Blood pressure in childhood

Epidemiological probes into the aetiology of high blood pressure

Cover:
"Diastole Systole" by Per Kirkeby. Oil on canvas, 150.5 x 122.5 cm. From the Semele-series. Courtesy of Mr. Kirkeby, Copenhagen, and Mr. Michael Werner of Galerie Werner, Cologne.

A.R. Penck wrote about Kirkeby's art: "... Do not diminish the intensity of observation. New and surprising possibilities could develop. The familiar image becomes unfamiliar, the unfamiliar intimate. Be on your guard for habit. The unusual lurks behind the boring colours...".

BLOOD PRESSURE IN CHILDHOOD

EPIDEMIOLOGICAL PROBES INTO THE AETIOLOGY OF HIGH BLOOD PRESSURE

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR IN DE
GENEESKUNDE
AAN DE ERASMUS UNIVERSITEIT ROTTERDAM
OP GEZAG VAN DE RECTOR MAGNIFICUS
PROF. DR. J. SPERNA WEILAND
EN VOLGENS BESLUIT VAN HET COLLEGE VAN DEKANEN.
DE OPENBARE VERDEDIGING ZAL PLAATSVINDEN OP
WOENSDAG 6 APRIL 1983 DES NAMIDDAGS
TE 3.45 UUR

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Albért Hofman

geboren te Hardenberg

PROMOTOR: PROF. DR. H.A. VALKENBURG

CO-REFERENTEN: PROF. DR. W.H. BIRKENHÄGER
PROF. DR. H.K.A. VISSER

"When I finally reckon up the number of questions that can be settled, doubts resolved, and obscure places made clear, ... , I find a field of such vast extent that, if I explored it fully in all directions, not only would this treatise of mine turn, contrary to my plan, into a full-sized book, but the rest of my life would perhaps not suffice for my writing of it".

William Harvey (1578 – 1657) *De Motu Cordis* (1628)

Dedicated to
my parents ;
and to M.H.P.

Acknowledgments

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Contents

Chapter 1

Introduction

High arterial blood pressure takes a heavy toll in western populations (1). Its causes are still largely unknown, but its sequelae, a variety of cardiovascular and renal diseases, have been referred to as "a modern scourge" (2). High blood pressure of unknown cause, or essential hypertension, is considered by most to be a quantitative deviation from the norm (3). Thus, the study of the distribution, determinants and development of blood pressure may provide knowledge about the aetiology and pathogenesis of high blood pressure.

The basic idea of this thesis is, that it is possible to learn something about the causes of essential hypertension by inquiries of the correlates and the course of blood pressure in early life, long before the consequences of high blood pressure have occurred and early enough to prevent them.

From this idea the questions follow naturally. What is the level of blood pressure in childhood? Does the level in childhood tell us something about the level in adulthood, when the diseases that are related to high blood pressure occur? What are the determinants, or correlates, of the level of blood pressure? Which factors predict change in blood pressure during childhood? And finally, can future hypertensives be detected early in life?

These questions will be dealt with in the following chapters, where reports of various studies are given. The *piece de résistance* of this thesis are investigations performed as part of the EPOZ study, the Epidemiological Preventive Organisation Zoetermeer. Further studies have been carried out in other populations. The different designs of these studies illustrate that an epidemiologist has many options as a student of disease aetiology. One study is experimental – a randomised trial of sodium intake and blood pressure in newborns. As the experiment serves as the 'gold standard' for any scientific research in epidemiology as well as elsewhere (4), I am glad

that an experimental study in the open population could be part of this thesis. The other investigations have been non-experimental, observational. Some studies were cross-sectional, others were planned according to a longitudinal research design. The longitudinal studies were of the case-control type and of the follow-up type. And finally, the follow-up studies have been retrospective and prospective. An overview of the various studies, with their design, population and type is given in the Table.

In *chapter 2* an investigation of the level of blood pressure in childhood and some of its correlates is reported. *Chapters 3* and *4* deal with putative determinants of blood pressure level. In *chapter 5* the change of blood pressure during childhood is studied. *Chapter 6* presents evidence on the determinants of blood pressure change. In *chapter 7* these findings are discussed in the context of the relation between blood pressure and atherosclerosis. *Chapter 8* gives a reappraisal of the formal aspects of the studies and in *chapter 9* the material aspects of the evidence are discussed and some suggestions for further research are presented.

References

1. Weinstein MC, Stason WB. *Hypertension: a policy perspective.* Cambridge, Mass: Harvard University Press, 1976.
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3. Pickering G. *High blood pressure.* 2nd ed. London: Churchill Ltd, 1968.
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Table
Studies of blood pressure in childhood reported in this thesis

Question	Type	Design	Population	Ch
What is the level of BP in childhood?	cross-sectional	BP measured in 3,924 youngsters, aged 5 – 19	Zoetermeer, 1975 – 1978	2
Is high plasma noradrenaline a cause of high BP?	'case-control'	Plasma noradrenaline measured in 38 'hypertensives' and 39 'normotensives' aged 13 – 23	Zoetermeer, 1978	3
Is a high cardiac output a cause of high BP?	'case-control'	Cardiac output measured in 41 'hypertensives' and 41 'normotensives', aged 13 – 23	Zoetermeer, 1978	3
	cross-sectional	Cardiac output and BP measured in 319 youngsters, aged 15 – 19	Boston, Mass, USA 1977 – 1979	3
Is high sodium intake a cause of high BP?	retro-spective follow-up	Measurement of BP in 348 youngsters, 7.7 – 11.7 years, living in three areas differing in drinking water sodium	Zeeland, Hazerswoude, 1979	4
	random-ized trial, experiment	Measurement of BP in 245 newborns on a normal-sodium, and 231 on a low-sodium diet for six months	Zoetermeer, 1980 – 1981	4
Is there BP-'tracking' or 'horse-racing' in childhood?	pro-spective follow-up	Annual measurement of BP in 596 youngsters, initially aged 5 – 19	Zoetermeer, 1975 – 1982	5
What causes BP to rise in childhood?	pro-spective follow-up	Annual measurement of BP in 596 youngsters, initially aged 5 – 19	Zoetermeer, 1975 – 1982	6

Chapter 2

The level of blood pressure in childhood

Hofman A, Valkenburg HA.
Distribution and determinants of blood pressure in free-living children. Results from an open population study of children aged 5 – 19 (EPOZ study).
In : Kesteloot H, Joossens JV, eds. *Epidemiology of Arterial Blood Pressure.* The Hague, Boston, London: M Nijhoff, 1980:99 – 117.

6. DISTRIBUTION AND DETERMINANTS OF BLOOD PRESSURE IN FREE-LIVING CHILDREN

Results from an open population study of children aged 5–19 (EPOZ Study)

A. HOFMAN and H.A. VALKENBURG

The growing popularity of the idea that the roots of atherosclerosis can be traced in young individuals has evoked many studies of cardiovascular risk indicators in childhood [1]. The finding of early lesions in the aorta and coronary arteries of children [2] and young adults [3] has led to the statement that atherosclerosis is a pediatric problem essentially [4]. Epidemiological research of determinants of atherogenesis in childhood can be motivated by two main objectives. Firstly, studies of the distribution and determinants of cardiovascular risk indicators can provide insight into the pathogenesis of atherosclerosis. Secondly, when atherosclerotic lesions are present in children, interventive measures implemented early in life can possibly prevent the development of atherosclerotic complications later.

With respect to blood pressure in childhood, the hypothesis has been proposed that overactivity of the sympathetic nervous system in youngsters sets the stage for hypertension in adults [5]. Furthermore, a specific hemodynamic pattern in children and young adults with raised blood pressure has been postulated, characterized by high cardiac output and normal peripheral resistance [6–10].

But before meaningful conclusions can be drawn on the development of essential hypertension in adults, the predictive value of blood pressure in childhood must be examined. Therefore a study emphasizing etiological aspects of atherosclerosis was designed to investigate the natural history ('tracking') of blood pressure and other risk indicators. The present report deals with the distribution of blood pressure in childhood, as well as with the determinants and the persistency of raised blood pressure over a short period of time. Also data on interrelations with other cardiovascular risk indicators and familial relationships of blood pressure are presented.

1. METHODOLOGY

1.1. Population

In the period between April 1975 and June 1978, the total population aged 5 or over of two districts (one rural and one urban) of a Dutch town was asked

H. Kesteloot, J.V. Joossens (eds.), Epidemiology of Arterial Blood Pressure, 99–117.

to take part in the Epidemiological Preventive Organization Zoetermeer (EPOZ). Data were collected on cardiovascular risk indicators, rheumatic and lung diseases, and urinary tract infections. Of the 13,462 persons who were invited 10,532 (78%) participated. Blood pressure was measured in 3942 children (82%) aged 5–19, out of 4806 eligible. The response rate was highest in children aged 5–9 (87%), intermediate in the age group 10–14 (84%), and lowest in 15–19 year olds (77%). The nonresponse in boys was somewhat higher than in girls, due to sex-specific differences in the age group 15–19. The primary nonresponse was about 5% higher in the rural than in the urban district.

All the children who belonged to the age- and sex-specific upper decile of the distribution of one or more of the cardiovascular risk indicators (systolic and diastolic blood pressure, total serum cholesterol, Quetelet index, and smoking habits) were selected for a tracking study. A control group was recruited at random from the remaining part of the same population. In total, 1435 children, initially aged 5–19, were selected for follow-up. The general protocol consisted of reexamination at four weeks after the initial measurement for blood pressure and cholesterol. Further on, the subjects got annual follow-up examinations for all risk indicators. Children with a blood pressure reading of 140 and/or 90 mmHg or over at the first examination round were followed for their blood pressure after 2, 4, and 26 weeks before entering the general protocol.

1.2. Methods

Blood pressure (BP) was measured in a strictly standardized protocol, using a random-zero sphygmomanometer [11], known to reduce observer bias. Two independent readings were taken, in time separated only by a count of the pulse rate. The mean of these two readings was used for BP calculation.

Eight well-trained paramedical observers measured BP on the left arm of a sitting subject, with the arm held at heart level. In general, the measurement was performed between 8 a.m. and 5 p.m., after a rest period of about 15 min in sitting position and before venipuncture.

Following published recommendations [12, 13], the largest cuff comfortably encircling the arm was used, which meant that, in general, children aged 5–9 were measured with a $23 \times 10\ cm^2$ cuff, while for subjects aged 10 or over, a cuff of $23 \times 14\ cm^2$ was used.

The first, fourth, and fifth Korotkoff sounds were noted. For diastolic pressure, the fifth Korotkoff sound was used in the analysis. A remarkably constant mean difference of 4 mmHg between fourth and fifth Korotkoff sounds was found in all age groups up to 65 years.

The absolute and relative measurement error was assessed from the dupli-

cate readings. A mean absolute error of ±9.0 mmHg was found for both systolic and diastolic pressure in subjects aged 5–19. The measurement error increased with age in both sexes, and varied between observers from ±7.3 to ±11.9 mmHg.

Serum total cholesterol was measured in plasma of nonfasting subjects with a modification [14] of an automated enzymatic method according to Kageyama [15], in the laboratory of the Department of Epidemiology, which participates in the standardization program of the WHO Lipid Centre in Prague.

Uric acid was measured by using an automated enzymatic method [16] in a Technikon Auto-analyzer II.

Weight and height were estimated while the subjects were without shoes and wearing indoor clothes. Quetelet index (weight/height^2) was used as an index for relative weight.

Smoking habits were determined for subjects aged 15 or over by means of a home-filled questionnaire. Children aged 5–14 were interviewed in absence of the parents in the examination center.

1.3. Data analysis

Data analysis was performed with an IBM-370 and a PDP-11/34 computer system. Standard statistical techniques were applied, using an SPSS or a BMD package [17, 18]. The household being the sampling unit, the EPOZ project is essentially a family study and therefore, whenever possible, the parents of all examined children were also studied.

Only the 1589 families on which BP data are available for both father and mother and at least one child were used in the family analysis. In these 1589 families, age-adjusted regression coefficients of BP of the parents and of all children aged 5 or over were calculated. Data on 1346 families are available with the first child aged 5–19 years. Age-specific Pearson correlation coefficients were calculated for BP of the first child, on the one hand, and the parents and sibs, on the other.

2. RESULTS

2.1. Mean values of blood pressure

In Figure 1 and Table 1, mean values of systolic and diastolic BP are presented for boys and girls aged 5–19. Systolic BP is slightly higher in girls up to 12 years of age, but a marked difference in systolic BP appears after the age of 13, when boys have 7–10 mmHg higher systolic BP than girls. This

Table 1. Age- and sex-specific mean values ±SD of systolic and diastolic blood pressure in children aged 5–19 ($n = 3924$) (EPOZ 1975–78).

Age	n		Systolic BP		Diastolic BP	
	Boys	Girls	Boys $m \pm$SD (CV%)[a]	Girls $m \pm$SD (CV%)	Boys $m \pm$SD (CV%)	Girls $m \pm$SD (CV%)
5	148	151	97 ± 9 (9)	97 ± 11 (11)	61 ± 9 (15)	60 ± 9 (15)
6	153	148	99 ± 10 (10)	99 ± 11 (11)	63 ± 9 (14)	63 ± 10 (16)
7	136	138	103 ± 10 (10)	104 ± 12 (12)	64 ± 10 (16)	65 ± 12 (18)
8	140	151	103 ± 12 (12)	105 ± 12 (11)	65 ± 9 (14)	66 ± 10 (15)
9	150	146	104 ± 12 (12)	106 ± 13 (12)	64 ± 9 (14)	65 ± 11 (17)
10	132	129	108 ± 12 (11)	109 ± 13 (12)	67 ± 9 (13)	64 ± 11 (17)
11	160	131	109 ± 11 (10)	110 ± 12 (11)	65 ± 11 (17)	66 ± 10 (15)
12	150	147	111 ± 13 (12)	114 ± 14 (12)	65 ± 10 (15)	68 ± 10 (15)
13	144	141	116 ± 14 (12)	116 ± 14 (12)	66 ± 11 (17)	68 ± 10 (15)
14	127	143	118 ± 14 (12)	116 ± 12 (10)	66 ± 10 (15)	69 ± 8 (12)
15	128	127	123 ± 14 (11)	116 ± 11 (9)	66 ± 11 (17)	68 ± 11 (16)
16	106	135	125 ± 14 (11)	118 ± 12 (10)	68 ± 11 (16)	69 ± 9 (13)
17	107	115	126 ± 13 (10)	121 ± 13 (11)	70 ± 11 (16)	70 ± 10 (14)
18	85	85	129 ± 15 (12)	122 ± 14 (11)	71 ± 9 (13)	71 ± 11 (15)
19	94	77	131 ± 15 (11)	120 ± 12 (10)	71 ± 10 (14)	70 ± 10 (14)
Total	1960	1964	113 ± 16 (14)	111 ± 15 (14)	66 ± 10 (15)	67 ± 10 (15)

[a] Percent coefficient of variation.

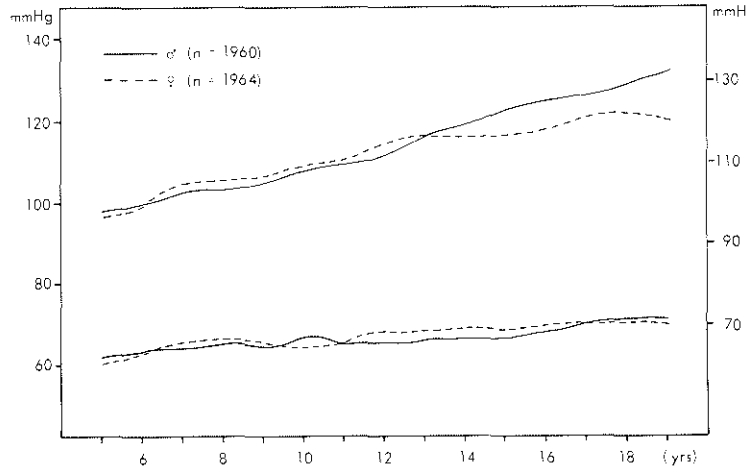


Figure 1. Age- and sex-specific mean values of systolic and diastolic blood pressure in children aged 5–19 (n = 3924) (EPOZ) 1975–78).

difference in systolic BP continues to exist until the end of the fourth decade, after which mean systolic BP of women increases over that of men.

No large differences in diastolic BP between the sexes are found in either children or adults. As a result of this, boys have considerably larger pulse pressures than girls between the ages of 13 and 43.

In Figure 2, the 5th, 50th, and 95th percentiles for systolic and diastolic BP versus weight are shown for both sexes. Weight was chosen as the reference variable, because it proved to be the best predictor of systolic and diastolic BP of all measured maturity indicators in this study. Besides that, it is standard practice in (school) health services to weigh children. In this presentation of percentiles, no adjustment for menarche was made. Such an adjustment would change the percentiles only slightly.

Only for systolic BP in boys is there an increase in absolute (mmHg) within-population variability, as indicated by the increasing standard deviations with age (Table 1).

When a relative measure of variability is applied (coefficient of variation), no differences in variability between the sexes and no increases with age are found. The relative variability of diastolic BP is considerably larger than that of systolic BP.

The age- and sex-specific distributions of both BP parameters are nearly normal. All distributions of systolic BP are slightly skewed to the right, while the distributions of diastolic BP are all (except the 15- to 19-year-old girls) skewed to the left.

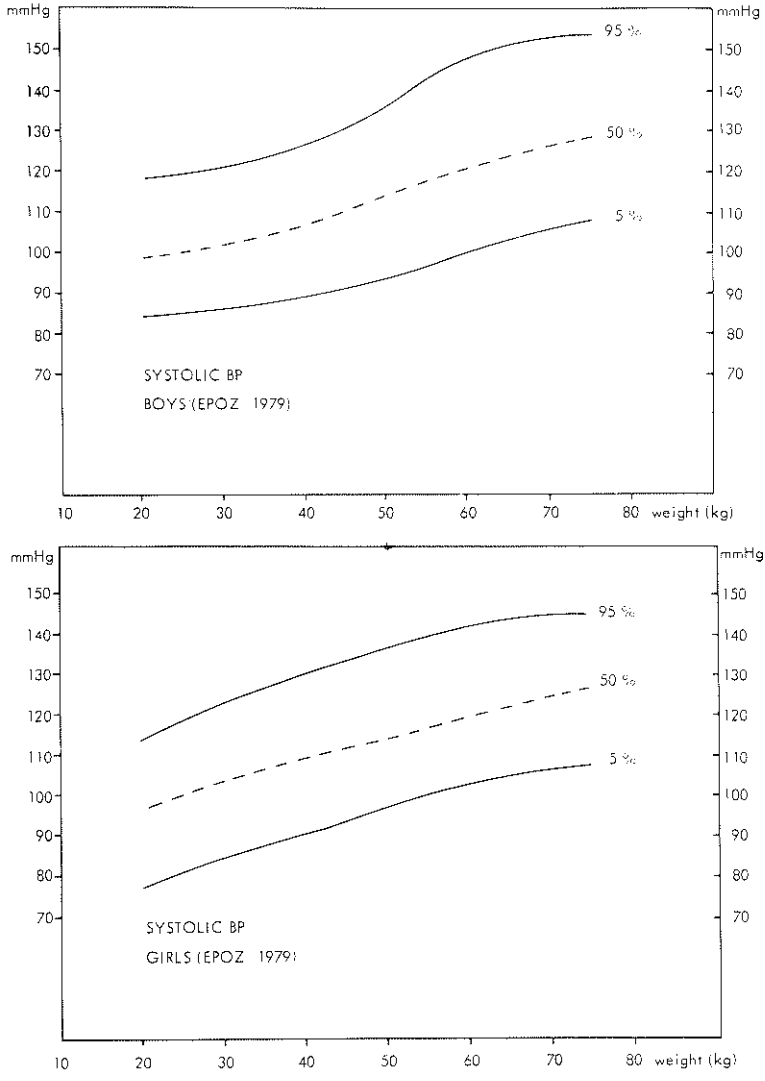
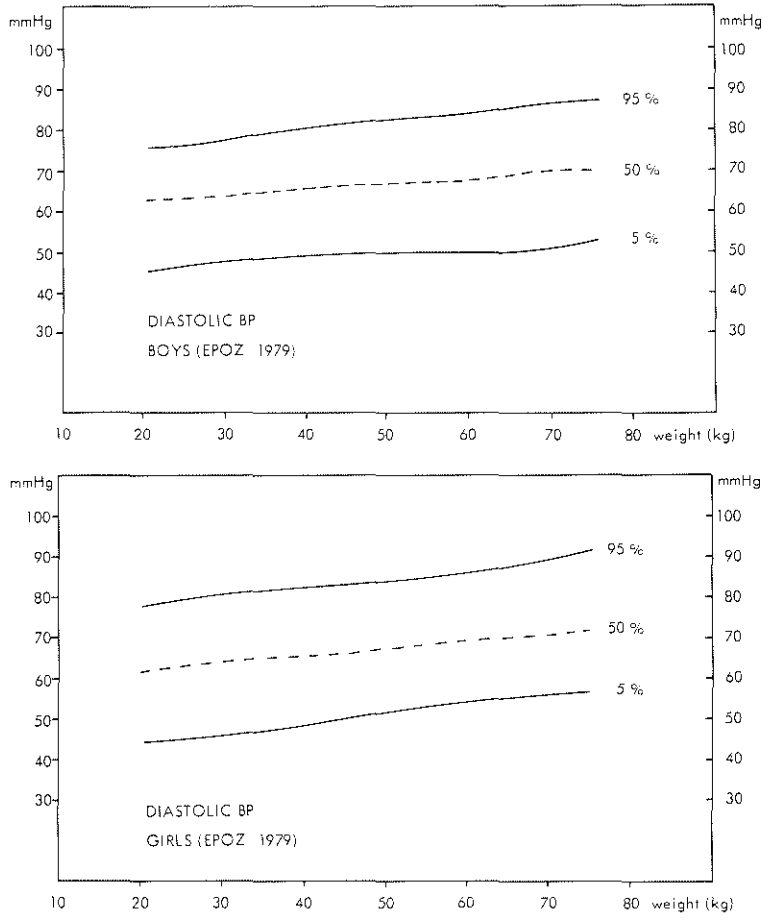


Figure 2. Systolic and diastolic blood pressure in boys and girls aged 5–19: 5th, 50th,

Children living in the rural district have higher mean systolic BP (114 vs 110 mmHg) than those in the urban district. This is true for both sexes and nearly all age groups. For diastolic BP and weight, no large differences are found between the districts.



and 95th percentiles of blood pressure with weight (n = 3924) (EPOZ 1975–78).

2.2. Prevalence of relatively high blood pressure

In Table 2, the percentages of children exceeding certain arbitrary cutoff points are shown. The cutoff levels recommended by WHO [19] for youngsters (140/90 mmHg) and adults (160/95 mmHg) are presented. The age dependency of BP in childhood is clearly demonstrated in these data. Over 20% of the boys aged 15–19 exceed 140/90 mmHg, while only 0.3% of the 5–9 year olds do so. Of the 15- to 19-year-old girls, 8.3% have a BP reading of 140/90 mmHg or over.

Table 2. Blood pressure in children aged 5–19: percentages at various cutoff points and follow-up ($n = 3924$) (EPOZ 1975–78).

Age	Total number in study	⩾140 and/or 90 %	⩾160 and/or 95 %	3× ⩾140/90 [a] % [b]
Boys 5–9	727	0.3	0.1	0.0
10–19	713	5.3	0.6	0.2
15–19	520	20.6	2.3	3.9
Total	1960	7.5	0.8	1.1
Girls 5–9	734	0.8	0.1	0.0
10–14	691	2.9	0.3	0.3
15–19	539	8.3	0.9	0.6
Total	1964	4.4	0.4	0.3

[a] Three times consecutively ⩾140 and/or 90 mmHg within a month.
[b] Total number corrected for loss at follow-up.

For an impression of the persistency of raised BP in childhood, the percentage of children who exceed 140/90 mmHg in all of three consecutive readings is also presented in Table 2. This criterion (or the 95th percentile) is sometimes advocated to define 'persistent hypertension' in childhood [13, 20]. Nearly 4% of the boys and 0.6% of the girls aged 15–19 had a BP level above 140/90 mmHg in all of three consecutive measurements, performed within a month.

2.3. Interrelations of cardiovascular risk indicators

Interrelations between various cardiovascular risk indicators were estimated by calculation of age-adjusted standardized regression coefficients of systolic and diastolic BP with total serum cholesterol, Quetelet index, and smoking habits (Table 3). Except for systolic with diastolic BP (0.52), the age-adjusted regression coefficients are very small. The positive association between serum total cholesterol and diastolic BP (0.13) is statistically significant with respect to this sample size, while the other smaller coefficients are not.

Table 3. Interrelations of cardiovascular risk indicators in children aged 5–19: age-adjusted standardized regression coefficients between blood pressure, cholesterol, smoking, and Quetelet index ($n = 3924$) (EPOZ 1975–78).

	Diastolic BP	Total cholesterol	Smoking habits [a]	Quetelet index [b]
Systolic BP	0.52	0.06	0.04	−0.01
Diastolic BP		0.13	0.04	−0.02
Total cholesterol			0.05	−0.02
Smoking habits				−0.02

[a] 3-Point scale: smoked never, in the past, now.
[b] Quetelet index = weight/height ^{2}.

2.4. *Family analysis*

Age is an important confounding variable in the relationship between BP of the parents and of their children. Therefore, overall age-adjusted (parent-child) regression coefficients were calculated. Between parents, a regression coefficient of 0.15 (systolic BP, $P<0.001$) and 0.11 (diastolic BP, $P<0.001$) is found. Overall age-adjusted father-child and mother-child regression coefficients are 0.13 ($P<0.001$) and 0.11 ($P<0.001$), respectively, for systolic BP. For diastolic BP, these overall coefficients are 0.11 ($P<0.001$) for both parent-child relations.

Table 4. Correlation coefficients between systolic and diastolic blood pressure of the first child with parents and siblings in three age groups (EPOZ 1975–78).

First child	Father	Mother	Second child	Third child
Systolic BP				
5–9 years	0.11[a] (417)	0.15[c]	0.40[c] (225)	0.34[a] (38)
10–14 years	0.17[b] (459)	0.26[c]	0.34[c] (422)	0.27[c] (172)
15–19 years	0.14[c] (470)	0.12[b]	0.25[c] (388)	0.16[b] (233)
Diastolic BP				
5–9 years	0.07 (417)	0.22[c]	0.17[b] (225)	0.29[a] (38)
10–14 years	0.17[c] (459)	0.26[c]	0.19[c] (422)	0.12 (172)
15–19 years	0.12[b] (470)	0.11[b]	0.21[c] (388)	0.11[c] (233)

[a] $P<0.05$;
[b] $P<0.01$;
[c] $P<0.001$.

Table 4 presents the various parent-sib and sib-sib correlations for both pressure parameters in three age groups. For the first child, the correlation with maternal BP is slightly larger than with BP of the father. No clear relationship with age of the first child can be shown except that the age group 10–14 years shows the largest coefficients. In general, the coefficients with siblings decrease with increasing difference in rank order. For systolic pressure, the magnitude of sib-sib correlations decreases with increasing age of the first child. This pattern is less clear for diastolic pressure, and the coefficients are not so large as for systolic BP.

2.5. *Determinants of blood pressure*

Correlation coefficients between systolic and diastolic BP and some anthropometric variables are presented in Table 5. All measured indicators of growth and physical maturity (age, height, weight and Quetelet index) have correlation coefficients with systolic BP of 0.5–0.6 and with diastolic BP of

Table 5. Correlation coefficients [a] of systolic and diastolic blood pressure with some variables, in children aged 5–19 ($n = 3914$) (EPOZ 1975 – 78).

	Systolic BP	Diastolic BP
Age	0.55	0.22
Sex	0.05	−0.03
Height	0.60	0.24
Weight	0.64	0.27
Quetelet index	0.55	0.25
Triceps skinfold [b]	0.16	0.08
Pulse rate	0.11	0.11

[a] Pearson test;
[b] $n = 2523$.

