-chemical evidence for a tubular innervation in the renal cortex in the monkey. J. Ultrastruct. Res. 41: 533, 1972.

MULLER, A. F. and VALLOTON, M. B. Mode d'action et régulation de l'aldostérone. Schweiz. Med. Wschr. 104: 905, 1974.

MURLOW, P. J. Rena, hormones. In: The Kidney. Ed. by Brenner, B. M. and Rector, F. C. W. B. Saunders Company, Philadelphia, London, Toronto. 1976.

NAGATSU, T., HIDAKA, H., KUZUYA, H. Inhibition of dopamine-beta-hydroxylase by fusaric acid (5-butylpicolinic acid) in vitro and in vivo. Biochem. Pharmacol. 19: 35, 1970.

NASH, F. D., ROSTORFER, H. H., BAILIE, M. D., WATHEN, R. L. and SCHNEIDER, E. G. Renin release: relation to renal sodium load and dissociation from hemodynamic changes. Circ. Res. 22: 473, 1968.
NESTEL, P. J. and DOYLE, A. E. The excretion of free noradrenaline and adrenaline by healthy young subjects and by patients with essential hypertension. Aust. Ann. Med. 17: 295, 1968.
NESTEL, P. J. Blood pressure and catecholamine excretion after mental stress in labile hypertension. Lancet I: 692, 1969.
NEWSOME, H. H. and BARTTER, F. C. Plasma renin activity in relation to serum sodium concentration and body fluid balance. J. Clin. Endocr. 28: 1704, 1968.
NEWTON, M. A. and LARAGH, J. H. Effect of corticotropin on aldosterone excretion and plasma renin in normal subjects, in essential hypertension, and in primary aldosteronism. J. Clin. Endocrinol. Metab. 28: 1006, 1968.
NGAI, S. H., DAIRMAN, W., MARCHELLE, M. and SPECTOR, S. Dopamine-beta-hydroxylase in dog lymph – effect of sympathetic activation. Life Sci. 14: 2431, 1974.
NICHOLLS, M. G., ESPINER, E. A. and DONALD, R. A. Aldosterone and renin-angiotensin responses to stimuli in patients with treated congestive heart failure. J. Lab. Clin. Med. June: 1005, 1976.
NIELSEN, I. and MØLLER, I. Simultaneous determination of renin activity and angiotensin concentration levels in human plasma. Acta Med. Scand. 182: 263, 1967.
NIELSEN, I. and MØLLER, I. The relationship between plasma renin activity and hemoconcentration. Acta Med. Scand. 183: 281, 1968'
NIELSEN, I. and JACOBSON, J. Plasma renin activity and aldosterone secretion rate in hypertension. Acta Med. Scand. 187: 401, 1970.
NIES, A. A. and SHAND, A. G. Clinical Pharmacology of propranolol. Circulation 52: 6, 1975.
NISSEN, O. I. The filtration fraction of plasma supplying the superficial and deep venous drainage area of the cat kidney.. Acta Physiol. Scand. 68: 275, 1966.
NISSEN, O. I. Changes in the filtration in the superficial and deep venous drainage area of the cat kidney due to fluid loading. Acta Physiol. Scand. 73: 320, 1968.
NOLLY, H. L., REID, I. A. and GANONG, W. F. Effect of theophylline and adrenergic blocking drugs on the renin response to norepinephrine in vitro. Circ. Res. 35: 575, 1974.
NOMURA, G., KUROSAKI, M., INASAKA, T., TAKABATAKE, T., DOHL, K. and TAKEUCHI, J. Intrarenal blood flow in essential hypertension. Nephron 13: 114, 1974.
NOMURA, G. L., TAKABATAKE, T., ARAI, S., UNO, D., SHOMAO, M., and HATTORI, N. Effect of acute unilateral renal denervation on tubular sodium reabsorption in the dog. Amer. J. Physiol. 232: F16, 1977.
NOSAKA, S. and OKAMOTO, K. Modified characteristics of the aortic baroreceptor in the spontaneously hypertensive rat. Jap. Circ. J. 34: 685, 1970.
NOSAKA, S. and WANG, S. C. Carotid sinus baroreceptor functions in the spontaneously hypertensive rat. Amer. J. Physiol. 222: 1079, 1972.
NOTH, R. H., LASSMAN, M. N., TAN, S. Y., FERNANDEZ-CRUZ, A. and MULROW, P. J. Low plasma renin activity (PRA) in normotensive subjects (abstract). Clin. Res. 23: 199, 1975.
NOTH, R. H. and MULROW, P. J. Serum dopamine-beta-hydroxylase as an index of sympathetic nervous activity in man. Circ. Res. 38: 3, 1976.
NOVAK, L. P., STRONG, C. G. and HUNT, J. C. Body composition in primary and secondary hypertension, in Hypertension '72, edited by Genest, J. and Koiw, E. Springer Verlag, New York, 444, 1972.
NOWACZYNSKI, W., KUCHEL, O. and GENEST, J. A decreased metabolic clearance rate of aldosterone in benign essential hypertension. J. Clin. Invest. 50: 2184, 1971.
OATES, H. F., STOKES, G. S. and GLOVER, R. G. Plasma renin response to acute blockade of angiotensin II in the anaesthetized rat. Clin. Exp. Pharmacol. Physiol. 1 (2): 155, 1974.
OELKERS, W., DUSTERDIECK, G. and MORTON, J. J. Arterial angiotensin and venous immunoreactive material before and during angiotensin infusion in man. Clin. Sci. 43: 209, 1972.
OELKERS, W., BROWN, J. J., FRASER, R., LEVER, A. F., MORTON, J. J. and ROBERSON, J. I. S. Sensitization of the adrenal cortex to angiotensin II in sodium-deplete man. Circ. Res. 34: 69, 1974.
OGIHARA, T. and NUGENT, C. A. Serum dopamine-beta-hydroxylase in three forms of acute stress. Life Sci. 15: 923, 1974.

OGIHARA, T., NUGENT, C. A., SHEN, S. W. and GOLDFEIN, S. Serum dopamine-beta-hydroxylase activity in parents and children. J. Lab. Clin. Med. 85: 566, 1975.

OKADA, T., FUJITA, T., OHTA, T. A 24-hour rhythm in huma serum dopamine-beta-hydroxylase activity. Experientia 30: 605, 1974.

OKAMOTO, K. and AOKI, K. Development of a strain of spontaneously hypertensive rats. Jap. Circ. J. 27: 282, 1963.

OMVIK, P., ENGER, E. and EIDE, I. Effect of sodium depletion on plasma renin concentration before and during adrenergic beta-receptor blockade with propranolol in normotensive man. Amer. J. Med. 61: 608, 1976.

OPARIL, S., VASSAUX, C., SANDERS, C. A. and HABER, E. Role of renin in acute postural homeostasis. Circulation 41: 89, 1970.

OTSUKA, K., ASSAYKEEN, T. A., GOLDFEIN, A. and GANONG, W. F. Effect of hypoglycemia on plasma renin activity in dogs. Endocrinology 87: 1306, 1970.

OTT, C. E., MARCHAND, G. R., DIAZ-BUXO, J. A. and KNOX, F. G. Determinants of glomerular filtration rate in the dog. Amer. J. Physiol. 231: 235, 1976.

OVERY, H. R., PFISTER, R. and CHIDSEY, C. A. Studies on the renal secretion of norepinephrine. J. Clin. Invest. 46: 482, 1967.

PADFIELD, P. L., NELSON, C. S., BEEVERS, D. G., HAWTHORNE, V. M., GREAVES, D. A., DUNCAN, S., BLYTH, M. and YOUNG, J. Hypertension and the renin-angiotensin system in an unselected population. In: Hypertension – its nature and treatment. Ed. by Burley, D. M., Birdwood, G. F. B., Fryer, J. H. and Taylor, S. H. Ciba laboratories, Horsham, 1975[a].

PADFIELD, P. L., BEEVERS, D. G., BROWN, J. J., DAVIES, D. L., FRASER, R., LEVER, A. F. and ROBERTSON, J. I. S. with SCHALEKAMP, M. A. D. H., KOLSTERS, G. and BIRKENHÄGER, W. H. Low-renin hypertension: a diagnostic entity attribute to mineral-corticoid excess? In: Hypertension. Its nature and treatment. Ed. by Burley, D. M., Birdwood, G. F. B., Fryer, J. H. and Taylor, S. H. Ciba Laboratories, Horsham, 1975[b].

PADFIELD, P. L., BEEVERS, D. G., BROWN, J. J., DAVIES, D. L., LEVER, A. F., ROBERTSON, J. I. S., SCHALEKAMP, M. A. D., and TREE, M. Is low-renin hypertension a stage in the development of essential hypertension or a diagnostic entily? Lancet I: 548, 1975[c].

PAGE, I. H. and HELMER, O. M. A crystalline pressor substance (angiotensin) resulting from the reaction between renin and renin activator. J. Exp. Med. 71: 29, 1940.

PAGE, I. H., KANEKO, Y. and McCUBBIN, J. W. Cardiovascular reactivity in acute and chronic renal hypertensive dogs. Circ. Res. 18: 379, 1966.

PANISSET, J. C. and BOURDOIS, P. Effect of angiotensin on the response to noradrenaline uptake in cat mesenteric blood vessels. Canad. J. Physiol. Pharmacol. 46: 125, 1968.

PARVING, H. H., NOGENSEN, C. E., JENSEN, H. A. E. and EVRIN, P. E. Increased urinary albumin excretion rate in benign essential hypertension. Lancet I: 1190, 1974[a].

PARVING, H. M., ROSSING, M. and JENSEN, H. A. E. Increased metabolic turnover rate and transcapillary escape rate of albumin in essential hypertension. Circ. Res. 35: 544, 1974[b].

PASSO, S. S., ASSAYKEEN, T. A., GOLDFEIN, A. and GANONG, W. F. Effect of alpha and beta-adrenergic blocking agents on the increase in renin secretion produced by stimulation of the medulla oblongata in dogs. Neuroendocrinology 7: 97, 1971.

PATERSON, J. W., CONOLLY, M. E., DOLLERY, C. T., HAYES, A. and COOPER, R. G. The pharmacodynamics and metabolism of propranolol in man. Pharmacol. Clin. 2: 127, 1970.

PATIL, P. N. Steric aspects of adrenergic drugs. VIII. Optical isomers of beta-adrenergic receptor antagonists. J. Pharmacol. Exp. Ther. 160: 308, 1968.

PEART, W. S. The renin-angiotensin system. Pharm. Rev. 17: 143, 1965.

PEDERSEN, E. B. Effect of sodium loading and exercise on renal haemodynamics and urinary sodium secretion in young patients with essential hypertension before and during propranolol treatment. Acta Med. Scand. 201: 365, 1977.

PEDERSEN, E. B. and CHRISTENSEN. Catecholamines in plasma and urine in patients with essential hypertension determined by double-isotope derivative techniques. Acta Med. Scand. 198: 373, 1975.

PEDERSEN, E. B. and KORNERUP, H. J. Renal haemodynamics and plasma renin in patients with essential hypertension. Clin. Sci. Mol. Med. 50: 409, 1976.
PETTINGER, W. A., CAMPBELL, W. B. and KEETON, K. Adrenergic component of renin release induced by vasodilating antihypertensive drugs in the rat. Circ. Res. 33: 82, 1973.
PETTINGER, W. A. and MITCHELL, H. C. Renin release, saralasin and the vasodilator-beta-blocker drug interaction in man. New Engl. J. Med. 292: 1214, 1975.
PETTINGER, W. A., KEETON, T. K., CAMPBELL, W. B. and HARPER, D. C. Evidence for a renal alpha-adrenergic receptor inhibiting renin release. Circ. Res. 38: 338, 1976.
PFEIFFER, J. B., WOLFF, H. G. and WINTER, O. S. Studies in renal circulation during periods of life stress and accompanying emotional reactions in subjects with and without essential hypertension; observations on the role of neural activity in regulation of renal blood flow. J. Clin. Invest. 29: 1227, 1950.
PICKERING, G. High blood pressure. Second edition 1968. Grune & Stratton, New York.
PITCOCK, J. A. and HARTROFT, P. M. The juxtaglomerular cells in man and their relationship to the level of plasma sodium and to the zona glomerulosa of the adrenal cortex. Amer. J. Pathol. 34: 863, 1958.
PITT, B., ELLIOT, E. C. and GREGG, D. E. Adrenergic receptor activity in the coronary arteries of the unanesthetized dog. Circ. Res. 21: 75, 1967.
PLANZ, G., WIETHOLD, G., APPEL, E., BOHMER, D., PALM, D. and GROBECKER, H. Correlation between increased dopamine-beta-hydroxylase activity and catecholamine concentration in plasma: Determination of acute changes in sympathetic activity in man. Europ. J. Clin. Pharmacol. 8: 181, 1975.
POMERANZ, B. H., BIRTCH, A. G. and BARGER, A. C. Neural control of intrarenal blood flow. Amer. J. Physiol. 215: 1067, 1968.
POWELL, C. E. and SLATER, I. H. Blocking of inhibitory adrenergic receptors by a dichloro analog of isoproterenol. H. Pharmacol. Exp. Ther. 122: 480, 1958.
PRATT, J. H., DALE, S. L. and MELBY, J. C. The effect of administered ACTH on aldosterone metabolism and secretion. J. Clin. Endocrinol. Metab. 42: 355, 1976.
PRICHARD, B. N. C. Beta adrenoceptor blocking drugs in hypertension. Ann. Acad. Med. Singapore 5: 59, 1976.
PRITCHARD, W. H., ECKSTEIN, R. W., MacINTYRE, W. J. and DABAJ, E. Correlation of renal blood flow determined by the single injection of Hippuran-I^{131} with direct measurements of flow. Amer. Heart J. 70: 789, 1965.
DE QUATTRO, V. and SJOERDSMA, A. Catecholamine turnover in normotensive man: Effects of antiadrenergic drugs. J. Clin. Invest. 47: 2359, 1968.
DE QUATTRO, V. and CHAN, S. Raised plasma-catecholamines in some patients with primary hypertension. Lancet I: 806, 1972.
DE QUATTRO, V. and MIURA, Y. Neurogenic factors in human hypertension: mechanism or myth. Amer. J. Med. 55: 362, 1973.
DE QUATTRO, V., CAMPESE, V., MIURA, Y. and MEIJER, D. Biochemical markers of sympathetic nerve activity and renin in primary hypertension. In: Pathophysiology and management of arterial hypertension. Ed. by Berglund, G., Hansson, L. and Werko, L. Lingren and Soner AB, Mohndal, 1975.
DE QUATTRO, V., CAMPESE, V., MIURA, Y. and MEYER, D. Increased plasma catecholamines in high renin hypertension. Amer. J. Card. 38: 801, 1976.
RAAB, D. The integrated role of catecholamines, mineralo-corticoids and sodium in blood pressure regulation and pathology. A working hypothesis. J. Mt. Sinai Hosp. 19: 233, 1952.
RAO, U. V. G. and WAGNER, H. N. Jr. Normal weights of human organs. Radiology, 102, 337, 1972.
REEVES, G. and SOMMERS, S. C. Sensitivity of the renal macula densa to urinary sodium. Proc. Soc. Exp. Biol. Med. 120: 324, 1965.
REID, I. A., SCHRIER, R. W. and EARLY, L. E. Effect of extrarenal beta-adrenergic stimulation on the release of renin. J. Clin. Invest. 51: 1861, 1972.
REID, J. L. and KOPIN, I. J. Significance of plasma dopamine-beta-hydroxylase as an index of sympathetic neuronal function. Proc. Natl. Acad. Sci. USA 71: 4394, 1974.
REID, J. L. and KOPIN, I. J. The effects of ganglionic blockade, reserpine and vinblastin on plasma catecholamines and dopamine-beta-hydroxylase in the rat. J. Pharmacol. Exp. Ther. 193: 748, 1975.

