CHAPTER SIX

Developmental Genetic Trends in Blood Pressure Levels and Blood Pressure Reactivity to Stress

HAROLD SNIEDER, LORENZ J. P. VAN DOORNEN, AND DORRET I. BOOMSMA

INTRODUCTION

This chapter has two main aims. The first is to describe the changes in heritability of blood pressure levels and blood pressure reactivity that occur during the life span. The second is to disentangle the genetic and nongenetic causes of stability and change in these parameters. In order to achieve these goals, both empirical studies and developmental models will be discussed.

After an initial examination of blood pressure levels and reactivity, the results of twin studies on subjects of different ages are compared to address the question of whether heritabilities are age-specific. The next section focuses on parent–offspring studies and studies with a special interest in age-dependent genetic and environmental effects. Following this presentation, the very limited number of longitudinal genetic studies of blood pressure are discussed, and an extended parent–offspring design is described and illustrated with relevant data from our own laboratory. This design, coupled with the appropriate modeling, shows how one can estimate genetic stability in the absence of longitudinal data.

HAROLD SNIEDER, LORENZ J. P. VAN DOORNEN, AND DORRET I. BOOMSMA • Department of Psychophysiology, Free University of Amsterdam, De Boelelaan 1111, 1081 HV Amsterdam, The Netherlands.

Behavior Genetic Approaches in Behavioral Medicine, edited by J. Rick Turner, Lon R. Cardon, and John K. Hewitt. Plenum Press, New York, 1995.

Finally, we discuss the implications of such studies and speculate about what directions such research might take in the future.

BLOOD PRESSURE LEVELS

Blood pressure levels have been shown to be related to the risk of coronary heart disease and stroke. Risk increases linearly from a systolic blood pressure (SBP) of 110 mm Hg on, and even increases progressively in the higher pressure range (Pooling Project Research Group, 1978; Kannel, 1976). In Western societies, blood pressure rises with age. This trend, however, is not a simple linear one, and it differs between males and females. In boys, a strong rise in SBP of about 15 mm Hg occurs in the first 8 weeks of life; in girls, this rise occurs earlier and is even steeper. In both sexes, SBP then remains stable until the age of 12 months. Diastolic blood pressure (DBP) declines after birth in both boys and girls, reaching its minimum in 2–3 months, but is back at birth level by the end of the first year. From then on, there is a gradual increase in SBP (+20 mm Hg) and DBP (+15 mm Hg) in both sexes until puberty.

During adolescence, SBP again rises, this time more steeply in boys than in girls. At the age of 20, SBP in boys is nearly 10 mm Hg higher than in girls, whereas DBP is only slightly higher (Lauer, Burns, Clarke, & Mahoney, 1991; Labarthe, Mueller, & Eissa, 1991; van Lenthe & Kemper, 1993). These sex differences remain until the age of 50.

During the middle-age period (40–60 years), SBP rises about 10 mm Hg in males, and the variance in values also increases. DBP levels and their variance remain fairly constant in this period (Pooling Project Research Group, 1978). Recently, these age trends in levels and variances during middle age were confirmed in a large Norwegian sample and shown to apply to females as well (Tambs et al., 1992). The SBP rise from 40 years of age on is steeper in females. After the age of 50, women have a higher SBP than men. Menopause as such does not seem to be responsible for this difference (Lerner & Kannel, 1986; Matthews et al., 1989). SBP, but not DBP, continues to rise until the age of 70. After this age, both SBP and DBP decline. In later life, females have higher SBP and DBP than males (Valkenburg, Hofman, Klein, & Groustra, 1980).

The age-specific increase in SBP and DBP, and the sex differences in this increase, suggest that different mechanisms have their influence on blood pressure in different periods of life and that they may not be the same, or have the same timing, in males and females. The balance between genetic and environmental influences on blood pressure thus may also vary as a function of age and sex. There may even be "critical periods" in which exposure to certain environmental factors, or the expression of particular genes, will have a decisive impact on future blood pressure, whereas exposure to the same factors in other stages of life may be relatively inconsequential (Unger & Rettig, 1990).

BLOOD PRESSURE REACTIVITY

Exaggerated cardiovascular reactivity to stress is hypothesized to play some role in the development of hypertension (Manuck, Kasprowicz, & Muldoon, 1990). Support for this idea is furnished by studies showing that increased cardiovascular reactivity to stress is associated with stronger rises of blood pressure with age. This was shown by Menkes et al. (1989) for the response to the cold pressor test and by Matthews, Woodall, and Allen (1993) for the response to mental stressors. Promising as these results may be, these observations do not necessarily imply a causal role of exaggerated stress reactivity for the development of high blood pressure. Such stress reactivity could be just a risk marker reflecting underlying structural or functional vascular changes (Folkow, Hallback, Lundgren, & Weiss, 1970; Adams, Bobik, & Korner, 1989).

When investigating the contribution of genetic factors to blood pressure reactivity, it is again of interest to know whether this influence varies with age. A change in reactivity with age would perhaps point to this possibility. A decline in heart rate responsiveness to mental stress with increasing age has been observed in several studies (Faucheux et al., 1989; Garwood, Engel, & Capriotti, 1982; Barnes, Raskind, Gumbrecht, & Halter, 1982; Furchtgott & Busemeyer, 1979; Gintner, Hollandsworth, & Intrieri, 1986). This observation fits the general finding of attenuated cardiac responsiveness to β-receptor agonists. For blood pressure reactivity, one would predict an increased stress reactivity with age on physiological grounds. α_1-Receptor-mediated functions are preserved with aging, whereas β-receptor-mediated vasodilation and arterial compliance decrease with age (Folkow & Svanborg, 1993). The empirical support for an age trend in blood pressure reactivity is, however, not convincing. Matthews and Stoney (1988) found larger SBP responses in adults as compared to children, but no association within the adult age range (31–62). Garwood et al. (1982) observed a small positive correlation of SBP reactivity with age ($r = 0.25$) in the range between 30 and 79 years. Other studies, however, found no age effect (Faucheux et al., 1989; Gintner et al., 1986; Steptoe & Ross, 1981). In none of these studies was DBP reactivity age-dependent.

The absence of a convincing age trend in blood pressure reactivity does not refute, however, the possibility that genetic or environmental influences on reactivity, or both, differ by age. A role for genetic factors in stress reactivity finds support in studies showing that a family history of hypertension in subjects who are still normotensive themselves is associated with higher blood pressure reactivity to stressors (De Visser, 1994).