0.2–0.3. The only exception is the skinfold above the triceps muscle as measured by caliper, which has very small coefficients with both systolic and diastolic BP (0.08–0.16). The magnitude of these coefficients can be partly explained by mutual interrelations. Therefore, a stepwise multiple regression analysis was performed with systolic and diastolic BP as dependent variables.

Table 6. Stepwise multiple regression of systolic and diastolic blood pressure in children aged 5–19 ($n = 3914$) (EPOZ 1975–78).

Independent vars	Systolic pressure Regression coefficients		Diastolic pressure Regression coefficients	
	Unstandardized	Standardized	Unstandardized	Standardized
Weight (kg)	0.58	0.60	0.19	0.31
Pulse rate (/30 s)	0.56	0.27	0.23	0.17
Sex [a]	2.24	0.07	−0.35	−0.02
Age (years)	0.29	0.08	0.27	0.01
Smoking habits [b]	−0.71	−0.04	−0.35	−0.03
Height (cm)	0.30	0.04	0.12	0.00
Intercept (mmHg)	54.12		47.96	
Cumulative R^2	0.47		0.10	

[a] 0 = girls, 1 = boys;
[b] 3-Point scale: never smoked, in the past, now.

Table 6 shows that by entering weight, pulse rate, sex, age, smoking habits, and height into the equation, 47% of systolic variability and only 10% of diastolic variability can be explained in youngsters aged 5–19. By far, the most important determinants of both BP parameters are *weight* and *pulse rate*. Weight has a standardized regression coefficient of 0.60 with systolic BP, and of 0.31 with diastolic BP. Pulse rate is also positively associated with systolic

and diastolic BP, having standardized coefficients of 0.27 and 0.17, respectively.

Parental blood pressure levels are positively associated with BP of their children, but the independent contribution is small as compared with weight and pulse rate. No relation between BP in children and the *profession* or *educational level* of their fathers is found in the multiple regression analysis.

Age per se, expressed by its linear term, makes only a very small independent contribution in explaining the variability of BP in childhood.

Smoking is negatively associated with both BP parameters. The standardized regression coefficients are small (−0.04 with systolic and −0.03 with diastolic BP) although statistically significant.

Of 526 girls aged 15–19 years from whom this information was obtained, 140 (26.6%) were using *oral contraceptives*. Pill users have significantly higher systolic (123 vs 118 mmHg) and diastolic (71 vs 69 mmHg) BP than nonusers. In a multiple regression analysis (Table 7), women taking oral contraceptives have 0.93 mmHg higher systolic BP than women of the same weight, pulse rate, smoking habits, and age, but not taking the pill.

Table 7. Stepwise multiple regression of systolic blood pressure in women aged 15–19 ($n = 526$) (EPOZ 1975–78).

Independent vars	Cumulative R^2	Regression coefficients	
		Unstandardized	Standardized
Weight (kg)	0.12	0.52	0.35
Pulse rate (/30 s)	0.23	0.52	0.33
Smoking habits[a]	0.23	−1.33	−0.09
Oral contraceptives	0.24	0.93	0.06
Age (years)	0.24	0.36	0.05
Height (cm)	0.24	0.10	0.01
Intercept		55.45	

[a] 3-Point scale: never smoked, in the past, now.

The age-adjusted regression coefficients between *uric acid* and systolic and diastolic BP are 0.13 and 0.05, respectively. Uric acid makes no statistically significant contribution to the multiple regression analysis.

2.6. 'Tracking' of blood pressure

For the analysis of 'tracking' of BP, the children in the control group were randomly supplied with a proportional number of children from the group in the upper decile of risk indicators, to provide a representative sample of the

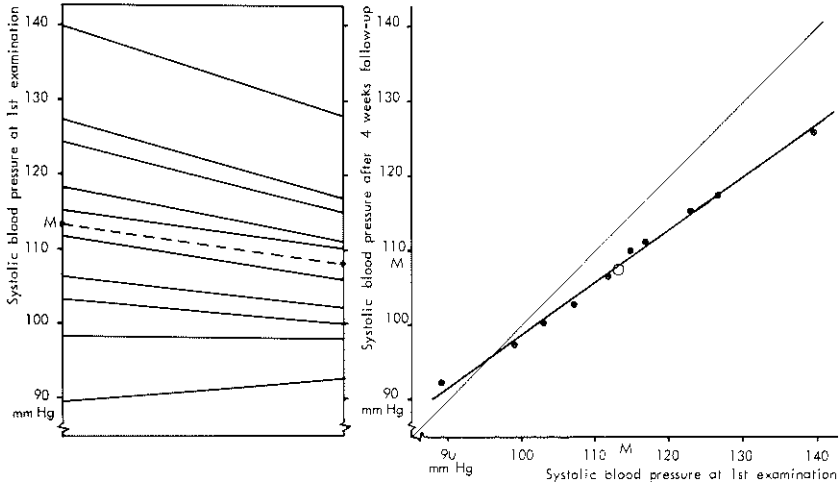


Figure 3. Systolic blood pressure at first examination and at follow-up after four weeks in a sample from the total initially examined population of children aged 5–19: mean values per decile at first examination and after 4 weeks ($n = 435$) (EPOZ 1975–78).

total population of children initially examined. In Figure 3, the mean values for systolic BP in the ten deciles at first examination and at follow-up at four weeks are presented. The overall mean value decreased from 113 mmHg to 108 mmHg, and a clear regression toward the mean is depicted. The regression line plotted in the right-hand part of Figure 3 presents no evidence for curvilinearity.

The variability of BP over time is also illustrated in Table 8. Tracking correlations are presented for the values at first examination and those at four-week follow-up. The correlation coefficients are larger for systolic than for diastolic BP (for the total group: 0.68 vs 0.41). The coefficient of pulse rate for the total group is 0.51.

Table 8. Tracking correlations [a] between initial examination and four-week follow-up in controls ($n = 435$) (EPOZ 1975–78).

Age	*n*	Systolic BP	Diastolic BP	Pulse rate
5– 9	139	0.53	0.48	0.42
10–14	159	0.55	0.34	0.48
15–19	137	0.63	0.31	0.54
Total	435	0.68	0.41	0.51

[a] Pearson test.

3. DISCUSSION

The *response rates* in various investigations of BP in childhood depend largely on the age of the subjects. In primary school children, the response rates are over 85% in most studies in the USA [21–25] as well as Europe [26–28]. By contrast, in adolescents and young adults, the response rates are below 80% in general [29–31]. The age-specific response rates in the EPOZ study reflect this general pattern.

In our tracking study in a rural and in an urban district, we have to cope with a very mobile study population. Although the results of follow-up can be influenced by this phenomenon, this is not the case for the prevalence data as presented in this paper. In our experience, home visits, with a personal approach to persuade youngsters to participate in the study, are very effective.

For systolic BP, a clear increase of *mean values* with age occurs in both sexes. The dissociation of mean values between the sexes after 13 years of age has been observed in various studies [21–24, 26] and can be explained only partly by weight differences. Its relevance is that during the 'incubation period' of atherosclerosis, males have higher BP levels than females, combined with higher mean values of total cholesterol and body mass index [32].

The comparison of our findings with other studies is hampered severely by differences in sampling frame, procedures, and methods. To exclude some dissimilarities, we compared our results with other open population studies only. Mean values of systolic BP were found to be higher in Tecumseh [21] and in the National Examination Survey [23, 24], about the same in Muscatine [29], and lower in whites in Bogalusa [22]. After correction for different definitions of diastolic BP, all American studies, except the National Examination Survey, found lower diastolic BP. Various school-based studies in European countries (UK, Ireland, Greece, FRG, GDR, Austria, Switzerland, and The Netherlands) [26–28, 31, 33–36] show large differences in mean values. Relatively high levels of systolic BP were found in Greece [36] and Austria [33], and low values in the UK [26] and Holland [27]. The gradient between the same age and sex group in these different studies is 15–20 mmHg. Unfortunately, the degree to which these differences are due to methodological dissimilarities cannot be estimated.

The within-population *variability* differs between both pressure parameters; diastolic BP having larger standard deviations. In both sexes, the variance of systolic BP increases with age. This phenomenon is more distinct for boys. The larger absolute variability in boys has been implicated in the origin of essential hypertension [20] and has been interpreted as an argument for the existence of a hyperkinetic phase in early essential hypertension.

However, when a measure of relative variability is used—the coefficient of variation—no clear difference in variability is found between the sexes. Hence, the increasing variability with age and the differences between the sexes, as reported above and in other studies, seem to be associated with higher mean values of systolic BP, and not with increasing variability per se. Mean values of diastolic BP increase only slightly with age, and no changes in absolute diastolic variability with age can be observed. This also supports the view that age is not related with BP variability per se.

As far as the *determinants* of BP are concerned, there is little doubt about the great importance of *genetic factors* [38]. This point has been stressed in particular by elegant adoption studies [39, 40], which indicate that about half of the variability of BP in children is genetically determined.

In our study as well as in others [41], there is a striking resemblance between the sex- and age-specific curves of mean systolic BP and mean uric acid values, especially in younger ages. Since mean values of uric acid are merely the result of endogenously determined factors, this is likely to be an expression of the impact of genetic factors. Our family analysis shows essentially the same pattern as reported from other investigations [21, 37, 42].

Weight has been reported from most other studies as being a very important independent variable in the explanation of BP variability in childhood. In relation with BP, it seems to be the best predictor of maturity [22, 37]. Age per se is unimportant in relation with BP.

Pulse rate is an important determinant of systolic and diastolic BP in this study and in others [30]. There are several possible explanations for this finding. Firstly, the association between pulse rate and BP can be an expression of excitation during the (first) BP examination. The fact that pulse rate makes an independent contribution to the explanation of systolic variability at the follow-up examination after four weeks, which is of about the same magnitude as of the first examination, contradicts this explanation. Secondly, it has been postulated that this association is a result of a hyperkinetic response of BP in childhood, which characterizes an early stage in essential hypertension. Published [43] and still unpublished data from a case-referent study of hemodynamic variables in our follow-up cohort do not support this hypothesis.

Smoking and the use of *oral contraceptives* have small and inverse effects on systolic BP. In the regression analysis, increased systolic BP is associated with the use of the pill, and with nonsmoking. Although the regression coefficients are small, these findings probably are important because of the short period of usage of the pill and the smoking of cigarettes in this age group.

A potentially important variable, currently under study in the same population of children, is *sodium intake* and its influence on the natural history of BP, and on the changes in BP values over time.

The study of the *natural history* of BP in adults as well as in children has gained much interest [44]. In 'tracking studies' devoted to this subject, the relative position of an individual in the distribution of BP is studied over time. In this way, an impression of the persistency of BP elevation can be obtained. In adults, correlation coefficients of about 0.6–0.7 have been found in various studies [45, 46]. In children, the situation is less clear. Some investigators reported tracking correlations in youngsters of 0.4–0.5 [46–48], while others found considerably smaller coefficients, varying from 0.2 to 0.4 [49–51].

In this paper, only data on short-term follow-up (after four weeks) are presented. Correlation coefficients of 0.7 for systolic BP and 0.4 for diastolic BP were found. Preliminary analysis of our data on longer follow-up periods shows coefficients of about 0.5 for systolic BP and 0.2 for diastolic BP, after two and three years of follow-up in children aged 5–19 [52]. The findings of regression toward the mean and decrease of mean BP after four weeks of follow-up are as expected. In this relatively short period of follow-up, the decreasing effect of the growing familiarity with the examination on mean BP level is more important than the process of maturation, which tends to increase BP over time.

The regression line of systolic BP, as shown in Figure 3, is linear, even in the highest deciles of BP levels. This linear regression in a nonintervened population is important for the interpretation of effects of interventive measures in hypertensive adults. When the same pattern of regression holds true for the adult population, the effect of intervention can be estimated by comparing the linearly extrapolated regression line from normotensives with the regression line obtained from hypertensives receiving therapy.

4. CONCLUSIONS

1) Persistently elevated BP is not uncommon in childhood, especially in boys aged 15–19.
2) There is no evidence for the increase in relative variability of BP with increasing age. Furthermore, in this respect there are no differences between the sexes and the BP parameters.
3) Mean systolic BP increases with age in both sexes. The increase is more marked in boys after 13 years of age, when a considerable dissociation between the sexes in mean systolic BP emerges. In both sexes, diastolic BP increases only slightly with age.
4) Weight, pulse rate, and parental BP levels are the most important determinants of BP in childhood. In a multiple regression analysis, a relatively

large part of systolic variability and only a small part of diastolic variability can be explained.

5) Smoking and the use of oral contraceptives have small, but independent, contributions in explaining systolic BP variability. Smoking is negatively associated and the use of oral contraceptives is positively associated with systolic BP.
6) 'Tracking' correlations of BP over a brief follow-up period (four weeks) are 0.68 for systolic BP, 0.41 for diastolic BP, and 0.51 for pulse rate. There is a clear regression toward the mean. Preliminary data about longer follow-up periods support the hypothesis of tracking of systolic BP.
7) The regression of BP at follow-up examination on the level at the initial examination is linear in the total population of nonintervened children.

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Chapter 3

Determinants of blood pressure level 1

Plasma noradrenaline, plasma renin and haemodynamics

Hofman A, Boomsma F, Schalekamp MADH, Valkenburg HA.
Raised blood pressure and plasma noradrenaline concentrations in teenagers and young adults selected from an open population.
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Raised blood pressure and plasma noradrenaline concentrations in teenagers and young adults selected from an open population

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Summary and conclusions

Plasma noradrenaline (PNA) concentrations were measured in 38 subjects aged 13-23, who were followed up for two to four years after an initial blood-pressure (BP) reading of 140/90 mm Hg or over was obtained, and in 39 age-matched controls from the same open population. Subjects who were hypertensive when the PNA concentration was measured had a significantly higher concentration (351 ± SE 26 pg/ml) compared with their controls (248 ± 29 pg/ml). Furthermore, in those subjects in whom the mean arterial pressure decreased by under 5% during the follow-up period the mean concentration was 363 ± 27 pg/ml, compared with 271 ± 29 pg/ml in their controls. PNA concentrations and systolic BP were positively correlated. A positive association between PNA concentrations and age was observed in the controls but not the subjects with hypertension, owing to the higher concentrations in younger hypertensive subjects.

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BMJ/240/79

These findings support the hypothesis that excessive sympathetic activity is related to early essential hypertension.

Introduction

Evidence is increasing that essential hypertension has its roots in childhood. Persistently raised blood pressure (BP) is not uncommon in children,[1-3] who tend to keep their relative positions in the distribution of BP over time,[4 5] possibly from the first months of life.[6] The hypothesis has been proposed that overactivity of the sympathetic nervous system plays an important part in the pathogenesis of essential hypertension in its early phase, and that other factors—for example, kidney changes—are more important later.[7] As a reflection of this, plasma catecholamine concentrations would be expected to be increased in young people with raised BP. Until now only studies of plasma catecholamine concentrations in adults[8-12] and a few adolescents[13] have been reported, and the data have been equivocal. We have measured the plasma noradrenaline (PNA) concentration in young people with potential hypertension and matched controls selected from the same population.

Subjects and methods

Blood pressure was measured as part of a tracking study of indicators of cardiovascular risk (EPOZ study) in 3924 children and teenagers initially aged 5-19, representing 82% of the population in that age group living in two districts in a Dutch town. Subjects with an initial BP reading of 140/90 mm Hg or over were re-examined at least five times during a follow-up period varying from two to four years. They were ranked, using the per cent decrease in mean arterial pressure (MAP; MAP = diastolic pressure + pulse pressure/3) during follow-up as compared with the initial examination. According to this ranking all subjects with the smallest (less than 5%) decrease in MAP over time (group 1) and all those with the largest decrease (more than 15%; group 2) were selected for estimation of PNA concentrations. Group 1 comprised 17 male and four female subjects, and group 2 comprised 12 male and five female subjects. All were aged 13-23, and physical examination and urine analysis showed no evidence of secondary hypertension. These subjects are referred to as "potential hypertensives."

Out of all the potential hypertensives, 18 (15 male) had a BP of 130/85 mm Hg or over when blood was sampled for estimation of PNA concentrations. These subjects are referred to as being hypertensives. Controls matched for age and sex were selected at random from the remainder of the same population. None of the subjects or controls received medication, and all were on their usual, unrestricted diets.

In a standardised protocol BP was measured by two trained observers, using a random-zero sphygmomanometer[16] with the subjects sitting. The Korotkoff sound V was noted as diastolic BP. The subjects were unaware of their BP group. They were asked not to eat, drink, or smoke for at least 90 minutes before the venepuncture, which was performed after 30 minutes' recumbency. Blood sampling was carried out only between 2 pm and 4 pm, when circadian variation is smallest,[16] and cases and controls were studied on the same occasions. Blood was collected in cold heparinised 10 ml tubes containing 15 mg glutathione and centrifuged immediately. The plasma was frozen to −20 C. PNA concentrations were measured by a modification of the radioenzymatic method of Henry *et al*,[17] in which phenylethanolamine-*N*-methyl transferase and tritiated *S*-adenosyl-L-methionine are used for *N*-methylation of PNA. The between and within coefficients of the measurement are below 10%.

Statistical analysis—Data analysis was performed with a BMD package implemented in a PDP11 computer. For group mean comparisons matched pairs were formed and the *t* test for unpaired observations with pooled variances was used. The P values correspond to a two-tailed test of significance. Due to missing values not all subjects could be used in group mean comparisons; this explains the differences in numbers in the various analyses.

Results

The distribution of PNA concentrations in potential hypertensives was more or less normal, with a slight skew to the right. In controls, however, a bimodal distribution was found (fig 1). No significant differences in mean PNA concentrations between the sexes were observed. The subjects who were hypertensive at the time of blood sampling had higher PNA concentrations than their matched controls. There were no significant differences in pulse rate and the number of cigarettes smoked daily (table I). When the two groups of potential hypertensives were pooled they had higher PNA concentrations than the controls (table II). This difference, however, was mainly due to the subjects who showed the smallest decrease in MAP over time (group 1), who differed from the controls in respect of the mean systolic BP and PNA concentration. By contrast, subjects in group 2 differed in respect of only mean diastolic pressure (fig 2).

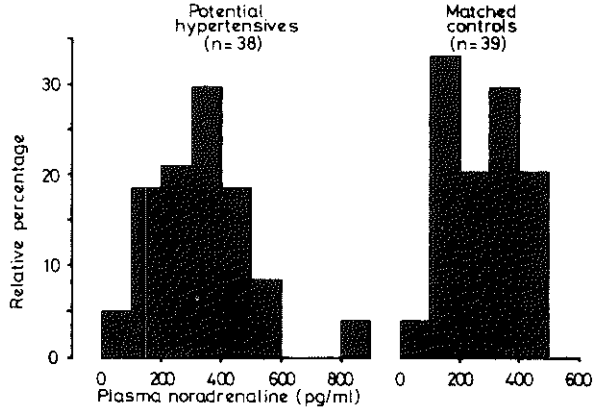

FIG 1—Distribution of plasma noradrenaline concentrations.

TABLE I—*Mean (± SE of mean) plasma noradrenaline (PNA) concentrations, blood pressure, and pulse rate in hypertensive subjects and age-matched controls*

	Hypertensive subjects* (n = 18)	Matched controls (n = 18)	P†
PNA (pg ml)	351 ± 26	248 ± 29	0·011
Blood pressure (mm Hg):			
Systolic	139 ± 2	125 ± 2	0·000
Diastolic	76 ± 2	73 ± 2	0·200
Pulse rate (beats min)	76 ± 3	72 ± 3	0·408
Age (years)	18·8 ± 0·8	18·4 ± 0·6	0·665

*Blood pressure 130 85 mm Hg or over at time of blood sampling for estimations of PNA concentrations.
†Two-tailed test.

TABLE II—*Mean (± SE of mean) plasma noradrenaline (PNA) concentrations and blood pressures in two groups of potential hypertensives aged 13-23 and their age-matched controls*

		Potential hypertensives	Matched controls	P‡
Group 1* (n = 19)	PNA (pg/ml)	363 ± 27	271 ± 29	0·027
	Blood pressure (mm Hg):			
	Systolic	134 ± 3	123 ± 2	0·005
	Diastolic	74 ± 3	72 ± 2	0·563
Group 2† (n = 17)	PNA (pg/ml)	305 ± 41	293 ± 28	0·802
	Blood pressure (mm Hg):			
	Systolic	126 ± 2	120 ± 2	0·076
	Diastolic	75 ± 2	67 ± 2	0·002
Total (n = 36)	PNA (pg/ml)	336 ± 24	281 ± 20	0·087
	Blood pressure (mm Hg):			
	Systolic	130 ± 2	122 ± 2	0·001
	Diastolic	74 ± 2	69 ± 2	0·025

*Subjects with initial BP of 140/90 mm Hg or more and smallest (less than 5%) decrease in mean arterial pressure during follow-up period.
†Subjects with initial BP of 140/90 mm Hg or more and largest (more than 15%) decrease in mean arterial pressure during follow-up period.
‡Two-tailed test.

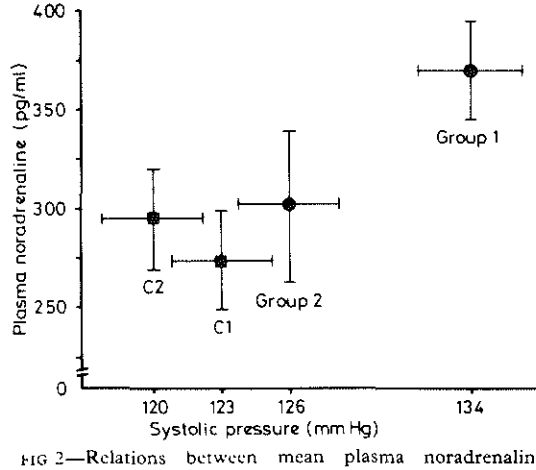

FIG 2—Relations between mean plasma noradrenaline concentrations and systolic blood pressure in subjects with smallest decrease in mean arterial pressure (MAP) over time (group 1 *v* controls (C1): P = 0·03) and subjects with largest decrease in MAP (group 2 *v* controls (C2): P = 0·8).

Figure 3 shows the PNA concentrations plotted against age. In the two groups of potential hypertensives no significant relation between these variables was found ($r = -0{\cdot}14$, $P = 0{\cdot}41$), but in the controls the PNA concentration was positively associated with age ($r = 0{\cdot}30$, $P = 0{\cdot}05$). No significant relation between the PNA concentration and BP emerged when subjects and controls were considered separately. When they were considered together a positive correlation could be shown between PNA concentrations and systolic BP ($r = 0{\cdot}21$, $P = 0{\cdot}06$) but not between PNA concentrations and diastolic pressure ($r = 0{\cdot}11$, $P = 0{\cdot}34$).

Correlation coefficients of PNA concentrations with pulse rate, pulse pressure, body-mass index, and number of cigarettes smoked daily did not reach significance.

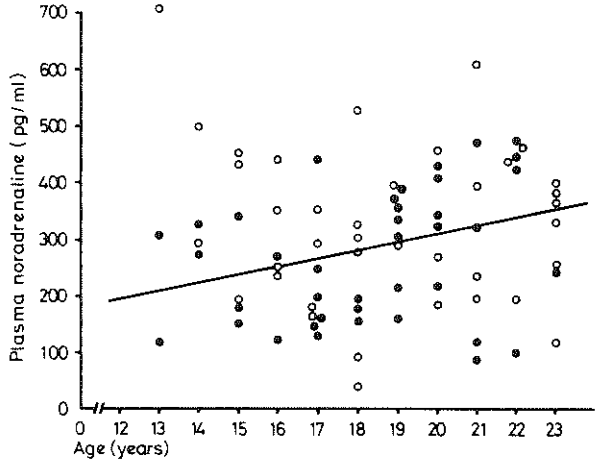

FIG 3—Relation between plasma noradrenaline concentrations and age. ○ = Potentially hypertensive subjects ($n = 38$; $r = 0{\cdot}14$, $P = 0{\cdot}41$). • = Matched controls ($n = 39$; $r = 0{\cdot}3$, $P = 0{\cdot}05$). Regression line of controls given by $y = 13{\cdot}1x - 40{\cdot}9$.

Discussion

In case-control studies recruiting suitable controls is crucial. The present study has an important advantage over others reported: both cases and matched controls were selected from the same open population in an epidemiological investigation, which enlarges comparability. Moreover, the relevant parameters were measured in a rigorously standardised protocol, known to reduce variability.[15 16 18] Studies in adults[10 12 13] have emphasised the need for careful age-matching. The present study shows a positive association between PNA concentrations and age in normotensive controls, even in the rather narrow age range of

13-23 years. This relation was not found in the potential hypertensives, suggesting altered sympathetic outflow in the early stages of essential hypertension.

Subjects who were hypertensive (according to an arbitrary cut-off) had clearly higher PNA concentrations than their matched controls. The subjects with the smallest decrease in MAP over time showed higher systolic BPs and concentrations of PNA than controls. The subjects with the largest decrease in MAP over time had a higher diastolic pressure than controls, but the PNA concentration was the same. These findings suggest that in teenagers and young adults a persistently raised BP is associated with increased PNA concentrations. Furthermore, systolic rather than diastolic pressure seems to be related to excessive sympathetic activity. This is also supported by the significant, albeit weak, association of systolic but not diastolic pressure with PNA concentrations. The different relations of PNA concentrations with systolic and diastolic pressures might explain the reported similarity of PNA concentrations in normotensive and hypertensive people,[10] because in that study subjects were primarily selected on the basis of high diastolic BP.

No differences in mean pulse rate between potential hypertensives and their controls were found. This was unexpected, since a positive association between pulse rate and BP in the young has been reported.[1] Nevertheless, the increased concentrations of PNA in subjects with raised BP shown in this study support the hypothesis that the sympathetic nervous system is important in the pathogenesis of essential hypertension.

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Haemodynamics, plasma noradrenaline and plasma renin in hypertensive and normotensive teenagers

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Summary

1. Plasma noradrenaline, active and inactive plasma renin, cardiac index and total peripheral vascular resistance were studied in 41 subjects, initially aged 10–19 years, who were followed up for at least 2 years after a blood pressure reading of 140 and/or 90 mmHg or more (initial hypertensives) and in 41 normotensive control subjects selected from the same population and matched for age, sex and body-mass index.

2. The initial hypertensive subjects had a lower mean cardiac index (3·63 ± SD 0·83 vs 4·00 ± 0·89 litre min^{-1} m^{-2}), a higher mean total peripheral resistance (26·8 ± 5·7 vs 22·8 ± 5·5 units) and a higher mean plasma noradrenaline concentration (336 ± 146 vs 281 ± 126 pg/ml) than the control subjects.

3. Mean plasma noradrenaline concentration was higher in initial hypertensive subjects with a high active renin concentration than in those with a normal renin concentration (442 ± 70 vs 324 ± 100 pg/ml).

4. A weight-adjusted standardized regression coefficient of 0·77 between active plasma renin concentration and left ventricular mass was found in normotensive control subjects.

5. These findings are at variance with the existence of a hyperkinetic phase in young hypertensive subjects and suggest that sympathetic overactivity may be related to early essential hypertension through increase of peripheral vascular resistance.

Key words: adolescence, blood pressure, cardiac index, hyperkinetic phase, noradrenaline, peripheral vascular resistance, renin.

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Introduction

Studies of the natural history of blood pressure in childhood have shown that a relatively high blood pressure tends to stay high over time [1–3]. In adolescents and young adults a hyperkinetic state, characterized by a high cardiac output and a normal peripheral vascular resistance, has been described as an important feature of the early stage of essential hypertension [4–12]. Furthermore the sympathetic nervous system has been implicated in the pathogenesis of essential hypertension. It has been postulated that increased sympathetic outflow in childhood sets the stage for essential hypertension in adults [13]. According to this view secondary changes in target organs, such as the kidney, occur later on in life and override the signs of sympathetic overactivity. It seems, therefore, attractive to study the early pathogenesis of essential hypertension in children and adolescents, in which these secondary changes due to hypertension have not yet occurred.