REID, J. L. Dopaminergic pathways and the pathophysiological significance. Clin. Sci. Mol. Med. 53: 303, 1977.
REID, W. D. and LARAGH, J. H. Sodium and potassium intake, blood pressure and pressor response to angiotensin. Proc. Soc. Exptl. Biol. Med. 120: 26, 1965.
REIS, D. J. and CUÉNOD, M. Central neural regulation of carotic baroceptor reflexes in the cat. Amer. J. Physiol. 209: 1267, 1965.
REMINGTON, J. W. and BAKER, C. H. Evaluation of blood volume measurement techniques. Circ. Res. 9: 60, 1961.
RENKIN, E. M. and GILMORE, J. P. Glomerular filtration. In: Handbook of Physiology. Sect. 8, Renal Physiology. Ed. by Orloff, J. and Berliner, R. W. American Physiological Society, Washington, D.C. 1973.
RENNICK, B. R. and PRYOR, M. Z. Effects of autonomic drugs on renal tubular transport of catecholamines in the chicken. J. Pharmacol. Exp. Ther. 148: 262, 1965.
REUBI, F. C. Renal hyperemia induced in man by a new phthlalazine derivative. Proc. Soc. Exp. Biol. Med. 73: 102, 1950.
REUBI, F. C. The late effects of hypertensive drugs therapy on renal functions of patients with essential hypertension. In: Essential Hypertension. An International Symposium. Berne, 1960 (Ed. by K. D. Bosch & P. T. Cottier) Springer, Berlin. 1960.
RICHARDSON, D., VETROVEC, W. and WILLIAMSON, W. C. In: Hypertension: Mechanisms and Management. ed. by G. Onesti, K. E. Kim and J. H. Moyer, Grüne and Stratton, New York, 1973[a].
RICHARDSON, D., STELLA, A., LEONETTI, G., BARTORELLI A. and ZANCHETTI, A. Renin release and renal vasomotor changes during stimulation of the brain stem in the cat. Clin. Sci. Mol. Med. 45 (Suppl. 1): 243s, 1973[b].
RICHARDSON, D., STELLA, A., LEONETTI, G., BARTORELLI, A. and ZANCHETTI, A. Mechanisms of renal release of renin by electrical stimulation of the brain stem in the cat. Circ. Res. 34: 425, 1974.
ROBERTSON, C. R., DEEN, W. M., TROY, J. L. and BRENNER, B. M. Dynamics of glomerular ultrafiltration in the rat. III. Hemodynamics and autoregulation. Amer. J. Physiol. 223: 1191, 1972.
ROCHLIN, D. B., SHOHL, T. and BLAKEMORE, W. S. Blood volume changes associated with essential hypertension. Surg. Gynec. Obstet. 111: 569, 1960.
ROJO-ORTEGA, J. M., HATT, P. Y. and GENEST, J. A propos de l'innervation des cellules juxtaglomerulaires. Etude au microscope electronique dans diverses conditions experimentales chez le rat. Pathol. Biol. (Paris) 16: 497, 1968.
ROMERO, J. C., STANELONI, R. J., DUFAU, M. L., DOHMEN, R., BINIA, A., KLIMAN, B. and FASCIOLO, J. C. Changes in fluid compartments, renal haemodynamics plasma renin and aldosterone secretion induced by low sodium intake. Metabolism 17: 10, 1968.
ROSEN, S. M., HOLLENBERG, N. K., DEALY, J. B. and MERRILL, J. P. Measurement of the distribution of blood flow in the human kidney using the intra-arterial injection. of ^{133}Xe. Relationship to function in the normal and transplanten kidney. Clin. Sci. 34: 287, 1968.
ROSENBLUM, R., TAI, A. R. and LAWSON, D. Dopamine in man: cardiorenal haemodynamics in normotensive patients with heart disease. J. Pharmacol. Exp. Ther. 183: 256, 1972.
ROSENTHAL, J., BOUCHER, R., NOWACZYNSKI, W. and GENEST, J. Acute changes in plasma volume, renin activity and free aldosterone levels in healthy subjects following frusemide administration. Canad. J. Physiol. Pharmacol. 46: 85, 1968.
ROSS, E. J. Total exchangeable sodium in hypertensive patients. Clin. Sci. 15: 81, 1956.
ROSS, S. B., WETTERBERG, L. and MYRHED, M. Genetic control of plasma dopamine-beta-hydroxylase. Life Sci. 12: 529, 1973.
ROSSET, E. and VEYRAT, R Release of renin by human kidney slices: In vitro effect of angiotensin II, norepinephrine and alodsterone. Rev. Eur. Etud. Clin. Biol. 16: 792, 1971.
ROTH, R. H. Action of angiotensin on adrenergic nerve endings: enhancement of norepinephrine biosynthesis. Fed. Proc. 31: 1358, 1972.
ROWE, G. G., CASTILLO, C. A., MAXWELL, G. M. and CRUMPTON, C. W. A hemodynamic study of hypertension including observations on coronary blood flow. Ann. Int. Med. 54: 405, 1961.

ROWLAND, M. Influence of route of administration on drug availability. J. Pharm. Sci. 61: 70, 1972.

RUSH, R. A. and GEFFEN, L. B. Radioimmunoassay and clearance of circulating dopamine-beta-hydroxylase. Circ. Res. 31: 444, 1972.

RYAN, G. B. and KARNOVSKY, M. J. Distribution of endogenous albumin in the rat glo- to norepinephrine and hemodynamic parameters in borderline hypertension. Amer, Heart J. 89: 480, 1975.

SAFAR, M., FENDLER, J. P., WEIL, B., IDATTE, J. M., BEUVE-MERY, P. et MILLIEZ, P. Etude hémodynamique de l'hypertension artérielle labile. Presse Med. 78: 111, 1970.

SAFAR, M. E., WEISS, Y. A., LEVENSON, J. A., LONDON, G. M. and MILLIEZ, P. L. Hemodynamic study of 85 borderline hypertensive patients. Amer. J. Card. 31: 315, 1973.

SAFAR, M. E., LONDON, G. M., WEISS, Y. A. and MILLIEZ, P. I. Vascular reactivity to norepinephrine and hemodynamic parameters in borderline hypertension. Amer. Heart. J. 89: 480, 1975.

SAFAR, M. E., CHAU, N. P., WEISS, Y. A., LONDON, G. M., and MILLIEZ, P. L., Control of cardiac output in essential hypertension. Amer. J. Card. 38: 332, 1976[a].

SAFAR, M. E., CHAU, N. P., WEISS, Y. A., LONDON, G. M., SIMON, A. Ch. and MILLIEZ, P. P. The pressure-volume relationship in normotensive and permanent essential hypertensive patients. clin. Sci. Mol. Med. 50: 207, 1976[b].

SALOMON, M. I., NARASIMHAN, P., BRUNO, M. S. and OBER, W. B. Renal lesion in essential hypertension. The problem of correlation between renal biopsy and clinical parameters. Angiology 13: 216, 1962.

SALT, P. J. and IVERSEN, L. L. Inhibition of the extraneuronal uptake of catecholamine in isolated rat heart by cholesterol. Nature New Biol. 238: 91, 1972.

SALVETTI, A., ARZILLI, F., RUSSO, R. and ZUCHELLI, G. C. Postural changes of plasma renin activity determined by radioimmunoassay. J. Nucl. Biol. Med. 15: 140, 1971.

SAMBHI, M. P., CRANE, M. G. and GENEST, J. Essential hypertension: new concepts about mechanisms. Amer. Int. Med. 79: 411, 1973.

SAMWER, K. F., SCHREIBER, M., MOLZAHN, M. and OELKERS, W. Pressor effects of angiotensin II in sodium replete and deplete rats. Pfluegers Arch. 346: 307, 1974.

SANDLER, M. and RUTHVEN, C. R. The biosynthesis and metabolism of the catecholamines. In: Progress in Medical Chemistry. Ed. by Ellis, G. P. and West, G. B. Butterworth, London. 1969.

SANNERSTEDT, R. Hemodynamic response to exercise in patients with arterial hypertension. Acta Med. Scand. 180; Suppl. 458: 1, 1966.

SANNERSTEDT, R. and CONWAY, J. Hemodynamic and vascular response to antihypertensive treatment with adrenergic blocking agents: A review. Amer. Heart J. 79: 122, 1970.

SANNERSTEDT, R., SIVERTSSON, R. and LUNDGREN, Y. Haemodynamic studies in young men with mild blood pressure elevation. Acta Med. Scand., Suppl. 602: 61, 1976.

SAPRU, H. N. and WANG, S. C. Modification of aortic baroreceptor resetting in the spon taneously hypertensive rat. Amer. J. Physol. 230: 664, 1976.

SATO, S., YOSHINAGA, K., WADA, Y., ISHIDA, N. and ITCH, C. Urinary excretion of catecholamines and their metabolites in normotensive and hypertensive patients. Tohoku J. Exp. Med. 75: 151, 1961.

SCHALEKAMP, M. A. D. H., SCHALEKAMP-KUYKEN, M. P. A. and BIRKENHÄGER, W. H. Abnormal renal haemodynamics and renin suppression in hypertensive patients. Clin. Sci. 38: 101, 1970.

SCHALEKAMP, M. A. D. H., KRAUSS, X. H., SCHALEKAMP-KUYKEN, M. P. A., KOLSTERS, G. and BIRKENHÄGER, W. H. Studies on the mechanism of hypernatriuresis in essential hypertension in relation to measurements of plasma renin concentration, body fluid compartments and renal function. Clin. Sci. 41: 219, 1971.

SCHALEKAMP, M. A. D. H. and BIRKENHÄGER, W. H. Renin levels in hypertension. New Eng. J. Med. 286: 1319, 1972.

SCHALEKAMP, M. A. D. H., SCHALEKAMP-KUYKEN, M. P. A., DE MOOR-FRUYTIER, M., MEININGER, Th., VAANDRAGER-KRANENBURG, D. J. and BIRKENHÄGER, W. H. Interrelationships between blood pressure, renin, renin substrate and blood volume in terminal renal failure. Clin. Sci. Mol. Med. 45: 417, 1973.

SCHALEKAMP, M. A. D. H., BIRKENHÄGER, W. H., KOSTERS, G. and LEVER, A. F. Pathogenetic aspects of low-renin hypertension. In: Hypertension – Current Problems, ed. by Distler, A. and Wolff, A. P. Georg Thieme, Stuttgart, 1974[a].
SCHALEKAMP, M. A. D. H., LEBEL, M., BEEVERS, D. G., FRASER, R., KOLSTERS, G. and BIRKENHÄGER, W. H. Body-fluid volumes in low-renin hypertension. Lacent II: 310, 1974[b].
SCHALEKAMP, M. A. D. H., BEVER DONKER, S. C., JANSEN-GOEMANS, A., FAWZI, T. D. and MULLER, A. Dissociation of renin and aldosterone during dehydration: Studies in a case of diabetes insipidus and adipsia. J. Clin. Endocrinol. Metab. 43: 287, 1976 .
SCHALEKAMP, M. A. D. H., BIRKENHÄGER, W. H., ZAAL, G. A. and KOLSTERS, G. Haemodynamic characteristics of low-renin hypertension. Clin. Sci. Mol. Med. 52: 405, 1977.
SCHANBERG, S. M., STONE, R. A., KISHMEN, N., GUNNELLS, J. C. and ROBINSON, R. R. Plasma dopamine-beta-hydroxilase: A possible aid in the study and evaluation of hypertension. Science 183: 523, 1974.
SCHANBERG, S. M. and KIRSHNER, N. Serum dopamine-beta-hydroxylase as an indicator of sympathetic activity and primary hypertension. Biochem. Pharmacol. 25: 617, 1976.
SCHNEIDER, E. G., LYNCH, R. E., WILLIS, L. R. and KNOX, F. G. The effect of potassium infusion on proximal sodium reabsorption and renin release in the dog. Kidney Int. 2: 197, 1972.
SCHOLER, D., BIRKHÄUSER, M., PEYTREMANN, A., RIONDEL, A. M., VALLOTTON, M. B. and MULLER, A. F. Response of plasma aldosterone to angiotensin II, ACTH and potassium in man. Acta Endocrinol. 72: 293, 1973.
SEALEY, J. E., CLARK, I., BULL, M. B. and LARAGH, J. H. Potassium balance and the control of renin secretion. J. Clin. Invest. 49: 2119, 1970.
SEALY, J. E., GERTEN-BANES, J. and LARAGH, J. H. The renin system: variations in man measured by radioimmunoassay or bioassay. Kidney Intern. 1: 240, 1972.
SELDINGER, S. I. Catheter replacement of the needle in percutaneous arteriography. A new technique. Acta Radiol. 39: 368, 1953.
SEN, S., FERRARIO, C. M. and BUMPUS, F. M. Alteration in the feedback control of renin release by an angio-tensin antagonist. Acta Physiol. Lat. Amer. 24 (5): 529, 1974.
SEVER, P. S., BIRCH, M., OSIKOWSKA, B. and TUNBRIDGE, R. D. G. Plasma-noradrenaline in essential hypertension. Lancet I: 1078, 1977.
SHADE, R. E., DAVIS, J. O., JOHNSON, J. A. and WITTY, R. T. Effects of renal arterial infusion of sodium and potassium on renin secretion in the dog. Circ. Res. 31: 719, 1972.
SHADE, R. E., DAVIS, J. O., JOHNSON, J. A., GOTSHALL, R. W. and SPIELMAN, W. S. Mechanism of action of angiotensin II and antidiuretic hormone on renin secretion. Amer. J. physiol. 224: 926, 1973.
SHADE, R. E. and GRIM, C. E. Suppression of renin and aldosterone by small amounts of DOCA in normal man. J. Clin. Endocr. 40: 652, 1975.
SHAND, D. G. and RANGNO, R. E. The disposition of propranolol. Elimination during oral absorption in man. Pharmacol. 7: 159, 1972.
SHAND, D. G. Pharmacokinetics of propranolol: a review. Postgrad. Med. J. 52 (suppl. 4): 22, 1976.
SHAW, D. B., KNAPP, M. S. and DAVIS, D. H. Variations of blood pressure in hypertensive during sleep. Lancet I: 797, 1963.
SHOCK, N. W. Inulin, diorast and urea clearance studies on aged human subjects. Fed. Proc. 4: 65, 1945.
SHOCK, N. W. Kidney function tests in aged males. Geriatrics 1: 232, 1946.
SIMKIN, B., BERGMAN, H. C., SILVER, H. and PRINZMETAL, M. Renal arteriovenous anastomoses in rabbits, dogs and human subjects. Arch. Int. Med. 81: 115, 1948.
SIMPSON, J. O. and DEVINE, C. E. The fine structure of autonomic neuromuscular contacts in arterioles of sheep renal cortex. J. Anat. 100: 127, 1966.
SIVERTSSON, R. and OLANDER, R. Aspects of the nature of the increased vascular resistance and increased "reactivity" to noradrenaline in hypertensive subjects. Live Sci. 7: 1291, 1968.
SIVERTSSON, R. The hemodynamic importance of structural vascular changes in essential hypertension. Acta Phyaiol. Scand. 79. Suppl. 343: 28, 1970.