Currently, we know very little about developmental trends in the heritability of important cardiovascular and other (psycho)physiological parameters, and we know even less about causes of stability and change in these variables. As stated, the age trends in blood pressure level may indicate the involvement of different genetic or environmental factors, or both, at different ages. The same applies to

the increases in phenotypic variance, especially for SBP, across the life span. This increase may be due to an increase in the amount of genetic variance, nongenetic variance, or both. Such changes in variance components can imply changes in heritabilities with age ($h^2 = Vg/Vp$, where h^2 = heritability, Vg = genetic variance, and Vp = total phenotypic variance) as well as differences in correlations among relatives of different ages. For example, if the amount of genetic variance is the same at different ages while the amount of environmental variance increases as people grow older, the covariance between parents and offspring will be the same as the covariance among siblings (assuming that the same genes are expressed at different ages and that shared environmental and dominance influences are negligible). However, the parent–offspring *correlation* will be lower than the sibling correlation, due to the increase in variance in the parental generation.

Changes in phenotypic variance and in the part of the variance that may be attributed to genetic and environmental factors, i.e., heritability and environmentality (Plomin, DeFries, & McClearn, 1990), may be detected in cross-sectional or longitudinal studies. However, only longitudinal studies, in which the same subjects are measured repeatedly, are informative about the stability of genetic and environmental factors. Contrary to popular points of view, genetically determined characteristics need not be stable, nor are longitudinally stable characteristics always influenced by heredity (Molenaar, Boomsma, & Dolan, 1991). During development, stability of a quantitative trait such as blood pressure may be due to stable environmental influences, while instability may be due to distinct subsets of genes turning on and off. This chapter considers the kinds of empirical evidence that will help us to understand the genetic and environmental influences on the stability and change of blood pressure as a dynamic characteristic.

TWIN STUDIES

Blood Pressure Levels

If twins within a specific age range are measured in studies estimating the genetic influence on blood pressure level, heritability values for this specific age range are obtained. The available twin studies are listed in Table 1. These studies did not take an explicit interest in age, but studies are listed in ascending order according to age of the twin sample.

Such a systematic overview of all studies may reveal any age-dependent trends in heritability. If studies considered sex differences in h^2, estimates for males and females are listed separately. The studies in Table 1 found no evidence for influence of shared family environment (c^2) on blood pressure. With respect to heritability estimates, the results are remarkably consistent: The majority of heritability estimates lie between 0.40 and 0.70 for both males and females, and no clear age trend in h^2 can be detected.

TABLE 1. Twin Studies Estimating Heritability in Systolic Blood Pressure and Diastolic Blood Pressure, in Ascending Order According to Age[a]

Investigator	Pairs of twins	Age		Sex	Heritability (h^2)	
		Mean (SD)	Range		SBP	DBP
Levine et al. (1982)	67 MZ, 99 DZ	? (?)	0.5–1.0	M & F	0.66	0.48
Schieken et al. (1989)	74 MZF, 71 MZM,	11.1 (0.25)	?	M	0.66	0.64
	31 DZF, 23 DZM, 52 DOS			F	0.66	0.51
McIlhany, Shaffer, &	47 MZF, 40 MZM,	14.0 (6.5)	5.0–50.0	M	0.41	0.56
Hines (1975)	36 DZF, 32 DZM, 45 DOS			F	0.78	0.61
Boomsma (see the	33 MZF, 35 MZM,	16.8 (2.0)	13.0–22.0	M	0.49	0.69
text) (1992)	29 DZF, 31 DZM, 28 DOS			F	0.66	0.50
Sims et al. (1987)	40 MZM, 45 DZM	19.4 (3.0)	?		0.68	0.76
Ditto (1993)	20 MZF, 20 MZM,	20.0 (5.0)	12.0–44.0	M	0.63	0.58
	20 DZF, 20 DZM, 20 DOS			F	0.63	0.58
Bielen et al. (1991)	32 MZM	21.7 (3.7)	18.0–31.0		0.69	0.32
	21 DZM	23.8 (3.9)				
Hunt et al. (1989)	73 MZM, 81 DZM	34.5 (9.5)	?		0.54	0.60
Slattery et al. (1988)	77 MZM, 88 DZM	? (?)	22.0–66.0		0.60	0.66
Snieder et al. (see the	47 MZF, 43 MZM,	44.4 (6.7)	34.0–63.0	M	0.40	0.42
text)	39 DZF, 32 DZM, 39 DOS			F	0.63	0.61
Feinleib et al. (1977)	250 MZM, 264 DZM	? (?)	42.0–56.0		0.60	0.61
Theorell, DeFaire, Schalling, Adamson, & Askevold (1979)	17 MZM, 13 DZM	62.0 (?)	51.0–74.0		0.00	0.00

[a] Abbreviations: (MZF) monozygotic females; (MZM) monozygotic males; (DZF) dizygotic females; (DZM) dizygotic males; (DOS) dizygotic opposite-sex; (SBP) systolic blood pressure; (DBP) diastolic blood pressure; (M) male; (F) female.

TABLE 2. Twin Studies Estimating Heritability in Systolic Blood Pressure and Diastolic Blood Pressure Reactivity, in Ascending Order According to Age[a]

Investigator	Pairs of twins	Age		Task	Sex	Heritability (h^2)	
		Mean (SD)	Range			SBP	DBP
McIlhany et al. (1975)	47 MZF, 40 MZM, 36 DZF, 32 DZM, 45 DOS	14.0 (6.5)	5.0–50.0	CP	M	0.36	0.53
					F	0.72	0.68
Boomsma (see the text) (1992)	33 MZF, 35 MZM, 29 DZF, 31 DZM, 28 DOS	16.8 (2.0)	13.0–22.0	RT	M	0.00	0.00
					F	0.00	0.00
				MA	M	0.44	0.38
					F	0.44	0.38
Ditto (1993)	20 MZF, 20 MZM, 20 DZF, 20 DZM, 20 DOS	20.0 (5.0)	12.0–44.0	MA	M	0.36	0.47
					F	0.36	0.47
				CT	M	0.00	0.34
					F	0.00	0.34
				IH	M	0.00	0.57
					F	0.00	0.57
				CP	M	0.38	0.81
					F	0.38	0.22
Shapiro et al. (1968)	7 MZF, 5 MZM	23.6 (?)	?	ST	M & F	0.70 (= MAP)	
	8 DZF, 4 DZM	21.9 (?)	?				
Smith et al. (1987)	82 MZM, 88 DZM	35.0 (?)	21.0–61.0	MA		0.48	0.52
Snieder et al. (see the text)	47 MZF, 43 MZM, 39 DZF, 32 DZM, 39 DOS	44.4 (6.7)	34.0–63.0	RT	M	0.37	0.23
					F	0.27	0.23
				MA	M	0.36	0.25
					F	0.36	0.25
Theorell et al. (1979)	17 MZM, 13 DZM	62.0 (?)	51.0–74.0	SI		0.00	0.00
Carmelli et al. (1991)	47 MZM, 54 DZM	62.4 (?)	59.0–69.0	MA		0.80	0.66

[a] Abbreviations: (CP) cold pressor task; (RT) reaction time task; (MA) mental arithmetic task; (CT) concept task; (IH) isometric handgrip; (ST) Stroop task; (SI) structured interview; (MAP) mean arterial pressure. See the Table 1 footnote for further abbreviations.