In the present study haemodynamics, assessed by echocardiography, plasma noradrenaline and active and inactive plasma renin were examined in teenagers with raised blood pressure and in normotensive control subjects matched for age, sex and body-mass index.

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Subjects and methods

Population

Blood pressure, serum total cholesterol, body-mass index and smoking habits were measured in 3924 children, aged 5–19 years, comprising 82% of the total free-living population of that age group in two districts of a Dutch town near The Hague [14]. All children in the upper decile of the distribution of one or more of these risk-indicators for cardiovascular diseases were selected for follow-up. A control group was randomly selected from the remaining part of the population. The resulting cohort of 1435 subjects was re-examined after 4 weeks and every year subsequently, to study the natural history ('tracking') of the risk-indicators. Subjects with secondary hypertension were removed from the follow-up cohort. The remaining children, both from the upper decile of the distribution of blood pressure and the control group, were reassured about their blood pressure and asked to participate in the follow-up study. No specific measures of intervention were taken. All children received the same general advice on life habits, especially dietary habits. Salt restriction was not stressed.

For the present study 85 subjects were selected from the follow-up cohort. These were all the children, aged 10–19 years, who had a blood pressure reading of 140 and/or 90 mmHg or more at the initial examination and who were followed up for at least 2 years. These 85 subjects were ranked according to the percentage decrease in mean arterial blood pressure (=diastolic pressure + pulse pressure/3) during follow-up. The percentage decrease in this was calculated by comparing the average mean arterial blood pressure over all follow-up examinations with that at the initial examination. Of the 85 children, 22 (17 boys) with less than a 5% decrease of mean arterial blood pressure over time and 19 subjects (13 boys) who had more than a 15% decrease were taken into the present study. Thus in total 41 children with a relatively high initial blood pressure, referred to as 'initial hypertensives', were selected for investigation of haemodynamics, plasma noradrenaline and plasma renin.

From the control group 41 control subjects were selected. They were matched for age, sex and body-mass index at the initial examination, had gone through the same follow-up regimen and were studied according to the same protocol as the cases. None of the children was on treatment and all had their usual unrestricted diets. The subjects were informed about the study in general terms and consent was obtained from all of them. In Table 1 the general characteristics of the initial hypertensive and the normotensive control subjects at the first examination are shown.

TABLE 1. *Characteristics of initial hypertensive and control subjects matched for age, sex and body-mass index at the first examination*

Results are means ± SD for 41 initial hypertensive and 41 control subjects.

Variables	Initial hypertensive	Control	2*P*
Systolic blood pressure (mmHg)	146 ± 13	119 ± 11	0·00
Diastolic blood pressure (mmHg)	73 ± 15	63 ± 9	0·00
Mean arterial pressure (mmHg)	98 ± 10	82 ± 8	0·00
Total serum cholesterol (mg/dl)	175 ± 24	173 ± 29	0·79
Serum uric acid (mg/dl)	4·74 ± 1·05	4·82 ± 0·93	0·72
Serum creatinine (mg/dl)	0·84 ± 0·15	0·83 ± 0·11	0·87
10^5 × Body-mass index (kg/cm^2)	212 ± 33	210 ± 33	0·85
Age (years)	16·4 ± 2·9	16·3 ± 2·6	0·72

Methods

All hypertensive and control subjects were examined between 14.00 and 16.00 hours and the same sequence of investigations was followed: 10 min of rest, blood pressure measurement, echocardiogram and venepuncture for a blood sample (40 ml) after 30 min recumbency.

Blood pressure. This was measured on the left arm by trained paramedical observers with a random-zero sphygmomanometer [15] with the children in a sitting position. The mean of two independent readings, which were separated by a count of the heart rate, was used for analysis. The fifth Korotkoff sound was taken as diastolic pressure.

M-mode echocardiography. This was performed by two experienced technicians with a commercially available echocardiograph [16]. End-diastolic left-ventricular diameter, end-systolic left-ventricular diameter, end-diastolic thickness of interventricular septum and posterior left-ventricular wall at three consecutive cardiac cycles were obtained directly from the echocardiogram by two observers. The mean of these readings was taken. The interobserver variation was below 5%. Cardiac index and total peripheral resistance were estimated by applying the formulae given in Table 2.

Plasma noradrenaline. Blood was collected in cold heparinized tubes containing 15 mg of glutathione, centrifuged immediately and frozen to −20°C for measurement of plasma norad-

TABLE 2. *Formulae applied for estimation of haemodynamic parameters from echocardiographic dimensions [23]*

BSA = Body surface area, according to Dubois & Dubois [33]; CI = cardiac index; ED = end-diastolic left-ventricular diameter; ES = end-systolic left-ventricular diameter; HR = heart rate; IVS = end-diastolic interventricular septum thickness; LVM = left-ventricular mass; LVPW = posterior left-ventricular wall; MAP = mean arterial pressure; TPR = total peripheral vascular resistance.

$$CI = [(ED^3 - ES^3) \times HR]/BSA \ (l\ min^{-1}\ m^{-2})$$
$$LVM = [(ED + IVS + LVPW)^3 - ED^3] \times 1{\cdot}05 \ (g)$$
$$TPR = MAP/CI \ (arbitrary\ units)$$

renaline concentration. A modification of the method of Henry, Starman, Johnson & Williams [17] was used. In this radioenzymatic method tritiated noradrenaline *N*-methyltransferase (EC 2.1.1.28, *S*-adenosyl-L-methionine : phenylethanolamine *N*-methyltransferase) was used for *N*-methylation of plasma noradrenaline. Some data on noradrenaline have been published elsewhere [18].

Active and inactive plasma renin. Blood was collected in ice-cold tubes containing disodium ethylenediaminetetra-acetate (EDTA) (5 nmol/l), centrifuged immediately and stored at −20°C for enzymatic measurement of active and inactive plasma renin concentrations. The measurement was performed by radioimmunoassay as described earlier [19] in which prorenin is activated by acidification to pH 3·3 [20]. Plasma renin concentration is expressed in μ-units of standard human kidney renin (MRC standard 68/356)/ml of plasma. The concentration of inactive renin was calculated by subtracting the value obtained after pH 7·5 treatment from the value at pH 3·3.

Data analysis

Group means are expressed with standard deviations (SD). For each variable only complete matched pairs were taken in the analysis and Student's *t*-test for unpaired observations with pooled variances was used after a stratified analysis of the matching variables revealed no differential effects. Not in all comparisons could 41 pairs of subjects be used due to missing values. *P* values corresponding to a two-tailed test of significance are given. Weight-adjusted standardized regression coefficients were calculated by entering weight as an independent variable in a multiple linear regression model.

Results

Blood pressure

Mean values of systolic and diastolic blood pressure at the first examination, during follow-up and at the occasion of the study of haemodynamics are presented in Fig. 1.

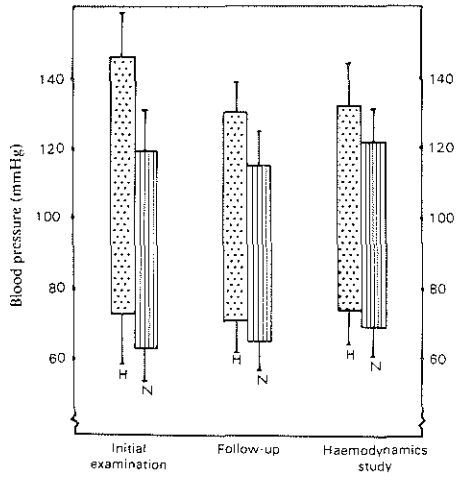

FIG. 1. Mean values of systolic and diastolic blood pressure at the initial examination, at follow-up and at the occasion of the present study of haemodynamics in initial hypertensive (H) and normotensive control (N) subjects.

In initial hypertensive subjects mean systolic blood pressure decreased from 146 ± 13 at the first examination to 130 ± 8 during follow-up and to 132 ± 12 at the occasion of the haemodynamics study. Mean diastolic blood pressure was 73 ± 15 at the initial examination, 71 ± 8 during follow-up and 74 ± 9 at the haemodynamics study. In the control subjects only small changes in mean systolic and diastolic blood pressure were found during follow-up. Mean systolic pressure changed from 119 ± 11 initially to 115 ± 9 during follow-up and 120 ± 10 at the study of haemodynamics, whereas mean diastolic pressure increased from 63 ± 9 initially to 65 ± 9 (follow-up) and 69 ± 8 (haemodynamics study).

Haemodynamics

Mean values of the haemodynamics in hypertensive and control subjects are shown in Table 3. Cardiac index was 3·63 litres min^{-1} m^{-2} in initial hypertensive and 4·00 litres min^{-1} m^{-2} in control subjects ($P = 0{\cdot}06$). Mean total peripheral vascular resistance was significantly higher in initial hypertensive subjects (26·8 ± 5·7 units) than in control subjects (22·8 ± 5·5) ($P = 0{\cdot}003$). The weight-adjusted standardized regression coefficient of systolic blood pressure with cardiac index was 0·22 (initial hypertensive subjects) and 0·27 (control subjects). With total peripheral

TABLE 3. *Mean values (±SD) of haemodynamics, plasma noradrenaline and plasma renin measured in 41 initial hypertensive and 41 control subjects*

Variables	Initial hypertensive	Control	2P
Systolic blood pressure (mmHg)	132 ± 12	122 ± 10	0·00
Diastolic blood pressure (mmHg)	74 ± 9	69 ± 8	0·01
Heart rate (beats/min)	73 ± 12	74 ± 12	0·74
Cardiac index ($l\,min^{-1}\,m^{-2}$)	3·63 ± 0·83	4·00 ± 0·89	0·06
Total peripheral resistance (units)	26·8 ± 5·7	22·8 ± 5·5	0·00
Active renin (μ-units/ml)	27·9 ± 14·9	30·7 ± 14·1	0·38
Inactive renin (μ-units/ml)	101·1 ± 62·2	82·7 ± 34·6	0·10
Plasma noradrenaline (pg/ml)	336 ± 146	281 ± 126	0·09
Age (years)	18·6 ± 2·9	18·4 ± 2·6	0·72

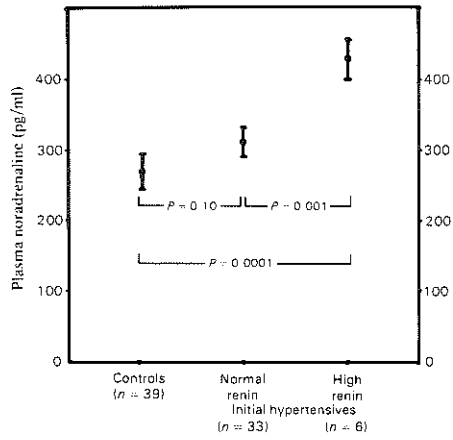

FIG. 2. Mean values ± SEM of plasma noradrenaline concentration in initial hypertensive subjects with high active-renin concentration (>45·0 μ-units/ml), compared with those with normal renin concentration and with control subjects.

resistance these coefficients were very small (−0·06 for initial hypertensive subjects and −0·04 for control subjects).

Plasma renin

In Table 3 the mean values of active and inactive plasma renin concentration are presented. No significant differences of active plasma renin between hypertensive and control subjects could be shown, but inactive plasma renin was higher in initial hypertensive subjects than that in control subjects (101·1 ± 62·2 vs 82·7 ± 34·6 μ-units/ml; $P = 0·10$). No relationship between plasma renin concentration and age was found. The regression coefficients between active and inactive plasma renin and systolic blood pressure were very small.

Plasma noradrenaline

Mean levels of plasma noradrenaline concentration were higher in initial hypertensive subjects than that in control subjects (336 ± 146 vs 281 ± 126; $P = 0·09$) as is shown in Table 3.

In control subjects none of the regression coefficients of plasma noradrenaline with heart rate and cardiac index reached statistical significance. They were −0·05 and 0·08 respectively.

Interrelation between plasma renin and noradrenaline

Mean values of plasma noradrenaline concentration in initial hypertensive subjects with high active plasma renin are compared with those with normal plasma renin concentration and with control subjects (Fig. 2). High renin concentration is defined arbitrarily as >45·0 μ-units/ml (mean + 1 SD in control subjects). Mean plasma noradrenaline concentration was 442 ± 70 pg/ml in high renin initial hypertensive ($n = 6$), 324 ± 100 in normal renin initial hypertensive ($n = 33$) and 281 ± 124 in control subjects. The weight-adjusted standardized regression coefficient between active plasma renin and left-ventricular mass was 0·77 in control subjects, whereas it was not significant in initial hypertensive subjects.

Discussion

The principal findings in the present study are that initial hypertensive teenagers tend to have a lower cardiac index, a higher total peripheral vascular resistance and a higher level of circulating catecholamines as compared with matched control subjects from the same population. Some methodological problems related to measurement of blood pressure and haemodynamics in teenagers must be considered, however.

When blood pressure in growing subjects is studied the comparability of hypertensive subjects and normotensive control subjects is a major concern. Slight differences in maturity may markedly influence physiological and other variables. In the present study hypertensive and

control subjects were derived from the same open population, were matched for age, sex and body-mass index and followed the same protocol, thus improving comparability.

The use of echocardiography in measuring left-ventricle dimensions and estimating haemodynamics is subject to discussion [21]. However, the measurement error due to echocardiographic estimation of haemodynamics affects hypertensive and control subjects to the same extent. Therefore, the comparison of the two groups is not likely to be biased by echocardiographic estimation of haemodynamics. A major advantage is the non-invasive character of the technique, especially when studying young normotensive subjects. Good agreement between left-ventricle dimensions as determined from echocardiography and angiocardiography has been demonstrated [21–23]. Under the assumption that the left ventricle has an ellipsoid form, which contracts symmetrically, the left-ventricular ejection fraction and myocardial mass can be estimated by formulae as presented in the Methods section. High regression coefficients between these parameters as estimated from echo- and angio-gram have been reported [22–24]. The reproducibility of echocardiographic measurement of left-ventricle dimensions in children is good [25, 26].

Despite the large variability of blood pressure, both within and between subjects, children tend to keep their relative positions in the distribution of blood pressure over time [1–3]. This large variability means that a number of children who were initially 'hypertensive' had become 'normotensive' at the moment of the study of haemodynamics. In the present study this was largely due to regression towards the mean in subjects selected on the basis of a high initial blood pressure. Furthermore the growing familiarity with the examination procedures during follow-up tends to decrease blood pressure values. Conversely, follow-up is associated with increase of blood pressure through aging. Differences between the subjects in change of blood pressure during follow-up should therefore at least in part be interpreted as an expression of variability of blood pressure *per se* and not solely (perhaps not even mainly) as a biological phenomenon in its own right. Accordingly, we refrained from labelling our study subjects as 'labile', 'borderline' or 'sustained' hypertensive.

Our results are at variance with the postulated existence of an hyperkinetic phase in early essential hypertension. The haemodynamics profile of our initial hypertensive teenagers resembles that of older hypertensive patients. We found a lower cardiac index combined with a higher total peripheral vascular resistance in initial hypertensive as compared with matched control subjects from the same population. It is important to emphasize that hypertensive and control subjects underwent the same number of follow-up examinations ,according to the same protocol. This may explain some of the differences of our findings with previous studies [4–9, 11] in which the control subjects were not part of a control group selected from the same population. Our findings are in agreement with reports of Laird & Fixler [27] and Goldring, Hernandez, Choi, Lee, Londe, Lindgren & Burton [28], who also estimated haemodynamics in hypertensive children by means of echocardiography.

In initial hypertensive subjects higher plasma noradrenaline concentrations were found than those in control subjects. Increased noradrenaline levels seem to be associated with raised systolic pressure in youngsters [18]. No significant differences in heart rate were found between hypertensive and control subjects. There are two possible explanations for these findings. The most likely is that the plasma noradrenaline elevation is preceding a higher blood pressure level and possibly is its cause. The findings of higher peripheral resistance and lower cardiac output suggest an adrenergic action on the arterial vasculature. There is no evidence for primary cardiac stimulation, as was described earlier in adults [29, 30]. On the contrary, the normal heart rate in hypertensive subjects and the absence of a significant influence of noradrenaline on cardiac index support an alternative hypothesis. The most likely mechanism seems to be stimulation of central origin, inducing noradrenaline release and peripheral vasoconstriction. It cannot be ruled out from this study, however, that the increase of noradrenaline is an effect and not a cause of the increased peripheral vascular resistance.

The finding of high levels of circulating catecholamines in initial hypertensive subjects with a high-renin concentration supports the view of Esler, Julius, Zweifler, Randall, Harburg, Gardiner & DeQuattro [31] that mild hypertension, characterized by a high level of plasma renin, is neurogenic in origin. A very high regression coefficient between active plasma renin and left ventricular mass was found in normotensive subjects. The magnitude of this association suggests a direct involvement of renin in cardiac physiology, as has been reported by Giacomelli, Anversa & Wiemer [32] from animal experiments.

In conclusion, we found no evidence for the existence of a hyperkinetic stage in early essential

hypertension. Our findings are in agreement with the hypothesis that sympathetic overactivity, perhaps through renin, plays an important part in the increase of peripheral vascular resistance and thereby of arterial blood pressure.

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Blood pressure and haemodynamics in teenagers

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SUMMARY It has been suggested that a hyperkinetic circulatory state, with high cardiac output, causes high blood pressure in childhood and, secondarily, in adulthood. We studied blood pressure and cardiac output in 319 subjects aged 15 to 19. Blood pressure was measured with an automated device; cardiac output was estimated by M-mode echocardiography and indexed by body surface area. The distribution of cardiac output was stratified using quartiles. Mean arterial pressure was virtually constant over these strata, with boys and girls showing essentially the same pattern. Linear regression of mean arterial pressure on cardiac output yielded a coefficient which was not significantly different from zero. A history of high blood pressure in the parents was positively associated with mean arterial pressure, but unrelated to cardiac output, in the offspring. This evidence does not support the hypothesis that the hyperkinetic circulatory state causes high blood pressure in childhood; rather, raised blood pressure in adolescents appears to relate to increased peripheral vascular resistance. Therefore, our findings lend support to the view that change in blood pressure over time is caused by a gradual increase in peripheral resistance beginning early in life.

It has been proposed that a "hyperkinetic" circulatory state[1] during youth, characterised by a high cardiac output, plays a part in the aetiology of high blood pressure.[2] Many children and adolescents with high blood pressure, sometimes referred to as "labile" or "borderline" hypertensives, are thought to have high cardiac output.[3] It has been suggested that an early rise in blood pressure, whether resulting from increased cardiac output or from other factors, causes alterations in the vascular wall[4] and/or the kidneys.[5] These alterations are held to be responsible for the increased peripheral resistance which accompanies high blood pressure in adults.[6]

To test whether a hyperkinetic circulatory state is a determinant of high blood pressure in the young, we examined blood pressure in relation to cardiac output in 319 subjects aged 15 to 19.

Subjects and methods

The subjects were participants of the Collaborative Perinatal Study,[7] in which pregnant women and those of their children born between 1959 and 1966 were studied in 12 medical centres in the USA. Eligible for the present study were white members of the Boston cohort of the Perinatal Study, born between 1959 and 1962, who had no known congenital anomalies and who had been re-examined as part of the Perinatal Study at 7 years of age. A sample of about 900 persons, unselected as to blood pressure, was invited by letter to take part in a study of cardiovascular risk indicators[8]; 456 persons responded and 380 were examined. This report deals with subjects who were 15·0 to 19·9 years of age at the time of the cardiovascular study (1977 to 1979). There were a total of 319 (168 male and 151 female) subjects. The majority (215) were 17 years of age.

Systolic and diastolic blood pressures were measured with a Narco Physiograph automated device as described earlier.[8] Diastolic pressure was based on the fifth phase of the Korotkoff sounds. The measurements were obtained between 8.00 and 9.30 am, with the subjects in a fasting state. All the readings were obtained with appropriately sized cuffs[9] and with the subjects in a recumbent position. Mean arterial pressure was computed by adding one third of the pulse pressure to diastolic pressure. A history of high blood pressure was obtained from the parents by interview.

Cardiac output was obtained by M-mode echocardiography, as described by Roelandt,[10] on the same occasion as when blood pressure was measured. Stroke volume was estimated by subtracting the cubed end-

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systolic diameter of the left ventricle from the cubed end-diastolic diameter. Heart rate was measured from the echocardiogram. An index of cardiac output was obtained by dividing it by body surface area, calculated according to Dubois and Dubois.[11]

The relation between cardiac output (index) and blood pressure was analysed in three ways. Firstly, we compared mean levels of mean arterial pressure among strata based on quartiles of cardiac output. Secondly, cardiac output of subjects with the highest values of mean arterial pressure was compared with that in the other study subjects. Thirdly, a linear regression analysis of mean arterial pressure on cardiac output was made. No age stratification or standardisation was applied because of the narrowness of the range of age.

Results

The values of mean arterial pressure ranged from 61 to 107 mmHg, with an average of 83·0. The average was higher for boys than for girls, because of a higher average systolic pressure. Mean cardiac output (index) was 3·15 l/min per m², with similar values for male and female subjects (Table 1).

Mean values of mean arterial pressure were virtually constant over the strata of cardiac output. Boys and girls showed essentially the same pattern (Table 2).

The subjects with the highest values of mean arterial pressure (90th centile or higher) had a mean cardiac output of 3·30 l/min per m² (95% CI: 3·01 to 3·59), whereas those with mean arterial pressure less than the 90th centile had a mean cardiac output of 3·14 (95% CI: 3·05 to 3·23). The difference between these means was not significantly different from zero.

Linear regression of mean arterial pressure on cardiac output yielded a coefficient of 0·6 mmHg/l per min per m² (95% CI: −0·6 to 1·8), which also was not significantly different from zero.

Table 1 *Blood pressure, heart rate, and cardiac output in subjects aged 15 to 19*

	Boys Mean±S D (n=168)	*Girls Mean±S D (n=151)*
Systolic blood pressure (mmHg)	127·7±11·6	117·4 ±10·7
Diastolic blood pressure (mmHg)	64·4± 9·2	63·9 ± 8·9
Mean arterial pressure (mmHg)	84·2± 8·2	81·7 ± 8·3
Heart rate (beats/min)	61·5±11·1	70·1 ±12·7
Cardiac output (l/min per m²)	3·2± 0·78	3·11± 0·82

Discussion

Our finding of no association between blood pressure and cardiac output in teenagers is at variance with previous studies[2 3 12] in which cardiac output was measured invasively. Recent investigations,[13 14] using non-invasive (echocardiographic) estimation of cardiac output, failed to show high cardiac output in children with relatively high blood pressure. In those studies the number of subjects was relatively small and "hypertensive" children were contrasted with normotensive controls. In the present study cardiac output was estimated in a study population unrestricted as to blood pressure, enabling evaluation of the trend of blood pressure over the whole range of cardiac output, with avoidance of the potential bias caused by varying familiarity of cases and controls with the procedures.

The study population comprised newborns enrolled in a large perinatal study[7] who were re-examined at age 7. An unselected sample was invited for the present study and in about 40% of the invited subjects both blood pressure and cardiac output were measured. No appreciable differences in blood pressure, heart rate, height, and weight at the age of 7 were found between those who took part in the present study and those who did not. Therefore, it seems unlikely that the procedure of subject selection has led to differential exclusion of teenagers with high blood pressure and high cardiac output.

The non-invasive measurement of cardiac output may be subject to criticism.[15 16] Though the measurement of cardiac output by echocardiography undoubtedly involves considerable random errors, this also is true when invasive techniques are employed. Nevertheless, stroke volume values obtained by angiocardiography and M-mode echocardiography have

Table 2 *Mean arterial pressure (mean±1 SEM) by categories of cardiac output*

Cardiac output		*Mean arterial pressure (mmHg)*					
Stratum	*Range* (l/min per m²)*	*Both sexes*		*Boys*		*Girls*	
		No.	*Mean±SEM*	*No.*	*Mean±SEM*	*No.*	*Mean±SEM*
I	(1·6–2·5)	79	82·8±0·9	42	85·2±1·1	37	82·4±1·4
II	(2·6–3·0)	80	82·3±1·1	42	83·9±1·4	38	79·4±1·4
III	(3·1–3·6)	80	82·9±0·9	42	83·5±1·2	38	81·5±1·3
IV	(3·7–5·5)	80	84·2±1·0	42	84·3±1·4	38	83·6±1·4
All strata	(1·6–5·5)	319	83·1±0·5	168	84·2±0·6	151	81·7±0·7

*Ranges for boys and girls separately were only slightly different from the ranges for boys and girls combined.

been shown to be in reasonably good agreement in adults[17] and children.[18] We used the cube method to calculate stroke volume[10]; application of the corrected cube method as suggested by Teichholz *et al.*[17] did not alter the observed regression coefficient between blood pressure and cardiac output. Though random errors in cardiac output tend to lead to an underestimate of the true relation with blood pressure, we believe that these errors are unlikely to be much larger in our study than in previous ones, in which cardiac output was measured invasively. We therefore think it improbable that information bias is responsible for our findings.

Epidemiological studies[19] have shown that levels of blood pressure in young people have good predictive value for later life. This "tracking" of blood pressure implies that the study subjects with the highest mean arterial pressure are likely to be future hypertensives. We found no difference between their average cardiac output and that of their counterparts with lower mean arterial pressure and this is in agreement with the finding of no association between levels of blood pressure and of cardiac output over the whole range of the latter.

Our study indicates that in adolescents a high blood pressure reflects high resistance of the vascular bed rather than high cardiac output. As there is evidence for high blood pressure to run in families,[20] one would expect high blood pressure in parents to be associated with high vascular resistance, and not with high cardiac output, in the offspring. The Fig. shows that this was the case in our subjects: children whose parents had a history of high blood pressure had higher mean arterial pressure and vascular resistance than children with no parental history of high blood pressure (Table 3).

The evidence presented here suggests that the hyperkinetic circulatory state does not have an important role in the aetiology of high blood pressure, since blood pressure in teenagers seems to be related to peripheral resistance, rather than to cardiac output. These results support the view that rises in blood pressure as people get older are caused by a gradual increase in peripheral resistance, which begins quite

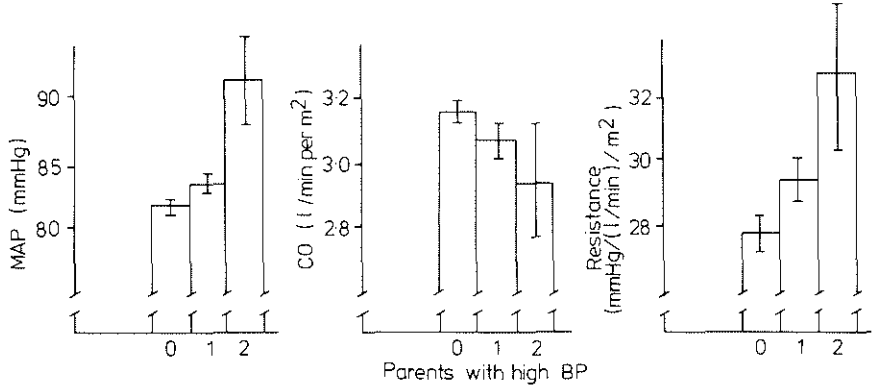

Fig. *Mean arterial blood pressure, cardiac output, and total peripheral resistance in teenagers, according to number of parents with a history of high blood pressure. Mean values are given with 1 SEM.*

Table 3 *Mean arterial pressure (mmHg), cardiac output (l/min per m²), and vascular resistance (mmHg/l per min per m²) in teenagers, according to history of high blood pressure in their parents*

History of high blood pressure	*No.*	*Mean arterial pressure*	*Cardiac output*	*Resistance**
		Mean±SEM	*Mean±SEM*	*Mean±SEM*
Neither parent	182	82·1±0·6	3·17±0·06	27·7±0·5
One parent	80	84·3±1·0	3·07±0·09	28·8±0·8
Both parents	11	90·2±3·1	2·91±0·28	32·3±2·5
Regression coefficient**		2·9±0·9	−0·11±0·09	1·5±0·8
($P_{(2)}$-value)***		(0·003)	(0·19)	(0·06)

*Computed as: resistance = mean arterial pressure/cardiac output.
**Trend of mean pressure, cardiac output, and resistance on history of high blood pressure in parents; coefficient obtained by weighted regression analysis, using the inverse of the variances as weights.
***Two-sided p value, computed using χ^2 test, 1 df, to test difference from zero.

early in life.