SJOERDSMA, A. Relationship between alterations in amine metabolism and blood pressure. Circ. Res. 9: 734, 1961.
SKINNER, S. L., McCUBBIN, J. W. and PAGE, I. H. Control of renin secretion. Circ. Res. 15: 64, 1964.
SKINNER, S. L. Improved assay methods for renin "concentration" and "activity" in human plasma. Circ. Res. 20: 391, 1967.
SKINNER, S. L., CRAN, E. J., GIBSON, R., TAYLOR, R., WALTERS, W. A. W. and CATT, K. J. Angiotensin I and II, active and inactive renin, renin substrate, renin activity and angiotensinase in human liquor amnii and plasma. Am. J. Obstr. and Gyn. 121: 626, 1975.
SLACK, B. L. and LEDINGHAM, J. M. The influence of sodium intake on the pressor response to angiotensin II in the unanaesthetized rat. Clin. Sci. Mol. Med. 50: 285, 1976.
SLEIGHT, P., ROBINSON, J. C., BROOKS, D. E. and REES, P. M. Carotid baroreceptor re-setting in the hypertensive dog. Clin. Sci. Mol. Med. 48 (Suppl. 2): 261, 1975.
SLOTKOFF, L. M., LOGAN, A., JOSE, P., D'AVELLA, J. and EISNER, G. M. Microsphere measurement of intrarenal circulation of the dog. Circ. Res. 28: 158, 1971.
SMIRK, F. J., VEALE, A. M. and ALSTAD, K. S. Basal and supplemental blood pressure in relationship to life expectancy and hypertension symptomatology. New Zld. Med. J. 58: 711, 1959.
SMITH, A. D. and WINKLER, H. Fundamental mechanism in the release of catecholamines. In: Handbook of Experimental Pharmacology (vol 33). Ed. by Blaschko, H. and Muscholl, E. Springer Verlag, Berlin. 1972.
SMITH, H. W., GOLDRING, W. and CHASIS, H. The measurement of the tubular excretory mass, effective blood flow and filtration rate in the normal human kidney. J. Clin. Invest. 17: 263, 1938.
SMITH, H. W., GOLDRING, W. and CHASIS, H. Role of the kidney in the genesis of hypertension. Bull. N. Y. Acad. Med. 19: 449, 1943.
SMITH, H. W. The Kidney, Structure and function in health and disease. Oxford Medical Publications. Oxford University Press, New York. 1951.
SMITH, J. J., BUSH, J. E., WIEDMEIER, V. T. and TRISTANI, F. E. Application of impedance cardiography to study of pastural stress. J. Appl. Physiol. 29: 133, 1970.
SNEDECOR, G. W. and COCHRAN, W. G. Statistical methods. The Iowa State University Press, Ames, Iowa, U.S.A. Sixth Edition, 1967.
SPANNER, R. Über Gefäßkurzschlüße in der Niere. Verh. Anat. Ges. 45: 81, 1938.
SPARK, R. F. and MELBY, J. C. Hypertension and low plasma renin activity: presumptive evidence for mineralocorticoid excess. Ann. Int. Med. 75: 831, 1971.
SPARK, R. F., O'HARA, C. M. and REGAN, R. M. Low-renin hypertension. Restoration of normotension and renin responsiveness. Arch. Int. Med. 133: 205, 1974.
SPARLING, C. M. Registratie en kwantitative interpretatie van kleurstof verdunningscurves, verkregen door reflectie-meting in rood of infrarood licht. Dissertatie Groningen. Van Gorkum, Assen, 1961.
STAFFURTH, J. S. and BIRCHALL, I. The measurement of the extracellular fluid volume with radioactive bromine. Clin. Sci. 19: 45, 1960.
STARKE, K., WERNER, U. und SCHÜMAN, H. J. Wirkung von Angiotensin auf Funktion und Noradrenalinabgabe isolierter Kaninchenherzen in Ruhe und bei Sympathicus-Reizung. Arch. Exp. Pathol. Pharmakol. 265: 170, 1969.
STARKE, K. Regulation of catecholamine release: alpha-receptor mediated feedback control in peripheral and central neurones. In: Frontiers in catecholamine research. Ed. by Usdin, E. and Snyder, S. H. Pergamon, New York. 1973.
STARKE, K. and MONTEL, H. Local feed-back mechanisms controlling the release of noradrenaline: Possible sites of action of antihypertensive drugs. In: Hypertension. Ed. by Distler, A. and Wolff, H. P. Georg Thieme, Stuttgart. 1974.
STARLING, E. H. The glomerular functions of the kidney. J. Physiol. London 24: 317, 1899.
STARR, I., DONAL, J. S., MARGOLIES, A., SHAW, R., COLLINS, L. H. and GAMBLE, C. J. Studies of heart and circulation in disease; estimation of basal cardiac output, metabolism, heart size and blood pressure in 235 subjects. J. Clin. Invest. 13: 561, 1934.
STEELE, J. M. Jr. and LOWENSTEIN, J. Differential effects of an angiotensin II analogue on pressor and adrenal receptors. Circ. Res. 35: 592, 1974.

STEIN, J. H., REINECL, J. H., OSGOOD, R. W., and FERRIS, T. F. Effect of acetylcholine on proximal tubular sodium reabsorption in the dog. Amer. J. Physiol. 220: 227, 1971.
STEIN, J. H., BONJARERN, S., MAUK, R. C. and FERRIS, T. F. Mechanism of redistribution of renal cortical blood flow during hemorrhagic hypotension in the dog. J. Clin. Invest. 52: 39, 1972.
STEINITZ, K. Zur Frage der Nierendurchblutung bei normalen Hypertonikern und Nierenkrankheiten. Acta Med. Scand. 109: 95, 1941.
STELLA, A., CAFIERO, F. and ZANCHETTI, A. Mechanisms of renin release in response to tilting and furosemide. Eur. J. Clin. Invest. 4: 349, 1974.
STELLA, A., CALARESU, F. and ZANCHETTI, A. Neural factors contributing to renin release during reduction in renal perfusion pressure and blood flow in cats. Clin. Sci. Mol. Med. 51: 453, 1976.
STJÄRNE, L. Mechanisms of catecholamine secretion. In: Frontiers in catecholamine research. Ed. by Usdin, E. and Snyder, S. H. Pergamon Press, N.Y., Toronto, Oxford, Sydney, Braunschweig, 1973.
STOCKIGT, J. R., COLLINS, R. D. and BIGLIERI, E. G. Determination of plasma renin concentration by angiotensin. I. Immuno-assay. Circ. Res. vol. 28 and 29, Suppl. II: 175, 1971.
STONE, R. A., GUNNELLS, J. C., ROBINSON, R. R., SCHANBERG, S. and KIRSHNER, N. Dopamine-beta-hydroxylase in primary and secondary hypertension. Circ. Res. 34/35 (suppl. 1): 47, 1974.
STOTT, A. W. and ROBINSON, R. Urinary normetadrenaline excretion in essential hypertension. Clin. Chim. Acta 16: 249, 1967.
STRANDHOY, J. W. Effects of prostaglandins E_1 and E_2 on renal sodium reabsorption and Starling forces. Amer. J. Physiol. 226: 1015, 1974.
STRANG, K. D., VANDONGEN, R., POESSÉ, M. H. and BIRKENHÄGER, W. H. Failure of alpha-adrenergic stimulation by phenylephrine to enhance renin secretion in the isolated rat kidney. Eur. J. Pharmacol. 45: 141, 1977.
STRANG, K. D. De rol van renale alpha-receptoren bij de regulatie van de reninesecretie door de geïsoleerde rattenier. Thesis, Rotterdam, 1978.
STREETEN, D. H. P., SCHLETTER, F. E., CLIFT, G. V., STEVENSON, C. T. and DALAKOS, T. G. Studies on the renin-angiotensin-aldosterone system in patients with hypertension and in normal subjects. Amer. J. Med. 46: 844, 1969.
STREWLER, G. J., HINRICHS, K. J., GUIOD, L. R. and HOLLENBERG, N. K. Sodium intake and vascular smooth muscle responsiveness to norepinephrine and angiotensin in the rabbit. Circ. Res. 31: 758, 1972.
STROOBANDT, R., FAGARD, R. and AMERY, A. Are patients with essential hypertension and low renin protected against stroke and heart attack? Amer. Heart. J. 86: 781, 1973[a].
STROOBANDT, R., FAGARD, R., ROUSSEL-DERUYCK, R. and AMERY, A. Plasma renin concentration in essential hypertension and incidence of stroke and heart attack. In: Ipertensione Arteriose, ed. by Zanchetti, A. Boehringer-Ingelheim, s.p.a., Firenze, 1973[b].
STUDNITZ, W. VON. Methodische und klinische Untersuchungen über die Ausscheidung der 3-Methoxy-4 Hydroxymandelsaure in Urin. Scand. J. Clin. Lab. Invest. 12 (suppl. 48): 3, 1960.
SUCK, A. S., MENDLOWITZ, M., WOLF, R. L. GITLOW, S. E. and NAFTCHI, N. E. Identification of essential hypertension in patients with labile blood pressures. Chest 59: 402, 1971.
SUTHERLAND, E. W. and RALL, T. W. The relations of adenosine-3', 5'-phosphate and phosphorylase to the actions of catecholamines and other hormones. Pharmacol. Rev. 12: 265, 1960.
SWALES, J. D. and THURSTON, H. Plasma renin and angiotensin II measurement in hypertensive and normal subjects: Correlation of basal and stimulated states. J. Clin. Endocrinol. Metab. 45: 159, 1977.
TAGAWA, H. and VANDER, A. J. Effect of acetylcholine on renin secretion in salt-depleted dogs. Proc. Soc. Exp. Biol. Med. 132: 1087, 1969.
TAGAWA, H., VANDER, A. J., BONJOUR, J. P. and MALVIN, R. L. Inhibition of renin secretion by vasopression in unanesthetized sodium-deprived dogs. Amer. J. Physiol. 220: 949, 1971.

TAKESHITA, A., TANAKA, S., KUROIWA, A. and NAKAMURA, M. Reduced baroreceptor sensitivity in borderline hypertension. Circulation 51: 738, 1975.

TALBOTT, J. H., CASTLEMAN, B., SMITHWICK, R. H., MELVILLE, R. S. and PECORA, L. Renal biopsy studies correlated with renal clearance observations in hypertensive patients treated by radical sympathectomy. J. Clin. Invest. 22: 387, 1943.

TALLEY, R. C., GOLDBERG, L. I., JOHNSON, C. E. and McNAY, J. L. A hemodynamic comparison of dopamine and isoproterenol in patients in shock. Circulation 39: 361, 1969.

TANAKA, K., OMAE, T., HATTORI, N. and KATSUKI, S. Renin release from ischemic kidneys following angiotensin infusion in dogs. Jap. Circ. J. 33: 235, 1969.

TANAKA, K. and PETTINGER, W. Renin release and ketamine-induced cardiovascular stimulation in the rat. J. Pharmacol. Exp. Ther. 188: 229, 1974.

TANIGAWA, H., ALLISON, D. J. and ASSAYKEEN, T. A. A comparison of the effects of various catecholamines ons plasma renin activity alone and in the presence of adrenergic blocking agents. In: Hypertension '72. Ed. by Genest, J. and Koiw, E. New York, Springer Verlag, 1972.

TAQUINI, A. C., WILLAMIL, M. F., ARAMENDIA, P., DE LA RIVA, I. J. and FERMOSO, J. D. Effect of postural changes on cardiac and renal function in hypertensive subjects. Amer. Heart J. 63: 78, 1962.

TARAZI, R. C., FROHLICH, E. D. and DUSTAN, H. P. Plasma volume in men with hypertension. New Eng. J. Med. 278: 762, 1968.

TARAZI, R. C., DUSTAN, H. P. and FROHLICH, E. D. Relation of plasma to interstitial fluid volume in essential hypertension. Circulation 40: 357, 1969.

TARAZI, R. C., DUSTAN, H. P., FROHLICH, E. D., GIFFORD, R. W. and HOFFMAN, G. C. Plasma volume and chronic hypertension. Arch. Int. Med. 125: 835, 1970.

TARAZI, R. C., FROHLICH, E. D. and DUSTAN, H. P. Plasma volume changes with long-term beta-adrenergic blockade. Amer. Heart J. 82: 770, 1971.

TARAZI, R. C. and DUSTAN, H. P. Beta adrenergic blockade in hypertension. Amer. J. Cardiol. 29: 633, 1972.

TARAZI, R. C., IBRAHIM, M. M., DUSTAN, H. P. and FERRARIO, C. M. Cardiac factors hypertension. Circ. Res. 34 and 35, Suppl. 1: 213, 1974.

TARAZI, R. C., MAGRINI, F. and DUSTAN, H. P. The role of aortic distensibility in hypertension. In: Recent Advances in hypertension, Ed. by Milliez, P. and Safar, M. Laboratories Boehringer-Ingelheim, Reims, 1975.

TAYLOR, S. H., DONALD, K. W. and BISHOP, J. B. Circulatory studies in hypertensive patients at rest and during exercise. Clin. Sci. 16: 351, 1957.

TELLEM, M. Progression of target organ damage from sustained diastolic hypertension. Amer. J. Cardiol. 17: 604, 1966.

TENG, H. C., SHAPIRO, A. P. and GROLLMAN, A. Volume of the fluid compartments in human and experimental hypertension. Metabolism 3: 405, 1954.

THORBURN, G. D., KOPALD, H. H., HERD, J. A., HOLLENBERG, M. O'MORCHOE, C. C. C. and BARGER, A. C. Intrarenal distribution of nutrient blood flow determined with Krypton^{85} in the unanesthetized dog. Circ. Res. 13: 290, 1963.

THURAU, K., DEETJEN, P. and KRAMER, K. Hämodynamik des Nierenmarks. II. Pflügers Arch. Ges. Physiol. 270: 270, 1960.

THURAU, K., SCHNERMANN, J., NAGEL, W., HORSTER, M. and WOHL, M. Composition of tubular fluid in the macula densa segment as a factor regulating the function of the juxta-glomerular apparatus. Circ. Res. 21, Suppl. II: 79, 1967.

THURAU, K., DAHLHEIM, H., GRUNER, A., MASON, J. and GRANGER, P. Activation of renin in the single juxtaglomerular apparatus by sodium chloride in the tubular fluid at the mascula densa. Circ. Res. 30, 31 (suppl. II): 182, 1972.

THURSTON, H. and LARAGH, J. H. Prior receptor occupancy as a determinant of the pressor activity of infused angiotensin II in the rat. Circ. Res. 36: 113, 1975.

THURSTON, H. Vascular angiotensin receptors and their role in blood pressure control. Amer. J. Med. 61: 768, 1976.

TIBBLIN, G., BERGENTZ, S. E., BJURE, J. and WILHELMSEN, L. Hematocrit, plasma protein, plasma volume and viscosity in early hypertensive disease. Amer. Heart J. 72: 165, 1966.

TIGERSTEDT, R. and BERGMANN, P. G. Niere und Kreislauf. Skand. Arch. Physiol. 8: 223, 1898.
TISCHER, C. C., BULGER, R. E. and TRUMP, B. F. Human renal ultrastructure. III. The distal tubule in healthy individuals. Lab. Invest. 18: 655, 1968.
TISCHER, C. C. Anatomy of the kidney. In: The kidney. Ed. by Brenner, B. M. and Rector, F. C. W. B. Saunders Company, Philadelphia, London, Toronto, 1976.
TOBERT, J. A., SLATER, J. D. H., FOGELMAN, F., LIGHTMAN, S. L., KURTZ, A. B. and PAYNE, N. N. The effect in man of (+)-propranolol and racemic propranolol on renin secretion stimulated by orthostatic stress. Clin. Sci. 44: 291, 1973.
TOBIAN, L. and BINION, J. T. Tissue cations and water in arterial hypertension. Circulation 5: 754, 1952.
TOBIAN, L. and BINION, J. T. Artery wall electrolytes in renal and DOC hypertension. J. Clin. Invest. 33: 1407, 1954.
TOBIAN, L. and REDLEAF, P. D. Ionic composition of the aorta in renal and adrenal hypertension. Amber. J. Physiol. 192: 325, 1958.
TOBAIN, L., TOMBOULIAN, A. and JANECEK, J. The effect of high perfusion pressure on the granulation of juxtaglomerular cells in an isolated kidney. J. Clin. Invest. 38: 605, 1959.
TOBIAN, L. Interrelationship of electrolytes, juxtaglomerular cells and hypertension. Physiol. Rev. 40: 280, 1960.
TOBIAN, L., JENECEK, J., TOMBOULIAN, A. and FERREIRA, D. Sodium and potassium in the walls of arterioles in experimental renal hypertension. J. Clin. Invest. 40: 1922, 1961.
TOBIAN, L. Relationship of juxtaglomerular apparatus to renin and angiotensin. Circulation 25: 189, 1962.
TOBIAN, L. J. A. Viewpoint concerning the enigma of hypertension. Amer. J. Med. 52: 595, 1972.
TRENDELENBURG, U. Classification of sympathomimetic amines. In: Handbook of experimental pharmacology. Vol. 33. Ed. by Blaschko, H. and Muscholl, E., Berlin, Springer Verlag, 1972.
TRUETA, J., BARCLAY, A. E., FRANKLIN, K. J., DANIEL, P. M. and PRICHARD, M. M. L. Studies of the renal circulation Blackwell Scientific Publications, Oxford. 1947.
TSAI, T. H. and FLEMING, W. W. The adrenotropic receptors of the cat uterus. J. Pharmacol. Exp. Ther. 143: 268, 1964.