Some caution concerning the interpretation of Table 1 is required. First, studies used different methods to estimate h^2. Second, there was wide variation in the composition of the twin samples in the studies: The age range within studies differs considerably, and results are more reliable for males, since the majority of studies used only male twins. Furthermore, results from studies with small sample sizes are clearly less reliable. Nevertheless, the absence of an age trend in h^2 in Table 1 seems to warrant the conclusion that the relative influence of genes on blood pressure does not change appreciably with age.

Blood Pressure Reactivity

Studies that have investigated genetic influence on blood pressure reactivity are scarce. Turner and Hewitt (1992) (see also Chapter 5) reviewed the twin studies of blood pressure response to psychological stress. They concluded that:

1. Blood pressure reactivity to psychological stress is moderately heritable.
2. A common environmental influence is highly improbable.
3. Sex differences are possible, but as yet unexplored.
4. Genotype–age interactions are probable, but they await systematic evaluation.

A first impression of this genotype–age interaction can be obtained by listing the twin studies in ascending order according to the subjects' ages (Table 2).

Heritability estimates of blood pressure reactivity vary between 0.00 and 0.81 and are far less consistent than estimates for blood pressure levels. As in Table 1, a trend in h^2 for blood pressure reactivity with age cannot be readily detected. In addition to the interpretational difficulties mentioned in relation to Table 1, interpretation of Table 2 is hampered by the use of different stress tasks across studies. Even the use of different stress tasks within the same study leads to different h^2 estimates (Ditto, 1993).

PARENT–OFFSPRING STUDIES

Blood Pressure Levels

Another approach to investigating the age dependency of genetic and environmental effects is to compare parent–offspring data with data from siblings or twins (Eaves, Last, Young, & Martin, 1978). If there is an age-dependent genetic or environmental effect on the phenotype, one would expect the parent–offspring correlation to be lower than sibling or dizygotic (DZ) twin correlations, as the latter are measured around the same age. This expectation was confirmed in a review by Iselius, Morton, and Rao (1983). They pooled the results from a number of studies and arrived at a mean correlation for 14,553 parent–offspring pairs of 0.165 for SBP and 0.137 for DBP. Corresponding values for 11,839 sibling and DZ twin pairs were 0.235 (SBP) and 0.201 (DBP).

If, on the other hand, parents and their offspring are measured at the same age, a rise in parent–offspring correlations toward levels similar to sibling correlations is to be expected. This expectation was supported by data from Havlik et al. (1979), who measured SBP and DBP for 1141 parent pairs aged 48–51. At 20–30 years later, blood pressures for 2497 of their offspring were measured. At this time, the offspring were of ages similar to those of their parents when they were measured. Parent–offspring correlations ranged between 0.13 and 0.25 for SBP and between 0.17 and 0.22 for DBP. These ranges were quite similar to the sibling-pair correlations, which were between 0.17 and 0.23 (SBP) and between 0.19 and 0.24 (DBP).

An alternative explanation for the lower parent–offspring correlation compared to the sibling or DZ twin correlation could be the influence of genetic dominance (Tambs et al., 1992). The similarity between parent–offspring and sibling correlations in the study of Havlik et al. (1979) suggests, however, that dominance variation is not important.

Lower values for parent–offspring correlations also lead to lower h^2 estimates for blood pressure in family studies (which usually measure pairs of subjects at different ages) compared with twin studies. Heritability estimates from family studies range from 0.17 to 0.45 for SBP and from 0.15 to 0.52 for DBP (Iselius et al., 1983; Hunt et al., 1989; Rice, Vogler, Perusse, Bouchard, & Rao, 1989; Tambs et al., 1992), while estimates from twin studies range from 0.40 to 0.78 for SBP and from 0.32 to 0.76 for DBP (see Table 1).*

Province and Rao (1985) modeled genetic and environmental effects on SBP in nuclear families as a function of age. Before estimating environmental and genetic parameters, they used a standardization method to adjust for the effect of age on the mean and the variance; this standardization leaves temporal trends in familial resemblance intact. They found some evidence for a temporal trend in h^2, reaching maximum values of about 0.45 between 20 and 40 years of age. These results conflict with the results presented in Table 1, in which an age trend could not be detected. Thus, parent–offspring studies suggest that age may influence genetic effects on blood pressure, whereas no such effects are clear in twin data.

Two types of age-dependent effect could offer an explanation for the lower parent–offspring correlation compared to the sibling and DZ twin-pair correlations. First, the influence of nonshared environmental factors could increase with age. Such an increase, however, would lead to a lower h^2. Second, different genes could influence blood pressure in childhood than in adulthood. This possibility is still compatible with the results of Table 1, as h^2 can remain stable across time even though different genes are influential at different times. The latter possibility is supported by data from Tambs et al. (1993). In a Norwegian sample with 43,751 parent–offspring pairs, 19,140 pairs of siblings, and 169 pairs of twins, correlations between relatives decreased as age differences between these relatives increased. A model specifying age-specific genetic additive effects and unique environmental effects fitted the data well.

*Results of Theorell et al. (1979) are not considered because of deviant sample characteristics.

This model also estimated the extent to which genetic effects were age-specific. As an example, the expected correlations for SBP and DBP in relatives with an age difference of 40 years were calculated. For SBP, 62% of the genetic variance at, for example, age 20 and at age 60 is explained by genes that are common to both ages, and 38% is explained by age-specific genetic effects. The same values for DBP were 67% and 33%, respectively. The model used by Tambs et al. (1993) assumes invariant heritabilities for blood pressure throughout life. This assumption proved to be valid for SBP, whereas for DBP a very slight increase in h^2 was detected.

On the basis of their results from a study of twins and their parents, Sims, Hewitt, Kelly, Carroll, and Turner (1986) found that the assumption that the same genes act in young adulthood and middle age would require a *decrease* in heritability from 0.68 to 0.38 from young adulthood to middle age for DBP. This reduction, however, would need to be accompanied by an *increase* in the contribution of individual environmental factors that would account for an increase in phenotypic variance as people grow older. The same pattern of observations was seen for SBP (Sims, Carroll, Hewitt, & Turner, 1987). Samples in the studies of Sims et al. (1986, 1987) were relatively small (40 monozygotic [MZ], 45 dizygotic [DZ] male twin pairs, and their parents), and thus their results carry less weight than those from the very large Norwegian sample (Tambs et al., 1993). However, on the basis of the relatively small study of Sims et al. (1986, 1987), Hewitt, Carroll, Sims, and Eaves (1987) presented an alternative hypothesis for increases in variance of blood pressure across the life span that could be tested in longitudinal studies using genetically informative subjects. They proposed a developmental model in which genetic effects on blood pressure are largely the same (pleiotropic) at different points in time, but not cumulative throughout