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Chapter 4

Determinants of blood pressure level 2

Sodium intake

Hofman A, Valkenburg HA, Vaandrager GJ.
Increased blood pressure in schoolchildren related to high sodium levels in drinking water.
J Epidemiol Community Health 1980;34:179–81.

Hofman A, Hazebroek A, Valkenburg HA.
A randomized trial of sodium intake and blood pressure in newborn infants.
JAMA (in press)

Journal of Epidemiology and Community Health, 1980, **34**, 179–181

Increased blood pressure in schoolchildren related to high sodium levels in drinking water

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SUMMARY The relationship between sodium in drinking water and blood pressure was examined in 348 schoolchildren aged 7·7 to 11·7 years. They were born and living in three areas with different levels of sodium in the public drinking water. Sodium content of the water was either long-term low, long-term high, or short-term high. The three communities are closely comparable according to demographic characteristics. The mean values of systolic and diastolic blood pressure were higher in the high sodium areas. After adjustment for dissimilarities in distributions of weight, height, pulse rate, age, family history of hypertension, and time of blood pressure measurement, these differences remained constant, ranging from 1·8 to 4·0 mm Hg. Girls and boys showed essentially the same differences. Mean 24-hour sodium excretion was somewhat higher in the long-term low area; no differences were found in sodium-creatinine ratio. The regression coefficients between sodium excretion and blood pressure were not significant. The findings from this retrospective follow-up study support the hypothesis that sodium intake influences blood pressure. The association seems to be of a relatively short-term nature, as no differences in blood pressure levels were found between the long-term and short-term high areas.

The role of high sodium intake in the pathogenesis of essential hypertension has been emphasised for a long time.[1] Epidemiologically this is mainly based on comparisons of the mean blood pressure levels of different populations with varying sodium intakes. Within populations, however, the results of blood pressure studies have been equivocal.[2–6] Most of these investigations were cross-sectional, relating a casual blood pressure reading to an estimate of sodium intake at the same time. The major problems of this approach are that the estimates of sodium intake are generally very crude; furthermore, the time-course of the relation between dietary sodium and blood pressure is not taken into account. Therefore, follow-up studies are preferable because these can provide insight into the temporal aspects of the relationship under study.

Calabrese *et al*[7] reported elevated blood pressure levels in adolescents living in a community with a high sodium content in the drinking water. In this paper data are presented from a retrospective follow-up study of blood pressure in Dutch schoolchildren living in areas with markedly different levels of sodium in the drinking water.

Material and methods

Blood pressure was measured in 348 children, born and still living in three rural Dutch communities. The areas with long-term low and long-term high sodium levels had experienced only minor changes in the drinking water content over the past 15 years. About one year before the study, the sodium levels in the short-term high community changed from approximately 1 to 7 mmol/l because of the introduction of NaOH as an ion-exchanger to soften the water.

The three areas are closely comparable according to demographic characteristics and no significant differences were found in the occupations of parents of the study children.

All children born between 1968 and 1971 and attending the eight largest primary schools in the areas were asked to participate. The response rate was 98% and the age of the children varied from 7·7 to 11·7 years.

Blood pressure was measured with a random-zero sphygmomanometer to reduce observer bias.[8] The readings were made by one observer, who was not aware of the sodium content of the drinking water. Blood pressure was measured in duplicate and the two readings were separated in time only by measurement of the heart rate. All subjects were studied within a two-week period in September 1979. Blood pressure was taken after at least five minutes of rest on the left arm of the sitting subject. Korotkoff sound V was taken as diastolic blood pressure and the

mean of the duplicate readings was used in the analysis.

Weight, height, and pulse rate were recorded. Sodium intake was estimated by measuring urinary sodium excretion. Sodium and potassium concentrations in a 24-hour urine sample were measured by flame-photometry. Urinary creatinine concentration was measured by an automated enzymatic method (Technicon). Only children exceeding an excretion of 0·16 mmol creatinine/24 hrs/kg body weight were taken into the analysis. A family history of hypertension was assessed by asking the parents whether they or the child's grandparents had ever received any anti-hypertensive medication.

Results

Mean blood pressure values were higher in the areas with high sodium levels in the drinking water (Table 1). These differences could have been due to unlike distributions of the determinants of blood pressure in the study communities, so adjustment was made for variables known to be determinants of blood pressure in childhood.[9] In a model for multiple linear regression the effect of residence on systolic and diastolic blood pressure was calculated, and adjustment was made for weight, height, pulse rate, age, family history of hypertension, and time of blood pressure measurement.

Table 1 *Mean blood pressure (±SD) values in three areas with different sodium levels in the drinking water*

	Long-term low	*Short-term high*	*Long-term high*
Systolic BP (mm Hg)	100·2±12·3	103·4±9·7	102·9±10·9
Diastolic BP (mm Hg)	57·4±8·6	59·3±9·4	59·5±7·8
Weight (kg)	33·5±6·7	32·0±6·4	32·1±6·2
Height (cm)	143 ±9	141 ±10	141 ±9
Age (years)	10·0±1·2	9·6±1·2	9·7±1·2
No.	110	112	126

Table 2 shows the differences between the mean values of systolic and diastolic blood pressure in high vs low sodium areas, before and after adjustment. All differences were statistically significant and ranged from 1·8 to 4·0 mm Hg.

No significant differences were found in mean blood pressure between children living in the long-term high and the short-term high areas. Girls and boys showed essentially the same adjusted effect of residence on systolic and diastolic blood pressure.

Mean values of 24-hour excretion of urinary sodium, potassium and creatinine are given in Table 3. The sodium excretion in 24 hours was larger in the long-term low area; no differences in potassium excretion were found. Mean creatinine excretion was larger in the long-term low area, but no significant differences in sodium-creatinine ratio were found between the communities. Adjustment for body weight and age slightly diminished the differences in sodium excretion between the areas. The standardised regression coefficients between urinary sodium excretion and systolic (b = 0·02) and diastolic (b = 0·01) blood pressure were non-significant.

Table 2 *Differences between mean blood pressure values in mm Hg: long-term high vs long-term low area, and short-term high vs long-term low area*

	Long-term high minus long-term low	
	Observed	*Adjusted†*
Systolic BP	2·7*	3·3***
Diastolic BP	2·1**	1·8*
	Short-term high minus long-term low	
	Observed	*Adjusted†*
Systolic BP	3·2**	4·0***
Diastolic BP	1·9*	2·3**

† Adjusted for weight, height, pulse rate, family history of hypertension, time of blood pressure measurement.
* P <0·10
** P <0·05
*** P <0·01 (two-sided t-test)

Table 3 *Mean values of electrolytes and creatinine in a 24-hour urine sample in three areas with different sodium levels in the drinking water*

	Long-term low	*Short-term high*	*Long-term high*
Na^+ (mmol/24 hrs)	109 ±40	88 ±39	98 ±39
K^+ (mmol/24 hrs)	43 ±15	37 ±23	42 ±17
Creatinine (mmol/24 hrs)	7·9±1·8	6·2±2·0	7·1±1·7
Na/creatinine ratio	14	14	14
N	107	104	123

Discussion

Our finding that blood pressure levels are higher in high sodium areas agrees with that of Calabrese *et al.*[7] However, there are three differences between our study and theirs.

In the American study no device was used to reduce observer bias in the measurement of blood pressure. If the observers were aware of the hypothesis the results could have been seriously distorted. Furthermore, the previous study considered blood pressure levels only in long-term high and low communities. Finally, Calabrese *et al*[10] found higher mean levels of excreted sodium in the

high sodium areas, but in our study the sodium excretion was somewhat larger in the low sodium community.

In the first period of life a child gets a relatively large part of his or her dietary sodium from water, at least when living in a high sodium region and receiving artificial feeding. As most Dutch formula feedings contain 10–20 mmol Na^+/l, the infant fed solely on the bottle in a high sodium area (5–10 mmol Na^+/l) obtains about 20–50% of its sodium from the water, compared with 5% in a low sodium community. However, this cannot explain our finding of similar blood pressure levels in the short-term high and the long-term high areas.

The collection of data on total intake of sodium is fraught with problems. Urinary sodium excretion was used as an indicator of total sodium intake. We considered direct estimation of sodium intake to be impossible, because of the crudeness of dietary recall and duplicate portion methods. We found no differences in sodium-creatinine ratio in the 24-hour urine. Unfortunately, the marked intra-individual variability of sodium intake implies that one 24-hour urine collection is not enough to estimate the relationship between sodium intake and blood pressure.[11] A considerable number of 24-hour urine collections is necessary to assess the true value of the association.[12] This would involve large practical problems in general population studies and emphasises the need for follow-up studies in this field, especially of the prospective type.

Nevertheless, the findings from this retrospective follow-up study support the hypothesis that blood pressure is related to sodium intake. The association seems to be of a relatively short-term nature: in the community with a recent change to high sodium levels the effect was discernible after one year. Evidence exists for early 'tracking' of blood pressure,[13] perhaps even from the first months of life,[14] so this could indicate that sodium intake is an important early determinant of 'tracking'. It may well be that genetic predisposition to high blood pressure expresses itself through environmental factors, especially high sodium intake, as early as the first period of life.

We thank the children who participated in the study, and Mrs. Wilma Haanen, Mrs. Ria Rijneveldshoek, Mr. Bram van Laar, Mr. A. M. de Brūyn, Dr. M. M. Dieleman, Dr. N. C. Lamaison van den Berg, and Dr. R. Bloembergen. We also thank Mr. W. Bessie of the WMZ Water Works. This study was supported in part by the Netherlands Prevention Fund.

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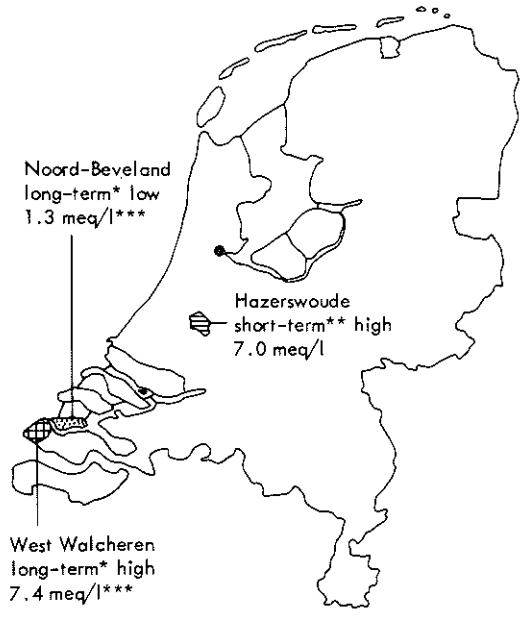

Figure
Three areas in the Netherlands with different levels of drinking water sodium

* at least 15 years
** about one year; sodium level 1 meq/l before
*** data from 1978

Note: The editor/publisher of the J Epidemiol Community Health have, erroneously and embarrassingly, not published this figure.

A randomized trial of sodium intake and blood pressure in newborn infants

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Abstract

We studied the effect of dietary sodium on blood pressure in a double-blind randomized trial with 245 newborn infants assigned to a normal-sodium diet and 231 to a low-sodium diet during the first six months of life. The sodium intake of the normal-sodium group was nearly three times that of the low-sodium group. Systolic blood pressure was measured every month from the first week until the 25th week. At 25 weeks systolic pressure was 2.1 mmHg lower in the low-sodium group than in the normal-sodium group ($p_1 = 0.01$). The difference between the groups increased significantly over the first six months of life. These observations are in agreement with the view that sodium intake is causally related to blood pressure level.
Key words: blood pressure, newborns, sodium intake

Introduction

The view that high sodium intake is involved in the etiology of high blood pressure is old,[1] but remains controversial.[2] The evidence consists of animal experiments[3] and of comparisons of blood pressure of populations differing in sodium intake.[4] Nearly all within-population studies have yielded negative results, perhaps partly due to large random errors in the measurement of sodium intake.[5] Some

trials have shown that high blood pressure may be successfully treated by severe[6] or moderate[7] sodium restriction. This does not necessarily imply that sodium is causally related to blood pressure, because different mechanisms might be involved in the etiology and the treatment of high blood pressure. To our knowledge no experimental evidence in humans for an etiologic role of sodium intake in high blood pressure has been presented until now.[8]

We conducted a double-blind trial to study the effect of sodium intake on the level and evolution of blood pressure in healthy newborn infants. They were randomly assigned to a group with a normal or a low amount of sodium in the diet during the first six months of life and their blood pressure was measured monthly.

Methods

Subjects

The study subjects were infants born to residents of Zoetermeer, a suburban residential area of about 60,000 inhabitants near The Hague in The Netherlands. Eligible were all infants delivered at home or in an outpatient clinic, between January 15 and December 15, 1980. Babies delivered in hospital (less than 50% of the deliveries in Holland) were not taken into the study. We contacted prospective parents in the seventh months of pregnancy and obtained informed consent from 476 of them (73% of those eligible). They were randomly assigned to a group receiving a normal-sodium diet (245) or a group with a low-sodium diet (231) starting immediately after birth. All parents who consented received a number ranging from 1 to 476, depending on the date of entry in the trial. Each number corresponded to a code for the sodium group, which was assigned by a random number generator. This code was only known to a co-worker who prepared the food-packets and who had no direct contact with the parents. Thus, neither the parents nor the investigators knew to which group an infant was assigned.

Dietary groups

All participants in the trial received formula milk (Almiron AB) and solid foods (Olvarit) free of charge for six months. The formula milk and solid foods were specially produced for this study. The mothers were allowed to breastfeed their babies, but urged not to give them any other foods than the ones they received in the trial, with the exception of fruit juices. The parents were adviced to start with solid foods in the 13th week after birth. The food was delivered at home by a study nurse who recorded each month the amount of formula milk and solid foods used. The mothers were asked to record any deviation from protocol in a special diary.

The normal-sodium formula contained an amount of sodium that was regular for Dutch formula milks (acid milks) commercially available during the study period. The sodium concentration of the low-sodium formula was similar to that of human milk and it was three times lower than that of the normal-sodium milk (6.3 vs. 19.2 mEq/l). The sodium concentration of the solid foods ranged, depending on the kind of vegetable, from 2.2 to 13.9 mEq/l (after demineralization) in the low-sodium group and from 22.6 to 76.5 mEq/l in the normal-sodium group. The sodium-potassium ratio was 0.67 for the low-sodium formula and 0.64 for the normal-sodium milk. The concentration of other minerals, proteins and lipids in both milks were very similar, with the exception of chloride (6.0 mEq/l in the low-sodium milk and 22.6 mEq/l in the normal-sodium formula).

The total intake of sodium for each baby during the first six months, was calculated from the amount of baby-food delivered to the mother, with allowance for breastfeeding. The allowance was based on the average amount of breastmilk consumed daily as reported by Jelliffe et al.,[9] multiplied by the sodium concentrations of breastmilk of the breastfeeding mothers in this study.[10] As the allowance is based on the average amount of consumed breastmilk, it is only an approximation of the true sodium intake by breastmilk. The average amount of sodium (SD) consumed during the first six months amounted to 0.89 (0.26) Eq Na^+ in the low-sodium group and 2.50 (0.95) in the normal-sodium group. The distributions of estimated sodium intake of both study groups are given in Table 1.

An infant in the normal-sodium group received on the average 72%

Table 1
Distribution of total sodium intake during the trial in the two study groups (in Eq Na^+)

Percentile	Low sodium (n = 231)	Normal sodium (n = 245)
10%	0.7	1.1
25%	0.8	1.7
50%	0.9	2.8
75%	1.0	3.2
90%	1.1	3.5

of its sodium from formula milk, 18% from solid foods and 10% from breastmilk. For the low-sodium group these figures were 72%, 5% and 23%, respectively. The average sodium excretion (S.D.) in three casual urine samples, collected in week 5, 13 and 21, was 11.1 (10.0) mEq/l in the low-sodium group and 22.7 (14.5) in the normal-sodium group.

Measurements
We measured blood pressure at seven occasions in each infant: in week 1, 5, 9, 13, 17, 21 and 25. A few infants were not measured in the first but in the second week of life. Four experienced study nurses, unaware of the diet-group of the babies, measured systolic blood pressure. They participated in bi-weekly training sessions in which they measured blood pressure in the same babies. During these sessions we found no systematic differences in blood pressure recorded by the different observers. Each nurse measured babies in both the normal-sodium and the low-sodium group. The same observer made all measurements in a single infant, with few

exceptions. The measurements were performed with a Parks 208A^R Doppler ultrasound device[11] connected to a random-zero sphygmomanometer.[12] This device only measures systolic blood pressure accurately. The measurement devices were calibrated regularlyregularly calibrated at the training sessions. All measurements were made on the right arm of a supine infant. In order to facilitate the procedures, blood pressure was measured with a 4 cm cuff at all occasions. The mean of three readings at each occasion was used in the analyses. In both study groups the measurements were made between 8 am and 7 pm. The readings were taken while the infants were awake and not crying, except for a few infants in the first two months who were measured while sleeping. Weight and length at birth were obtained from the midwives.

Data-analysis

The sample size for this study was calculated to detect a difference in systolic blood pressure between the groups at 25 weeks of 3 mmHg, with sodium groups.

The analyses were based on all subjects in whom blood pressure readings were obtained, i.e., infants who deviated from the protocol were included. This is in accordance with the 'intention-to-treat' principle in the analysis of clinical trials,[13] in which all those assigned to a certain treatment are analysed according to that treatment. Newborns who received other foods than those prescribed in the trial for more than seven days were considered to be deviators from the protocol. Table 2 shows that at 25 weeks 8.2% of the babies in the normal-sodium group and 10.6% of those in the low-sodium group deviated from the protocol. At 25 weeks four infants in the normal-sodium group (1.6%) and six in the low-sodium group (2.6%) could not be measured. This was due to death (1 in normal-sodium and 1 in low-sodium group), severe diseases (2 and 3) and migration (1 and 2).

We computed the observed difference of mean systolic pressure between the sodium groups at each occasion of measurement, i.e., at week 1, 5, 9, 13, 17, 21 and 25. These differences were adjusted for

Table 2
*Number of infants, proportion receiving breastfeeding, proportion deviating from protocol and average body weight in the study groups at week 1 and 25**

Variable	Sodium group	Week	
		1	25
Number examined	Normal	245	241
	Low	231	225
Breastfeeding %	Normal	72	15
	Low	68	13
Deviation from protocol (%)**	Normal	0.8	8.2
	Low	2.6	10.6
Mean (SD) body weight (g)	Normal	3421(481)	7184(805)
	Low	3466(429)	7302(722)

* more detailed tables available upon request.

** as obtained from food diaries.

SD indicates standard deviation.

slightly different distributions of length and weight at birth, differences in average recorded blood pressure by the observers and systolic pressure in the first week, using a model for multiple linear regression with systolic blood pressure as the outcome variable. An indicator for sodium group (0 = low, 1 = normal) was entered as independent variable, together with length at birth (cm), weight at birth (gr), blood pressure in the first week (mmHg) and indicator variables for the blood pressure observers (0,1). The estimate of the regression coefficient for sodium group yielded by this model served as the adjusted difference between the sodium groups. The observed and adjusted differences between the groups are given with a 90% confidence interval (CI) and a p-value corresponding to a one-tailed test of significance (p_1).

Separately we analysed the trend of the difference between the sodium groups over the first six months of life by adding an interaction-term to a model for linear regression of blood pressure on time and sodium group.[14] To overcome the non-linear increase of blood pressure over time we transformed all blood pressure values to z-scores.

Results

Weight and length at birth, as well as parental blood pressure and other measured characteristics of the parents were distributed similarly in the two groups (Table 3).
The percentage of breastfeeding mothers decreased from about 70% in the first week to 14% in the 25th week (Table 2). The proportion of subjects deviating from the protocol was similar in the two groups (Table 2). Average body weight at the various occasions was not different among the study groups, except at weeks 21 and 25 when it was slightly larger in the low-sodium group (Table 2).

Mean values of systolic blood pressure at various occasions are given in Table 4.

Table 3
Characteristics of infants and their parents after randomization

Characteristic	Statistic	Normal sodium (n = 245)	Low sodium (n = 231)
Gender ratio	% M:F	51:49	52:48
Length at birth	Mean in cm (SD)	50.9 (2.2)	51.0 (2.1)
	Median (cm)	51	51
	10th centile (cm)	48	48
	90th centile (cm)	54	53
Weight at birth	Mean in gr (SD)	3421(481)	3466(429)
	Median (gr)	3400	3450
	10th centile (gr)	2800	2900
	90th centile (gr)	4000	4000
Age of mother	Median (yrs)	28	28
Smoking mother	% ever	49	43
	% during pregnancy	33	28
Systolic BP			
Mother	Mean in mmHg (SD)	105.4 (9.9)	106.2 (9.6)
Father	Mean in mmHg (SD)	124.7(11.6)	126.4(14.4)
Diastolic BP			
Mother	Mean in mmHg (SD)	66.8 (8.0)	66.6 (8.3)
Father	Mean in mmHg (SD)	75.5 (9.1)	76.8(10.6)

SD indicates standard deviation.

Table 4
Mean systolic blood pressure of the two sodium groups

Week	Normal-sodium group			Low-sodium group		
	n	Mean	SD	n	Mean	SD
1	245	87.7	19.7	231	87.0	19.5
5	243	101.9	18.6	227	102.5	19.0
9	237	108.8	14.8	227	108.3	14.9
13	243	111.9	13.4	228	111.3	13.7
17	234	113.4	13.6	224	112.4	11.9
21	241	114.9	11.0	224	113.5	12.2
25	241	116.1	11.2	225	114.1	11.9

SD indicates standard deviation.

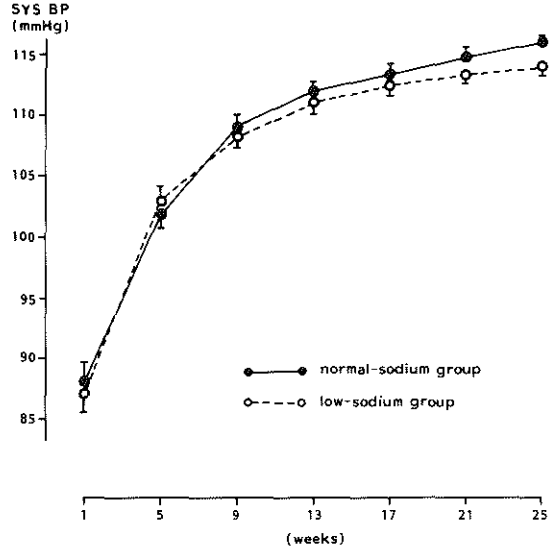

Figure
Systolic blood pressure (± 1 standard error) of infants receiving a normal-sodium or a low-sodium diet

Table 5
Observed and adjusted differences in mean systolic blood pressure between the study groups (normal – sodium minus low – sodium group) at various occasions

Week	Observed difference (mmHg)		Adjusted difference* (mmHg)	
	Mean	90% CI	Mean	90% CI
1	0.7	−2.3 to 3.7	**	
5	−0.6	−3.4 to 2.2	−0.4	−2.1 to 2.9
9	0.5	−1.8 to 2.8	0.4	−1.7 to 2.5
13	0.7	−1.4 to 2.8	0.6	−1.4 to 2.6
17	1.0	−1.0 to 3.0	1.2	−0.6 to 3.0
21	1.4	−0.4 to 3.2	1.7	0.0 to 3.4
25	2.0	0.2 to 3.8	2.1	0.5 to 3.7

* adjusted for observers, weight, length at birth and systolic blood pressure in the first week.

** systolic blood pressure in the first week is a determinant in the model.

90% CI indicates 90% confidence interval.

Systolic blood pressure increased with age in both groups, but less in the low-sodium group than in the normalsodium group (Figure). An additional analysis in which only the newborns with a blood pressure reading at all occasions were included, yielded essentially the same results. The differences of mean systolic pressure between the groups are given in Table 5.

At 25 weeks systolic pressure was 2.0 mmHg lower in the low-sodium group ($p_1 = 0.03$). The linear trend of the difference between the groups over time was different from zero ($p_1 = 0.04$). The adjusted differences were slightly larger than the observed ones and amounted to 2.1 mmHg at 25 weeks ($p_1 = 0.01$). The adjusted differences also increased significantly over the first six months ($p_1 = 0.025$).

Comment

The main finding in this study is that sodium intake is associated with systolic blood pressure early in life. The difference between the two study groups, albeit small, increased with months of life, thereby suggesting a dose-response relation. Although the magnitude of the effect is small, this experiment is in agreement with the view of a causal connection between dietary sodium and blood pressure. There is evidence for a moderately high predictive value of blood pressure in childhood for future blood pressure.[15] Therefore, our observations suggest that dietary sodium plays a part in the etiology of high blood pressure and the rise of blood pressure with age.

There are two reasons why we think that the difference between the study groups is not only statistically significant, but also relevant. Firstly, one expects the difference to increase with life. Secondly, in dicussing the 'high risk' and the 'whole population' approach in prevention, Rose[16] has estimated that the number of lifes saved by current antihypertensive treatment might be equalled by a downward shift of the whole blood pressure distribution of 2 – 3 mmHg. Thus, in the long run even a decrease of 2 mmHg, when maintained, may contribute considerably to the prevention of cardiovascular disease.

The most important difference between this study and previous ones on the relation between sodium intake and blood pressure in humans, lies in its experimental nature. We were able to reach a two- to threefold difference in sodium intake between both groups. The subjects were succesfully randomized, as evidenced by the similarity of baseline characteristics in the study groups. Systolic blood pressure was measured with a device that given readings which are in good

agreement with intra-arterial readings.[11] The increase of blood pressure in the first months of life corresponds with earlier reports.[15] Average systolic pressure in the first month was similar to that reported previously. From the second to the sixth month mean systolic pressure was higher in our study than in most previous ones. We attribute this to the use of a small cuff in all measurements during the first six months.[17] However, the endpoint in this trial, the difference between group means, is not biased by such a procedure.

The study population comprised newborn infants born at home or in an outpatient clinic. Babies delivered in hospital were not eligible. It is conceivable that this has resulted in exclusion of some mothers with high blood pressure, who more often have clinical deliveries in Holland. One could argue that this might produce an underestimate of the effect of sodium on blood pressure, because of the differential exclusion of possible sodium-susceptibles. It is also likely that our analysis, with inclusion of the deviators from the protocol, produced an underestimate of the true effect of sodium on blood pressure. A separate analysis, with exclusion of protocol-deviators, showed at 25 weeks an observed difference between the sodium groups of 2.8 mmHg (with a standard error of 1.1; $p_1 = 0.005$) and an adjusted difference of 2.9 mmHg (standard error 1.0; $p_1 = 0.002$).

Dahl et al.[3] inferred from their experiments in rats that part of the human population might be genetically susceptible to high intake of sodium. An analysis in subgroups with and without evidence for familial high blood pressure showed no different trend of systolic pressure over time for the subgroups. However, the sample size of this study does not permit proper subgroup analyses and we suggest therefore with reserve that we found no evidence for genetic sodium-susceptibility.