TUCCI, J. R., ESPINER, E. A., JAGGER, P. I., PAUK, G. L. and LAULER, D. P. ACTH stimulation of aldosterone secretion in normal subjects and in patients with chronic adrenocortical insufficiency. J. Clin. Endocrinol. Metab. 27: 568, 1967.
TUCK, M. L., WILLIAMS, G. H., CAIN, J. P., SULLIVAN, J. M. and DLUHY, R. G. Relation of age, diastolic blood pressure and known duration of hypertension to presence of low-renin essential hypertension. Amer. J. Card. 32: 637, 1973.
TUCK, M. L., DLUHY, R. G. and WILLIAMS, G. H. A specific role for saline on the sodium ion in the regulation of renin and aldosterone secretion. J. Clin. Invest. 53: 988, 1974.
UEDA, H., YASUDA, H., TAKABATAKE, Y., IIZUKA, M., IIZUKA, T., IHORI, M., YAMAMOTO, M. and SAKAMOTO, Y. Increased renin release evoked by mesencephalic stimulation in the dog. Jap. Heart J. 8: 498, 1967.
UEDA, H., YASUDA, H., TAKABATAKE, Y., IIZUKA, M., IIZUKA, T., IHORI, M. and SAKAMOTO, Y. Observations on the mechanism of renin release by catecholamines. Circ. Res. 26, 27 Suppl. II: 195, 1970.
ULRYCH, M., HOFMAN, J. and HEJL, Z. Cardiac and renal hyperresponsiveness to acute plasma volume expansion in hypertension. Amer. Heart J. 68: 193, 1964.
ULRYCH, M., FROHLICH, E. D., DUSTAN, H. P. and PAGE, I. H. Immediate hemodynamic effects of beta-adrenergic blockade with propranolol in normotensive and hypertensive man. Circulation 37: 411, 1968.
ULRYCH, M. Plasma volume decrease and elevated Evans blue disappearance rate in essential hypertension. Clin. Sci. Mol. Med. 45: 173, 1973.
VALTIN, H. Structural and functional heterogenety of mammalian nephrons. Amer. J. Physiol. 233: F491, 1977.
VANDER, A. J. and MILLER, R. Control of renin secretion in the dog. Amer. J. Physiol. 207: 537, 1964.
VANDER, A. J. Effect of catecholamines and the renal nerves on renin secretion in anesthetized dogs. Amer. J. Physiol. 209: 659, 1965.

VANDER, A. J. and GEELHOED, G. W. Inhibition of renin secretion by angiotensin II. Proc. Soc. Exp. Biol. Med. 120: 399, 1965.
VANDER, A. J. Control of renin release. Physiol. Rev. 47: 359, 1967.
VANDER, A. J. and LUCIANO, J. R. Effects of mercurial diuresis and acute salt depletion on renin release in dog. Amer. J. Physiol. 212: 651, 1967[A].
VANDER, A. J. and LUCIANO, J. R. Neural and humoral control of renin release in salt depletion. Circ. Res. 20, 21, (suppl. II): 69, 1967[b].
VANDER, A. J. Inhibition of renin release in the dog by vasopressin and vasotocin. Circ. Res. 23: 605, 1968.
VANDER, A. J. and CARLSON, J. Mechanism of the effects of furosemide on renin secretion in anesthetized dogs. Circ. Res. 25: 145, 1969.
VANDER, A. J. Direct effects of potassium on renin secretion and renal function. Amer. J. Physiol. 24: 455, 1970.
VANDONGEN, R., PEART, W. S. and BOYD, G. W. Adrenergic stimulation of renin secretion in the isolated perfused rat kidney. Circ. Res. 32: 290, 1973.
VANDONGEN, R. and PEART, W. S. The inhibition of renin secretion by alpha-adrenergic stimulation in the isolated rat kidney. Clin. Sci. Mol. Med. 47: 471, 1974.
VANDONGEN, R., PEART, W. S. and BOYD, G. W. Effect of angiotensin II and its non-pressor derivatives on renin secretion. Amer. J. Physiol. 226: 277, 1974.
VANDONGEN, R. Inhibition of renin secretion in the isolated rat kidney by antidiuretic hormone. Clin. Sci. Mol. Med. 49: 73, 1975.
VANDONGEN, R. and GREENWOOD, D. M. The stimulation of renin secretion by nonvaso-constrictor infusions of adrenaline and noradrenaline in the isolated rat kidney. Clin. Sci. Mol. Med. 49: 609, 1975.
VANDONGEN, R., POESSÉ, M., STRANG, K. D. and BIRKENHÄGER, W. H. Evidence that "inactive" renin is produced outside the kidney of the rat. Clin. Sci. Mol. Med. 53: 189, 1977.
VARNAUSKAS, E. Studies in hypertensive cardiovascular disease with special reference to cardiac function. Scand. J. Clin. Lab. Invest. 7 Suppl. 17: 1, 1955.
VATNER, S. F., FRANKLIN, D., VANCITTERS, R. L. and BRAUNWALD, E. Effects of carotid sinus nerve stimulation on the coronary circulation of the conscious dog. Circ. Res. 27: 11, 1970.
VENNING, E. J., DYRENFURTH, I., DOSSETER, J. B. and BECK, J. C. Influence of alterations in sodium intake on urinary aldosterone response to corticotropin in normal individuals and patients with essential hypertension. metabolism 11: 254, 1962.
VEYRAT, R., BRUNNER, H. R., MANNING, E. L. et MULLER, A. F. Inhibition de l'activité de la rénine plasmatique par le potassium. J. Urol. Nephrol. (Paris) 73: 271, 1967.
VEYRAT, R. and ROSSET, E. In vitro renin release by human kidney slices: effect of norepinephrine, angiotensin II and I, and aldosterone. In: Hypertension '72. Ed. by Genest, J. and Koiw, E. New York, Springer Verlag, 1972.
VIDEBACK, J., CHRISTENSEN, N. J. and STERNDORFF, B. Serial determination of plasma catecholamines in myocardial infarction. Circulation 46: 846, 1972.
VIVEROS, O. H., ARQUEROS, L. and KIRSHNER, N. Release of catecholamines and dopamine-beta-oxidase from the adrenal medulla. Life Sci. 7: 609, 1968.
VIVEROS, O. H., ARGUEROS, L., CONNETT, R. C. and KIRSHNER, N. Mechanism of secretion from the adrenal medula. IV. The fate of the storage vesicles following insulin and reserpine administration. Mol. Pharmacol. 5: 69, 1969.
VLACHAKIS, N. D., SCHIAVI, P., MENDLOWITZ, M., DE GUIA, D. and WOLF, R. L. Hypertension and anxiety. Amer. Heart J. 87: 518, 1974.
WÄGERMARK, J., UNGERSTEDT, U. and LJUNDQUIST, A. Sympathetic innervation of the juxtaglomerular cells of the kidney. Circ. Res. 22: 149, 1968.
WALKER, W. G., HORVATH, J. S., MOORE, M. A., WHELTON, P. and RUSSELL, R. P. Relation between plasma renin activity, angiotensin and aldosterone and blood pressure in mild untreated hypertension. Circ. Res. 38: 470, 1976.
WALSER, M., DUFFY, B. J. and RIFFIN, H. W. Body fluids in hypertension and mild heart failure. J.A.M.A. 160: 858, 1956.
WATHEN, R. L., KINGSBURY, W. S., STOUDER, D. A., SCHNEIDER, E. G. and ROSTORFER, H. H. Effects of infusion of catecholamines and angiotensin II on renin release in anesthetized dogs. Amer. J. Physiol. 209: 1012, 1965.

WATKINS, B. E., DAVIS, J. O., FREEMAN, R. H. and LOHMEIER, T. E. Mechanism of action of calcium to decrease renin release (Abstract). Feder. Proc. 35: 619, 1976.
WEIDMANN, P., DE MYTTENAERE-BURSZTEIN, S., MAXWELL, M. H. Effect of aging on plasma renin and aldosterone levels in normal man. Kidney Intern. 8: 325, 1975.
WEIDMANN, P., HIRSCH, D., BERETTA-PICCOLI, C. and REUBI, F. C. Interrelations among blood pressure, blood volume, plasma renin activity and urinary catecholamines in benign essential hypertension. Amer. J. Med. 62: 209, 1977.
WEINBERGER, M. H., DOWDY, A. J., NOKES, G. W. and LUETSCHER, J. A. Plasma renin activity and aldosterone secretion in hypertensive patients during high and low sodium intake and administration of diuretics. J. Clin. Endocrinol. 28: 359, 1968.
WEINBERGER, M. H., AOI, W. and HENRY, D. P. Direct effect of beta-adrenergic stimulation on renin release by the rat kidney slice in vitro. Circ. Res. 37: 318, 1975.
WEINBERGER, M. H., AOI, W.L WADE, M. B., USA, T., GRIM, C. E., DENTINO, M. E. and LUFT, F. Renin-like activity (RLA) in anephric man. (Abstract) Kidney Intern. 10: 537, 1976.
WEINSHILBOUM, R. M. NGUYEN, B. T., JOHNSON, D. G., KOPIN, J. J. and AXELROD, J. Proportional release of norepinephrine and dopamine-beta-hydroxylase from sympathetic nerves. Science. 174: 1349, 1971.
WEINSHILBOUM, R. M. and AXELROD, J. Serum dopamine-beta-hydroxylase. Decrease of chemical sympathectomy. Science 173: 931, 1971[a].
WEINSHILBOUM, R. M. and AXELROD, J. Reduced plasma dopamine-beta-hydroxylase activity in familial dysautonomia. New Eng. J. Med. 285: 938, 1971[b].
WEINSHILBOUM, R. M., RAYMOND, F. A., ELVEBACK, L. R. and WEIDMAN, W. H. Serum dopamine-beta-hydroxylase activity: Sibling-sibling correlation. Science 181: 943, 1973.
WEISS, S. and ELLIS, L. B. Quantitative aspects and dynamics of the circulatory mechanism in arterial hypertension. Amer. Heart. J. 5: 448, 1930.
WENTING, G. J., VERHOEVEN, R. P., MAN IN 't VELD, A. J., BIRKENHÄGER, W. H. and SCHALEKAMP, M. A. D. H. Aldosteron bij hypertensie: rol van ACTH bij primair hyperaldosteronisme. Ned. T. v. Gen. 120: 727, 1976.
WERKÖ, L. and LAGERLÖF, J. Studies on the circulation in man. cardiac output and blood pressure in the right auricle, right ventricle and pulmonary artery in patients with hypertensive cardiovascular disease. Acta Med. Scand. 133: 427, 1949.
WERMUT, M. and WOJCICKI, M. Suicidal attempt with propranolol. Brit. Med. J. 3: 591, 1969.
WESSON, L. G. Physiology of the human kidney. Grune and Stratton, Inc. New York, London, 1969.
WEST, M. J., SLEIGHT, P. and HONOUR, A. J. Clinical trial of the beta-adrenoreceptor-blocking agent tolamolol with the use of 24 hour blood pressure recordings. Clin. Sci. Mol. Med. 51: 545s, 1976.
WESTER, A., ZAAL, G. A., DE LEEUW, P. W. and BIRKENHÄGER, W. H. Haemodynamic and endocrinological changes during antihypertensive treatment with a new vasodilator substance (L6250) and propranolol. Clin. Sci. Mol. Med. 51 (suppl. 3): 605s, 1976.
WESTER, A., ZAAL, G. A., DE LEEUW, P. W., FALKE, H. E. and BIRKENHÄGER, W. H. Haemodynamic and endocrinological changes during antihypertensive treatment with a new vasodilator substance (L6150) and propranolol. In: Interference with mechanisms in hypertension. Ed. by Birkenhäger, W. H. and Vandongen, R. Rotterdam, 1976.
WESTERMAN-VAN DER HORST, H. J. Dissertatie Rotterdam, 1975.
WETTERBERG, L., ABERG, H., ROSS, S. B. Plasma dopamine-beta-hydroxylase activity in hypertension and various neuropsychiatric disorders. Scand. J. Clin. Lab. Invest. 30: 283, 1972.
WEZLER, K. und BÖGER, A. Die Dynamik des arteriellen Systems. Der arterielle Blutdruck und seine Komponenten. Ergebn. Physiol. 41: 292, 1939.
WIDIMSKI, J., FEJFARVAO, H. M. und FEJFAR, Z. Der jugendliche Hochdruck. Arch. Kreisl. Forsch. 28: 100, 1958.
WIGGERS, C. J. The dynamic of hypertension. Amer. Heart J. 16: 515, 1938.
WILLIAMS, G. H., ROSE, L. I., DLUHY, R. G., McCAUGHN, D., JAGGER, P. I., HICKLER, R. B. and LAULER, D. P. Abnormal responsiveness of the renin-aldosterone system to acute stimulation in patients with essential hypertension. Ann. Intern. Med. 72: 317, 1970.

WILLIAMS, G. H., LAULER, D. P. and DLUHY, R. G. Aldosterone responses to volume manipulation: normal man, hypertension. In: Hypertension. Ed. by Genest, J. and Koiw, E. Springer, Berlin, 1972.
WILLIAMS, G. H., McDONNELL, L. M., RAUX, M. C. and HOLLENBERG, N. K. Evidence for different angiotensin II receptors in rat adrenal glomerulosa and rabbit vascular smooth muscle cells: Studies with competitive antagonists. Circ. Res. 34: 384, 1974.
WILLIAMS, G. H. and HOLLENBERG, N. K. Accentuated vascular and endocrine response to SQ 20881 in hypertension. New Eng. J. med. 297: 184, 1977.
WILLIAMS, L. T., SNYDERMAN, R. and LEFKOWITZ, R. J. Identification of beta-adrenergic receptors in human lymphocytes by (–) (^{3}H) alprenol binding. J. Clin. Invest. 57: 1975.
WINER, N., CHOKSKI, D. S., YOON, M. S. and FREEDMAN, M. D. Adrenergic receptor mediation of renin secretion. J. Clin. Endocr. 29: 1168, 1969.
WINER, N., CHOKSKI, D. S. and WALKENHORST, W. G. Effects of cyclic AMP, sympathomimetic amines, and adrenergic receptor antagonists on renin secretion. Circ. Res. 29: 239, 1971.
WISENBAUGH, P. E., GARST, J. B., HULL, C., FREEDMAN, R. J., MATTHEWS, D. N. and HADADY, M. Renin, aldosterone, sodium and hypertension. Amer. J. Med. 52: 175, 1972.
WITTY, R. T., DAVIS, J. O., JOHNSON, J. A. and PREWITT, R. L. Effects of papaverine and hemorrhage on renin secretion in the nonfiltering kidney. Amer. J. Physiol. 221: 1666, 1971.
WITTY, R. T., DAVIS, J. O., SHADE, R. E., JOHNSON, J. A. and PREWITT, R. L. Mechanisma regulating renin release in dogs with thoracic caval constriction. Circ. Res. 31: 339, 1972.
WOLF, R. L., MENDLOWITZ, M. and ROBOZ, J. A new test for primary hypertension. The apparent norepinephrine secretion rate in normotensive and hypertensive man. J. Clin. Invest. 46: 1134, 1967.
WOODS, J. W., LIDDLE, G. W., STANT, E. G., MICHELAKIS, A. M. and BRILL, A. B. Effect of an adrenal inhibitor in hypertensive patients with suppressed renin. Arch. Int. Med. 123: 366, 1969.
WOODS, J. W., PITTMAN, A. W., PULLIAM, C. C., WERK, E. E., WAIDIR, W. and ALLEN, C. A. Renin profiling in hypertension and its use in treatment with propranolol and chlorthalidone. New Engl. J. Med. 294: 1137, 1976.
WOOTEN, G. F. and CARDON, P. V. Plasma dopamine beta-hydroxylase activity. Arch. Neurol. 28: 103, 1973.
WURTMAN, R. J. Catecholamines. New Engl. J. Med. 273: 746, 1965.
YAMAGUCHI, T., OMAE, T. and KATSUKI, S. Quantitative determination of renal vascular changes related to age and hypertension. Jap. Heart J. 10: 248, 1969.
YAMAGUCHI, N., DE CHAMPLAIN, J. and NADEAU, R. Correlation between the response of the heart to sympathetic stimulation and the release of endogenous catecholamines into the coronary sinus of the dog. Circ. Res. 36: 662, 1975.
YAMAGUCHI, N., DE CHAMPLAIN, J. and NADEAU, R. A. Regulation of norepinephrine release from cardiac sympathetic fibers in the dog by presynaptic alpha- and beta-receptors. Circ. Res. 41: 108, 1977.
YAMAMOTO, K., HASEGAWA, T., MIYASAKI, M. and UEDA, J. Control of renin secretion, in the anesthetized dog. Relationship between renin secretion, plasma sodium concentration and G.F.R. in the perfused kidney. Jap. Circ. J. 33: 593, 1969.
YASUE, H., TOUYAMA, M., SHIMAMOTO, M., KATO, H., TANAKA, S. and AKIYAMA, F. Role of autonomic nervous system in the pathogenesis of Prinzmetal's variant form of angina. Circulation 50: 534, 1974.
YASUE, H., TOUYAMA, M., KATO, H., TANAKA, S. and AKIYAMA, F. Prinzmetal's variant form of angina as a manifestation of alpha-adrenergic receptor-mediated coronary artery spasm: documentation by coronary arteriography. Amer. Heart J. 91: 148, 1976.
YUN, J. C. H., DELEA, C. S., BARTTER, F. C. and KELLY, G. Increase in renin release after sinoaortic denervation and cervical vagotomy. Amer. J. Physiol. 230: 777, 1976.
ZAAL, G. A., STRANG, K. D., KOLSTERS, G., SCHALEKAMP, M. A. D. H. and BIRKENHÄGER, W. H. Haemodynamic changes during reversible hypertension due to liquorice ingestion. Neth. J. Med. 16: 169, 1973.