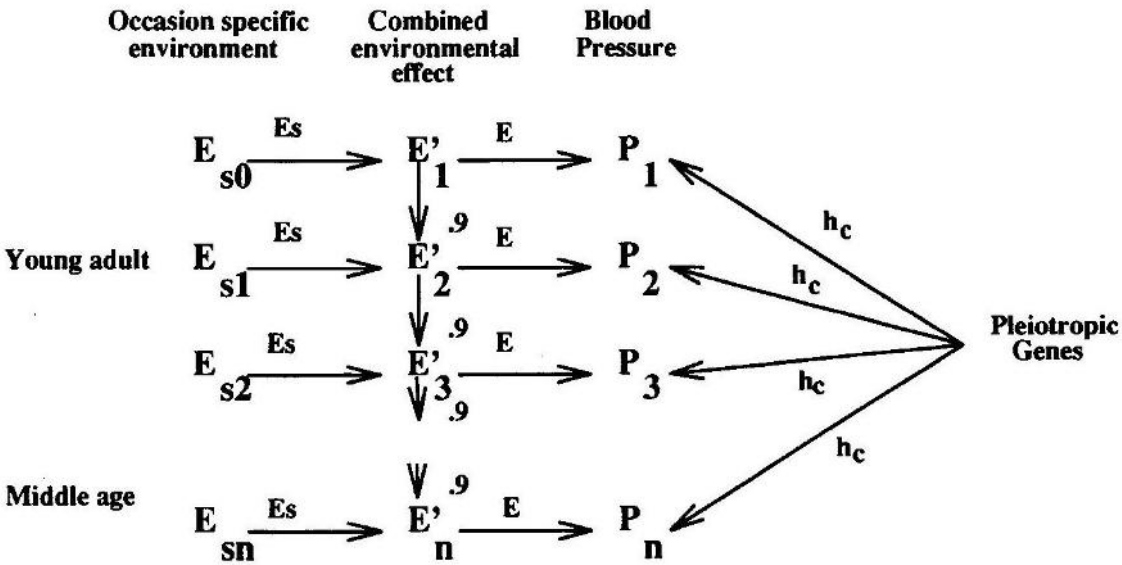

FIGURE 1. A developmental genetic model for adult blood pressure. Reprinted by permission from J. K. Hewitt, D. Carroll, J. Sims, and L. J. Eaves, "A Developmental Hypothesis for Adult Blood Pressure," *Acta Geneticae Medicae et Gemellologiae*, vol. 36, pp. 475–483. Copyright 1987 Associezione Instituto di Genetica Medica e Gemellologia Gregorio Mendel.

adulthood. Specific environmental influences are transient in their occurrence, but their impact is transmitted across occasions (Fig. 1).

Although it was restricted to twins aged in their late 40s and older and therefore did not cover the early adult to middle-aged period, the one reported longitudinal twin study (Colletto, Cardon, & Fulker, 1993)—which is discussed below—appears to disconfirm this hypothesis, finding little evidence for such a transmission or accumulation of environmental influences.

Blood Pressure Reactivity

The few parent–offspring studies reported to date will not permit a reliable conclusion about age-dependent genetic effects on blood pressure reactivity, and the comparison of parent–offspring with sibling or DZ twin correlations is difficult because of this paucity of studies. Moreover, the published studies to date have generally found low, or unstable, familial correlations, and quantitative genetic model-fitting has not been attempted. Matthews et al. (1988) conducted a study in which 145 families were measured using serial subtraction, mirror image tracing, and an isometric handgrip task. Only the correlation of SBP reactivity to the isometric handgrip was significant for parent–offspring as well as sibling pairs. Ditto (1987) investigated similarities in 36 sibling pairs (aged 18–21) in cardiovascular reactivity to four different stress tasks: a conceptual task, a mental arithmetic task, an isometric handgrip task, and a cold pressor task. Only one significant sibling correlation was found for DBP reactivity to the cold pressor task (0.40).

Ditto and France (1990) compared correlations in a group of 30 young (mean age: 26) and 30 middle-aged (mean age: 52) spouse pairs. Spouse correlations in blood pressure reactivity to a mental arithmetic and an isometric handgrip task were small and did not increase as a function of the number of years of living together. This suggests that the influence of a common environmental factor is small or even nonexistent, thereby offering support for the second conclusion of Turner and Hewitt (1992): that shared environment plays only a minor role in determining individual differences in blood pressure reactivity.

LONGITUDINAL STUDIES: BLOOD PRESSURE LEVELS

While we know of no longitudinal studies of genetic and environmental influences on blood pressure reactivity, two such studies have been reported for blood pressure levels. In such studies, variables are measured on repeated occasions, over an extended period, in the same subjects. A resulting matrix of correlations across occasions often conforms to what is referred to as the *simplex* pattern, in which correlations are maximal among adjoining occasions and decrease as the time between measurements increases. Such data may be described by autoregressive models in which some random change in the underlying phenotype, distinct from measurement errors, is introduced on each occasion. The underlying

phenotype continually changes, making measurements from adjacent time periods more similar than those from more remote ones. This autoregressive simplex model can be generalized to the genetic analysis of longitudinal data, providing information on genetic stability across time (Boomsma & Molenaar, 1987).

Although they did not exploit these modern methods of time series analysis, Hanis, Sing, Clarke, and Schrott (1983) studied genetic and environmental influences on familial aggregation, coaggregation, and tracking (intraindividual correlation over time) of SBP and weight. The study started with a sample of 998 full sibs and first cousins from 261 families of whom 601 were measured on 4 occasions. Data from occasions 1 and 2 were analyzed together as Group 1, and those from times 3 and 4 were similarly analyzed as Group 2. Models were fit first to Group 1 and then to Group 2. With respect to tracking, 59% of the SBP-tracking correlation (0.33) and 60% of the weight-tracking correlation (0.89) were attributable to genetic effects. Relationships between SBP and weight remained stable over time. Two shortcomings of this study, however, should be noted: the short period of follow-up (4 years) and the subjects' young age. Subjects were measured during preadolescence (from 9.2 to 13.3 years), whereas it is likely that the development of blood pressure can be divided into a preadult and an adult phase (Hewitt et al., 1987).

During adulthood, the developmental genetics of blood pressure might be similar to that recently reported for the body mass index; although the overall heritability remains relatively constant from young adulthood on, there are nevertheless additional genetic influences acting in middle age independent of those that influence young adults (Fabsitz, Carmelli, & Hewitt, 1992). This possibility has been given support by the report of Colletto et al. (1993), who analyzed SBP and DBP for 254 MZ and 260 DZ male twin pairs assessed in middle age (mean age: 48 years) and again 9 years and 24 years later. Using a time series analysis of genetic and environmental components of variation, they found that shared family environmental effects were absent and that specific environmental influences were largely occasion-specific. In contrast, genetic influences were in part the same across adulthood (60% of genetic variation at the later ages was already detected in middle age) and in part age-specific (the remaining 40% of the genetic variation at later ages was unrelated to that expressed earlier). Despite these changing genetic influences, the estimated heritabilities remain relatively constant across ages at around 0.5.