Two main mechanisms for the sodium-blood pressure relation have been proposed. One is that high sodium intake leads to expansion of the extracellular fluid volume,[18] the other that sodium has a direct influence on peripheral vascular resistance, perhaps through calcium.[19] Although this study was not designed to differentiate between these hypotheses, one would expect expansion of the extracellular volume to manifest itself through a larger mean

body weight in the normal-sodium group. As the average body weight was similar in the study groups (or even somewhat smaller in the normal-sodium group) we speculate that our observations are consistent with the view that peripheral resistance is influenced by sodium intake.

In summary these findings support the view that sodium intake is causally related to blood pressure level. Moderation of sodium intake starting very early in life might contribute to prevention of high blood pressure and of rise of blood pressure with age.

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Chapter 5

Change of blood pressure in childhood

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The natural history of blood pressure in childhood

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Abstract

To find out whether there is a relation between the level of blood pressure in childhood and later on in life, and whether future hypertensives can be identified early in life, we selected a random sample of 596 Dutch children. At the first examination they were 5 – 19 years of age. In 386 of them (65%) at least five consecutive annual blood pressure measurements were made between 1975 and 1982. The stability of a child's position in the blood pressure distribution ('tracking') was studied by linear regression of follow-up blood pressure on initial blood pressure. Tracking coefficients were 0.4 to 0.6 mmHg/mmHg for systolic pressure, and 0.2 to 0.5 mmHg/mmHg for diastolic pressure after four years of follow-up. Twenty-seven per cent of the boys and 44% of the girls who were in the upper 10% of the systolic blood pressure distribution at the first examination were also there after four years. For diastolic pressure these figures were 25% and 22%, respectively. These observations indicate that there is a moderate degree of blood pressure tracking in childhood. They further imply that it is impossible to detect future hypertensives early in life by measurement of blood pressure only.
Key words: blood pressure; childhood; predictive value; tracking

Introduction

Epidemiologic studies of blood pressure in childhood may provide insight in the etiology as well as in the possibilities of prevention of essential hypertension and of atherosclerotic diseases. They are mainly motivated by two questions:

(1) is there a relation between blood pressure in childhood and later on in life, i.e., does a child maintain his or her position in the distribution of blood pressure over time?

(2) is it possible to detect children who are at high risk to develop high blood pressure later in life?

To find out whether the roots of essential hypertension can be traced in childhood, and whether future hypertensives can be identified early in life, we designed a prospective follow-up study of blood pressure in youngsters. A random sample of 596 subjects, initially aged 5 – 19, was selected from a general Dutch population, and in 386 of them at least five consecutive annual blood pressure measurements were made.

Materials and methods

Population

The study population comprised all 5 – 19 year olds living in one of two study districts of the Dutch town of Zoetermeer from 1975 to 1979. Zoetermeer is located near the Hague, and had about 55,000 inhabitants in the initial stage of the study. The study population was invited to take part in a survey of risk-indicators for cardiovascular disease. In the age category of 5 – 19 years 5,670 subjects were eligible, and blood pressure was measured in 4,649 of them (82 per cent). Response rates were 87 per cent (in those aged 5 – 9), 83 per cent (10 – 14) and 77 per cent (15 – 19).

Of the initially examined youngsters, those who were in the upper ten per cent of one or more of the distributions of blood pressure, serum total cholesterol, body mass index or smoking habits were selected for yearly follow-up, together with an approximately ten per cent random sample of the remaining 5 – 19 years olds. In total 1,597

subjects were selected for follow-up and 596 of them are a random sample of all initially examined youngsters. This group of 596 youngsters comprised all children in the ten per cent random sample, with a proportionate suppletion of children in the upper stratum of the distributions of risk-indicators for cardiovascular disease. Children with secondary hypertension were removed from the follow-up cohort. The subjects received no specific intervention as part of this study.

This paper deals with 386 of the 596 subjects (65 per cent) of whom we obtained a complete string of blood pressure readings to at least the fourth year of follow-up (for numbers see Table 1).

Table 1
Number of subjects in whom at least five consecutive annual blood pressure readings were obtained

	Boys	Girls
5 – 9	52	49
10 – 14	80	70
15 – 19	75	60
Total	207	179

There were 207 boys who fullfilled this criterion, out of 301 eligible (69 per cent), and 179 girls, out of 295 (61 per cent). Two-hundred-and-ten youngsters did not meet the eligibility criterion for one of the following reasons: (1) 35 had not yet had their follow-up exam after four years at the time when this analysis was performed; (2) in 82 subjects one or more blood pressure readings were missing, but the children were not lost to follow-up; (3) 93 subjects were lost to follow-up; this was mainly due to migration and only in a few cases

to refusal to participate any further. We found no evidence for large differences in systolic and diastolic blood pressure at the first examination between those who were eligible for this analysis and those who were not.

Measurements

Measurements were made four weeks after the initial examination and furtheron at yearly intervals. At each occasion systolic and diastolic blood pressure were measured together with body weight and height, and pulse rate, as described previously (1,2). Blood pressure of the parents of the study subjects was measured at the initial examination. Systolic and diastolic blood pressure were measured with a random-zero sphygmomanometer (3). The subjects were measured at the left arm, while in the sitting position and after at least 15 minutes of rest. Blood pressure was measured before venipuncture. Eight paramedical co-workers, who participated in blood pressure training sessions, made the readings. Children aged 5 – 9 were measured with a 23 x 10 cm^2 cuff, the older subjects with a 23 x 14 cm^2 cuff, according to published recommendations (4,5). Two readings were made, in time only separated by a count of the pulse rate. In the analyses the average of these two readings was used. Diastolic blood pressure was based on the fifth Korotkoff sound. Body weight and height were measured with the subjects wearing indoor clothes, without shoes.

Data-analysis

We transformed the blood pressure readings into z-scores based upon means and standard deviations of systolic and diastolic pressure for boys and girls in five three-years age categories (5 – 7 yrs, 8 – 10 yrs, etc.). Our data-analytic approach was twofold. Firstly, to assess the stability of a child's rank in the blood pressure distribution over time (often referred to as 'tracking'), we regressed systolic and diastolic pressure at the various follow-up examinations, expressed as z-scores, on blood pressure at the initial exam. This yielded age-standardized regression coefficients, which we used as estimates of the magnitude of tracking of blood pressure over time. Secondly, in an attempt to assess the predictive value of a relatively high blood pressure, we

computed the fraction of those in the upper stratum of the blood pressure distribution at the first exam who were also in that upper stratum four years later.

Results

Average values of systolic and diastolic blood pressure at the initial examination and at the follow-up examinations are given in Tables 2 and 3.

Mean systolic and diastolic pressure decreased considerably from the initial exam to the four-weeks exam in all categories of age and gender. After the four-weeks exam, systolic and diastolic pressure increased steadily, with the largest increment in the first and second year of follow-up. The distributions of blood pressure were approximately normal in all categories of age and gender, and in all examination rounds. Figure 1 shows the change in blood pressure over a period of five years for each of the three age cohorts (5 – 9, 10 – 14 and 15 – 19 years at the first examination).

Coefficients of linear regression of blood pressure at follow-up examinations on initial blood pressure are given in Tables 4 and 5. These 'tracking' coefficients amounted to 0.4 to 0.6 for systolic blood pressure, and to 0.2 to 0.5 for diastolic blood pressure after four years. As shown in Figures 2 and 3, these coefficients decreased only slightly after the four-weeks examination.

The coefficients were somewhat larger in older subjects, particularly in girls. There was no association between the magnitude of tracking and body weight and pulse rate at the first examination, or blood pressure of the parents: the coefficients were not different in those with a relatively large body weight, pulse rate or parental blood pressure, from those without these characteristics (data not given, but available upon request).

Estimates of the predictive value of relatively high blood pressure are given in Tables 6 and 7.

Youngsters in the upper one-third of the distribution of systolic blood pressure at the initial exam, were also in the upper one-third after four years in 61 per cent (boys) and 58 per cent (girls). For diastolic blood

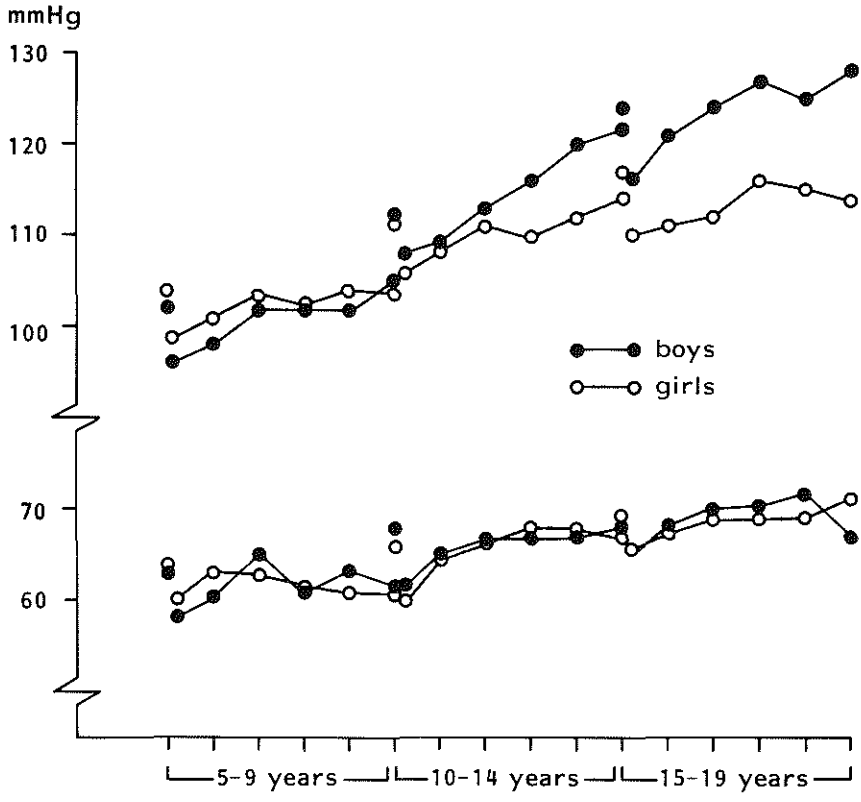

Figure 1
Cohort analysis of blood pressure in childhood. Average systolic and diastolic pressure over a five year period for three age-cohorts of Dutch children, 1975 – 1982. Blood pressure at the 4-weeks examination is used as the first value. The unconnected points indicate the initial readings
Note: The 'dip' of systolic blood pressure between the cohorts of 10 – 14 years and 15 – 19 years may be explained by somewhat different age-distributions. The average age of the 15 – 19 years cohort at the first examination was 17.1 years, whereas the average age of the 10 – 14 years cohort at the 5-years follow-up examination was 17.7 years.

Table 2
Systolic blood pressure (mean & S.D. in mmHg) at various examinations in 386 Dutch youngsters, initially aged 5 – 19

Sex	Examination	5 – 9 yrs		10 – 14 yrs		15 – 19 yrs	
		M	SD	M	SD	M	SD
Boys	Initial	102	12	112	13	124	13
	4 wks	96	11	108	11	116	15
	1 yr	98	10	109	12	121	13
	2 yrs	102	9	113	13	124	12
	3 yrs	102	11	116	14	127	12
	4 yrs	102	11	120	15	125	12
	5 yrs*	105	11	122	11	128	15
Girls	Initial	104	13	112	12	117	13
	4 wks	99	10	106	12	110	11
	1 yr	101	12	109	14	111	11
	2 yrs	103	10	111	11	112	11
	3 yrs	102	11	110	9	116	11
	4 yrs	104	12	112	10	115	12
	5 yrs*	104	12	114	9	114	12

* based on a smaller number of subjects.

Table 3
Diastolic blood pressure (mean & S.D. in mmHg) at various examinations in 386 Dutch youngsters, initially aged 5 – 19

Sex	Examination	5 – 9 yrs		10 – 14 yrs		15 – 19 yrs	
		M	SD	M	SD	M	SD
Boys	Initial	63	10	68	9	68	11
	4 wks	58	10	62	11	65	10
	1 yr	61	9	65	10	68	10
	2 yrs	65	10	67	9	70	9
	3 yrs	61	9	67	9	70	9
	4 yrs	63	7	67	10	72	9
	5 yrs*	62	8	68	10	67	7
Girls	Initial	64	11	66	10	69	10
	4 wks	60	11	60	11	65	9
	1 yr	63	9	65	10	68	10
	2 yrs	63	10	67	9	69	9
	3 yrs	61	9	68	8	96	9
	4 yrs	61	8	68	7	69	9
	5 yrs*	61	8	67	8	71	9

* based on a smaller number of subjects.

Table 4
Coefficients of linear regression (in mmHg/mmHg and with standard error) of systolic pressure at follow-up examinations on systolic pressure at the initial examination, in 386 Dutch youngsters initially aged 5 – 19

Exam	5 – 9 yrs		10 – 14 yrs		15 – 19 yrs		All ages	
	b	SE	b	SE	b	SE	b	SE
Boys								
4 wks	0.66	0.13	0.47	0.09	0.70	0.09	0.60	0.06
1 yr	0.44	0.13	0.48	0.11	0.69	0.12	0.53	0.07
2 yrs	0.46	0.13	0.46	0.11	0.37	0.11	0.43	0.07
3 yrs	0.26	0.14	0.39	0.11	0.49	0.11	0.39	0.07
4 yrs	0.41	0.12	0.55	0.10	0.42	0.10	0.47	0.06
5 yrs*	0.25	0.14	0.58	0.12	0.48	0.15	0.45	0.08
Girls								
4 wks	0.50	0.13	0.57	0.11	0.51	0.11	0.53	0.07
1 yr	0.39	0.14	0.44	0.12	0.70	0.09	0.51	0.07
2 yrs	0.41	0.14	0.57	0.11	0.62	0.09	0.55	0.07
3 yrs	0.48	0.14	0.47	0.11	0.73	0.09	0.57	0.06
4 yrs	0.48	0.14	0.26	0.12	0.59	0.10	0.44	0.07
5 yrs*	0.35	0.18	0.33	0.16	0.33	0.14	0.34	0.09

* based on a smaller number of subjects.

Table 5
Coefficients of linear regression (in mmHg/mmHg and with standard error) of diastolic pressure at follow-up examinations on diastolic pressure at the initial examination, in 386 Dutch youngsters initially aged 5 – 19

Exam	5 – 9 yrs		10 – 14 yrs		15 – 19 yrs		All ages	
	b	SE	b	SE	b	SE	b	SE
Boys								
4 wks	0.17	0.14	0.27	0.13	0.40	0.11	0.29	0.07
1 yr	0.16	0.14	0.35	0.13	0.42	0.11	0.31	0.07
2 yrs	0.21	0.16	0.46	0.11	0.41	0.11	0.38	0.07
3 yrs	0.18	0.14	0.18	0.12	0.37	0.11	0.25	0.07
4 yrs	0.34	0.11	0.21	0.12	0.21	0.10	0.25	0.07
5 yrs*	– 0.10	0.16	0.11	0.17	0.40	0.15	0.15	0.09
Girls								
4 wks	0.53	0.15	0.42	0.12	0.42	0.12	0.45	0.07
1 yr	0.47	0.13	0.39	0.12	0.49	0.12	0.44	0.07
2 yrs	0.30	0.15	0.25	0.12	0.57	0.10	0.37	0.07
3 yrs	0.25	0.14	0.26	0.13	0.48	0.11	0.33	0.07
4 yrs	0.20	0.13	0.33	0.12	0.53	0.11	0.36	0.07
5 yrs*	0.14	0.17	0.51	0.17	0.40	0.14	0.34	0.09

* based on a smaller number of subjects.

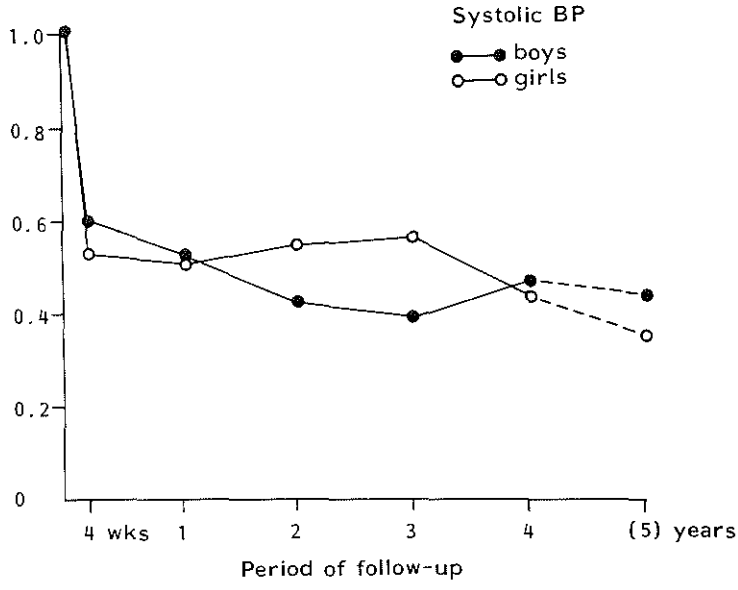

Figure 2
'Tracking' of systolic blood pressure in Dutch youngsters, initially aged 5 – 19. Age-standardized linear regression coefficients (mmHg/mmHg) of follow-up blood pressure with blood pressure at the first examination
Note: The 5-years follow-up data are based on a smaller number of children.

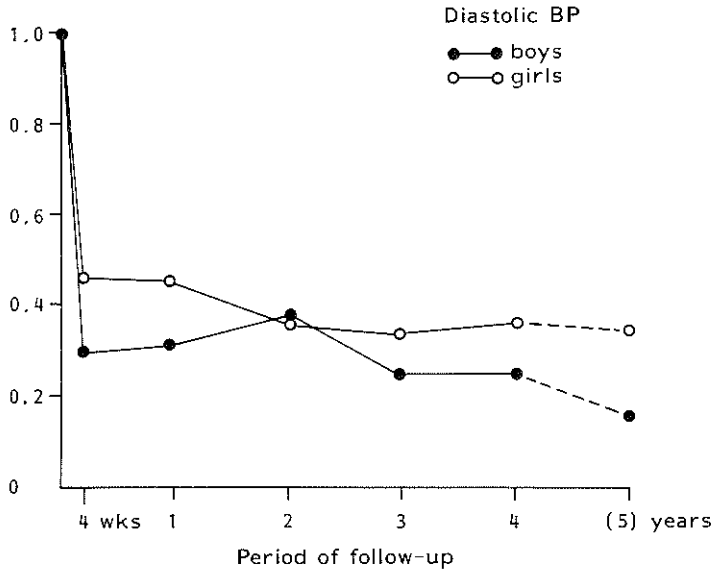

Figure 3
'Tracking' of diastolic blood pressure in Dutch youngsters initially aged 5 – 19. Age-standardized linear regression coefficients (mmHg/mmHg) of follow-up blood pressure with blood pressure at the first examination
Note: The 5-years follow-up data are based on a smaller number of children.

Table 6
Predictive value of high blood pressure in Dutch youngsters, initially aged 5 – 19 : upper one-third of the distribution*

Blood pressure	Age (yrs)	Boys		Girls	
Systolic BP	5 – 9	54%	(25 – 81)**	56%	(30 – 80)
	10 – 14	54%	(33 – 73)	39%	(20 – 61)
	15 – 19	64%	(43 – 82)	65%	(41 – 85)
	Total	61%	(48 – 72)	58%	(44 – 70)
Diastolic BP	5 – 9	50%	(22 – 76)	63%	(35 – 85)
	10 – 14	40%	(21 – 61)	43%	(23 – 66)
	15 – 19	56%	(35 – 76)	58%	(34 – 80)
	Total	48%	(36 – 60)	55%	(42 – 68)

* Predictive value defined as: proportion of those in upper one-third of the distribution of blood pressure at the initial examination who were also in the upper one-third after four years.

** Between brackets: 95% confidence interval of percentage based upon binomial distribution.

pressure these figures were 48 per cent for boys and 55 per cent for girls. The predictive value of a blood pressure reading in the upper one-tenth of the distribution of systolic pressure was 27 per cent (boys) and 44 per cent (girls). These figures amounted to 25 per cent (boys) and 22 per cent (girls) for diastolic pressure. Table 8 shows that repetition of blood pressure measurement added little to the predictive value of blood pressure for those in the upper one-third of the distribution.

Table 7
Predictive value of high blood pressure in Dutch youngsters, initially aged 5 – 19 : upper one-tenth of the distribution*

Blood pressure	Boys	Girls
Systolic BP	27% (11 – 50)**	44% (22 – 69)
Diastolic BP	25% (9 – 49)	22% (6 – 48)

* Predictive value defined as: proportion of those in upper one-tenth of the blood pressure distribution at the first examination who were also in the upper one-tenth after four years.

** Between brackets: 95% confidence interval of percentage based upon binomial distribution.

Discussion

Insight in the etiology of essential hypertension, and in the possibilities of prevention of high blood pressure may be gained by inquires of blood pressure in childhood. For the sake of clarity it is worthwhile to consider separately what the implications of the present report are for the etiology and for the individual prevention of high blood pressure. For etiology an important question is, whether there is 'tracking': does a child maintain his or her position in the blood pressure distribution over time? As to individual prevention the concern is with identifying children who are the future hypertensives.

Table 8
Predictive value of repeatedly high pressure in Dutch youngsters, initially aged 5 – 19 : upper one-third of the distribution initially and after 4-weeks*

Blood pressure	Boys		Girls	
Systolic BP	64%	(46 – 79)**	64%	(44 – 81)
Diastolic BP	62%	(38 – 82)	44%	(26 – 62)

* Predictive value defined as: proportion of those in upper one-third of the blood pressure distribution at the initial examination and at the four-weeks examination who were also in the upper one-third after four years.

** Between brackets: 95% confidence interval of percentage based upon binomial distribution.

Before we discuss our observations on tracking and on the predictive value of high blood pressure in childhood, we have to consider some methodological issues.

The analyses in this paper are based upon a random sample of initially examined youngsters. Response rates were relatively high and therefore we think this sample to be roughly representative of the source population. Only 65 per cent of the sample was included in the present analysis, and loss-to-follow-up might leave us with biased tracking coefficients and estimates of predictive value. However, we consider it unlikely that the magnitude of the bias is large, given the similarity of initial blood pressure values among those lost-to-follow-up and those not. Furthermore, only a limited number of children were lost-to-follow-up sensu strictu; most of them only had some missing values.

Repeated measurements of a variable like blood pressure, with a large within-subject variation and measurement error, pose their own analytical problems. Measurement error causes an underestimate of the true tracking coefficients of blood pressure. This has other implications for etiologic research than for individual prevention. For etiologic research the true tracking coefficients are of concern, and they are most likely larger than the empirical ones presented in this paper. But for preventive activities the empirical estimates of the predictive value of high blood pressure are of interest, as they address the issue of early detection of hypertensives in a realistic context, i.e., with measurement error and misclassification.

Our observations suggest that there is tracking of blood pressure to a moderate extent. The coefficients are of a magnitude which has been reported previously for children and adolescents – in fact they closely resemble the findings in the Muscatine study (6). The coefficients in youngsters are considerably lower then those reported from studies in adults. There seems to be consensus in the literature that tracking coefficients in childhood are about 0.4 to 0.6 for systolic blood pressure and 0.2 to 0.4 for diastolic pressure (6 – 12; see (13) for a review). An interesting finding in our study is that 15 – 19 year old girls, who have reached their 'adult' blood pressure levels, also have 'adult' tracking coefficients of 0.6 to 0.7, whereas boys of the same age, with still increasing blood pressure with age, have considerably lower coefficients. This confirms a finding reported by Rosner et al. (9).

The predictive value of relatively high blood pressure for future blood pressure is relatively low and it is hardly increased by repeating the measurements. Comparison of the predictive value with other studies is only meaningful when the same cut-off points of the blood pressure distribution are used. With that in mind the predictive value in our study of youngsters in the upper one-tenth of the distribution, ranging from 22 to 44 per cent is slightly higher than reported by Zinner et al. (reanalysis ref. 7), Clarke et al. (6) and Bringgold et al. (14). The predictive value seems to be larger when the cut-off level is higher, as evidenced by the larger O/E-ratio for those in the upper one-tenth of the distribution than those in the upper one-third (see Table 9).

That repeated measurements add little to the predictive value of high

Table 9
Ratio of observed and expected number of cases (O/E) in the upper stratum of the blood pressure distribution four years after the initial examination

Blood pressure	Boys	Girls
	O/E	O/E
Systolic BP		
Upper one-third	1.85	1.76
Upper one-tenth	2.74	4.40
Diastolic BP		
Upper one-third	1.45	1.67
Upper one-tenth	2.48	2.23

blood pressure is unexpected on a priori grounds. It might be partly due to sampling error; the estimates are, as exemplified by the wide confidence intervals, rather imprecise.

As to the implications for the etiology of essential hypertension these observations buttress the view that its roots can be traced in childhood. For the individual prevention of high blood pressure these data imply that it is as yet impossible to detect future hypertensives early in life by measuring blood pressure. It is only at an age of 15 that the predictive value has a magnitude (especially in girls) which

perhaps makes identification of those who will have high blood pressure later in life possible. The predictive value may be increased by considering other variables, but until now we have failed to identify the relevant ones. These observations indicate that large scale screening programs to detect future hypertensives at a school age have little merit. All in all this means that up to an age of 15 individual prevention has little meaning. If anything, preventive measures should be directed towards the whole population of youngsters (15).

Acknowledgments

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Chapter 6

Determinants of blood pressure change

Hofman A, Valkenburg HA.
Determinants of change in blood pressure during childhood.
Am J Epidemiol (in press).

Determinants of change in blood pressure during childhood

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Abstract

The determinants of change in blood pressure during childhood were studied in 596 Dutch children, aged 5 – 19. They were randomly selected from a general population and this report deals with 462 of them (78%), who had three to seven annual measurements of blood pressure between 1975 and 1982. The rate of change in blood pressure was obtained by least-squares regression of blood pressure on time for each subject. Initial level of blood pressure was associated negatively with subsequent change in systolic and diastolic pressure, even after adjustment for regression towards the mean. Parental blood pressure and initial body weight were related positively, but weakly, to the rate of blood pressure change. Initial serum uric acid was associated positively with change in blood pressure in girls only. Vascular reactivity, as measured by the cold pressor test, was not related to the rate of change in blood pressure. The same applied to pulse rate, the use of tobacco, coffee and oral contraceptives. The finding that children with the highest initial levels of blood pressure did not have the largest subsequent increase suggests that there is no 'horse-racing' of blood pressure during childhood. There is some evidence that the relation between initial level and subsequent change in blood pressure is modified by age.

Key words: blood pressure; blood pressure, change; body weight; childhood; cold pressor test; parental blood pressure; regression towards the mean; uric acid

Introduction

In most populations the average level of blood pressure increases with age (1). As early as the first decades of this century it was shown that the rise is especially marked in childhood (2,3). Yet, the causes of this increase are still largely unknown.

It has been postulated that the rate of change in blood pressure, rather than the level of blood pressure, characterizes an individual (4). If the rate of change in blood pressure is assumed to be constant for each individual and if blood pressure at birth is assumed to be the same for each individual, the initial level of blood pressure at any age is expected to be positively associated with the subsequent change in pressure (figure 1). This has indeed been found in adults (4,5), but it has not been studied in children.

The determinants of the *level* of blood pressure in childhood have received ample attention. Body weight, pulse rate, gender and parental blood pressure are associated with level of blood pressure in childhood, whereas studies of cigarette-smoking, sodium intake, alcohol consumption and serum uric acid in relation to blood pressure level have yielded conflicting results (1,6). By contrast, the determinants of *change* in blood pressure during childhood have not been studied extensively.

This paper deals with the relation between initial level and subsequent change in blood pressure, as well as with other putative determinants of change in blood pressure during childhood. We studied 596 Dutch children, initially aged 5 – 19, who were randomly selected from a general population and had three to seven annual measurements.