ZACHARIAS, F. J., COWNE, K. J., PRESTT, J., VICKERS, J. and WALLS, B. G. Propranolol in hypertension: A study of long-term therapy, 1964–1970. Amer. Heart J. 83: 755, 1972.

ZANCHETTI, A., BACCELLI, G., GUAZZI, M. and MANCIA, G. In: Hypertension: Mechanisms and Management. Ed. by G. Onesti, E. E. Kim and J. H. Moyer. Grüne and Stratton, New York, 1973.

ZANCHETTI, A., STELLA, A., LEONETTI, G., MORGANTI, A. and TERZOLI, L. Control of renin release: a review of experimental evidence and clinical implications. Am. J. Cardiol. 37: 675, 1976.

ZEHR, J. E. and FEIGL, E. O. Suppression of renin activity by hypothalamic stimulation. Circ. Res. 32 (suppl. I): 17, 1973.

ZEHR, J. E., HASBARGEN, J. A. and KURZ, K. D. Reflex suppression of renin secretion during distention of cardiopulmonary receptors in dogs. Circ. Res. 38: 232, 1976.

ZIMMERMAN, B. G. and GISSLEN, J. Pattern of renal vaso-constriction and transmitter release during sympathetic nervous system. J. Pharmacol. Exp. Ther. 163: 320, 1968.

ZIMMERMAN, B. G., GOMER, S. K. and LIAO, J. C. Action of angiotensin on vascular adrenergic nerve endings: facilitation of norepinephrine release. Fed. Proc. 31: 1344, 1972.

ZINNER, S. H., LEVY, P. S. and KASS, E. A. Familial aggregation of blood pressure in childhood. New Eng. J. Med. 284: 401, 1971.

ZUBERBUHLER, R. C. and BOHR, D. F. Responses of coronary smooth muscle to catecholamines. Circ. Res. 16: 431, 1965.

APPENDIX

Table A-1.

Variations of cardiac output measured by the impedance method on two separate days.

Nr.	First measurement l/min.	Second measurement l/min.
1	4,8	4,6
2	4,8	4,6
3	5,0	4,2
4	4,8	6,4
5	3,4	3,8
6	4,6	5,0
7	7,4	7,6
8	5,5	5,8
9	5,0	4,2
10	3,0	3,0
11	5,4	4,8
12	3,8	4,1
13	5,2	5,3
14	7,0	6,8
15	6,6	6,0
16	4,6	3,1
17	5,7	5,8
18	5,6	5,1
19	3,7	3,3
20	5,8	6,0
21	5,4	5,2
22	4,7	6,4
23	4,3	3,8
Mean and S.D.	5,0±1,1	5,0±1,2

Standard deviation of the paired observations, calculated as $\sqrt{d/2n}$ (where d is the difference of the two measurements and n is the number of observations) is 0,5 l/min. or 10%.

Table A-2.

Variations in glomerular filtration rate when measured on two separate days.

Nr.	Method	First measurement ml/min.	Second measurement ml/min.
1	^{57}Co	145	118
2	^{57}Co	177	165
3	^{57}Co	108	112
4	^{57}Co	117	96
5	^{57}Co	89	97
6	^{57}Co	89	85
7	Inulin	106	105
8	Inulin	102	110
9	Inulin	112	120
10	Inulin	74	93
11	Inulin	122	134
Mean and S.D.		113 ± 28	112 ± 22

Standard deviation of the paired observations: 9,5 ml/min. or 8,8%.

Table A-3.

Variations in renal plasma flow when measured on two separate days.

Nr.	First measurement ml/min.	Second measurement ml/min.
1	361	320
2	369	364
3	671	689
4	493	535
5	391	304
6	480	507
7	200	192
8	405	403
9	671	749
10	1196	1200
11	248	304
12	645	621
13	369	379
14	579	589
15	363	352
16	519	541
Mean and S.D.	498±233	503±242

Standard deviation of the paired observations: 27 ml/min. or 6,8%.

Table A-4.

Differences in estimated renal plasma flow when measured after renal arteriography and on a separate day, as an isolated procedure.

Nr.	Control ml/min.	After angiography ml/min.
1	655	696
2	304	304
3	693	556
4	483	457
5	643	592
6	347	390
7	624	488
8	535	526
9	373	332
10	476	407
11	493	481
12	364	375
13	499	524
14	208	221
15	437	434
16	424	422
17	595	473
18	485	421
19	419	507
20	556	486
Mean and S.D.	481±126	455±105

Standard deviation of the paired observations: 46 ml/min. or 8,8%.

Table A-5.

Variations in intrarenal blood flow during two successive measurements with a fifteen-minute interval.

Nr	C_1 First ml./min./100g	C_1 Second ml./min./100g	M.B.F. First ml./min./100g	M.B.F. Second ml./min./100g	% C_1 First	% C_1 Second
1	356	353	327	325	92	92
2	316	342	265	306	81	89
3	489	418	417	363	84	86
4	534	519	514	461	96	88
5	248	334	214	286	85	84
6	357	411	332	374	92	90
7	307	351	271	311	87	88
8	349	288	240	255	57	88
9	543	451	460	410	84	90
10	378	342	318	291	83	84
11	436	433	380	395	85	91
12	438	421	399	354	91	84
13	408	409	352	342	86	83
14	306	268	285	249	92	93
Mean	378	373	328	326	85	88
and S.D.	97	73	97	72	9	3

Standard deviation for the paired observations:

C_1 : 35 ml/min/100 g or 10 %

MBF : 29 ml/min/100 g or 9 %

%C_1 : 7% (without pat. 8) : 3%

V

Table A-6.

Variations in plasma volume determination on two separate days.

Nr.	First determination ml.	Second determination ml.
1	2678	2470
2	1255	1261
3	2821	3086
4	2895	3046
5	3960	3925
6	3005	2909
7	2061	2273
8	2306	2387
9	2083	2135
10	2184	2033
11	3071	3328
12	2401	2507
13	3700	3805
14	2690	2678
15	2084	1884
16	2970	3163
Mean and S.D.	2635±666	2680±707

Standard deviation of the paired observations: 110 ml. or 4,2%.

Table A-7.

Variations in the determination of the extracellular volume on two separate days.

Nr.	First determination l.	Second determination l.
1	6,4	6,9
2	14,6	13,5
3	18,8	15,6
4	9,6	9,6
5	10,4	10,0
Mean and S.D.	12,0±4,8	11,1±3,4

Standard deviation of the paired observations: 1,1 l or 7,1% .

Table A-8.

Variations in the plasma level of total renin concentration on two separate days.

Nr.	First sample ng/ml.hr.	Second sample ng/ml.hr.
1	13,0	14,0
2	19,4	16,3
3	15,5	8,3
4	4,3	3,3
5	10,7	12,8
6	8,7	8,8
7	3,5	3,4
8	2,9	2,5
9	11,6	10,9
10	7,7	6,9
11	9,5	9,7
12	3,6	3,7
13	4,3	5,4
14	8,0	8,3
15	9,4	8,6
16	5,0	4,5
17	13,5	13,0
18	10,3	10,4
19	8,7	7,7
20	5,8	11,4
21	1,4	2,0
22	3,6	4,4
23	17,4	13,7
24	8,3	9,1
25	5,3	5,0
26	8,6	6,9
27	25,9	23,0
28	11,5	9,0
29	10,8	8,1
Mean and S.D.	9,2±5,5	8,7±4,6

Standard deviation of the paired observations: 1,6 ng/ml.hr. or 16%.

Table A-9.

Variations in the plasma level of active renin concentration on two separate days.

Nr.	First sample μU/ml.	Second sample μU/ml.
1	15,2	22,6
2	24,0	20,4
3	13,6	10,4
4	24,7	28,6
5	43,5	53,6
6	30,7	25,3
7	20,1	17,0
8	5,6	7,1
9	6,5	5,6
10	19,3	20,2
11	14,0	12,1
12	70,3	73,4
13	20,6	19,8
14	27,6	26,5
Mean and S.D.	24,0±16,6	24,5±18,4

Standard deviation of the paired observations: 3,0 μU/ml. or 14% .

Table A-10.

Variations in the plasma level of aldosterone on two separate days.

Nr.	First sample ng/100 ml.	Second sample ng/100 ml.
1	14,2	10,7
2	31,8	10,4
3	10,0	9,1
4	18,3	17,2
5	32,2	25,7
6	15,6	9,0
7	5,0	5,3
8	9,6	7,2
9	13,4	11,2
10	15,2	15,6
11	10,1	13,5
12	11,1	15,3
13	3,9	4,7
14	8,9	14,7
15	12,1	7,4
16	13,3	11,8
17	5,3	27,4
18	18,9	23,6
19	9,8	9,8
20	10,4	12,7
21	21,8	12,5
22	16,4	15,4
23	11,2	10,8
24	6,5	7,4
25	4,6	2,7
26	7,3	6,5
27	11,4	13,6
28	13,5	11,6
29	7,5	11,2
30	14,0	16,2
31	7,3	6,8
32	9,0	8,7
33	10,9	13,6
Mean and S.D.	12,4±6,6	12,1± 5,6

Standard deviation of the paired observations: 4,5 ng/100 ml. or 28%.

Table A-11.

Variations in the plasma level of noradrenaline on two separate days.

Nr.	First sample ng/ml.	Second sample ng/ml.
1	0,19	0,20
2	0,60	0,52
3	0,17	0,14
4	0,26	0,30
5	0,21	0,20
6	0,12	0,13
7	0,33	0,32
8	0,27	0,28
9	0,48	0,54
10	0,40	0,58
11	0,35	0,31
12	0,16	0,21
Mean and S.D.	0,30±0,14	0,31±0,16

Standard deviation of the paired observations: 0,05 ng/ml. or 12% .

Table A-12.

Individual (raw) data obtained in normotensive control subjects.

Nr.	Sex	Age	B.S.A.	R.P.F.	R.B.F.	Co	G.F.R.	Inulin	P.V.	B.V.	E.C.V.	T.P.R.C.	A.P.R.C.	P. Aldo	P. Nor.
1	F	16	151						2062	3618					
2	M	18	173						3081	5312					
3	F	19	157						2495	3960					
4	F	19	204						2550	4250					
5	F	20	176						2512	4052					
6	M	21	171									136	22	22,6	0,25
7	M	22	166						2859	4929					
8	M	22	173									220	67	27,5	0,34
9	M	23	197						2760	4678	11,9				
10	M	23	186						2985	5632	13,2				
11	M	24	181	656	1171	124						120			
12	F	24	173											7,9	
13	F	26	173	521	868				2595	4325		101	63	16,0	0,18
14	M	27	177						2645	4560	13,2				
15	M	27	211						2895	4907	14,6				
16	F	28	171						2430	4190					
17	M	28	173											9,9	
18	M	30	186						2775	4784	9,8				
19	F	30	173									25	9	4,7	0,21
20	M	31	176						2780	5148	12,3				
21	M	31	176	835		143						135			
22	M	31	173											15,7	
23	M	32	199						3004	5270	15,8	219			
24	M	32	175						2780	5148	12,3				
25	M	32	164						2373	3955					
26	M	33	173	556	1158				2128	4433		270		12,8	
27	M	34	173						2401	4140					
28	F	35	181						3100	5167					
29	M	35	173										31	8,9	
30	F	37	161						2323	3872					
31	M	38	180						2519	4269	12,3	231			
32	M	38	173						3071	5388					
33	M	39	191						2648	4904	10,6	106			
34	M	39	197						2697	4732	14,1	225			
35	M	39	173						2084	3932					
36	M	41	206						3320	6036	14,7				
37	F	42	165						2590	4317	8,5				
38	M	42	186						3863						

Nr.	Sex	Age	B.S.A.	R.P.F.	R.B.F.	Co	G.F.R.	Inulin	P.V.	B.V.	E.C.V.	T.P.R.C.	A.P.R.C.	P.Aldo	P. Nor.
39	M	42	181						2685	4331	12,5				
40	F	43	173											3,8	
41	F	43	173											8,7	
42	F	44	184						2448	3948					
43	M	46	176						2419	4320	10,9				
44	F	46	173									99	13	6,4	0,20
45	M	47	176	583	940	136			2600	4407	13,2				
46	M	48	206						3318	5530					
47	M	50	169						3018	4868					
48	F	52	176						2212	3814					
49	F	52	165						2755	4238					
50	F	52	148						2606	4343					
51	M	52	192	384	674	112	118		3264	5829	11.7	82		5,0	
52	M	53	187	521	930	112	129		1809	3174	10,8	272			
53	M	54	208	887	1478	135						50			
54	M	54	173									211	23	5,3	0,14
55	M	54	173											12,6	
56	M	56	174						2330	4315	11.0	142			
57	F	56	185						2725	4007					
58	M	58	189						3419	5605					
59	F	58	173									80	8	3,2	0,19
60	F	60	151						2678	3800					
61	M	60	186						3669	5396					
62	M	61	179	387	667		91					298	75	14,6	0,57
63	M	62	184						3143	5238					
64	M	62	173									46	16	17,7	0,23
65	F	63	154	303	473	122	77		2164	3548	9,6	51			
66	F	63	202						2690	4410					
67	M	64	212	559	1016	152	115					278			
68	F	65	173											14,6	
69	M	67	200	490	891		98					252			
70	F	68	159						3120	4800					
71	F	69	157						2306	3719					
72	F	71	172						2785	3868					
73	M	72	172	268	412		70					78		1,1	
74	F	72	173											10,9	
75	M	74	173											11,4	
76	F	80	173											25,8	

Table A-13.