A COMPROMISE: ESTIMATION OF AGE-DEPENDENT GENETIC AND ENVIRONMENTAL EFFECTS WITHOUT A LONGITUDINAL DESIGN

Though twin–family designs are advantageous in that they yield additional information from the parents of the twins (Sims et al., 1986, 1987; Eaves, Fulker, & Heath, 1989; Boomsma, 1992), a disadvantage of this design is the underlying assumption that the same genes are expressed in parents and their offspring. Stated differently, the assumption is that the correlation between genetic effects during

childhood and adulthood equals unity. To test this assumption rigorously, longitudinal data from genetically informative subjects are needed. However, a less expensive and less time-consuming option is to extend the parent–offspring design to include, in addition to younger twins and their parents, a group of middle-aged twins of the same age as those parents (Stallings, Baker, & Boomsma, 1989).

This extended design, which includes young twins, their parents, and twins of the same age as the parents, can take account of the possibility that the correlation between genetic effects during adolescence and adulthood does not equal unity. The model can be written as:

$$Rpo = 0.5 \times Rg \times H1 \times H2 \quad (1)$$

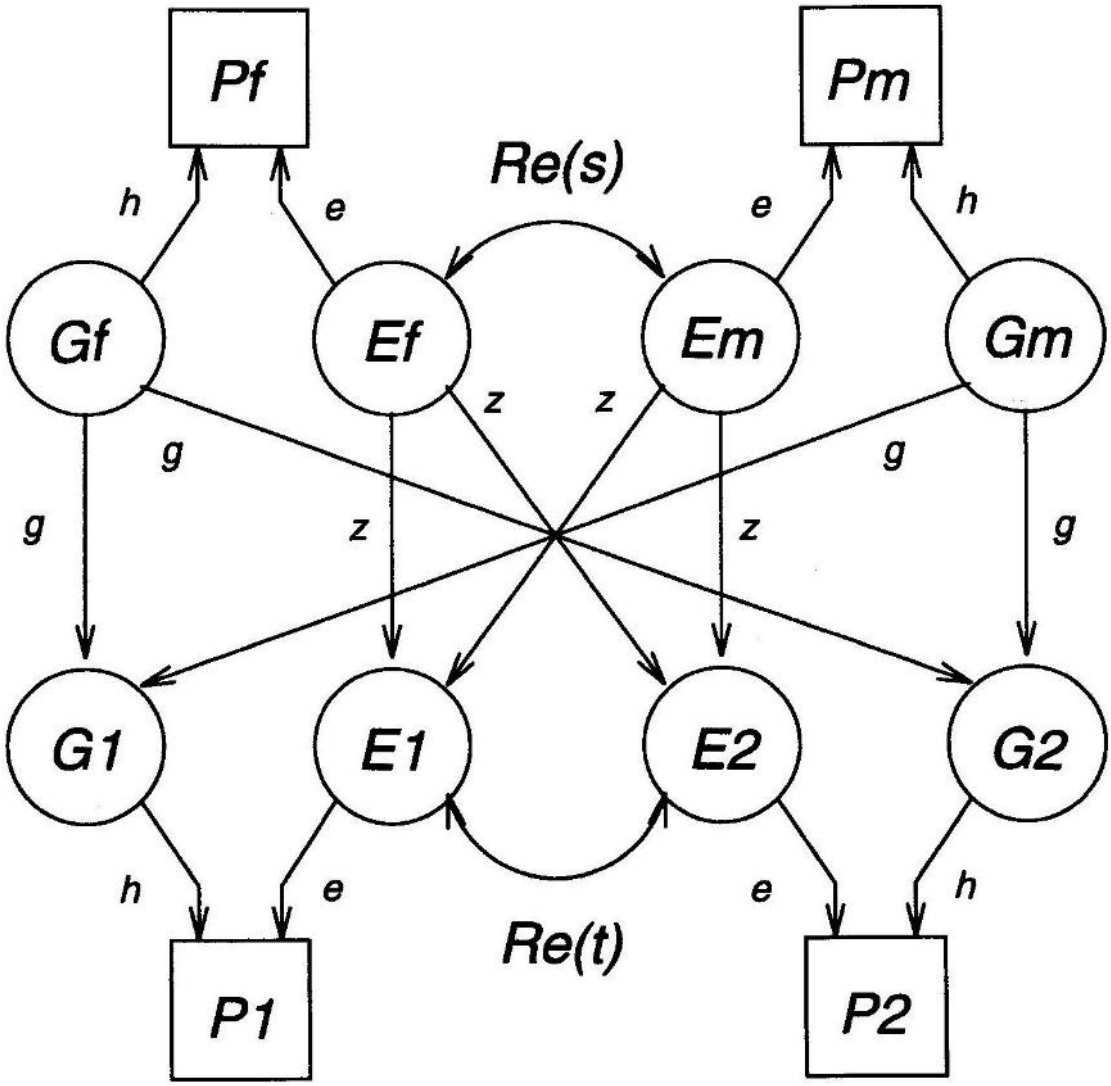

FIGURE 2. Parent–offspring model. (*P*) Observed phenotypes of father (*f*), mother (*m*), twin 1 (*1*) and twin 2 (*2*). (*G, E*) Latent genotype and total environment. (*g*) Modeling of genetic transmission from parents to offspring; (*z*) modeling of nongenetic transmission from total parental environment to offspring environment, in this case modeled to be equal for fathers and mothers. [*Re(s)*] Correlation between total environments of spouses; [*Re(t)*] correlation between residual environments of twins.

where *R*po is the parent–offspring correlation, *R*g is the genetic correlation across time (which is 1 if the same genes are expressed during adolescence and adulthood), *H*1 is the estimate of genetic influence during adolescence, and *H*2 is the estimate of genetic influence during middle age. *H*1 and *H*2 are equal to the square root of the corresponding heritabilities and can both be estimated with a univariate analysis for the adolescent and middle-aged twin groups, respectively. As *R*po is observed, *R*g is the only unknown left, which allows one to test whether *R*g differs from unity (Fig. 2). Figure 2 depicts the parent–offspring model as outlined by Boomsma, van den Bree, Orlebeke, and Molenaar (1989). In this model, the impact of total parental environment on offspring environment is considered, and the spouse correlation [*Re(s)*] is modeled as a correlation between total environments. The total environmental offspring correlation consists of a part that is accounted for by parental influences {through the environmental transmission parameter (*z*) and a part independent of the resemblance with their parents [*Re(t)*]}.