Materials and methods

Population

The study was carried out among residents of two districts of Zoetermeer, which is a suburban residential area with about 55,000 inhabitants near the Hague in the Netherlands. All persons who were 5 – 19 years of age between 1975 and 1979, were invited to participate

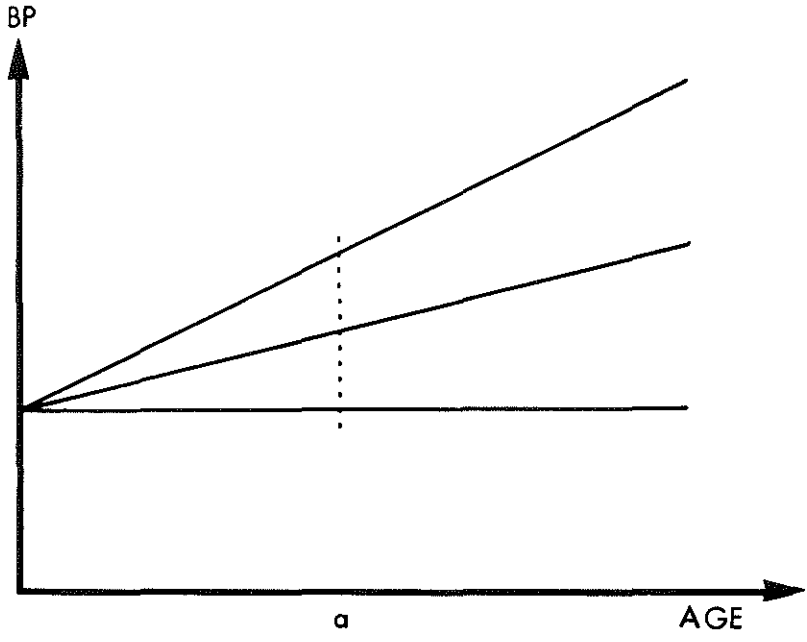

Figure 1
Blood pressure and age, model 1 :
the relation between initial level of BP and the subsequent change in BP is positive at any age a

in a study of blood pressure and other risk-indicators for cardiovascular disease, as described previously (7,8).

Blood pressure was measured in 4,649 subjects, out of 5,670 eligible (82 per cent). Response rates ranged from 77 per cent among those aged 15 – 19 years, to 87 per cent among children 5 – 9 years of age. Of the initially examined subjects 1,597 were selected for annual follow-up and 596 of them are a random sample of the initially examined children. This report deals with 462 of these 596 children

(78 per cent) who underwent at least three yearly exams between 1975 and 1982. The 134 subjects who did not qualify for the present analysis had essentially the same mean systolic and diastolic pressure at the initial exam as the 462 subjects who had at least three yearly exams. The loss to follow-up was largely due to migration. Children with secondary hypertension were removed from the follow-up cohort. No intervention measures were taken and all children received the same general advice about life habits.

Measurements

All children selected for follow-up were reexamined four weeks after the initial exam and subsequently at yearly intervals. At each annual exam information was obtained about blood pressure, height, weight, serum total cholesterol, serum uric acid, serum creatinine, smoking habits and use of coffee, alcohol and oral contraceptives.

Systolic and diastolic pressure were measured with a random-zero sphygmomanometer (9), as described earlier (7). Blood pressure was measured on the left arm of a child in a sitting position after 15 minutes of rest and before veni-puncture. Eight nurses made the measurements. The readings were obtained using the largest cuff which comfortably encircled the arm (10). This implies that, generally, children aged 5 – 9 years were measured with a 23 x 10 cm^2 cuff, whereas for older children a cuff of size 23 x 14 cm^2 was used. The average of two readings which were separated by a count of the pulse rate, was used in the analyses. Diastolic pressure was based on the fifth Korotkoff sound. At the examination four weeks after the initial exam a cold pressor test was carried out, as described by Hines and Brown (11). Blood pressure of the parents was measured in the same way as the children's and generally at the occasion at which the first exam of the child took place. Height and weight were measured with the subjects wearing indoor clothes without shoes. The consumption of tobacco and coffee was determined by questionnaire in subjects aged 15 or over and by interview in children aged 5 – 14 in absence of their parents. In girls who had had menarche, the use of oral contraceptives was assessed by questionnaire. Uric acid in serum was measured using a method described previously (7).

Data-analysis

We performed linear regression of blood pressure on time for each individual using the least-squares approach. This yielded a slope and an intercept, which served as measures of the rate of change and the estimated initial level of pressure, respectively. As the present analysis was restricted to subjects who underwent at least three yearly exams, three to seven annual readings were available in each individual. The value obtained four weeks after the first examination was used as the observed initial value to reduce the effect of unfamiliarity with the procedures.

The relation between the initial level of blood pressure and subsequent change was studied by regressing the individual slopes on the intercepts. This yielded a regression coefficient which is affected by regression towards the mean, i.e., is less positive or more negative than the true coefficient of regression of change on initial level. Blomqvist (12) developed a method in which the ratio of the average residual variance of the individual regressions of blood pressure on time and the variance of the estimated initial values is used to obtain the true coefficient of regression of slope on initial level. In the Appendix the statistical model underlying this procedure is described.

We investigated the determinants of the rate of change of blood pressure by performing multiple linear regression of the individual slopes on the determinants measured at the first examination. We included the initial level of blood pressure in the model and therefore the coefficients represent the effect of a determinant on the rate of blood pressure change conditional on initial level. The regression coefficients are presented with their standard errors (SE), for six categories of age and gender. The analysis was based on subjects with three to seven annual blood pressure readings. The findings were essentially the same when we restricted the analysis to those with five or seven annual readings.

Results

Level of blood pressure

Mean systolic and diastolic pressure at the first examination are given in table 1. Systolic and diastolic pressure were similar in boys and girls in the 5 – 9 and 10 – 14 age groups. Mean systolic pressure in 15 – 19 years old boys was considerably higher than in girls.

Table 1
Blood pressure (mmHg) at the initial examination according to age and gender

Age in years	Boys					Girls				
		Systolic BP		Diastolic BP			Systolic BP		Diastolic BP	
	(n)	Mean	SD	Mean	SD	(n)	Mean	SD	Mean	SD
5 – 9	(60)	101	11	63	10	(65)	102	13	63	11
10 – 14	(89)	112	13	68	9	(87)	112	11	66	10
15 – 19	(87)	124	13	68	11	(74)	117	12	69	10

Change in blood pressure

The average rate of blood pressure increase during childhood, as measured by the slope of the individual linear regression of blood pressure on time, is given in table 2. For systolic pressure it was 2.6 mmHg/yr in boys and 1.0 mmHg/yr in girls. The average increase in

diastolic pressure was 0.6 mmHg/yr in boys, and 0.3 mmHg/yr in girls.

Table 2
Mean annual change in BP (mmHg/yr) according to age and gender

Age in years	Systolic BP				Diastolic BP			
	Boys		Girls		Boys		Girls	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
5 – 9	1.2	0.4	0.9	0.4	0.1	0.4	−0.4	0.5
10 – 14	3.2	0.4	1.1	0.3	0.4	0.4	1.0	0.3
15 – 19	2.9	0.4	1.0	0.3	1.0	0.4	0.3	0.3
Total	2.6	0.1	1.0	0.1	0.6	0.1	0.3	0.1

Determinants of change in blood pressure
Initial level of blood pressure. The observed coefficients of regression of the individual slopes on the intercepts were negative for boys and girls in all age categories. After adjustment for regression towards the mean the coefficients remained negative, although the difference from zero was only statistically significant in the youngest age groups (table 3). The coefficients became less negative with increasing age.
Parental blood pressure. Linear regression of the individual slopes on the average blood pressure of the parents yielded coefficients which were generally positive, but small (table 4). For systolic pressure in children aged 5 – 9 and for diastolic pressure in those aged 10 – 14 the

Table 3
Adjusted † coefficients ※ ((mmHg/yr)/mmHg) of linear regression of rate of change of BP on initial level of BP

Age in years	Systolic BP				Diastolic BP			
	Boys		Girls		Boys		Girls	
	b	SE	b	SE	b	SE	b	SE
5 – 9	−0.18***	0.05	−0.04	0.09	−0.17**	0.06	−0.29***	0.07
10 – 14	−0.06	0.06	−0.05	0.05	−0.06	0.06	−0.16**	0.05
15 – 19	−0.05	0.04	−0.02	0.05	−0.07	0.06	−0.12	0.11
Total	−0.11***	0.03	−0.05	0.03	−0.11***	0.03	−0.14***	0.04

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

† According to Blomqvist (12).

※ Adjusted for age.

coefficients were significantly different from zero. With the age categories combined, the coefficients were significantly different from zero, except for systolic blood pressure in boys. A difference of 10 mmHg in parental blood pressure was associated with a mean difference in change of systolic and diastolic pressure of about 0.3 to 0.4 mmHg/yr. The use of another index for parental blood pressure (160 and/or 95 mmHg or higher, or treatment for high blood pressure, as compared to lower parental blood pressure) yielded similar results.

Table 4
Coefficients † ((mmHg/yr)/mmHg) of linear regression of rate of change of BP in children on BP of their parents ⚒

Age in years	Systolic BP				Diastolic BP			
	Boys		Girls		Boys		Girls	
	b	SE	b	SE	b	SE	b	SE
5 – 9	0.056*	0.028	0.074**	0.028	0.046	0.028	0.035	0.032
10 – 14	0.025	0.033	0.003	0.024	0.070*	0.028	0.063*	0.028
15 – 19	0.021	0.033	0.022	0.027	0.034	0.036	– 0.018	0.038
Total	0.026	0.019	0.033*	0.015	0.045*	0.018	0.044*	0.018

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

† Adjusted for differences in initial BP, initial weight, initial height and age at first exam.

⚒ Average BP of father and mother.

Body weight and height. Initial body weight (measured at first exam) was positively related to the rate of change of systolic and diastolic pressure in older boys and girls (table 5). A difference of 10 kg in body weight, adjusted for differences in initial blood pressure, height and age, was associated with a mean difference in change of systolic and diastolic pressure of about 0.5 to 0.7 mmHg/yr in boys and girls aged 5 – 19. Initial body height was only significantly positively related to change in systolic pressure, when all age categories were combined. For diastolic pressure no association was found. These relations were observed after adjusting for differences in initial pressure, age and

body weight. Additional analyses, with adjustment for various indices of obesity (weight/height^2 and weight/height^3), showed similar results. More detailed tables are available upon request.

Table 5
Coefficients † ((mmHg/yr)/kg) of linear regression of rate of change of BP on initial body weight

Age in years	Systolic BP				Diastolic BP			
	Boys		Girls		Boys		Girls	
	b	SE	b	SE	b	SE	b	SE
5 – 9	0.11	0.08	0.00	0.09	0.07	0.06	−0.06	0.08
10 – 14	0.14**	0.05	0.05	0.04	0.08*	0.04	0.04	0.03
15 – 19	0.01	0.04	0.10**	0.04	0.04*	0.02	0.07*	0.03
Total	0.07*	0.03	0.07*	0.03	0.05**	0.02	0.06**	0.02

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

† Adjusted for differences in initial BP, initial height and age at first exam.

Serum uric acid. The level of serum uric acid at the initial exam was positively related to change in blood pressure in boys and girls. After adjustment for initial body weight this association remained statistically significant in girls only with all age categories combined (table 6).
Other determinants. The consumption of tobacco or coffee at the first examination was unrelated to subsequent change in blood pressure. The same applied to pulse rate and to indices of vascular reactivity as derived by the cold pressor test. Users of oral contraceptives at the

Table 6
Coefficients † ((mmHg/yr)/(mMol/ltr)) of linear regression of rate of change of BP on initial serum uric acid

Age in years	Systolic BP				Diastolic BP			
	Boys		Girls		Boys		Girls	
	b	SE	b	SE	b	SE	b	SE
5 – 9	5.8	6.6	1.4*	0.6	−5.2	4.9	8.0	4.8
10 – 14	−7.5	8.4	1.4	5.8	0.7	5.0	3.0	4.8
15 – 19	−6.9	7.8	8.2	8.5	2.6	4.9	11.1	6.5
Total	−4.6	4.2	7.6*	3.7	−1.1	2.7	7.7*	3.0

* $p < 0.05$

† Adjusted for differences in initial BP, initial weight and height, and age at first exam.

initial exam had no larger increase of blood pressure than non-users.

Discussion

Interest in the relation between level and change in blood pressure stems from the conceptualization of the change of blood pressure with age as depicted in figure 1. This model is a modification of a similar one proposed by Fletcher et al. (13) for pulmonary function. The model has two basic features: (1) it postulates a constant rate of blood

pressure change and (2) the same starting level of blood pressure, e.g. at birth, for each individual. If the model holds, one would expect the initial level of blood pressure at any age to be positively related to subsequent change. This has been referred to as 'horse-racing' (13).

Unfortunately, the analytic approach to the relationship between initial level and change in blood pressure is not straight-forward. It is complicated by the phenomenon of regression towards the mean. We used the method of Blomqvist (12) to obtain the maximum likelihood estimate of the true regression coefficient of blood pressure change on initial level (see Appendix). As has been pointed out previously (5,14), this procedure is preferable in some senses to (1) regression of change on observed initial level, to (2) regression of change on mean blood pressure level as suggested by Oldham (15) and to (3) regression of blood pressure change, computed without observed initial blood pressure, on observed initial blood pressure, as employed by Feinleib et al. (16).

A further problem is that every model known to us assumes independence of errors and this seems intuitively unjustified. However, in our data we found no firm evidence that errors in blood pressure, measured over a period longer than one year apart, were correlated. The correlation between initial and subsequent blood pressure remains constant after one year and therefore we are confident that the coefficients given in table 3 reflect the true relation between initial level and subsequent change and are not merely analytic artefacts.

Our finding of no positive relation between initial level and change in blood pressure in youngsters is at variance with two previous studies in adults. From a study among residents of Gothenburg, initially aged 50 years, Svardsudd and Tibblin (5) reported a positive relationship for systolic pressure and a negative one for diastolic pressure. Wu et al. (6) analyzed data collected in Framingham and found a positive association between initial level and subsequent change in systolic pressure in all but one categories of age (35 years and over) and gender. Sparrow et al. (17) recently reported a study in Bostonian men in which they found a negative association between blood pressure change and initial blood pressure.

Their findings are hard to interpret, however, because they did not adjust for regression towards the mean.

Further evidence originates from re-analysis of a study reported by Jenss (18) in 1934. Jenss analyzed blood pressure data collected on 1,139 U.S. Army officers in whom an average of 9.4 blood pressure readings was obtained over an average period of 12.3 years. She computed a least-squares slope of blood pressure on age for each officer, calculated a 'theoretical' initial blood pressure using the intercepts, and correlated the slopes with the estimated initial values. We re-analyzed her data using the method according to Blomqvist (12) and the results are presented in table 7. Two conclusions emerge from Jenss' study. First, after adjustment for regression towards the mean the coefficients remain negative, especially in the younger age categories. Second, this re-analysis indicates that, as expected, the impact of regression towards the mean is very small when a multitude of observations is available.

What is the explanation of Jenss' and our finding of no positive association between change in blood pressure and initial level in youngsters? There is evidence that the basic features of the proposed concept are untenable, at least in childhood. The assumption that blood pressure at birth is the same for all individuals is quite unrealistic. It seems likely that the 'constitutional' or 'genetic' level of blood pressure has about the same variance as can be observed in the first decade of life. A more realistic modification of the proposed model is presented in figure 2.

From this model one can deduce that the empirical relation between initial level and change in blood pressure is modified by age: the older the study subjects are, the more positive the coefficients of the relation between initial level and change in blood pressure will be. This is in accordance with findings for men in Framingham (5), with Jenss' findings (18) and with our findings. Moreover, although there are no data available about the relation between the rate of increase of blood pressure in childhood and later on in life, it is unlikely that the rate of change is constant over time.

The average blood pressure values of youngsters in our study are in agreement with those reported from most other studies in the U.S.A. and Europe (7). As to the determinants of blood pressure

Table 7
Rate of change of systolic blood pressure in relation to estimated initial level in 1,139 U.S. Army officers, studied by Jenss (18)

Initial age in years	Observed correlation coefficient		Observed* regression coefficient		Adjusted** regression coefficient	
	r	SE	b	SE	b	SE
20 – 24	– 0.66	0.07	– 0.07	0.01	– 0.05	0.01
25 – 29	– 0.46	0.06	– 0.05	0.01	– 0.03	0.01
30 – 34	– 0.51	0.05	– 0.04	0.01	– 0.02	0.01
35 – 39	– 0.45	0.06	– 0.04	0.01	– 0.01	0.01
40 – 44	– 0.42	0.06	– 0.04	0.01	– 0.01	0.01
45 – 49	– 0.36	0.07	– 0.04	0.01	– 0.01	0.02
50 – 54	– 0.35	0.11	– 0.03	0.01	0.00	0.02

* Calcuted using correlation coefficient and standard deviations of initial level and slopes, given by Jenss (18).

** According to Blomqvist (12); $a_1 = 0.06$, $a_2 = 0.38$, and λ is assumed to be 0.5 (see Appendix).

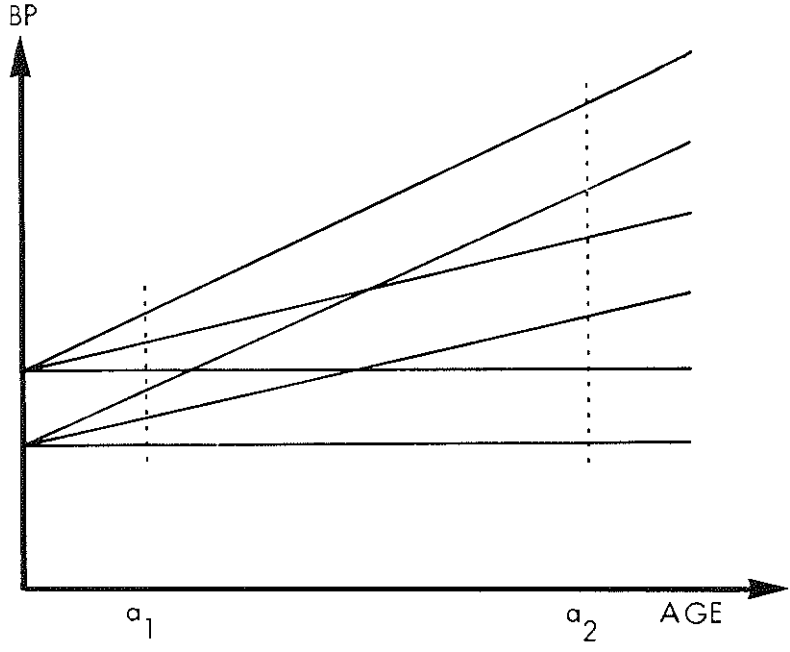

Figure 2
Blood pressure and age, model 2 :
the relation between initial level and subsequent change in BP is stronger at age a_2 than at age a_1, i.e., age modifies the relation between initial BP level and subsequent change

change, parental blood pressure is positively related to the rate of increase of blood pressure in their children, but the magnitude of the association is small. This is in agreement with previous studies in which familial aggregation of blood pressure in children was observed (19). Generally, these studies too showed very small coefficients of regression of children's blood pressure on parental blood pressure (20). Body weight is a determinant of blood pressure change in older children. No explanation is as yet available for this association, although it has been suggested that body weight might be related to hemodynamic variables as well as sodium intake (6). The finding of a positive relation between body height and change in systolic pressure partly confirms Voors' (21) contention that stature and blood pressure are positively associated in childhood. Vascular reactivity, as measured by the cold pressor test, was not a predictor of blood pressure change in our study and this agrees with the findings of Harlan et al. (22) in young men. The initial level of serum uric acid was strongly related to subsequent blood pressure change in children, but in boys this association disappeared when initial body weight was taken into account. However, in girls the positive association remained when controlling for body weight.

These findings suggest that children with the highest initial level of blood pressure do not have the largest subsequent increase, i.e., there is no evidence for 'horse-racing' of blood pressure in childhood. Parental blood pressure, body weight and serum uric acid (in girls) are predictors of change in blood pressure during childhood.

Acknowledgments

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Appendix

The statistical model assumed here has been described previously by Feinleib et al. (16) and Blomqvist (12) and applied by Svardsudd and Tibblin (4) and Wu et al. (5). In brief, it can be described as follows.

Let Y_{ij} be the observed blood pressure of the ith individual ($i=1,...,n$) at time t_j ($j=1,...,k$; $t_1=0$). Y_{ij} is assumed to be linearly regressed on time:

$$Y_{ij} = M_i + b_i t_j + e_{ij},$$

where M_i and b_i are the true initial blood pressure and the true slope, respectively, and e_{ij} are independent $N(O,\sigma_e^2)$. The vectors e_{ij} and (M_i,b_i) are assumed to be independent.

The true regression coefficient b_t of b_i on M_i is given by:

$$b_i = a + b_t(M_i - M) + d_i,$$

where M is the average true initial blood pressure value and d_i are independent $N(O,\sigma_d^2)$, and also independent of M_i.

Blomqvist (12) showed that the maximum likelihood estimate of b_t can be obtained through adjustment of the observed regression coefficient b_o, as follows:

$$b_t = (b_o + a_1\lambda)/(1 - a_2\lambda)$$

where λ is the ratio of the error variance $\hat{\sigma}_e^2$, estimated by the mean of the residual mean squares of each individual regression of blood pressure on time, and the sample variance of the estimated initial blood pressure values, the intercepts; and where

$$a_1 = \bar{t}/\Sigma(t_j - \bar{t})^2 \text{ and}$$
$$a_2 = \Sigma t_j^2/\Sigma(t_j - \bar{t})^2.$$

Chapter 7

Blood pressure and atherosclerosis

Hofman A.
Blood pressure and atherosclerosis. A proposal.

Blood pressure and atherosclerosis
A Proposal

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Abstract

This paper addresses the relations between blood pressure, atherosclerosis and cardiovascular disease. It proposes that departure from the genetically determined blood pressure level, the genetic track, determines cardiovascular risk. Direction, pattern and timing of this departure influence atherogenesis, and thereby the occurrence of cardiovascular disease. Subjects who are young when they deviate from the genetic track are thought to be at a higher risk to develop cardiovascular disease than those who deviate later in life. The implications of this proposal are that the relation between blood pressure and atherosclerosis and in particular the pattern and timing of blood pressure change should receive more scientific attention. For prevention the implication is that intervention might be guided best by knowledge of individual patterns of blood pressure change, particularly in young people. This proposal casts some doubt on the effectiveness of the 'whole population approach' in the prevention of cardiovascular disease.

Introduction

Blood pressure research has been unsuccessful in providing a generally accepted causal explanation for the relation between arterial blood pressure and morbidity and mortality of

cardiovascular diseases. In this paper the reasons for this phenomenon will be examined. It will be argued that the current thinking about blood pressure is still mainly in qualitative terms and that there is little emphasis in research on the role of blood pressure in atherogenesis. A general concept about the relation of blood pressure and atherosclerosis will be proposed, in which findings in experimental studies are combined with results of epidemiologic investigations. Its implications for both etiologic research and prevention will be discussed briefly.

The State of the Art

Pickering-Platt revisited.

In 1968 Sir George Pickering wrote: "The 'disease' essential hypertension representing the consequences of raised pressure without evident cause is thus a type of disease not hitherto recognized in medicine in which the defect is one of degree not of kind, quantitative not qualitative... It is apparently difficult for doctors to understand because it is a departure from the ordinary process of binary thought to which they are brought up... Quantity is not an idea that is as yet allowed to intrude. Medicine in its present state can count up to two but not beyond" (1). Since 1968 much lip-service has been paid to Pickerings view that essential hypertension represents a quantitative deviation from the norm and that blood pressure should be seen as a graded physiologic characteristic. Still, the current literature is dominated by thinking in qualitative terms. In the report of the Hypertension Task Force of the U.S. National Heart, Lung and Blood Institute, dated 1979, terms like 'persistent', 'sustained', 'labile' and 'borderline' hypertension are used abundantly (2). In most papers reporting blood pressure research two entities are displayed: 'hypertensives' and 'normotensives'. Hypotheses about the causes of increase of blood pressure are often expressed in qualitative terms. Studies of the course of blood pressure early in life are performed "to observe the early onset of hypertension and to be able to define essential hypertension as a disease in childhood" (3). It seems that, as

a rule, blood pressure increase is considered as a qualitative rather than a quantitative phenomenon.

High blood pressure is not a problem per se

A second idea to be confronted with the current literature is that high blood pressure is not a problem in its own right. This has been recognized in the report of the Hypertension Task Force (2), but no conclusions have been drawn from this notion. It is by virtue of its putative association with morbidity and mortality of mainly cardiovascular diseases that blood pressure has gained interest. Especially its role in athero- and thrombogenesis seems important, because it is largely through the relation between blood pressure and atherosclerosis that the study of blood pressure becomes relevant. Strangely enough atherosclerosis seems to be considered a side issue in current hypertension research, as evidenced by the already mentioned report of the Hypertension Task Force (2). In 125 pages summarizing the state of the art in blood pressure research only two paragraphs (0.4%) are explicitly devoted to the role of blood pressure in atherogenesis. The situation has not changed very much since Dustan wrote in 1974 that research efforts "have not begun to explain why hypertension plays such an important role in the pathogenesis of atherosclerosis and its complications" (4).

No general concept

A third notion when examining the current activities is the apparent lack of a unifying concept in blood pressure research. Again the report of the Task Force (2) may serve as an illustration. The scientific summaries, provided by subgroups of the Task Force, have headings like 'hemodynamics', 'pediatrics', 'neural control of the circulation', 'pregnancy', 'salt and water', 'vascular smooth muscle' and 'obesity'. This overtly inconsistent taxonomy – or better, this lack of taxonomy – reminds one of the parable of the "Blind men and the Elephant", in which each blind man is convinced that he is describing the elephant correctly by touching part of it (5). General concepts have been proposed in the past – the debate between Platt and Pickering is a case in point (6). Epidemiologists have not been very active in stating a general theory about the relation between blood pressure

and atherosclerosis, although the importance of such a theory has been recognized (7,8).

A concept

In the remainder of this paper a conceptualization of the relations of blood pressure, atherosclerosis and cardiovascular diseases will be developed. As a point of departure some consistently corroborated hypotheses will be considered (9).

Elements of the concept

It is generally agreed upon that the level of blood pressure is to a certain extent genetically determined. There seems to be a moderate amount of stability of rank of an individual's pressure. This stability is often referred to as 'tracking' and it is stronger in adults than in children (10). Average blood pressure levels remain, after a rapid increase in the first months of life, constant until the age of about 4 years (11). Then a gradual increase of average blood pressure begins (12).

There is agreement upon the notion that changes in total peripheral resistance are crucial in the longterm regulation of blood pressure and it is generally accepted that the contractile apparatus of the smooth muscle cells of the vasculature plays a role as final common path for various effectors. The impact of both structural and functional factors (9,13,14) in vascular smooth muscle regulation is well-documented. Electrolytes and catecholamines are predominant among the postulated physiologic correlates of smooth muscle activity, but a host of other humoral and neurogenic variables have been implicated in the regulation of the contractile status of the vasculature and thereby of total peripheral resistance.

At the beginning of life major alterations take place in the vascular wall (9). After a period (2 – 6 months) of rapid development of the wall layers, notably the media, an equilibrium is set, in which the wall structure corresponds to a basic smooth muscle tone (9,13,15 – 16). The pressure level related to this equilibrium may be referred to as the 'genetic track', and it seems largely determined by the structure of the vascular wall (9,14). In the course of life various environmental

factors influence the contractile apparatus, thereby changing peripheral resistance. This change of the resistance of the vascular bed results from an interplay of the structurally determined basic tone and vascular reactivity, and the potential functional effectors of the contractile apparatus of the smooth muscle cell. This leads to change of blood pressure and thereby to departure from the genetic track. Renal control mechanisms may play a part in the initiation of the deviation from the genetic track, but probably the kidneys are more important as the rise of blood pressure advances (9).