Individual (raw) data, obtained in the patients with essential hypertension. (group I)

Nr.	Sex	Age	B.S.A.	M.A.P.	H.R.	C.O. Dye.	C.O. Imp.	T.P.R.	P.V.	B.V.
1	M	17	190	105	82	8,2		1024	2914	5024
2	M	18	172	120	103		7,3	1315	2432	4504
3	F	19	162	123	88		5,4	1822	2392	4054
4	M	21	193	95	59		4,2	1810	3303	5795
5	M	21	201	121	84	6,85		1407	3842	7115
6	F	22	152	115					2207	3560
7	M	23	205	104	70	3,86		2155	2971	5305
8	M	23	195	130	60	5,8		1793	2918	5305
9	F	23	164	130	86	4,3		2419	1780	2825
10	M	23	187	95	70		7,7	987	2726	4956
11	F	24	172							
12	M	24	193	105	110	9,1		923		
13	M	24	193	105	105	7,6		1105	3180	4818
14	M	24	157	105	80	5,92		1412	1957	3495
15	F	24	157	115	66		4,6	2000	2483	4356
16	M	25	190	125		8,4		1192	2747	5087
17	F	25	180	116	70	4,2		2200	2370	3823
18	M	25	228	118	70	5,93		1592	2924	5221
19	M	25	169	110						
20	M	26	193	120	60	6,0		1600		
21	M	26	200	129	60		5,28	1955	2994	5758
22	M	26	215						2970	5500
23	F	27	170						2327	4082
24	M	27	197	127	115	7,2		1411	3288	5573
25	F	27	167	124	80	4,98	6,6	1992	2431	4191
26	M	28	210	122	58		7,8	1251	3634	6730
27	M	28	195	121	75	5,58		1735	2360	4214
28	M	28	204	105	90	7,8		1077	3070	5117
29	F	28	166	114		10,4		877	3148	4919
30	M	29	226	112	90	7,37		1216	2994	4990
31	M	29	200	114	109		5,28	1720	3431	5916
32	M	29	170	92	85	8,7	8,8	846	2565	4750
33	F	29	162	107	64				2407	3946
34	M	29	218	117	72		4,2	2229	3366	5905
35	M	29	173			7,7			2660	5216
36	M	30	200	137	78		5,5	1993	3100	5849
37	F	30	160						2295	3825
38	M	30	203						2967	5395
39	F	30	152	160	72	4,6		2783	2184	3702
40	M	31	183	115	75		4,6	2000	2571	4944
41	M	31	184	120	78	7,1		1352	2660	4361

E.C.V.	G.F.R. Cyano.	G.F.R. Inulin.	R.P.F.	R.B.F.	R.V.R.	F.F.	Ren. Fract.	T.P.R.C.	P.Aldo
10,7	127	121	684	1140	7368	0,18	14	15,9	
		100	549	980	9796	0,18	13	11,4	5,1
	121	108	667	1093	9003	0,16	20	4,1	21,6
		143	676	1186	6408	0,21	28	17,4	9,8
12,4	122	76	660	1217	7921	0,18	18	10,2	
9,3	86	80	396	660	13939	0,20		7,4	
		137	568	1014	8205	0,24	26	7,9	15,2
12,6	125		577	1089	9550	0,22	19	5,3	5,1
9,8	95		484	849	12250	0,20	20	5,3	
			816	1511	5030		20	14,8	34,1
	143		779			0,18		4,3	
13,9	155		1023	1764	4762	0,15	23	8,0	
8,9	66	87	440	733	11405	0,20	12	13,2	
		101	444	783	12218	0,23	16	9,3	8,0
			731	1354	7386		16	15,0	
11,1	121	105	540	870	10608	0,19	21	8,0	
	133		752	1367	6906	0,18	23	8,0	
			844	1407	6254			15,9	24,8
			757	1402	6847		23	16,0	
		160	660	1200	8600	0,24	23	15,7	7,5
12,5	129	131	749	1362		0,17		24,6	
								17,4	13,2
13,6		130	980	1849	5495	0,13	26	12,2	
9,6	106	98	387	645	15380	0,25	13	14,4	
			707	1309	7456		17	7,5	21,7
13,2	112		505	1082	8946	0,19	19	10,7	
10,8	165		773	1487	5649	0,21	19	6,7	
			847	1366	6676		13		
9,8	161		907	1744	5138	0,18	24	8,7	
		141	888	1531	6108	0,16	29	11,8	13,7
		105	535	892	8251	0,20	10	8,3	10,4
		117	667	1112	7698	0,18	28	5,4	
		141	561	1058	8847	0,25	25	13,3	29,2
			693	1308	8379		24	10,3	8,9
9,8	100	99	491	767		0,20		3,5	
12,6	107	118	493	836		0,24		7,8	
9,6	93	74	363	648	19753	0,20	14	3,6	
9,6		99	505	935	9840	0,20	20	13,0	6,3
10,0	133		671	1137	8433	0,20	16	5,3	

Nr.	Sex	Age	B.S.A.	M.A.P.	H.R.	C.O. Dye.	C.O. Imp.	T.P.R.	P.V.	B.V.
42	F	31	170	124	85	5,28		1879	2684	3834
43	M	31	193						2981	5323
44	F	31	155	140	88	6,7		1672	2028	3325
45	M	31	191	100	102		4,1	1951	2328	4392
46	M	32	183	97	85	7,1		1096	2618	4292
47	M	33	195	143		7,0		1634		
48	M	34	187	105	85	3,8	4,2	2210	2702	5004
49	F	34	156						2138	3341
50	M	34	216	105	63	7,15		1170	3615	6342
51	M	34	173	132	71	7,55		1393		
52	F	34	172	138	89	4,82	5,64	2290	2944	4826
53	F	35	174						2678	4463
54	M	35	206	125	86	7,4		1351	2955	5008
55	M	35	180						2805	5009
56	F	35	172	100	75	6,95		1151	2770	4074
57	M	35	169	80		6,62		967	2790	4359
58	M	35	200	115	60	4,6		2000		
59	M	36	198	105	50		5,3	1585	3196	5510
60	M	36	186						3100	5741
61	F	36	143	145	92	5,35		2168	2000	3077
62	F	36	151	115	96		4,9	1877	2175	3686
63	M	36	194	104	90	7,9		1053	2805	5100
64	F	36	151	116		5,3		1751	2067	3230
65	M	37	194	100	67	5,8		1379	2660	4508
66	F	37	179	110	92		6,2	1419	2664	4298
67	M	37	202	108					3621	6706
68	M	37	204	102	74	6,5		1249	3211	5838
69	M	37	182	107	58		5,2	1646		
70	F	37	153	113	76		3,9	2318	2292	3952
71	F	38	194	110		4,7		1872	2895	4991
72	M	38	188	103	57		3,49	2361	3095	6448
73	M	39	182	140	52		5,1	2196	2619	4762
74	M	39	174	113		8,1		1116	2745	4733
75	F	39	144	139	56		2,99	3719	2341	4335
76	F	39	160	140		6,0		1867	2688	4556
77	M	39	188	97	88	6,62		1184	3838	6505
78	F	39	152		70	6,8	4,3		1964	3168
79	F	40	162	127	59	4,2		2419	2295	3531
80	M	40	204	110	69		4,6	1913	2851	5002
81	F	40	175	124	90	4,82		2058	2336	4028
82	M	41	192	120	87	3,96		2424	2274	3610

E.C.V.	G.F.R. Cyano.	G.F.R. Inulin.	R.P.F.	R.B.F.	R.V.R.	F.F.	Ren. Fract.	T.P.R.C.	P.Aldo
7,4	97		587	947	10475	0,10	18	20,8	
	80		573	1023	10498	0,14	15	6,9	
			424	800	10000		20	21,3	31,5
18,7	75		472	726	10722	0,16	10	9,7	
		120	586	1126	7247	0,20	26	8,8	6,4
	76	70	295	492		0,24		11,2	
16,9	144		716	1256	6662	0,20	18	13,0	
10,3								17,2	
10,8		165	528	866	12748	0,31	18	14,1	6,9
16,7	134		709	1289	7758	0,19	17	6,1	
9,6								8,6	16,0
11,3	115		585	929	8611	0,20	13	3,6	
	105		653	1146	5585	0,16	17	5,5	
	110		436	838	10979	0,25	18	12,6	
		126	483	833	10084	0,26	16	7,7	7,4
	132	129	608	1086		0,21		14,0	
10,9	107		336	560	20714	0,32	10	5,7	
		106	539	914	10666	0,20	19	8,3	12,2
9,5	118		458	777	10708	0,26	10	9,7	43,1
9,6	85		371	580	16000	0,23	11	6,1	8,5
15,5	123		677	1167	6855	0,18	20	8,0	
			524	832	10577		13	3,4	9,4
12,3	140	128	575	1065	8133	0,22		15,0	7,5
	135		573	1042	7793	0,24	16	5,5	
			290	547	15649		11	6,8	9,4
			420	724	12486		19	9,5	13,4
13,0	148		720	1241	7091	0,21	26	5,6	
		139	555	1156	7128	0,25	33	12,4	9,8
11,0									
			225	409	22103		5	16,0	
9,1		75	313	559	19893	0,24	19	12,3	7,5
	119		547	977	11464	0,22	16	8,0	
9,8	124		559	1055	7355	0,22	16	9,1	
			493	808			12	3,7	11,7
8,0	98		411	663	15324	0,24	16	6,4	
		142	607	1104	7971	0,23	24	9,5	1,9
9,6	60		200	339	29263	0,30	7	13,4	16,8
		117	519	944	10169	0,23	24	9,6	

Nr.	Sex	Age	B.S.A.	M.A.P.	H.R.	C.O. Dye.	C.O. Imp.	T.P.R.	P.V.	B.V.
83	M	41	212	178	72	5,88		2422		
84	M	41	202	115	100	7,4		1243	3045	5342
85	M	41	207	102	60		5,8	1379	2888	5251
86	F	41	158	136	90	4,29	5,7	2536	2894	5675
87	F	42	191						2636	4321
88	M	42	214	130	68		4,7	2213	3618	6238
89	M	43	190	102	64		4,4	1855	2680	5154
90	M	43	210						3086	5321
91	M	43	204	150					3420	6453
92	M	43	207	134		7,2		1489	3968	6613
93	M	43	208	125	53		5,7	1754	3385	6387
94	M	43	212	134		6,5		1649	4093	6822
95	F	43	162	115						
96	F	43	162							
97	M	43	204						2605	4915
98	M	43	191	109	70	4,79		1820	2680	4786
99	M	44	206	100	48		5,1	1569	3732	6547
100	F	44	176						2223	3705
101	F	44	184	126		5,2		1938	2951	4611
102	F	44	173	125						
103	M	44	212							
104	F	44	185	160	74	7,85		1631	2933	4583
105	F	45	190	127	86		5,1	1992	3257	5428
106	M	45	185	140					2748	4738
107	M	45	206	100	63		3,6	2222	3430	6236
108	F	45	176	116		3,7		2508	2274	3728
109	M	45	183	122	70		7,0	1379	2452	4228
110	M	45	224	120	93	7,8		1231	3104	5352
111	F	45	185	122	86		5,1	1914	2431	4502
112	F	45	160	120	64		6,1	1574	2492	4224
113	M	45	206	119	75	6,87		1386	4055	6758
114	M	45	195	130					3336	6415
115	M	45	193	120					3206	6165
116	F	45	144						1731	2984
117	F	46	177	142	79		4,2	2705	3163	4792
118	M	46	197						2501	4631
119	M	47	208	130	60		3,9	2667	3384	6385
120	F	47	157	117	74		4,2	2229	2485	4284
121	M	47	215	124	96	7,73		1283	3290	5672
122	F	47	170						3473	5343
123	F	47	163	131	68	3,48		3011	2359	3932

E.C.V.	Cyano.	G.F.R. Inulin.	R.P.F.	R.B.F.	R.V.R.	F.F.	Ren. Fract.	T.P.R.C.	P.Aldo
10,9	120	106							
14,7	143		743	1376	6686	0,19	19	5,4	
		125	561	1020	7843	0,22	18	9,9	16,9
8,6	125	118	376	684	15906	0,31	16	8,6	21,4
10,2	120		645	1057		0,19	26	5,4	
			736	1247	8340		27	2,1	19,4
		120	586	1126	7247	0,20	26	8,8	6,4
	139		673	1202		0,21		8,3	
13,8	134		557	1051	11418	0,24		7,0	
			608	1067	10047		15	8,8	
10,9		122	555	1009	9911	0,22	18	16,9	12,1
			773	1356	7906		21		
			328	547				3,6	
	75		229	352		0,33		2,6	
13,5	185		599	1175		0,31		9,8	
7,4	117	116	521	883	9875	0,22	18	11,6	18,3
		146	577	1030	7767	0,25	20	8,5	6,3
			361	645				2,5	
13,9			507	805	12522		15	5,5	
13,9	124		453	719	13908	0,27		5,0	5,6
	167		763	1339		0,22		5,3	
12,8	154		828	1335	9588	0,19	17	5,0	
		147	608	1030	9864	0,24	20	4,0	13,7
7,6	116	113	537	1013	11056	0,21		9,8	
		129	581	1056	7576	0,22	29	7,3	11,8
	108		381	646	14365	0,28	17	3,5	
		107	333	608	16132	0,32	9	9,0	34,2
14,1	164		783	1450	6621	0,21	19	7,5	
			490	846	11537		17	11,3	4,8
		100	487	812	11823	0,21	13	7,9	12,7
10,5	146	158	420	712	13371	0,35	10	8,6	
12,3		110	427	854	12178	0,26		3,6	
12,2	141	127	504	933	10289	0,25		9,4	14,8
6,6								8,0	32,4
		106	368	566	20071	0,29	13	6,6	44,9
8,0	89	107	247	441		0,43		8,8	15,6
		128	576	1087	9568	0,22	28	5,0	4,7
		103	432	708	13220	0,24	17	7,5	7,0
14,6	129	138	620	1048	9466	0,22	14	10,6	
			241	389					
								15,8	

Nr.	Sex	Age	B.S.A.	M.A.P.	H.R.	C.O. Dye.	C.O. Imp.	T.P.R.	P.V.	B.V.
124	F	47	148	117	53	3,66	3,7	2546	2069	3567
125	F	47	169	116		4,6		2017	2924	4716
126	M	47	184	120	63		4,2	2286	3641	6743
127	M	47	196	113	73		6,0	1507	3263	5438
128	M	47	183	129	85	5,07		2034	2203	3865
129	F	47	146	144	72	3,97		2902	1840	3345
130	M	48	167	95	61		3,6	2111	2865	5026
131	F	49	174	146	71	4,33		2697		
132	F	49	175	120		6,0		1600		
133	M	49	202	100	87		3,7	2162	3229	5665
134	F	49	170	131					2752	4300
135	F	50	180	122	72	3,76		2596	2450	3952
136	M	50	169	132	74	4,34		2439	2939	4453
137	M	50	207	160		5,61		2282	3720	6414
138	F	50	185	118	70	4,26	3,9	2216	3011	5018
139	F	50	183	130	85	5,07		2051	2900	4915
140	M	50	216	120	88		7,1	1352	3405	5974
141	F	50	160	150	90	4,46		2691		
142	M	50	173	122	68		4,2	2324	3568	6732
143	F	50	163	154	66	3,47	5,43	3550		
144	F	50	148	158	65	2,62		4824	2442	4361
145	F	50	162	150	53		5,0	2400	2290	4256
146	M	50	184	120	53		5,4	1778	2804	5392
147	F	50	154	150	100	4,82		2490	2510	3984
148	F	51	168	127	60	6,55		1545	2059	3321
149	M	51	166						2395	4202
150	M	52	182	137	58		4,1	2673	2585	4700
151	M	52	170	170	62		5,5	2472	3365	5608
152	F	52	161						2594	3991
153	M	52	179						2111	4491
154	F	52	154	135	56		4,1	2634	2298	3379
155	M	53	185	163	76	5,12		2552	3381	5367
156	F	53	179	127	66		7,2	1411	2517	4195
157	F	53	182	125	80	5,4		1852	2995	4680
158	M	53	206	138	70	5,05		2178	3783	6522
159	F	53	167	120	82		4,4	2182	2580	4868
160	M	53	170	130		6,3		1651	2758	4925
161	M	53	227							
162	F	53	178						2571	4215
163	F	53	190	169	90		3,7	3643	3093	5333
164	M	53	179							