In the extended model, parameters are estimated by using information from 10 groups: 5 groups of young twins and their parents and 5 middle-aged twin groups, grouped according to the sex and zygosity of the twins. In this multigroup design, path coefficients for the parents equal those of the middle-aged twins. The genetic transmission from parents to offspring is modeled by the *g* coefficient. This *g* coefficient equals 0.5 *R*g and *g* equals 0.5 if the same genes are expressed in adolescence and adulthood {as *R*g equals 1 in that case [see equation (1)]}. A prerequisite for the application of this model is a significant parent–offspring resemblance, which implies significant heritabilities in both childhood and adulthood and a substantial genetic correlation across time [see equation (1)].

Blood Pressure Levels

This approach was adopted in the modeling of our own data. Data were combined from two different research projects. In the first project (Boomsma, 1992), SBP and DBP were measured in a group of adolescent twins and their parents. In the other project (which is still in progress), blood pressure data from twins in the same age range as the parents were collected. Some characteristics of the subject groups are shown in Table 3.

TABLE 3. Number of Pairs, Mean Age, Standard Deviations, and Age Range of Included Subject Groups

		Age	
Subject group	*N*	Mean (SD)	Range
Young twins	156	16.7 (2.0)	13–22
Parents	156	46.8 (6.3)	35–65
Middle-aged twins	200	44.4 (6.7)	35–62

TABLE 4. Number of Individuals and Mean Systolic and Diastolic Blood Pressures and Standard Deviations for Males and Females in the Three Subject Groups

	Males					Females				
Subject group	*N*	SBP	(SD)	DBP	(SD)	*N*	SBP	(SD)	DBP	(SD)
Young twins	160	119.8	(8.8)	65.8	(6.8)	152	114.9	(6.5)	67.6	(5.1)
Parents	156	128.2	(10.6)	80.7	(8.0)	156	125.7	(14.1)	77.6	(9.9)
Middle-aged twins	189	127.4	(10.8)	78.6	(8.7)	211	122.1	(13.5)	74.2	(10.3)

Blood pressure was measured three times by the Dinamap 845XT, using oscillometric techniques, while subjects rested and were comfortably seated in a sound-attenuated cabin for 8.5 minutes. In the first project only, this condition was repeated once. One average SBP value and one average DBP value for the rest condition were calculated in all groups. Mean values and standard deviations of SBP and DBP for males and females in the three subject groups are presented in Table 4. Both means and standard deviations of SBP and DBP are larger in the parents and the middle-aged twin group compared to the young twin group.

Before genetic modeling using LISREL VII (Jöreskog & Sörbom, 1988), blood pressure data were corrected for body weight. Maximum-likelihood estimates of parent–offspring correlations are shown in Table 5.

For SBP, the model in which the spouse correlation was set to zero fitted best. In the best-fitting model for DBP, the spouse correlation was set to zero and the four different parent–child correlations were set equal. Models in which parent–child correlations were set to zero fitted significantly less well for both SBP and DBP (Table 5), which means that there is a significant parent–offspring correlation.

As stated earlier, $H1$ and $H2$ (Equation [1]) can be estimated with a univariate analysis within the adolescent and middle-aged twin groups, respectively. Twin correlations of both groups are shown in Table 6. The pattern of correla-

TABLE 5. Models for Systolic and Diastolic Blood Pressure Rendering Maximum-Likelihood Estimates of Parent–Offspring Correlations[a]

Measure	*R*sp	*R*fs	*R*fd	*R*ms	*R*md	χ^2	*df*	*p*
SBP	0.06	0.17	−0.02	0.22	0.44	39.36	36	0.32
	0	**0.16**	**−0.04**	**0.21**	**0.44**	**39.88**	**37**	**0.34**
	0	0.19	0.19	0.19	0.19	55.41	40	0.05
	0	0	0	0	0	72.36	41	0.00
DBP	−0.04	0.08	0.13	0.30	0.26	25.54	36	0.90
	0	0.09	0.14	0.30	0.27	25.78	37	0.92
	0	**0.20**	**0.20**	**0.20**	**0.20**	**29.50**	**40**	**0.89**
	0	0	0	0	0	45.94	41	0.28

[a]Correlations: (*R*sp) spouse; (*R*fs) father–son; (*R*fd) father–daughter; (*R*ms) mother–son; (*R*md) mother–daughter. The best-fitting models are in **boldface** type.

TABLE 6. Twin Correlations for Systolic and Diastolic Blood Pressure in Both Young Twins and Middle-Aged Twins

Zygosity and sex[a]	Young twins			Middle-aged twins		
	Number of pairs	SBP	DBP	Number of pairs	SBP	DBP
MZF	33	0.51	0.49	47	0.50	0.59
DZF	29	0.33	0.40	39	0.42	0.28
MZM	35	0.49	0.61	43	0.44	0.44
DZM	31	0.53	0.56	32	0.16	0.23
DOS	28	0.37	0.32	39	0.23	0.21

[a] See the Table 1 footnote for abbreviations.

tions as shown in Table 6 is indicative of genetic influences on blood pressure, as MZ twin correlations are larger than DZ twin correlations. Standardized estimates from univariate analyses are shown in Table 7 for young and middle-aged twins.

For both young and middle-aged twins, models estimating additive genetic (G) and environmental (E) factors fitted beset. For both groups, a G and E model that allowed heritabilities to be different in males and females gave the best account of the data.

Under these conditions of a significant parent–offspring resemblance and significant heritabilities in both childhood and adulthood, it is possible to fit the extended model (Fig. 2) and estimate the value of the genetic transmission coefficient. Results are shown in Table 8.

TABLE 7. Standardized Estimates of Best-Fitting Univariate Models for Systolic and Diastolic Blood Pressure in Twins[a]

Measure	h^2_m	e^2_m	h^2_f	e^2_f	χ^2	df	p
			Young twins				
SBP[b]	0.49	0.51	0.66	0.34	7.80	12	0.80
DBP[c]	0.69	0.31	0.50	0.50	5.81	12	0.93
			Middle-aged twins				
SBP[d]	0.40	0.60	0.63	0.37	23.98	12	0.02
DBP[d]	0.42	0.58	0.61	0.39	7.84	12	0.80

[a] Abbreviations: (h^2_m) heritability for males; (e^2_m) unique environmental variance for males; (h^2_f) heritability for females; (e^2_f) unique environmental variance for females.
[b] For SBP, absolute genetic variance is equal for males and females.
[c] For DBP, absolute unique environmental variance is equal for males and females.
[d] For both SBP and DBP, absolute unique environmental variance is equal for males and females.