Proposal

It is postulated here that the blood pressure level of the genetic track has no bearing on the probability of developing cardiovascular disease. It provides the 'background' risk. It is departure from the genetic track in the course of life that determines the cardiovascular risk. Thus, blood pressure change – deviation from the genetic track – modifies the risk, through acceleration and aggravation of atherogenesis and thrombogenesis. A subject with a basic smooth muscle tone corresponding to a genetic systolic level of 110 mmHg has, according to the outlined concept, the same (background) risk as a person with a genetic level of 80mmHg.

Change of blood pressure

How does change of blood pressure, defined as departure from the genetic track, affect the probability of developing cardiovascular disease? First of all it has to be stated what is meant by change of blood pressure. In the context of atherogenesis change of pressure is referred to as the long-term average change of the long-term average true blood pressure of a subject in a resting state. Long-term may be loosely defined in terms of at least months. The 'genetic track' level is the blood pressure level corresponding to the basic smooth muscle tone determined largely by the structure of the vascular wall. 'Attained' blood pressure is referred to as the pressure level reached after a certain defined time period. Direction, pattern, timing and effect on disease risk of change in blood pressure will now be

described seriatim. It will lead to some refinement of the proposal presented above.

Direction of blood pressure change

Positive change, viz. increase of blood pressure, is related to increase of risk of cardiovascular diseases. Increase not necessarily implies change of position in the distribution, but it implies departure from the genetic track. When every subject experiences the same rate of increase no change of relative position in the distribution will occur. It may seem redundant to relate increase of pressure to increase of risk, but no logical necessity excludes the possibility that decrease in the level of a variable is associated with increased disease risk. As an illustration may serve that the U-shaped relation of serum total cholesterol with cancer mortality, as observed by some (17), may result from such a state.

Pattern of blood pressure change

It seems natural to propose that the cardiovascular risk is a function of the magnitude and course of the departure of blood pressure from the genetic track. This implies that the probability of developing cardiovascular diseases is related to the integral of the function describing the deviation over time. The implicit assumption is that deviation from the genetic track is quantitatively related to the extent of atherosclerotic lesions. There is some evidence that this relationship is linear (18). Figure 1 presents three possible patterns of change.

There may be abrupt, cascadic or gradual change. These patterns may be described, of course not exhaustingly, as 'causes' of increase: 'experimental', 'neurogenic', 'sodium'. Figure 2 visualizes two patterns of gradual change.

When all subjects deviate with the same rate of increase from the genetic track (Figure 2a) no change of position in the blood pressure distribution will occur over time. Different rates of increase lead to change of position (Figure 2b). This is sometimes referred to as 'horse-racing' (19,20). Another possibility, and a rather likely one, is that the increase in non-linear, i.e., that the rate of increase varies with age.

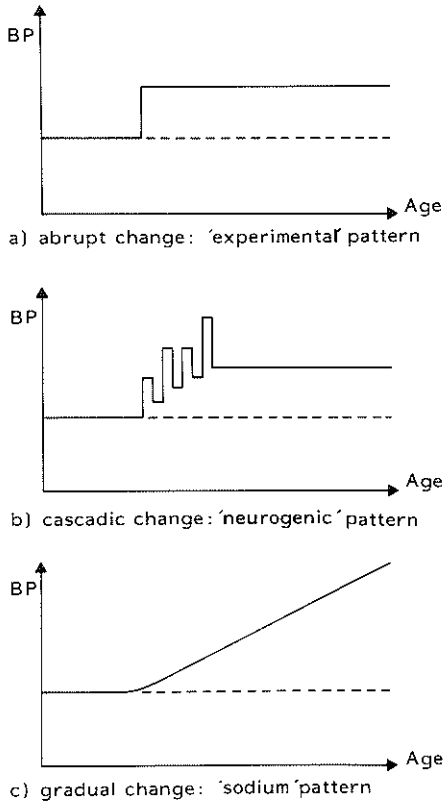

Figure 1
Different patterns of change in blood pressure with age

Timing of blood pressure change

Given the same rate of increase of pressure the relation between the timing of increase (age at initiation) can be thought of as non-influential on, or as a modifier of the extent of atherosclerotic lesions. There is evidence to take the latter view (21), and to propose different cardiovascular risks for 'early' and 'late' increasers. It is likely that pressure increase has different effects on atherogenesis and thrombogenesis at various ages depending on the stage of atherogenesis (16). It might well be that early increase *accelerates* the transition from fatty streaks into fibrous plaques through increase of

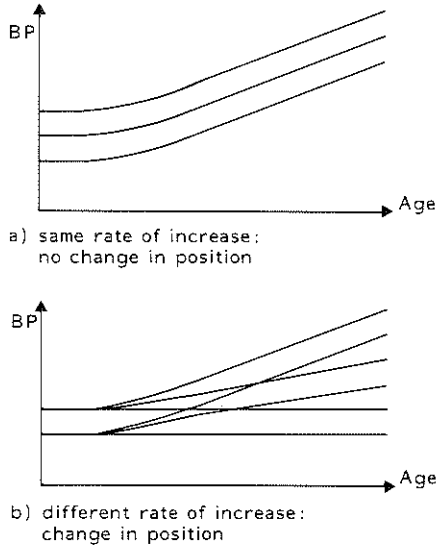

Figure 2
Different patterns of gradual change in blood pressure with age

vascular (endothelial) permeability and subsequent lipid deposition (16). It is likely that the earlier this pressure increase takes place, the more fatty streaks will be involved and the more atherosclerotic lesions will occur. Late increase of pressure may play a part in *aggravating* the effects of fibrous plaques by transition of plaques into complicated lesions through hemorrhage and ulceration of the plaques.

Risk and blood pressure change

Two elements of the outlined concept have bearing on the relation between blood pressure change and cardiovascular risk. Firstly, the magnitude of deviation from the genetic track is thought to be linearly related to the extent of atherosclerosis. Secondly, the modifying effect of age at initiation of pressure increase on risk implies that, given the same rate of increase, an increase in childhood is associated with more atherosclerosis than the same increase later in life.

The relation between amount of atherosclerosis (A) and its determinants *in each individual* may be formalized as follows:

$$A = b_o + b_1 T_{ia} (BP_a - BP_g) + b_2 I$$

in which T_{ia} is the time between initiation of pressure increase and reaching the 'attained' pressure, BP_a the 'attained' pressure, BP_g the genetic track level and I the age at initiation of the increase.

When b_3 denotes the individual rate of blood pressure rise, then

$$BP_a = BP_g + b_3 T_{ia}$$

Therefore

$$A = b_o + b_1 b_3 T_{ia}^2 + b_2 I$$

In figure 3 subjects a and b, with different pattern or timing blood pressure rise, have the same cardiovascular risk.

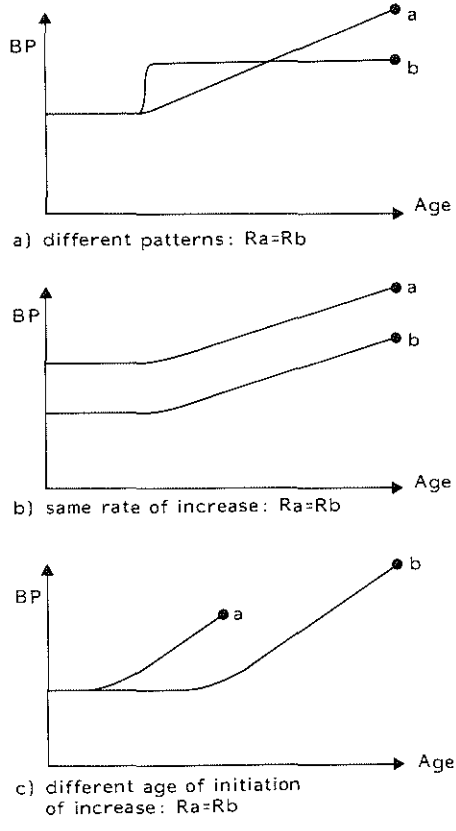

Figure 3
Pattern and timing of change in blood pressure and cardiovascular disease risk

Comparison of concepts

It seems that the widely held view about the relation between atherosclerosis, blood pressure and cardiovascular risk is that the *level* of blood pressure is linearly related to cardiovascular disease risk. It may be asked, then, what the advantage is of the outlined view, which relates *change* of blood pressure to cardiovascular risk.

The relation between attained blood pressure and cardiovascular risk would be linear according to the level-concept. According to the change-proposal the proportion of blood pressure 'increasers' goes up with attained blood pressure level (see Figure 2b). On the assumption of a constant rate of blood pressure increase the fraction of increasers rises linearly with the level of attained pressure. However, in the upper strata of attained level there is a predominance of large increasers. Therefore, the average amount of pressure increase per subject rises exponentially with attained level. Thus, the change-concept predicts an exponential increase of cardiovascular risk with attained level of blood pressure. This agrees with observations in epidemiologic studies, in which an exponential (log-linear) relation between 'attained' pressure and cardiovascular disease risk has been found (22,23).

It has been observed that the differences between the average blood pressure of patients with coronary heart disease, as compared with non-cases, increases with age (24). This is predicted by the change-concept, in which the age at initiation of blood pressure change affects the risk. In early increasers a relatively small rise is responsible for the same atherogenic effect as a large rise in late increasers. Thus, late increasers will not only develop atherosclerotic complications later, but also have experienced a larger increase in blood pressure (Figure 3c).

The strength of the association between blood pressure and risk tends to decrease with age (22). For example, in the Framingham Heart Study the upper strata of the blood pressure distribution of those who were 35 years of age at the first examination consisted mainly of early increasers. The upper strata of the distribution of those aged 55 at the first examination comprised also late increasers, and according to the change-concept this weakens the relation between blood pressure level and risk.

Implications

It seems that the relation between blood pressure and atherosclerosis deserves more scientific attention than it has received until now. Current epidemiologic research in this area focusses on the natural history of blood pressure in childhood (25). Potentially the ongoing studies can serve both etiologic research and preventive activities by examining patterns of blood pressure change. One of the implications of the proposed concept is that emphasis should be put upon describing various patterns of blood pressure change over time. Until now natural history ('tracking') studies have generally been reported in terms of measures of stability of rank. Recognition of patterns of blood pressure change may provide a quantitation of the exposure of the circulation to potentially injurious 'non-normal' pressure. Investigations of the effect of timing of blood pressure increase merits attention.

The major implication for prevention of cardiovascular diseases seems to be that intervention might be guided best by knowledge of individual pressure patterns. Blood pressure change, not merely a 'high' level, may be the starting point of intervention, particularly in young adults. It is at place here to subtlilize this statement by dividing between early and late increasers. In late increasers the 'attained' blood pressure level might be used for intervention. In early increasers, however, detection of change might be a crucial prerequisite for preventing the transition of fatty streaks into fibrous plaques.

The outlined concept has some bearing on the scientific rationale of the 'whole population approach' in prevention (26,27). Reduction of cardiovascular risk is related to decrease of blood pressure in increasers only and the fraction of increasers becomes larger with increasing 'attained' level. The lower strata of the distribution of 'attained' blood pressure consist mainly of subjects in which the cardiovascular risk cannot be reduced, because they are at their genetic tracks. Thus, the basic assumption in comparing the effect of the 'whole population approach' to that of the 'high risk strategy', namely that reducing blood pressure gives a proportionate reduction in cardiovascular risk, might not be warranted.

Discussion

The outlined concept is proposed to provide a scheme which may be modified. One of the necessary alterations might be the consideration of a genetically determined (fixed) rate of increase of total peripheral resistance, and thereby of blood pressure. In fact the described concept can be viewed as a simple case, in which the genetic track has zero rate of increase. However, generalization of the concept does not affect the basic idea that departure from the genetic track is related to the extent of atherosclerosis and that early increase of blood pressure is more harmful than late increase.

Another point is that the effects of other variables have not been taken into consideration. It might well be that the proposed relations between blood pressure, atherosclerosis and cardiovascular disease are modified by other risk-indicators for cardiovascular disease.

Finally, the change-concept has not the pretention of explaining the myriad of observations in blood pressure and atherosclerosis research. And although it is consistent with many findings in experimental and observational studies, the empirical evidence directly favouring it is rather limited. It seems that reanalysis of some of the prospective follow-up studies of risk-indicators for cardiovascular disease might be promising in this respect.

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Chapter 8

Reappraisal of the evidence 1
Formal aspects

This thesis presents evidence on blood pressure in childhood originating from a variety of studies. In this chapter the formal aspects of these investigations will be reviewed. The design of the studies, the methods and data-analysis, and the inference based upon them, will be discussed.

Study design

In 1954 Cornfield wrote that "we all have a vague feeling that if we can make an event occur, we understand it better than if we simply observe it passively" (1,2). The studies described in the previous chapters are, with the exception of the trial of sodium intake and blood pressure in newborns (chapter 4), observational in character. A major problem of non-experimental probes into disease aetiology has been stated by Feinstein and Horwitz (3). "Since neither observational cohort studies, nor case-control studies are conducted under experimental circumstances, the results may not always accurately reflect what might be found with a randomized experiment, which serves as the scientific 'gold standard' in cause-effect research". The validity of observational epidemiological research has to be secured by avoidance of bias in the design of the investigation, or by 'control' of bias, if possible, in its analysis. The validity of the studies on which this thesis is based will be discussed under Methods. Three comments have to be made about their designs.

The study in which plasma noradrenaline was measured in 'hypertensive' and 'normotensive' youngsters (chapter 3) has been labelled a 'case-control' study. This might give rise to some

misunderstanding. In epidemiology a case-control study is generally referred to as a study in which a certain exposure is compared between cases and non-cases. Conceptually this is a longitudinal design, the idea being that exposure in the past has led to the disease. In our study noradrenaline and blood pressure were measured simultaneously. Operationally the study was therefore cross-sectional, but the concept behind it was longitudinal, assuming that a high mean noradrenaline level at the occasion of blood pressure measurement reflects a long-term high level in the past, which might have led to an increase of blood pressure. As will be discussed in chapter 9, this assumption might be unwarranted. The study design does not permit us to rule out the possibility that a high noradrenaline level is an epiphenomenon of the procedures, rather than a long-term cause of high blood pressure.

In the study of haemodynamics and blood pressure (chapter 3) the prime question was whether a high cardiac output, i.e., a hyperkinetic circulatory state, in childhood, causes high blood pressure in adulthood. This question might be answered by comparing blood pressure in adults, who had a high versus a normal cardiac output as children (and were otherwise comparable). An experimental study seems unfeasible in this context. A first approximation to the experiment would be a prospective follow-up study, with measurement of cardiac output in childhood, and assessment of the blood pressure status in adulthood. This would take at least 15 years of follow-up. As a second approximation we performed a cross-sectional study (chapter 3) in which we measured cardiac output and blood pressure simultaneously. A preferable approximation to the experiment might be a retrospective follow-up study, using data on cardiac output which have been collected in the past for other purposes, e.g. for the evaluation of what turned out to be 'innocent' cardiac murmurs in children. This would yield the same length of follow-up within a considerably shorter study period.

The design of the prospective follow-up study (chapters 5 & 6) may be criticized in that it was non-symmetrical in sampling: we selected subjects in the upper ten per cent of the blood pressure distribution together with a random sample of the remaining youngsters. We might have selected subjects from the lower ten per cent, and perhaps

ten per cent from the distribution around the median. If blood pressure would have been the only outcome variable in this study this might have been the most efficient approach in terms of precision. But the prospective follow-up study focussed also on other risk-indicators for cardiovascular disease, like serum cholesterol, body mass index and smoking habits. The chosen design was efficient in that the reference group could also serve for the study of these risk-indicators.

Methods

Population

In the first phase of the EPOZ study, from April 1, 1975 to June 30, 1978, blood pressure was measured in 3,924 youngsters, out of 4,806 eligible, who lived in one of the two study districts in Zoetermeer and who were 5 – 19 years of age at January 1, 1975. These numbers correspond to those given in chapters 2 & 3.

In 1978 and 1979, all 5 – 19 year olds who migrated into one of the study districts between January 1, 1975 and July 1, 1978, or who became 5 years of age in that period were also asked to participate in the EPOZ study. There were 864 children who qualified, and in 725 of them (84 per cent) blood pressure was measured. Thus, in total 4,649 out of 5,670 children were studied. The analyses in chapters 5 & 6 are based on a sample of these children.

Measurement of blood pressure

As the outcome variable in this study was blood pressure, it is at place to discuss its measurement. Measurements were done by eight paramedical co-workers in the initial phase of the EPOZ study (1975 – 1978), and by two of them in the years thereafter. Two readings were obtained in time only separated by a count of the pulse rate. The measurements were done with a random-zero device (4). The duplicate readings enabled us to gain some insight in the random error of blood pressure measurement (5). We defined measurement error as the difference of the two readings as a proportion of the average blood pressure of each subject. This is, of course, only an approximation of the true measurement error, as it does include (very)

short-term biological variability. The average of this quantity was expressed in per cent. For systolic pressure it ranged from 4.3 to 8.0 per cent for the eight observers (the average of the observers was 6.1 per cent), for diastolic pressure (phase IV) from 5.1 to 10.8 per cent (average 7.9 per cent) and for diastolic pressure (phase V) from 5.3 to 11.1 per cent (average 8.0 per cent). The average errors in systolic and diastolic pressure of boys and girls were very similar. From 5 to 19 years of age the error did not vary with age, but after 19 years the increase with age was considerable (5). We based all our analyses of diastolic pressure on the fifth sound according to Korotkoff. The mean difference between the fourth and the fifth Korotkoff sound was 4.0 mmHg for both boys and girls. This difference did not increase with age.

Accuracy

The accuracy of the parameter estimates has to be discussed in terms of validity (is there systematic deviation from the true value of the estimate?) and precision (how large is the random error?) of each of the studies.

In the cross-sectional study (chapter 2) precision poses no problem. The sample size is large enough to yield precise estimates. Comparison with other studies shows that it is unlikely that the estimates of mean blood pressure are heavily biased (6,7), although systematic deviation from the true value can not be ruled out in the absence of a simultaneously used 'gold standard'.

In the retrospective follow-up study on drinking water sodium and blood pressure (chapter 4) the inference largely rests on the validity of the comparison of the study areas. The use of a random-zero device and the blinding of the blood pressure observers for sodium levels of the drinking water makes it unlikely that information bias has occurred. Bias due to different distributions of other (unmeasured) determinants of blood pressure in the study areas cannot be ruled out. The sample size in this study was large enough to yield precise estimates.

In the 'case-control' study of haemodynamics, plasma noradrenaline, plasma renin and blood pressure (chapter 3) random error in blood pressure measurement decreases the contrast in blood

pressure between 'hypertensives' and 'normotensives' due to imperfect 'case'-definition. This tends to dilute a true relation between blood pressure and its putative determinants. In essence this also is a matter of precision, as increase of the sample size would increase the statistical power to detect these smaller differences.

In the cross-sectional study of haemodynamics and blood pressure in teenagers (chapter 3) random error in the estimation of cardiac output (not of blood pressure) might lead to an underestimate of the true relation between cardiac output and blood pressure. It is highly unlikely, however, that random error would lead to no difference in mean blood pressure when comparing the lower and the upper stratum of cardiac output.

In the prospective study on the natural history of blood pressure in childhood (chapter 5) the estimates of 'tracking' and 'predictive value' are influenced by random error in the measurement of blood pressure. This dilutes the true 'tracking' coefficients of blood pressure towards the null-value, and thus underestimates the stability of blood pressure rank over time. The 'predictive value' is estimated in a realistic context, with random error, and therefore these estimates are the meaningful ones.

In the experimental study of sodium intake and blood pressure in newborns (chapter 4) random error in blood pressure measurement affects the precision of the estimates of the difference between the sodium groups and thereby the statistical power of the study. The sample size calculation for this study turned out to be unrealistic in two ways. Firstly, the standard deviation of blood pressure was larger than expected (12 mmHg versus 10 mmHg at 25 weeks). Secondly, the difference between the sodium groups was somewhat smaller, at least in the analysis according to the 'intention-to-treat' principle, than anticipated.

Data-analysis

A guiding principle in analysing the data has been the intuitive acceptability and intelligibility of the data-analytical approach. The only notable exception to this rule has been the employment of Blomqvist's method to adjust for regression towards the mean. This

procedure is not very transparent in how it accomplishes its mission. Unfortunately, I am not familiar with an intuitively more appealing approach which yields mathematically similar results. The method suggested by Feinleib et al. (8), in which the change of blood pressure is computed without the initial reading on which it is regressed, has more appeal than Blomqvist's approach and yields unbiased, but unfortunately and expectedly, less precise estimates (9).

We have mainly used regression analysis to describe associations. Regression analysis has two major advantages over correlation analysis. Firstly, regression coefficients are independent of the study design, and secondly, they may be interpreted quantitatively in cause-and-effect terms (mean change in Y given unit change in X).

A final point concerns the 'case-control' study of haemodynamics and blood pressure (chapter 3), and in particular the relation between total peripheral resistance (TPR) and mean arterial pressure (MAP). In the analysis blood pressure was regressed on TPR. This is wrong. The issue is that TPR is computed as the ratio of MAP and cardiac output (CO) and thus MAP is regressed on MAP/CO. It can be shown (see Appendix 1) that the coefficient yielded by this regression is given by

$$b = (s^2_{map}/s^2_{tpr})(\overline{CO}_h)^{-1}$$

in which s_{map} denotes the standard deviation of MAP, s_{tpr} indicates the standard deviation of TPR, and $\overline{CO}_h$ denotes the harmonic mean of CO. This regression coefficient contains no empirical information. Fortunately, this mistake does not influence the inference based on this study. It is perhaps at place to add that a similar reasoning applies to regression of CO on TPR. Graphic representations of the relation between CO and TPR for various levels of MAP, which have been presented in the literature (10 – 13, reviewed in 14), appear not to hold empirical information either, although they may be proper illustrations of the theoretical relation between CO and TPR. The basic problem is that we are as yet unable to measure TPR in humans. It seems that extension of our knowledge of the haemodynamics of blood pressure awaits developmment of techniques for direct measurement of peripheral vascular resistance in humans.

Inference

Evidence in conflict with priors

The retrospective follow-up study on drinking water sodium and blood pressure (chapter 4) gave evidence that was clearly in conflict with prior views. Our observation of higher mean blood pressure in an area with high drinking water sodium was certainly unexpected, as we had designed the study mainly to refute a previous investigation (15). Since our confirmative report one 'negative' and one 'positive' study has been published (16,17). Two reviews have been devoted to the subject, also differing in outlook (18,19). One might ask what the approach to inference should be in cases like this (and there must be many). It seems that a Bayesian approach is quite suited for the matter at hand. Miettinen (20) suggested the following. If we leave the critical issue of internal validity of the study aside for the moment, than it is possible to compute the posterior probability of a specified hypothesis, given a prior probability and the evidence presented as a likelihood ratio of the probability of the data on the null-hypothesis and on the specified hypothesis. If we specify as our hypothesis that high drinking water sodium causes an increase in systolic pressure of $3-4$ mmHg, we can compute a (minimum) likelihood ratio. This relates to a maximum posterior probability of the specified hypothesis, which can be obtained for different priors, as shown in Appendix 2. For example, with a prior probability of the stated hypothesis of 0.01, the maximum posterior probability given the data presented in chapter 4 would be 0.10.

Evidence in conflict with previous findings

Our studies do not support the view that a high cardiac output, i.e., a hyperkinetic phase, in childhood, is a determinant of high blood pressure later on in life. This is at variance with many previous observations (see chapter 3 and (14) for a review), and it is reasonable that one of the pioneers in the field of haemodynamics and blood pressure in childhood asked me to explain this (Widimski, personal communication).

(Note: Professor Widimski's remark springs of course from an altogether different spirit than the one that led Sir George Pickering

to fill his typewriter with vitriol. In "High Blood Pressure" (21) he presented his view about the distribution of blood pressure and remarked: "The hypothesis just outlined has been greeted by medical scientists 'as a glimpse into the obvious', and by physicians as 'dangerous nonsense because it is against accepted teaching', a criticism voiced by an eminent Russian at the Prague conference in 1960. I treasure it – as from one revolutionary to another")

A problem is that not only the findings are different, but also the design and methods of the studies. In most of the previous studies cardiac output was measured invasively. As suggested in chapter 3, it is quite possible that the normotensive reference subjects were more familiar with the procedures than the normotensive youngsters, and this may have has led to a lower cardiac output in normotensives. Furthermore, it might well be that young people with relatively high blood pressure react with a higher cardiac output than normotensive youngsters, when invasive procedures are used. This might not be the case when non-invasive techniques are employed. This notion agrees with the view of Birkenhäger and de Leeuw (22), who suggested that high cardiac output might be an epiphenomenon of the procedures rather than an important stage in the aetiology of essential hypertension.

Evidence is redundant

To some the evidence presented on a causal relation between sodium intake and blood pressure is redundant. The argument goes like this: "We know that sodium restriction may lower blood pressure in patients with high blood pressure, therefore there must be an aetiological relation between sodium intake and blood pressure". This is a case of confusing clue and cure. There is indeed quite some evidence that sodium restriction lowers blood pressure in some patients with high blood pressure. But this does not necessarily imply that sodium intake is also a cause of high blood pressure, as different mechanisms might be involved in the aetiology and the treatment of high blood pressure.

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Appendix 1

Let cardiac output (CO) be a random variable X, mean arterial pressure (MAP) a random variable Y, and total peripheral resistance (TPR) Y/X. Assume X and Y to be independent.
The covariance of Y and Y/X is given by

$$\begin{aligned}\mathrm{cov}(Y,YX^{-1}) &= E(Y^2X^{-1}) - E(Y)E(YX^{-1}) \\ &= E(Y^2)E(X^{-1}) - E(Y)E(Y)E(X^{-1}) \\ &= (E(Y^2) - (E(Y))^2)E(X^{-1}) \\ &= \mathrm{var}(Y)E(X^{-1}) \\ &= \mathrm{var}(Y)(\overline{X}_h)^{-1}\end{aligned}$$

The regression coefficient b of Y on Y/X is given by

$$\begin{aligned}b &= \mathrm{cov}(Y,YX^{-1})(\mathrm{var}(YX^{-1}))^{-1} \\ &= (\mathrm{var}(Y)/\mathrm{var}(YX^{-1}))\,(\overline{X}_h)^{-1}\end{aligned}$$

Therefore, $b = (s^2_{map}/s^2_{tpr})(\overline{CO}_h)^{-1}$

Appendix 2

Miettinen (20) suggested the following approach.
Bayes' theorem can be expressed as follows:

$$P_2 = (1+((1-P_1)/P_1)LR)^{-1}$$

in which P_1 and P_2 are the prior and posterior probabilities, respectively, of a specified hypothesis. LR, the likelihood ratio, is the ratio of the probability of the data given the null-hypothesis and the probability of the data given the specified hypothesis. V_0 is the variance of the parameter on the null-hypothesis, V_1 the variance on the specified hypothesis. The minimum likelihood ratio is given by

$$LR_{min} = (V_1/V_0)\exp(-0.5\chi^2)$$

In chapter 4 the adjusted difference of mean systolic blood pressure between the area with a longterm high level of drinking water

sodium and a longterm low concentration was 3.3 mmHg, with a standard error of the difference of 1.5 mmHg, $\chi^2 = 4.84$. V_1/V_0 is approximated by 1. This yields a minimum LR of 0.09, corresponding to maximum posterior probabilities given below.

Prior Probability	Posterior Probability
0.10	0.55
0.05	0.37
0.01	0.10

Chapter 9

Reappraisal of the evidence 2
Material aspects

Referring to the questions posed in the Introduction of this thesis, the evidence presented in the previous chapters may be summarized as follows.

1. Blood pressure in childhood rises with age.
2. This rise is most likely due to an increase of peripheral vascular resistance.
3. The level of blood pressure is causally related to sodium intake.
4. The level and rise of blood pressure are related to body weight.
5. The level of blood pressure in childhood is probably related to the level of circulating catecholamines.
6. But not to cardiac output.
7. There is 'tracking' of blood pressure in childhood.
8. There is no 'horse-racing' of blood pressure in childhood.
9. Future hypertensives cannot be detected in childhood by measuring blood pressure.