E.C.V.	G.F.R. Cyano.	G.F.R. Inulin.	R.P.F.	R.B.F.	R.V.R.	F.F.	Ren. Fract.	T.P.R.C.	P.aldo
	94	92	425	733	12715	0,22	20	3,6	10,6
			427	712	13034		15	2,3	8,4
		116	433	787	12198	0,27	19	7,0	3,4
		156	580	1094	8263	0,27	18	4,2	8,6
	119		614	1059	9737	0,19	21	16,8	
	98	88	361	656	17561	0,24	17	6,7	10,1
		112	480	842	9026	0,23	23	4,3	11.8
10,6	110		479	812	14384	0,23	19	3,9	
14,8	97		333	564	17021	0,29	9		
		122	500	926	8639	0,24	25	8,7	14,8
10,2	93		351	585	17915	0,26		8,0	
	111		407	656	14878	0,27	17	2,4	
10,4	87		405	614	17199	0,21	14	5,3	
15,6	110		490	817	15667	0,22	15	2,1	
								15,6	
12,7	114		515	888	11712	0,22	18	2,4	
		138	892	1538	6242	0,15	22	10,9	16,6
10,6		70	129	215	55814	0,54	5	7,8	
		128	540	982	9939	0,24	23	13,4	20,4
	72	81	289	535	23028	0,28	15	15,9	11,8
7,0								3,8	
		108	455	784	15306	0,24	16	2,2	18,5
		101	423	769	12484	0,24	14	13,9	6,3
	124		600	952	12605	0,21	20	3,1	
10,7	107	85	361	547	18501	0,24	8	5,5	
8,7									
			435	806	13598		20	4,4	24,3
		123	360	600	22667	0,34	11	10,7	31,9
	65		268	454		0,24			
			415	883				10,0	
9,4		86	418	597	18090	0,21	15	6,8	7,3
12,8								26,6	3,1
			320	525	19352		7	1,4	13,3
11,2	142		475	779	12837	0,30	14	3,0	
15,6	141	125	513	933	11790	0,24	18	9,6	
7,9		95	261	458	20961	0,36	10	4,1	17,9
			619	1263	8234		20	11,5	
	160		608	1105		0,26		5,5	23,3
11,8			633	1055				14,9	
16,2		127	587	962	14012	0,22	26	9,0	15,2
	100		407	678		0,25		16,0	

Nr.	Sex	Age	B.S.A.	M.A.P.	H.R.	C.O. Dye.	C.O. Imp.	T.P.R.	P.V.	B.V.
165	M	54	212	140	74	6,53		1715	3657	5541
166	F	54	158	123	64		3,9	2523	2162	3664
167	M	54	202	120		5,2		1846	3940	6678
168	M	54	183						2911	4852
169	M	54	191	138	110	5,08		2181	3152	5530
170	M	55	181						3198	5922
171	M	55	197	131		7,8		1344	3150	5250
172	F	55	184	144	58	3,62	3,69	3182	2680	4542
173	M	55	173	140		3,9		2872	2323	4224
174	M	55	200	125	70	6,4		1562	3751	6820
175	M	55	180	135	180	5,85		1846	2918	4784
176	M	55	226	129	62	3,62		2851	3083	5929
177	M	56	173	110	78		6,8	1294	2713	5024
178	M	56	184	147	66		4,6	2557	3106	5860
179	F	56	154	115	64	3,08		2987	2360	3471
180	F	56	190	120	78	5,3		1811	2545	
181	M	56	202						3289	6206
182	M	57	199	87	60	4,3	4,0	1619	2154	3916
183	F	57	161	165					2042	3582
184	F	57	173	126	63	5,13	4,1	1965	2349	4271
185	M	58	186	145		5,4		2148	2545	4314
186	M	58	167	145	72		5,5	2109	3334	4976
187	M	58	194	122	63	4,08		2402	3145	5616
188	M	58	189	121	58		5,1	2115	3073	5587
189	M	58	155	100	72		3,0	2667	1929	3162
190	F	58	158	102	61				2751	4510
191	M	58	160	155					2254	4098
192	M	58	178	112	69				2930	5140
193	M	58	187	120	59		4,8	2000	3694	6369
194	M	59	202	120						
195	M	59	189							
196	M	60	195	135	54		5,1	2118	3613	6229
197	M	60	177	160					2654	4825
198	M	60	202							
199	M	60	208	160					2177	3456
200	M	60	208	140		7,1		1577	2955	5095
201	M	60	174	110	87		3,4	2588	2970	4869
202	F	61	174	145	65	4,1		2829	3000	4688
203	F	61	171	134	95	8,8	5,7	1218	2336	4247
204	M	61	208	130		6,5		1600		
205	F	62	168	175	87	3,66		3825		

E.C.V.	G.F.R. Cyano.	G.F.R. Inulin.	R.P.F.	R.B.F.	R.V.R.	F.F.	Ren. Fract.	T.P.R.C.	P.Aldo
	120		501	759	14756	0,24	12		
			410	707	13918		18	3,7	22,1
15,7	175		627	1140	8421	0,28	22	3,4	
12,1								6,1	11,7
	114	96	341	631		0,28		16,1	6,7
15,2	130		568	979	10705	0,23	13	4,4	
10,1		70	353	579	19896	0,20	16	8,7	8,3
12,4	112		355	645	17364	0,32	17	4,3	
12,5	155		632	1170	8547	0,25	18	6,4	
	134		465	861	12544	0,29	15	2,4	
13,9	151		456	894	11544	0,33	25	11,1	
		103	303	561	15686	0,34	8	12,4	10,9
		91	329	621	18937	0,28	14	15,9	9,4
8,8	96		484	793	11602	0,20	26	2,2	
19,9								2,5	
			419	776	8969		18	8,3	15,6
		53	115	202	65347	0,47		12,2	39,4
7,7		64	307	512	19688	0,21	10	8,6	30,8
15,2	123		412	736	15761	0,30	14	5,3	
		82							
		114	541	984	9959	0,21	24	12,5	6,5
		101	339	605	18282	0,30	12	15,8	15,0
		87	479	785	10191	0,18	26	15,2	10,1
		105	440	710	11493	0,24		5,7	
8,9	88	75	305	555	22342	0,25		5,8	
		114	368	634	14132	0,31		8,9	18,5
		95	339	584	16438	0,28	12	11,4	9,9
	128		387	717	13389	0,33		3,2	
	117	110	455	812		0,24		8,6	
		102	345	595	18151	0,30	12	6,2	5,8
9,7	118		413	700	18286	0,29		7,8	
	141		359	665		0,39		9,1	
14,5	166	113	567	930	13763	0,20		3,6	
16,5	155		493	1059	10576	0,26	15	5,4	
		122	519	865	10173	0,24	25	4,3	15,6
12,7	127		553	916	12664	0,25	22	2,8	
			442	807	13333		9	12,7	14,6
	132		509	893	11646	0,26	14	4,0	
9,9	113		188	308	45455	0,60	8	6,4	

Nr.	Sex	Age	B.S.A.	M.A.P.	H.R.	C.O. Dye.	C.O. Imp.	T.P.R.	P.V.	B.V.
206	M	63	187						2108	4216
207	M	63	203	175	82	5,85		2393		
208	M	63	200	129	59	4,71		2191	3309	5515
209	F	64	175	140	80		5,1	2196	2890	4661
210	F	64	168							
211	M	64	212							
212	M	64	204	132	70	5,99		1763	2990	5537
213	M	66	189	137	69		5,9	1858	2839	5357
214	M	66	206	148	72	4,04		2941	3917	6528
215	F	68	166	183					2439	4435
216	F	69	165	142	52		2,82	4028	2730	4789
217	F	69	204	127					3028	5047
218	F	69	174	132	80		4,8	2200	2588	4540
219	F	70	168	122						
220	F	70	200	127	69		6,33	1605	3198	5243
221	F	70	164						2874	4790
222	M	70	179	120	79	5,35	5,1	1794	2847	5272
223	M	72	198	128	66		3,6	2844	3711	6084
224	F	73	176	134	67	4,68		2299	2895	4523
225	M	73	181	130	90		5,8	1793	2842	5573
226	M	74	190	130						

E.C.V.	G.F.R. Cyano.	Inulin.	R.P.F.	R.B.F.	R.V.R.	F.F.	Ren. Fract.	T.P.R.C.	P.Aldo
11,9	99	127	329	621		0,39		8,1	
14,8	125		425	708	19774	0,29	12	1,8	
12,8	135		449	748	13797	0,30	16	2,3	
	85	70	237	389	28792	0,30	8	8,1	12,6
	82		308	550		0,27			
	152	115	559	1016		0,21			
12,9	108		463	874	12082	0,23	15	10,9	
	102	111	453	871	12583	0,25	15	14,1	18,8
	132	135	339	566	21367	0,40	14	5,6	2,1
9,4	91	80	227	420	34857	0,35		9,1	
10,9		75	200	339	33510	0,38	12	20,1	36,9
12,2	74	74	189	295		0,39		11,0	
		102	301	528	20000	0,34	11	2,0	
	120	110	367	655	14901	0,30		10,5	
11,1		63	209	332	30602	0,30	5	10,8	11,2
								17,1	
		110	312	578	16609	0,35	11	9,7	21,5
			477	782	13095		22	3,4	9,0
	145	102	391	611	17610	0,26	13	14,6	13,8
8,7		90	352	618	16828	0,26	11	13,6	10,3
	73	134	524	873	12308	0,26		11,2	

Table A-14.

Variability of blood pressure.
Numbers refer to patients in table A-13.

	SYSTOLIC		DIASTOLIC		MEAN		
Nr.	max.	min.	max.	min.	max.	min.	basal
1	165	125	105	75	122	90	122
5	200	160	130	110	150	127	127
6	190	140	100	60			
8	175	100	120	70	137	87	113
10	165	120	125	80			
11	180	100	115	70			
19	200	120	130	70	157	87	112
20	210	125	130	75			
22	185	135	115	85	133	108	110
23	180	135	110	65			
24	180	95	110	50			
27	260	175	130	90	163	127	146
28	150	130	105	90	120	102	103
29	172	85	94	40	120	55	77
30	200	130	125	90	150	107	117
31	175	105	115	65	133	77	117
32	155	115	105	85	122	98	101
36	190	150	115	90			
40	190	130	110	80	133	97	107
41	230	125	120	80	157	98	116
42	160	90	105	55	123	68	87
43	180	110	120	60	140	77	77
44	160	85	105	40	118	62	73
45	220	145	130	100	158	118	132
50	155	85	105	65	122	75	91
55	190	120	120	90			
57	250	195	135	120	170	150	167
59	200	120	145	80			
64	185	120	110	80	133	95	100
65	220	140	140	85	153	107	126
66	150	115	105	65	113	85	85
67	205	115	130	65			
73	200	120	130	90	147	103	129
76	205	150	135	95	145	112	135
77	260	150	140	95	170	113	164
79	155	120	120	80			
84	150	105	100	70	113	85	101
86	200	100	120	65	140	77	111
88	210	120	120	70	150	87	112
89	185	105	100	70			
90	160	100	100	60	117	70	91

	SYSTOLIC		DIASTOLIC		MEAN		
Nr.	max.	min.	max.	min.	max.	min.	basal
94	220	135	140	100	163	112	138
97	230	130	135	100			
98	180	120	130	90			
99	195	120	120	75	142	90	120
104	190	120	110	75			
105	180	75	120	40	137	55	77
110	190	150	125	100	143	117	133
111	200	140	120	95	140	112	130
123	175	100	100	60			
124	210	110	120	60			
127	170	110	130	85			
129	200	100	115	50	132	65	104
133	200	100	80	40			
136	200	135	135	90	155	107	115
137	170	120	105	80	123	93	93
145	200	130	115	70			
147	150	125	100	85	117	103	117
149	260	215	140	110			
152	160	100	110	45			
153	210	145	140	100			
154	180	100	100	60	123	83	95
156	220	100	125	45	140	67	101
157	220	160	140	110	155	127	141
167	205	150	130	105	153	120	133
168	150	110	110	75	123	87	100
171	205	110	130	70			
173	175	130	125	90			
185	170	110	120	65			
199	175	135	130	100	145	112	113
204	190	105	120	75	140	85	118
205	160	110	110	70			
206	205	140	115	85			
207	210	135	120	95	150	112	112
210	155	102	90	54	107	71	84
212	180	125	125	75	142	92	100
214	160	105	125	70	127	82	101
215	195	140	120	100	142	113	113
224	170	90	100	50	120	63	85
225	165	100	100	45	110	68	92
229	160	130	110	85	130	100	113

Table A-15.

Individual (raw) data, obtained in the patients with essential hypertension. (group II)

Nr.	Sex	B.S.A.	Age	M.A.P.	C.O. Dye.	C.O. Imp.	T.P.R.	P.V.	B.V.
1	M	193	21	95		4,2	1810	3303	5795
2	M	193	21	88		6,1	1154	3011	5018
3	M	220	27	105		4,0	2100		
4	M	210	28	122		7,8	1251	3634	6730
5	M		28			4,3			
6	M	169	29	87		4,5	1564	2565	4750
7	M	218	29	117		4,2	2229	3366	5905
8	M	200	30	137		5,5	1993	3100	5849
9	M			115					
10	M	183	31	115		4,6	2000	2571	4944
11	M	191	31	100		4,1	1951	2328	4392
12	F	181	31	112		3,8	2358	2549	4395
13	F	178	33	105		6,0	1400	3139	5232
14	F	172	34	138	4,8	5,6	2295	2944	4826
15	F	178	34	120		4,3	2233	3028	4884
16	M	198	36	105		5,3	1585	3196	5510
17	F	179	37	110		6,2	1419	2664	4299
18	M	188	38	103		3,5	2361	3095	6448
19	F	144	39	139		3,0	3719	2341	4335
20	F	168	39	115		3,7	2486	2424	4253
21	F	145	39	112		6,8	1318	1904	
22	M	221	40	110				3791	6893
23	M	214	42	130		4,7	2213	3618	6238
24	F	160	44	100		4,8	1667	1487	
25	F	185	45	122		5,1	1914	2431	4502
26	M	216	45	110		5,3	1660	1170	
27	F	177	46	142		4,2	2705	3163	4792
28	M	202	46	102		6,2	1316	3505	6491
29	M	208	47	130		3,9	1507	3384	6385
30	F	157	47	107		4,2	2038	2485	4284
31	M		47						
32	M	184	47	120		4,2	2286	3641	6743
33	M	167	48	95		2,9	2621	2865	5026
34	M	183	48	148		3,9	3036	3303	5795
35	M	171	48	115				2297	4417
36	M	202	49	100		3,7	2162	3229	5665
37	F	162	50	150		5,0	2400	2290	4256
38	M	208	51	110		4,5	1956	3556	6838
39	M	194	51	117		3,7	2530	2820	5127
40	M	182	52	137		4,1	2673	2585	4700
41	M	170	52	170		5,5	2472	3365	5608

G.F.R.	R.P.F.	R.B.F.	R.V.R.	F.F.	T.P.R.C.	A.P.R.C.	P. aldo	P. nor.
143	676	1186	6408	0,21	218	58	9,8	0,20
136	571	936	7521	0,24	169	36	4,6	0,12
	975	1773	4738		99	15	11,2	0,12
	707	1309	7456		94	26	21,7	
					119	40	9,0	0,17
106	493	880	7909	0,22	194	75	31,8	0,44
141	561	1058	8847	0,25	166	66	29,2	0,21
	693	1308	8379		129	61	8,9	0,33
					176	71	18,7	0,51
99	505	935	9840	0,20	162		6,3	0,23
	424	800	10000		259	41	31,5	0,30
	500	862	10394		36	8	2,0	0,14
	772	1287	6527		65		23,7	0,20
165	528	866	12776	0,31	176		6,9	0,10
	564	910	10549		45	25	13,4	0,42
126	483	833	10084	0,26	109	47	7,4	0,26
	524	832	10577		42	18	9,4	0,34
139	555	1156	7128	0,25	155		9,8	0,25
75	313	559	19893	0,24	154		7,5	0,11
	447	784	11735			12	15,4	0,31
	384	674	13294		265		8,4	0,36
	545	991	8880		66	10	12,5	0,20
	736	1247	8340		26	7	19,4	0,34
	493	747	10710		108	41	4,6	0,37
	499	846	11537		185	64	2,4	0,17
	657	1195	7364		92	19	13,2	0,32
106	368	566	20071	0,29	82		44,9	0,40
	595	1102	7405		131	45	6,2	0,17
128	576	1087	9568	0,22	62		4,7	0,13
103	432	708	12090	0,24	94		6,9	0,10
					38	9	6,8	0,21
116	433	787	12198	0,27	88			0,33
112	480	842	9026	0,23	54	15	11,8	0,20
	263	453	26137		90	34	34,7	0,12
	556	1069	8606		144	33	11,4	0,35
122	500	926	8639	0,24	109	48	14,8	0,25
108	455	784	15306	0,24	28		18,5	0,12
	563	1083	8126		121	30	12,5	0,20
	507	922	10152		66	31	14,5	0,28
	435	806	13598		55		24,3	0,28
123	360	600	22667	0,34	134	49	31,9	0,44