TABLE 8. Standardized Estimates of Best-Fitting Extended Models for Systolic and Diastolic Blood Pressure[a]

	Parents[b]				Offspring[c]							
Measure	h^2_m	e^2_m	h^2_f	e^2_f	h^2_m	e^2_m	h^2_f	e^2_f	g	χ^2	df	p
SBP												
$g = 0.5$	0.26	0.74	0.57	0.43	0.47	0.53	0.65	0.35	0.50	81.35	59	0.029
g free	0.25	0.75	0.62	0.38	0.49	0.51	0.66	0.34	0.38	79.66	58	0.031
DBP												
$g = 0.5$	0.29	0.71	0.55	0.45	0.69	0.31	0.50	0.50	0.50	42.31	59	0.950
g free	0.38	0.62	0.60	0.40	0.70	0.30	0.51	0.49	0.36	39.56	58	0.970

[a] See footnote *a* in Table 7 for abbreviations. The best-fitting model in which the genetic transmission coefficient (g) is fixed at 0.5 and the one in which g is estimated are shown.
[b] For both SBP and DBP, absolute unique environmental variance is equal for males and females.
[c] For SBP, absolute genetic variance is equal for males and females; for DBP, absolute unique environmental variance is equal for males and females.

Models that estimated the genetic transmission coefficient fitted slightly better than models in which g was fixed at 0.5 for both SBP and DBP. This difference, however, was not significant, which means that a model with a g equal to 0.5 cannot be rejected on the basis of these data. The possibility that the same genes are active in parents and their offspring can therefore not be excluded. Although not visible in Table 8 (which present only standardized estimates), the increase in SBP and DBP variance with age (see Table 4) was explained in the best-fitting models by an increase in both genetic and unique environmental variance for females and, for males, an increase in unique environmental variance only. As a consequence, h^2 in males is smaller in the combined parent/middle-aged twin group compared to the h^2 in the young twins.

These results accord with data from Sims et al. (1986, 1987), who studied a group of male twins and their parents and also suggested a decrease in h^2 caused by an increase in unique environmental variance from young adulthood to middle age. In the models in which g was estimated rather than fixed at 0.5, g was estimated to be 0.38 for SBP and 0.36 for DBP (but not significantly different from 0.5). This result means that the genetic correlation across time [Rg from equation (1)] equals 0.76 for SBP and 0.72 for DBP. The slightly lower values found by Tambs et al. (1993) (0.62 for SBP and 0.67 for DBP) might be explained by the larger age difference (40 years) in their example, compared to the age difference between parents and offspring in this study (30 years).

To conclude: The slightly better fit of models estimating a genetic transmission coefficient offered some evidence, but not definitive evidence, that different genes influence blood pressure in childhood and in adulthood. The decrease of h^2 in males with age could be explained by an increase in unique environmental variance. The h^2 in females did not change with age, as unique environmental and genetic variance increased proportionally.

TABLE 9. Number of Individuals and Mean Systolic and Diastolic Blood Pressure Reactivity to a Reaction Time and a Mental Arithmetic Task and Standard Deviations for Males and Females in the Three Subject Groups

Subject group	Males				Females			
	N	SBP	(SD)	DBP (SD)	*N*	SBP	(SD)	DBP (SD)
Young twins								
RT	160	6.5	(5.4)	4.7 (3.7)	152	5.4	(5.6)	3.8 (3.4)
MA	160	10.0	(6.9)	7.8 (4.7)	152	9.6	(7.9)	7.3 (4.4)
Parents								
RT	156	5.7	(6.5)	3.3 (3.7)	156	4.6	(6.7)	1.8 (3.8)
MA	156	12.5	(8.1)	6.7 (4.1)	156	11.1	(9.0)	5.0 (4.3)
Middle-aged twins								
RT	189	7.9	(8.5)	3.7 (5.9)	211	6.7	(9.0)	3.2 (5.4)
MA	189	11.1	(10.2)	6.5 (7.0)	211	9.7	(10.4)	6.5 (6.8)

Blood Pressure Reactivity

Subjects were exposed to two mental stress tasks: a choice reaction time (RT) task and a pressured mental arithmetic (MA) task (for a detailed description of these tasks, see Boomsma, van Baal, & Orlebeke, 1990). Each task lasted 8.5 minutes, during which blood pressure was measured 3 times. In the first project only, tasks were repeated once. For each task, one average SBP and one average DBP value were calculated in all groups. Blood pressure reactivity was calculated as the absolute difference between blood pressure level during the tasks and during the resting period. Mean values and standard deviations of SBP and DBP reactivity to both tasks are presented in Table 9.

In all subject groups and in both sexes, SBP and DBP reactivity during the

TABLE 10. Best-Fitting Models for Systolic and Diastolic Blood Pressure Reactivity to a Reaction Time and a Mental Arithmetic Task Rendering Maximum-Likelihood Estimates of Parent–Offspring Correlations[a]

Measure	*R*sp	*R*fs	*R*fd	*R*ms	*R*md	χ^2	*df*	*p*
SBP								
RT	0	0.11	0.11	0.11	0.11	29.05	40	0.90
MA	0	0.13	0.13	0.13	0.13	42.69	40	0.36
DBP								
RT	0	0	0	0	0	76.94	41	0.00
MA	0	0	0	0	0	53.77	41	0.09

[a]See the Table 5 footnote for correlation abbreviations.

TABLE 11. Twin Correlations for Systolic and Diastolic Blood Pressure Reactivity to a Reaction Time and a Mental Arithmetic Task in Young Twins and Middle-Aged Twins

Zygosity and sex[a]	Young twins					Middle-aged twins				
	Number of pairs	SBP		DBP		Number of pairs	SBP		DBP	
		RT	MA	RT	MA		RT	MA	RT	MA
MZF	33	0.37	0.33	0.07	0.27	47	0.15	0.33	0.36	0.16
DZF	29	0.41	0.49	0.25	0.41	39	−0.23	0.00	−0.15	0.09
MZM	35	0.30	0.51	−0.04	0.33	43	0.54	0.48	0.19	0.32
DZM	31	0.16	0.07	−0.07	0.06	32	0.03	−0.38	0.19	−0.03
DOS	28	0.35	0.07	0.24	0.12	39	0.29	0.29	0.04	−0.02

[a] See the Table 1 footnote for abbreviations.

MA task was greater than during the RT task. Blood pressure responses to the tasks in males were slightly higher than in females. DBP reactivity in both sexes and to both tasks was somewhat larger in the young twins compared to the parents and middle-aged twins. Such a pattern was absent for SBP reactivity.

Maximum-likelihood estimates of parent–offspring correlations are shown in Table 10. In the best-fitting model for SBP reactivity to both tasks, the spouse correlation was set to zero and the four different parent–child correlations were set equal. For DBP reactivity to both RT and MA tasks, models in which spouse and parent–child correlations were set to zero gave the most parsimonious account of the data. This result means that there is no significant parent–offspring correlation for DBP reactivity. Univariate analyses for blood pressure reactivity to both tasks were executed to estimate $H1$ and $H2$ [equation (1)] within the adolescent and middle-aged twins groups, respectively. Twin correlations of both groups are shown in Table 11. No clear overall pattern pointing to either genetic

TABLE 12. Standardized Estimates of Best-Fitting Univariate Models for Systolic and Diastolic Blood Pressure Reactivity to a Reaction Time and a Mental Arithmetic Task in Young Twins[a]

Measure	h^2	c^2	e^2	χ^2	df	p
SBP						
RT	—	0.31	0.69	3.94	13	0.99
MA	0.44	—	0.56	25.63	13	0.02
DBP						
RT	—	—	1.00	23.21	14	0.06
MA	0.38	—	0.62	12.98	13	0.45

[a] Abbreviations: (h^2) heritability; (c^2) shared environmental variance; (e^2) unique environmental variance.