In this chapter the material aspects of the evidence will be reviewed and annotated, and some suggestions for further research will be given. The findings will be discussed under four headings: blood pressure and growth, blood pressure and the hyperkinetic circulation, blood pressure and catecholamines, and blood pressure and sodium.

Blood pressure and growth

There is little doubt that in childhood blood pressure rises with age. To my knowledge all studies of blood pressure in children have shown an increase of systolic pressure with age, perhaps with one exception (1). This is not to say that the causes of this rise are known. It is likely that the rise of blood pressure largely reflects an increase of total peripheral resistance with age. This is not demonstrated beyond any doubt, because this contention is a matter of inference, and it must be, as we are unable to measure peripheral resistance in humans. Thus, according to this view the causes of rise of vascular resistance are also the causes of blood pressure rise. A major concern is, whether there is a genetically determined increase of resistance with age, or whether the rise results from environmental influences. This question is still unanswered for blood pressure rise. As to blood pressure level there is little doubt that it is to a certain extent genetically determined.

We have tackled this question of nature or nurture using data collected in the EPOZ study. We felt that increase in skeletal age per unit chronological age might serve as an indicator of the underlying, genetically determined growth rate. Therefore, if blood pressure rise would be mainly a matter of nature, we would expect a bigger rise in blood pressure in those with a large increase in skeletal age in a certain time period, than in those with a small increase in skeletal age. We were able to evaluate this in our prospective follow-up study and some preliminary results of the analysis will be presented here.

In all children who were 5 – 14 years of age initially and who were selected for yearly follow-up, skeletal age was determined at each follow-up examination, when they had not yet reached skeletal maturity. Skeletal age was determined using a radiograph of the hand and wrist according to the procedures and the rating system of Tanner et al. (2). All children in whom at least two measurements of bone age at consecutive years were available, were divided into two categories: those with an increase in skeletal age larger than the increase in chronological age (which was about one year, depending on the time elapsed between the examinations), and those in which the increase in bone age was smaller than the increase in chronological age. We found no differences in the average increase in systolic and diastolic

blood pressure between these groups (Hofman & Adams, unpublished). This applied to boys as well as girls. Stratification for body weight or change in body weight yielded similar results. This observation needs further data-analytical scrutiny, but it seems a promising approach to distinguish between the effects of nature and nurture on blood pressure rise.

If the rise in blood pressure is not mainly genetically determined, as these findings seem to indicate, then what are its causes? Body weight is the strongest known correlate of blood pressure level in childhood. This knowledge has been extended with the observation in this study that initial body weight is also a predictor of blood pressure change in childhood. One of the key questions is whether a high body weight causes high blood pressure, or whether blood pressure and body weight are related because they are both associated with another variable. Langford (3) mentions Cushing's syndrome, in which high cortisol levels increase both blood pressure and body weight. The finding that body weight is a predictor of blood pressure rise supports the proposition that these variables are causally connected. In our prospective follow-up study we will be able to evaluate putative meachanisms by which body weight affects blood pressure: plasma catecholamines, estrogens and insulin (3). Furthermore, change in body weight has to be related to blood pressure change. As discussed in chapter 7, it might be worthwhile to study patterns of blood pressure change in relation to outcome variables like blood pressure level and, if possible, indices for atherosclerosis. Labarthe (4) plans to study these aspects of the relation between blood pressure and growth.

Finally, technological advances might favour the epidemiological study of blood pressure in childhood. Continuous blood pressure registration seems a promising approach, although not yet on a very large scale. And perhaps the advances in echography may provide us within the foreseeable future with a non-invasive means to study the development of atherosclerosis early in life.

Blood pressure and the hyperkinetic circulation

In 1943 Starr and Jonas (5) used the term 'hyperkinemia' to describe a circulatory condition with a high cardiac output. Gorlin (6) introduced the term 'hyperkinetic heart syndrome' in 1962, to characterize a patient with a high cardiac output. He did not describe any signs related to the 'syndrome'. In a recent editorial (7) the ordeal was that "to judge by the scanty published work, this condition is neither homogeneous, nor well-defined". In chapter 3 I have implicitly defined the hyperkinetic circulation as a high output state. The hyperkinetic circulatory state differs from the hyperkinetic heart syndrome in that most authors have reported increased oxygen consumption in subjects with a hyperkinetic circulation, whereas patients with the hyperkinetic heart syndrome have a low arterio-venous oxygen difference, suggesting luxury perfusion (8). It might be asked what the long-term consequences of a hyperkinetic circulation are, in particular with reference to the development of high blood pressure.

There are two main views about the role of haemodynamics in the course of blood pressure in childhood (see 8,9,10 for reviews). The Figure shows these competing hypotheses. The *first* one states that there is a gradual increase of peripheral vascular resistance with age. According to this view, at all ages high blood pressure is related to high resistance. As discussed in chapter 3, some studies in children and adolescents in which cardiac output was measured non-invasively, have supported this hypothesis. The *second* hypothesis maintains that a hyperkinetic circulatory state, characterized by high cardiac output, leads to high blood pressure in childhood. This causes secondary changes in the circulation and in particular in the vasculature, which in turn lead to a combination of high blood pressure and high resistance in adulthood. According to this view there is a reversal of the haemodynamics profile in the development of high blood pressure. In chapter 3 of this thesis the previous investigations in youngsters which have supported this hypothesis have been reviewed. Other studies in older patients with 'borderline' or 'labile' hypertension have been interpreted as supporting this view (9,11). The two hypotheses agree on the endresult (in adults high

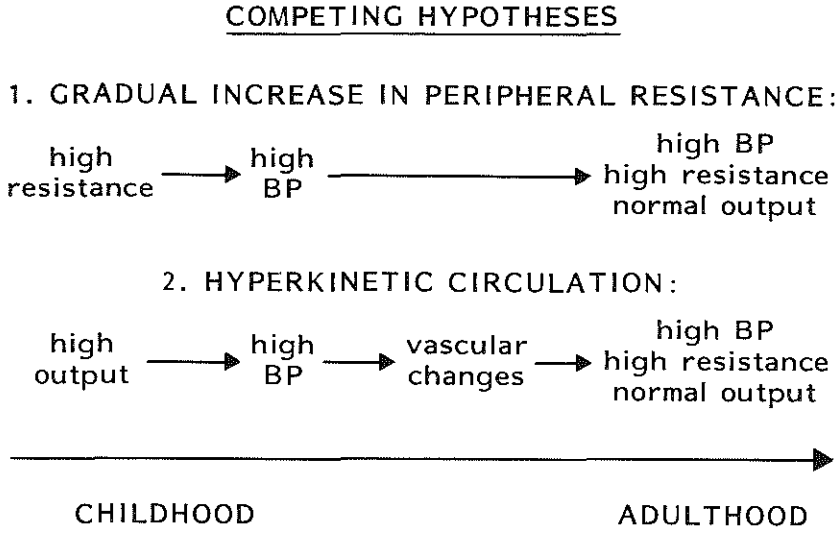

Figure
Haemodynamics, blood pressure and age: two competing hypotheses.

pressure is related to high resistance), but they disagree on the initiator of high blood pressure (high resistance or high cardiac output).

The studies reported in this thesis are at variance with the view that a hyperkinetic circulation in childhood is a determinant of high blood pressure in adults. They lend credence to the hypothesis that blood pressure rise is caused by an increase of peripheral vascular resistance. It might be that the high cardiac output in young hypertensive subjects as observed in earlier studies is due to differential arousal of

the subjects by the invasive methods used to measure cardiac output. These previous findings might therefore be an epiphenomenon of the procedures, rather then supporting the view that the hyperkinetic circulation is an early determinant of high blood pressure. The fact that virtually all studies in which a normal average cardiac output in hypertensive youngsters was found, employed a non-invasive (echocardiographic) method to measure cardiac output, points in this direction. Further investigations, of the retrospective follow-up type as outlined in chapter 8 might shed some light on this equivocal evidence.

An additional point is that this reasoning seems to have implications for the concept of 'borderline' hypertension. Julius and Schork (11) have suggested that there is merit in viewing this as a separate entity, and one of their main arguments was that 'borderline' and 'established' hypertensives have a different haemodynamics profile, i.e., a high cardiac output in 'borderline' hypertensives and a low (or normal) cardiac output in 'established' hypertensives, as compared to normotensives. Labarthe (12) has rejected this view, arguing that 'borderline' hypertension is only quantitatively and not qualitatively different from 'established' hypertension. The previous discussion, suggesting that high cardiac output in 'borderline' hypertension might be an epiphenomenon rather than an important stage in the aetiology of high blood pressure, would seem to support Labarthe's view.

Blood pressure and catecholamines

Since the remarkable discovery by Oliver (13) of the effect of an extract of the adrenal medulla on blood pressure, there is growing evidence that the sympathetic nervous system is implicated in the pathogenesis of high blood pressure (10,14,15). It is not clear whether sympathetic activity only aggravates high blood pressure, or also plays a part in the initiation of blood pressure rise (14). Many aspects of its link with the central nervous system still need elucidation. But in his monumental review of the physiological aspects of primary hypertension Folkow (10) considers it an "acknowledged fact" that

there is a connection between "excitatory psychoemotional influences" and blood pressure.

It has been suggested that overactivity of the sympathetic nervous system in childhood is an important factor in the pathogenesis of early essential hypertension (16). According to this view secondary changes in target organs, e.g. the kidneys, occur later on in life and override the signs of increased sympathetic outflow. The observations presented in chapter 3 support the view that sympathetic activity might be an early determinant of blood pressure rise, in particular of systolic pressure. But although our findings in teenagers have been closely confirmed by others (17), the evidence remains weak. Goldstein (18,19) has reviewed 64 papers on plasma noradrenaline in essential hypertension. In only 39% of the studies a statistically significant elevation of plasma noradrenaline in hypertensives as compared to normotensives was reported. An interesting observation was that virtually all studies in youngsters revealed significantly higher noradrenaline levels in hypertensives than in normotensives.

The overriding concern in evaluating the findings remains that the higher levels of plasma noradrenaline in teenagers may be caused by differential arousal of 'hypertensives' and 'normotensives' during blood pressure measurement and veni-puncture. In that case the higher level of circulating catecholamines does not reflect a causal connection between the sympathetic nervous system and blood pressure, but is an epiphenomenon of the procedures. However, I consider it unlikely that this applies to our study. Firstly, the hypertensive and normotensive youngsters in our study were selected from the same population and, more importantly, underwent the same examinations according to the same protocol in the same number of years. Secondly, we found no significant difference in pulse rate between hypertensive and normotensive subjects, and this is strong evidence against differential arousal.

Blood pressure and sodium

The view that high sodium intake is implicated in the aetiology of high blood pressure has protagonists (20,21,22), as well as antagonists (23,24,25). The evidence in its favour consists of three elements. Firstly, there is evidence originating from animal experiments. Dahl et al. (26) were able to induce hypertension in Brookhaven rats by salt-loading. However, it is questionable whether Dahl's hypertension-sensitive strain is the relevant model for human essential hypertension. As pointed out by Swales (24), hypertension can develop in some animal models despite severe salt depletion. Secondly, there have been observational studies in human populations. Comparisons of populations differing in sodium intake have revealed a higher proportion of subjects with high blood pressure in populations with a high average sodium intake than in those with low sodium intake (27,28 see 20,21,29 for reviews). Of course, these populations differ in other characteristics as well. Studies within populations have, with few exceptions, yielded negative results (30). This is perhaps to a large extent due to big random errors in the measurement of sodium intake. And thirdly, some studies of patients with high blood pressure have suggested that hypertension may be treated successfully by severe (31) or moderate (32 – 35) sodium restriction. However, as different mechanisms might be involved in the causation and in the treatment of high blood pressure, this observation does not necessarily imply that sodium intake is aetiologically related to high blood pressure.

Our study of blood pressure and sodium intake in newborns (chapter 4) presents experimental evidence in humans for an aetiological role of sodium intake in high blood pressure. Although this study points to sodium intake as a clue for high blood pressure, it does not provide insight in the mechanisms according to which sodium might be linked to blood pressure. We have argued that the evidence is in agreement with the view that sodium has a pressor effect. It might be that high sodium intake affects blood pressure through increase of vascular resistance, rather than through expansion of the extracellular fluid volume. This contention is highly speculative, but there is some evidence that electrolytes, notably

calcium, magnesium and sodium are implicated in peripheral control of blood pressure, by a direct effect on vascular resistance and reactivity (36,37,38). A potentially important avenue for further research seems to be the study of interaction between sodium intake and catecholamines as pressor substances (39). This could perhaps lead to some insight in which individuals are suspectible to high sodium intake. It is also possible that investigations of various defects in cellular electrolyte transport will shed some light on this question of sodium susceptibility, although it is unlikely that they will play a major role in the early detection of hypertensives (40).

Another important question is whether sodium restriction might be a cure. We have to distinguish between two strategies: one directed towards high risk individuals, patients with hypertension, and another towards the whole population. There is growing evidence that sodium restriction lowers blood pressure in some hypertensive patients (31 – 35). However, it is as yet unknown which patients will benefit from lowering sodium intake, and who will not. There is no evidence yet in youngsters to support the view that sodium restriction might be beneficial. It seems that an intervention trial in young hypertensives has merit, particularly because one is cautious to prescribe anti-hypertensives to young people. As far as the whole population is concerned, the benefits of sodium restriction are uncertain. Moreover, very little is known about possible adverse effects of lowering sodium intake. This underscores the notion that further study is needed before drastic public health measures to lower the sodium intake of the general population are taken.

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Chapter 10

Summary

The basic idea of this thesis is that it is possible to learn something about the aetiology and pathogenesis of high blood pressure by inquiries of the distribution, determinants and course of blood pressure early in life, at a time that the sequelae of high blood pressure have not yet occurred *(chapter 1)*.

Blood pressure was measured in 3,924 subjects, aged 5 – 19, living in one of two study districts in the Dutch town of Zoetermeer, where most of the studies reported in this thesis have been conducted *(chapter 2)*. Average systolic pressure rose from 100 mmHg in girls and boys at an age of 5 to 115 mmHg in 20 years old women and 130 mmHg in 20 years old men. Mean diastolic pressure increased in both boys and girls from 60 mmHg at an age of 5 to 70 mmHg at an age of 20. Body weight, pulse rate and parental blood pressure were the most important correlates of blood pressure level in childhood. Smokers had lower average systolic and diastolic blood pressure levels than non – smokers. Young women who used oral contraceptives had a higher mean systolic pressure than girls who did not take oral contraceptives.

Plasma noradrenaline and cardiac output were measured in 41 young people with a relatively high blood pressure and in 41 normotensive youngsters *(chapter 3)*. The level of plasma noradrenaline was considerably higher in hypertensive youngsters than in their normotensive counterparts. Mean cardiac output was lower in hypertensives than in normotensives.

In 319 Bostonian adolescents cardiac output and blood pressure were studied. Cardiac output was measured non – invasively by M – mode echocardiography. Blood pressure did not vary with cardiac output *(chapter 3)*.

The putative relation between sodium intake and blood pressure

was studied by comparing blood pressure levels in children who were living in three areas with different sodium concentrations of the drinking water *(chapter 4)*. Mean values of systolic and diastolic pressure were 1.8 to 4.0 mmHg lower in the low sodium area than in the two low sodium areas.

In an experimental investigation sodium intake and blood pressure were studied in newborn infants *(chapter 4)*. In a double-blind randomised trial 245 newborns received a normal-sodium diet and 231 a low-sodium diet during the first six months of life. The sodium intake of the normal-sodium group was nearly three times that of the low-sodium group. After 25 weeks systolic pressure was 2.1 mmHg lower in the low-sodium group than in the normal-sodium group. The difference between the sodium groups increased significantly over the first six months of life.

The natural history of blood pressure in childhood was studied in 596 young people, a random sample of those examined initially *(chapter 5)*. In 386 of them at least five consecutive annual blood pressure measurements were made. The stability of a child's position in the blood pressure distribution ('tracking') was studied by linear regression of follow-up blood pressure on initial blood pressure. 'Tracking' coefficients were 0.4 to 0.6 mmHg/mmHg for systolic pressure and 0.2 to 0.5 mmHg/mmHg for diastolic pressure after four years of follow-up. Twenty-seven per cent of the boys and 44 per cent of the girls who were in the upper ten per cent of the distribution of systolic blood pressure at the first examination were also there four years later. For diastolic pressure these figures were 25 per cent and 22 per cent, respectively.

The determinants of change in blood pressure during childhood were studied in the same 596 youngsters *(chapter 6)*. Three to seven annual blood pressure readings were obtained from 462 of them. Initial blood pressure level was associated negatively with subsequent change in systolic and diastolic pressure, even after adjustment for regression towards the mean. Parental blood pressure and initial body weight were related positively, but weakly, to the rate of blood pressure change. Initial serum uric acid was associated positively with change in blood pressure in girls only.

A conceptualization of the relations between blood pressure,

atherosclerosis and cardiovascular disease is proposed in *chapter 7*. It is suggested that departure from the genetic blood pressure track determines cardiovascular risk. Subjects who are young when they deviate from the genetic track are thought to be at a higher risk to develop cardiovascular disease than those who deviate later in life. The main implication of this proposal is that intervention might be guided best by knowledge of individual patterns of blood pressure change, particularly in young people.

The formal aspects of the studies reported in this thesis are discussed in *chapter 8*. In *chapter 9* the material aspects of the evidence are reviewed and some suggestions for further studies are given.

The inference based on the evidence given in the previous chapters may be summarized as follows.

1. Blood pressure in childhood rises with age.
2. This rise is most likely due to an increase of peripheral vascular resistance.
3. The level of blood pressure in causally related to sodium intake.
4. The level and rise of blood pressure are related to body weight.
5. The level of blood pressure in childhood is probably related to the level of circulating catecholamines.
6. But not to cardiac output.
7. There is 'tracking' of blood pressure in childhood.
8. There is no 'horse – racing' of blood pressure in childhood.
9. Future hypertensives cannot be detected in childhood by measuring blood pressure.

Chapter 11

Samenvatting

Het uitgangspunt van dit proefschrift is, dat het mogelijk is om iets te weten te komen over de etiologie en pathogenese van essentiële hypertensie door de verdeling, de determinanten en het beloop van de bloeddruk vroeg in het leven te bestuderen, op een moment dat de gevolgen van hoge bloeddruk nog niet zijn opgetreden *(hoofdstuk 1)*.

De bloeddruk werd gemeten bij 3.924 5 – 19 jarigen die woonden in Zoetermeer, waar de meeste van de onderzoekingen die in dit proefschrift worden gerapporteerd, hebben plaatsgevonden *(hoofdstuk 2)*. De gemiddelde systolische bloeddruk steeg van 100 mmHg bij meisjes en jongens van 5 jaar tot 115 mmHg bij 20 – jarige vrouwen en 130 mmHg bij 20 – jarige mannen. De gemiddelde diastolische druk steeg zowel bij meisjes als bij jongens van 60 mmHg op 5 – jarige leeftijd tot 70 mmHg op het 20e jaar. Het lichaamsgewicht, de polsfrequentie en de bloeddruk van de ouders waren de belangrijkste determinanten van het niveau van de bloeddruk op de kinderleeftijd. Rokers hadden een lagere gemiddelde systolische en diastolische bloeddruk dan niet – rokers. Jonge vrouwen die orale contraceptiva gebruikten, hadden een hogere systolische druk dan vrouwen die dat niet deden.

Het plasma noradrenaline gehalte en de cardiac output werden gemeten bij 41 jongeren met een relatief hoge bloeddruk en bij 41 normotensieve leeftijdgenoten *(hoofdstuk 3)*. Het niveau van het noradrenaline was aanzienlijk hoger bij hypertensieve dan bij normotensieve teenagers. De gemiddelde cardiac output was lager bij hypertensieven dan bij normotensieven.

Bij 319 Bostonse adolescenten werd de samenhang tussen de cardiac output en de bloeddruk bestudeerd. Cardiac output werd non – invasief vastgesteld via M – mode echocardiografie. De bloeddruk varieerde niet met de cardiac output *(hoofdstuk 3)*.

Het mogelijke verband tussen de consumptie van natrium en de bloeddruk werd onderzocht door de bloeddruk te vergelijken van kinderen die woonden in drie gebieden met een verschillende natrium concentratie van het drinkwater *(hoofdstuk 4)*. De gemiddelde waarden van de systolische en diastolische bloeddruk waren 1.8 tot 4.0 mmHg lager in het gebied met de lage natrium concentratie dan in de twee andere gebieden.

In een experimenteel onderzoek werden de natrium inname en de bloeddruk bestudeerd bij zuigelingen *(hoofdstuk 4)*. In een dubbelblinde gerandomiseerde trial kregen 245 babies een voeding met een normaal zoutgehalte, terwijl 231 babies een voeding met een verlaagde zoutconcentratie kregen, gedurende de eerste zes levensmaanden. De natriumconsumptie in de normale zoutgroep was ongeveer drie keer zo hoog als in de lage zoutgroep. Na 25 weken was de systolische bloeddruk 2.1 mmHg lager in de lage zoutgroep dan in de normale zoutgroep. Het verschil tussen de groepen nam gedurende de eerste zes maanden toe.

Het natuurlijk beloop van de bloeddruk op de kinderleeftijd werd onderzocht bij 596 Zoetermeerse jongeren van 5 – 19 jaar die een aselecte steekproef vormden van degenen die oorspronkelijk onderzocht waren *(hoofdstuk 5)*. Bij 386 van hen werden tenminste vijf opeenvolgende jaarlijkse bloeddukmetingen verricht. De stabiliteit van de plaats van een kind in de bloeddrukverdeling ('tracking') werd onderzocht door lineaire regressie van de bloeddruk bij de vervolgonderzoekingen op de bloeddruk bij het eerste onderzoek uit te voeren. De 'tracking' coefficienten waren 0,4 tot 0,6 mmHg/mmHg voor de systolische bloeddruk en 0,2 tot 0,5 mmHg/mmHg voor de diastolische druk na vier jaar. Zevenentwintig procent van de jongens en 44 procent van de meisjes die bij het eerste onderzoek tot de bovenste tien procent van de bloeddrukverdeling behoorden, waren daar ook na vier jaar. Voor de diastolische bloeddruk waren deze getallen respectievelijk 25 procent en 22 procent.

De determinanten van verandering van de bloeddruk op de kinderleeftijd werden bestudeerd bij dezelfde 596 jongeren *(hoofdstuk 6)*. Bij 462 van hen werden drie tot zeven jaarlijkse bloeddrukmetingen verkregen. De bloeddruk bij het eerste onderzoek had een negatieve samenhang met de verandering van de systolische

en diastolische bloeddruk daarna, zelfs na correctie voor regressie naar het gemiddelde. De bloeddruk van de ouders en het lichaamsgewicht bij het eerste onderzoek waren zwak positief verbonden met de verandering van de bloeddruk. Het urinezuurgehalte van het serum bij het eerste onderzoek was bij meisjes positief geassocieerd met verandering van de bloeddruk.

Op de samenhang tussen bloeddruk, atherosclerose en hart – en vaatziekten wordt in *hoofdstuk 7* ingegaan. Gesuggereerd wordt dat afwijking van het 'genetische bloeddrukspoor' het risico op hart – en vaatziekten bepaalt. Personen die op jonge leeftijd van hun 'spoor' afwijken, worden geacht een groter risico op een hart – en vaatziekte te hebben dan zij die dat op latere leeftijd doen. De belangrijkste implicatie van dit voorstel is dat het de voorkeur verdient interventie op jonge leeftijd uit te voeren op geleide van individuele patronen van verandering van de bloeddruk.

De formele kenmerken van de verschillende onderzoekingen worden besproken in *hoofdstuk 8*. In *hoofdstuk 9* worden de materiële aspecten van het bewijsmateriaal belicht en enige suggesties voor verder onderzoek gedaan.

De gevolgtrekkingen, die gebaseerd zijn op de bewijslast in de vorige hoofdstukken, kunnen als volgt worden samengevat.

1. De bloeddruk bij kinderen stijgt met de leeftijd.
2. Deze stijging is hoogstwaarschijnlijk het gevolg van een stijging van de perifere vaatweerstand.
3. De hoogte van de bloeddruk hangt oorzakelijk samen met de consumptie van natrium.
4. Het niveau en de stijging van de bloeddruk zijn gerelateerd aan het lichaamsgewicht.
5. De hoogte van de bloeddruk op jonge leeftijd is waarschijnlijk verbonden met het gehalte van circulerende catecholaminen.
6. Maar niet met de cardiac output.
7. Er is 'tracking' van de bloeddruk bij jongeren.
8. Er is geen 'horse – racing' van de bloeddruk op de kinderleeftijd.
9. Toekomstige patienten met hoge bloeddruk kunnen niet worden opgespoord door op de kinderleeftijd de bloeddruk te meten.

Epilogue

On April 3, 1957, Gajdusek wrote in a letter to Smadel: "I have the 'real thing' in my hands ... I tell you, Joe, this is no wild goose chase, but a really big thing. Everything in my medical training makes me confident ... This class of illness is not my specialty, but I can handle research on it as well as anyone". Gajdusek was able 'to handle research' on kuru better than anyone, and in 1976 it earned him a Nobel prize for his discovery of the slow-virus aetiology of the disease. To me Gajdusek's words embody some salient characteristics of epidemiology. Epidemiologic research focusses on the occurrence of illness and recovery as a function of determinants. As a student of disease aetiology, the epidemiologist can serve as the *trait d'union* between the formal and material aspects of a particular problem. This is not an easy mission. I have sometimes felt as a shaky rope-dancer over the gap between subject matter knowledge and statistical expertise. Perhaps the main hazard to an epidemiologist is to lean too heavily on methodological dogma. This may result in very broad statements with little empirical content. The only way I can think of to overcome this imminent danger, is to gain subject matter knowledge.

It is not to me to judge whether in this thesis the gap between formal and material elements of the problem has been bridged satisfactorily. But I can say that for me the work has been, intellectually and otherwise, very gratifying. There were, of course, moments of exception. I once received a review of a paper in which the following qualification was a relatively mild one: "This is an extremely confusing paper with several statistical subsets in which the subjects are constantly jumping between groups". This extinguished the fun for a moment. (It is only fair to say that the paper benefited substantially from the reviewer's vitriolic remarks. It is now part of this thesis.)

I have been in the luxurious position of close contact with 'patients', as well as with data-analytical facilities. I have learned, that these are important prerequisites for epidemiological research. Direct contact with the study subjects is quintessential. It is hard to get a feel for the data when the only place to meet them is the computer room. On the other hand, it is profitable to have direct access to computer experts. Too often a complicated data-analytical solution may be replaced by a simpler one through sharing some background knowledge with that very special breed, the software writers.

Many people have contributed to this work, but it is at place to first of

all thank the children who participated in these studies. I hope that, in the end, they will benefit from them.

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Curriculum vitae

Albert Hofman werd in 1951 te Hardenberg geboren. Hij behaalde er in 1968 het hbs−b diploma en begon daarna met de medische studie aan de Rijksuniversiteit te Groningen. Hij legde in 1974 met goed gevolg het doctoraal examen af en werd in 1976 tot arts bevorderd. Tijdens zijn opleiding maakte hij deel uit van het bestuur van de Faculteit der Geneeskunde en van de redactie van de Groningse Universiteitskrant. Na een klinisch assistentschap in de afdeling Interne Geneeskunde van het Academisch Ziekenhuis te Groningen werd hij in 1977 wetenschappelijk medewerker aan het Instituut Epidemiologie van de Rotterdamse Erasmus Universiteit. Onder leiding van Prof. Dr. H.A. Valkenburg werd hij opgeleid tot epidemioloog. Deze opleiding voltooide hij met een research fellowship bij Prof. O.S. Miettinen in het Department of Epidemiology (Prof. B. MacMahon) van de Harvard School of Public Health te Boston.

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