Nr.	Sex	B.S.A.	Age	M.A.P.	C.O. Dye.	C.O. Imp.	T.P.R.	P.V.	B.V.
42	F	167	53	120		4,4	2182	2580	4868
43	M	173	56	110		6,8	1294	2713	5024
44	F	162	56	113		5,8	1559	1832	
45	M		56						
46	F	165	57	135		4,2	2588	2674	5045
47	M	195	57	130		4,4	2364	3222	5461
48	M	155	58	100		3,0	2667	1929	3162
49	M	178	58	112				2930	5140
50	M	187	59	128		4,9	2090	3300	5893
51	M	174	60	110		3,4	2588	2970	4869
52	M	195	60	135		5,1	2118	3613	6229
53	M	182	61	113		3,6	2511		
54	M	182	61	143		4,6	2487	3144	5716
55	M	191	63	167				1805	
56	M	178	67	140				2974	5041
57	F		68						
58	F		72			4,1			
59	F	170	73	130		3,2	3250		

G.F.R.	R.P.F.	R.B.F.	R.V.R.	F.F.	T.P.R.C.	A.P.R.C.	P. aldo	P. nor.
98	261	458	20961	0,36	51		17,9	0,93
103	303	561	15686	0,34	155		10,9	0,18
	330	579	15613		67	6	7,5	0,55
					13	8	23,7	0,12
62	205	347	31170	0,30	148		5,1	0,11
	540	915	11366		136	35	2,0	0,19
87	479	785	10191	0,18	190	71	10,1	0,76
114	368	634	14132	0,31	111	40	18,5	0,28
	290	509	20118		70	36	9,9	0,20
122	519	865	10173	0,24	54		15,6	0,19
102	345	595	18151	0,30	78		5,8	0,20
	452	853	10598			31	13,5	0,48
	240	436	26239		50		15,2	0,31
	348	621	21514		58	13	5,9	0,34
90	269	472	23729	0,33	82		12,2	0,18
					62	11	53,4	0,29
					66	15	4,9	0,41
	245	395	26329		41		11,5	0,15

Table A-16.

Follow-up of intrarenal haemodynamics.

Nr.	Age	C_1	C_2	M.B.F.	% C_1
1	25	526	25	488	92
	29	376	38	350	93
2	41	366	71	328	89
	46	327	27	263	76
3	34	486	28	422	86
	40	384	28	331	85

Table A-17.

Intrarenal haemodynamics and arterio-venous levels of total and active renin and noradrenaline in untreated patients with essential hypertension.

Nr.	Sex	Age	B.S.A.	T.R.B.F.	C_1	C_2	M.B.F.	% C_1	M.A.P.
1	M	18	172	980	271	61	233	83	120
2	M	21	193	856	512	69	447	86	105
3	M	29	170	877	376	38	350	93	86
4	M	30	197	1049	784	59	718	91	104
5	M	31	191	740	240	56	190	75	98
6	M	36	198	862	361	26	244	66	69
7	M	40		915					100
8	F	45	181	890	352	42	324	91	118
9	M	45	216	1195	497	44	435	87	110
10	M	46	202	906	366	27	328	89	120
11	M	47		1600					100
12	M	57	195	880	360	40	304	84	130
13	F	65		795					105
14	F	68	180	544	284	47	231	79	100

	TOTAL RENIN CONCENTRATION			ACTIVE RENIN CONCENTRATION			NORADRENALINE CONCENTRATION		
Nr.	periph.	art.	ven.	periph.	art.	ven.	periph.	art.	ven.
3	104	103	118	32	43	47	0.26	0,33	0,28
5	266	242	245	41	45	45	0,30	0,30	
7	66	66	70	10	11	12	0,17	0,15	0,22
8	185	122	144	64	50	70		0,12	0,14
9	108	92	109	19	18	25	0,22	0,16	0,18
10	155	136	165	49	45	48	0,13	0,17	0,20
11	39	44	51	11	18	21	0,21	0,16	0,22
12	120	156	148	35	35	48	0,19	0,23	0,28
13	86	87	106	18	20	23	0,63	0,61	0,64
14	64	66	72		12	17	0,38	0,33	0,29

Table A-18.

Sequential values for renin (active and total), aldosterone and noradrenaline before and during tilting.

	Control	Tilting 30°			Tilting 60°		
Nr. Nor.							
1	0,17	0,26	0,28		0,36	0,33	0,23
2	0,18	0,32	0,40	0,52	0,70	0,80	
3	0,51	0,63	0,58	0,58	0,85	0,81	0,84
4	0,18	0,34	0,18		0,24		
5	0,12	0,12	0,12	0,14	0,19	0,25	
6	0,48	0,50	0,56	0,49	0,48	0,44	0,45
Nr. T.P.R.C.							
1	119	104	203		318	392	199
2	101	121	138	114	174	219	
3	176	164	125	180	164	205	192
4	167	211	230		256		
5	13	26	26	23	25	35	
6	27	58	30	33	30	42	33
Nr. A.P.R.C.							
1	40	54	62		141	233	82
2	63	72	109	95	150	206	
3	71	95	87	92	111	155	159
4	18	31	45		51		
5	8	9	10	12	14	19	
6			13	20	18	21	22
Nr. aldo							
1	9,0	7,6	37,8		62,8	81,0	50,0
2	16,0	22,1	41,6	65,8	68,0	115,9	
3	18,7	24,5	30,1	26,3	41,0	50,5	34,5
4	5,3	8,5	21,0		20,4		
5	23,7	16,7	18,1	21,6	27,2	30,4	
6	6,5	4,3	5,7	11,3	5,7	6,5	4,6

Table A-19.

Individual data obtained in patients with essential hypertension before and after treatment (for 2 weeks) with propranolol.

Nr.	Sex	Age	M.A.P.		H.R.		C.O.		G.F.R.		R.P.F.	
			B.	A.	B.	A.	B.	A.	B.	A.	B.	A.
1	M	18	120	92	103	79	7,3	7.7	100	120	549	668
2	M	21	88	85	57	43	6,1	4,5	136	156	571	611
3	M	25	125	120			8,4	6,0			731	757
4	M	28	122	102	58	47	7,8	5,2			707	655
5	M	29	92	95	85	52	8,8	6,0	105	105	535	512
6	M	29	117	82							561	732
7	F	31	140	110	88	65	6,7	4,2	80	94	573	583
8	M	31	115	103					99	95	505	512
9	M	31	100	100	102	54	4,1	3,6			424	372
10	M	34	105	91	65	68	7,2	6,3	144	141	716	697
11	M	36	105	88	62	48	5,3	7,1	126	121	483	444
12	F	37	110	88	92	58	6,2	5,4			524	512
13	M	38	103	82	57	51					555	643
14	F	39							119	98	547	623
15	F	40	127	92	59	44	4,2	4,2	98	98	411	375
16	M	42	130	132	68	48	4,7	4,4			736	584
17	F	44	160	130	74	56	7,8	4,8	154	160	828	471
18	M	45	120	102	93	62	7,8	5,2	164	137	783	692
19	F	45	122	113	86	70	5,1	6,5			499	317
20	M	45	100	113	63	51					581	443
21	M	47	129	126	85	63	5,1	4,0	119	120	614	463
22	M	47	120	93	63	47	5,1	4,7	116	107	435	493
23	M	48	95	93	61	61	3,6	3,7			480	487
24	M	48	148	107	57	47	4,2	3,3			263	246
25	M	49	100	110	87	68	3,7	3,7	122	119	500	409
26	F	50	122	133	72	66	3,8	3,4	111	108	407	284
27	F	50	150	130	53	48	5,0	3,4	108	112	455	400
28	M	51	110	102							563	578
29	M	52	137	128	58	46	4,1	3,5			435	462
30	M	52	170	138	62	54	5,5	4,1	123	76	360	367
31	F	53	168	137	90	62			127	120	587	544
32	M	54	140	110	74	55	6,5	6,4	120	119	501	472
33	F	56	115	125	64	50	3,1	4,4	96	103	484	544
34	M	56	110	105	78	40			103	105	303	279
35	M	58	100	82	72	60	3,0	3,4	87	82	479	364
36	M	58	112	123	69	53			114	119	368	380
37	M	58	120	134	68	52	3,6	3,9			504	432
38	M	59	128	103	59	47	4,5	5,8			290	336
39	M	60	110	93	87	64	3,4	4,2	122	110	519	488
40	M	60	140	140	54	51	3,5	4,4	102	108	345	328
41	M	67	140	130	89	64	3,9	2,9	90	99	269	264

P.V.		T.P.R.C.		A.P.R.C.		P. aldo		P. nor.	
B.	A.	B.	A.	B.	A.	B.	A.	B.	A.
2432	2760	141	98			4,2	4,0		
3011	3250	169	176	36	47	4,6	4,9	0,12	0,17
		188	200						
3634	3229	94	108	26	26	21,7	9,4	0,20	0,17
2565	2905	114	150	32	33	10,4	6,1	0,28	0,25
3366	3264	166	161	66	61	29,2	20,0	0,40	0,23
2028	2025	86	86						
2571	2554	163	138			6,3	1,8	0,23	
2328	2516	259	228	41	40	23,5	12,2	0,30	0,12
		162	150						
3196	3089	96	79	47	20	7,4	12,0	0,26	0,21
2664	2611	42	80	18	24	9,4	2,0	0,34	0,33
3095	3010	155	166	65	46	9,8	7,0	0,25	0,29
2688	2620	100	74						
2295	2397	80	100						
3618	3705	26	34	7	5	19,4	13,4	0,34	0,25
2933	3300	62	32						
3104	3359	94	134						
2431	2813	156	166	12	39	4,7	3,9	0,20	
3430	3640	91	91			11,8	4,7	0,29	0,29
3641	3213	88	84			3,4	6,7	0,33	0,44
2865	2898	45	40	15	12	10,6	4,0	0,20	0,23
3303	3891	90	138	34	35	34,7	3,7	0,12	0,15
3229	3639	109	103	48	11	14,8	4,3	0,25	0,20
2450	2595	30	24						
2298	2525	28	36	5	6	18,5	1,7	0,12	0,26
3566	3576	121	144	30	33	12,5	7,9	0,24	0,18
2585	2988	55	56			24,6	15,3	0,28	0,28
3365	3173	128	96	49	8	31,9	17,6	0,44	0,51
3093	3062	113	100			15,2	19,3		
3657	3854								
2360	2485	28	60						
2713	2815	155	134	40	34	10,9	6,5	0,18	0,13
1929	1895	190	141	71	48	10,1	3,0	0.76	0,58
2930	3405	111	46	40	11	18,5	11,0	0,28	0,28
		75	81			4,9	2,0		
3300	3175	70	90	36	18	15,8	18,0	0.13	0,22
		54	55	17	14	15,6	9,6	0,19	0,39
3613	3732	78	64			5,8	7,0	0,20	0,20
2974	3191	82	84			12,2	20,6	0,18	0,20

Table A-20.

Variability of blood pressure before and after treatment with propranolol.
Numbers refer to patients in table A-19.

	Syst. max.		Syst. min.		Diast. max.		Diast. min.		Mean max.		Mean min.		Mean basal	
Nr.	B.	A.	B.	A.	B.	A.	B.	A.	B.	A.	B.	A.	B.	A.
1	170	150	120	115	105	90	80	70	123	110	93	92	93	103
2	185	140	120	110	110	95	80	70	133	110	95	83	120	115
3	205	160	115	120	130	110	65	60						
4	185	160	135	110	115	90	85	65	133	108	108	77	110	85
5	150	140	115	100	105	95	65	60	113	107	85	73	85	73
6	180	170	125	120	125	120	75	70	142	137	92	87	100	107
8	150	135	130	110	105	95	90	60	120	108	102	77	103	93
11	175	130	105	100	115	90	65	55	133	103	77	70	117	70
12	155	130	115	105	105	95	85	65	122	103	98	80	101	88
13	180	170	110	110	120	100	60	80	140	120	77	93	110	115
19	200	180	140	120	120	110	95	70	140	133	112	93	130	110
20	175	160	130	130	120	130	100	100	138	140	100	113	140	140
22	175	150	135	110	130	100	100	80	145	117	112	90	140	120
23	150	140	105	100	100	90	70	65	113	103	85	77	101	78
24	220	170	160	110	140	115	100	80	167	130	122	90	147	115
25	150	140	110	100	110	110	75	60	123	120	87	73	120	130
27	205	190	150	140	130	125	105	95	153	143	120	110	180	190
29	260	220	175	150	130	110	90	75	163	133	127	107	146	125
30	250	200	195	165	135	125	120	105	170	147	150	128	240	200
31	245	220	200	175	160	135	130	110	183	163	153	132	183	163
34	165	150	125	115	105	105	75	70	122	120	90	85	122	120
35	150	110	125	95	100	75	85	70	117	87	103	78	117	82
36	210	210	135	160	120	135	95	105	150	160	112	123	112	140
38	200	160	140	105	130	120	95	55	147	128	112	75	124	101
39	160	125	130	115	110	95	85	80	130	105	100	92	113	105
40	210	225	150	170	120	125	90	95	141	158	112	127	170	190
41	205	180	155	140	115	110	75	70	145	133	103	93	200	170

Table A-21.

Intrarenal haemodynamics and arterio-venous levels of total and active renin and noradrenaline in patients with essential hypertension who have been treated with propranolol.

Nr.	Sex	Age	B.S.A.	T.R.B.F.	C_1	C_2	M.B.F.	% C_1	M.A.P.
1	M	27		1329	408	36	352	86	95
2	M	28	209	1243	384	44	353	91	108
3	F	31		860	436	64	380	85	100
4	M	31	184	914	691	46	543	77	103
5	M	33	184	736	291	40	250	84	127
6	F	34		906	438	31	399	91	90
7	F	38	168	666	329	45	286	85	132
8	M	38	189	1076	548	30	502	91	93
9	M	45	206	820	337	41	303	89	113
10	M	46	202	969	498	37	436	87	99
11	M	47	192	667	268	39	220	80	135
12	F	48	181	381	297	77	183	51	131
13	M	48							
14	F	49			350	40	302	85	96
15	M	49			408	31	335	81	105
16	M	51	182	591	266	34	211	77	129
17	F	53		793	307	55	272	87	115
18	M	53	197	461	435	63	345	77	110
19	M	56	190	742	436	28	400	91	113
20	M	56							95
21	M	58	155	543	344	44	300	86	59
22	M	58	201	708	329	26	291	88	134
23	M	58	191	778	318	75	248	72	122
24	M	61			385	19	334	86	145
25	M	67		611	175	29	150	85	120

	TOTAL RENIN CONCENTRATION			ACTIVE RENIN CONCENTRATION			NORADRENALINE CONCENTRATION		
Nr.	periph.	art.	ven.	periph.	art.	ven.	periph.	art.	ven.
1.	118	159	139	24	17	22	0,09	0,09	0,11
3.	135	122	126	12	10	12	0,14	0,26	0,31
6.	45	49	54	7	8	7	0,32	0,20	0,21
10.	21	20	21				0,18	0,22	0,20
14.	112	108	114	18	20	20	0,42	0,28	0,26
15.	182	172	178	32	38	38	0,42	0,43	0,59
16.	18	36	40				0,28	0,28	0,54
20.	50	48	48	7	4	3			
21.	144	159	169	58	71	98	0,58	0,31	0,17
24.	106	116	133	26	40	39	0,75	0,68	0,78
25.	54	55	55	21	9	11	0,14	0,14	0,16