TABLE 13. Best-Fitting Univariate Models for Systolic and Diastolic Blood Pressure Reactivity to a Reaction Time and a Mental Arithmetic Task in Middle-Aged Twins[a]

Measure	h^2_m	e^2_m	h^2_f	e^2_f	χ^2	*df*	*p*
SBP							
RT[b]	0.37	0.63	0.27	0.73	27.58	12	0.01
MA	0.36	0.64	0.36	0.64	26.63	13	0.01
DBP							
RT	0.23	0.77	0.23	0.77	23.12	13	0.04
MA	0.25	0.75	0.25	0.75	10.78	13	0.63

[a]See footnote *a* in Table 7 for abbreviations.
[b]For SBP reactivity to the RT task, absolute unique environmental variance is equal for males and females.

or common environmental influences could be detected in these correlations. Some correlations were even negative.

Results of univariate analyses are shown in Table 12 for young twins and in Table 13 for middle-aged twins. For the young twins (Table 12), best-fitting models for the two stress tasks (RT and MA) and the two reactivity measures (SBP and DBP reactivity) did not show a consistent pattern. For the SBP reactivity to the RT task, a model invoking shared environment (*C*) and nonshared environmental (*E*) factors fitted best. A model estimating *E* only gave the best fit for the DBP reactivity to the RT task. For SBP and DBP reactivity to the MA task, a *G* and *E* model fitted best to the data. Best-fitting models were thus different for the two tasks.

For middle-aged twins (Table 13), a *G* and *E* model gave the best fit in all four conditions. For SBP reactivity to the RT task, this model allowed heritabilities to be different in males and females.

As mentioned earlier, two conditions have to be met to be able to fit the extended model (Fig. 2) and estimate a genetic transmission coefficient. These requirements were not met: No significant parent–offspring correlations were found for DBP reactivity to RT and MA tasks, and no heritabilities were found for SBP and DBP reactivity to the RT task in the young twins. Only for SBP reactivity to the MA task was the parent–offspring correlation greater than zero and heritabilities found in childhood and in adulthood.

The picture is thus very far from clear for blood pressure reactivity. For SBP reactivity, a significant parent–offspring correlation was found; for DBP reactivity, no such correlation was found. Different models fitted best for different tasks, and for the same task, different models fitted best in young and in middle-aged twins.

DISCUSSION

This chapter has examined whether and how underlying genetic or environmental influences, or both, lead to stability or change across the life span in

individual differences in blood pressure level and blood pressure reactivity to stress. Different types of genetic studies and models investigating changes with age of heritability of blood pressure level and reactivity were discussed to shed some light on this question.

In twin studies of blood pressure level, no age trend in h^2 could be detected. Findings in family studies of lower parent–offspring compared to sibling and DZ twin correlations indicate, however, that age may influence genetic or environmental effects on blood pressure level. This age dependency could take two forms: The influence of unique environmental factors could increase with age, or different genes could influence blood pressure in children and adults. For both possibilities, some evidence was found in the literature (Sims et al., 1986, 1987; Tambs et al., 1993). However, an increase of unique environmental variance in adulthood, without a commensurate increase in genetic variance, would lower the heritability estimate, and the lack of an age trend in h^2 in twin studies is inconsistent with this prediction. On the other hand, the twin data are not inconsistent with the hypothesis of genes switching on and off with age, because the overall influence of genes can remain stable even though different genes are responsible for the effect.

Modeling of our own data gave some evidence, but not definitive evidence, that different genes are active during childhood and adulthood. However, a fall in h^2 with age in males could be explained by a rise in unique environmental variance, thus supporting the other possible age effect. In females, because environmental and genetic variance increased proportionally, heritability did not change with age. It seems that at least in males, both age-dependent effects on SBP and DBP level could act simultaneously: Different genes influence blood pressure in children and adults, and unique environmental variance increases with age.

As for blood pressure reactivity, in twin studies, no age trend in h^2 could be detected either, and the few family studies reported did not allow any conclusions about age dependency.

Furthermore, the picture that arises from modeling of our own data is far from clear. A significant parent–offspring correlation was found for SBP reactivity, but not for DBP reactivity. Different models fitted best in young and middle-aged twins, and in young twins, the best-fitting models for both SBP and DBP reactivity were different for the two tasks. This finding is somewhat unexpected if it is assumed that responses to mental tasks represent the underlying general propensity of subjects to be reactive or not. The same task dependency of heritability estimates was observed by Ditto (1993): The SBP response to a concept formation task showed no heritability, whereas the response to a mental arithmetic task did.

A reason for these differences might be that the blood pressure response is a composite of several contributing mechanisms that may differ between tasks (see, for example, Turner [1994] and Chapter 5). In one task, vascular processes may be the main determinant of the blood pressure elevation, while cardiac involvement

may be more prominent in another task. If the genetic contribution to cardiac and vascular reactivity is different, this difference will lead to different heritability estimates of the blood pressure response to these tasks. Studying the genetic contribution to blood pressure reactivity is, in fact, studying the combined genetic effects on several intermediate phenotypes such as vascular reactivity and baroreflex sensitivity. Future studies will have to measure the genetic contributions to the response of cardiac sympathetic (pre-ejection period) and parasympathetic indices [respiratory sinus arrythmia (Boomsma et al., 1990)] and to the response of indices of peripheral resistance and cardiac output. Such studies may reveal why heritability estimate for reactivity differ between stressors. Moreover, more knowledge of the genetics of these intermediate phenotypes will bring the genetic approach close to the crucial questions in hypertension research.

There is growing evidence that in contrast to earlier ideas, baroreceptor sensitivity and cardiac and vascular structural changes (all of which influence reactivity) have a genetic component (Weinstock, Weksler-Zangen, & Schorer-Apelbaum, 1986; Harrap, Van der Merwe, Griffin, MacPherson, & Lever, 1990; Unger & Rettig, 1990; Parmer, Cervenka, & Stone, 1992) and, moreover, are not merely a consequence of elevated pressure but may precede a rise in pressure and thus have an etiological role. The study of the genetics of blood pressure levels and of its age and sex dependency will benefit from measuring intermediate phenotypes in addition to blood pressure. Clearly, the genetic variance in blood pressure reflects the genetic variance of its determinants. A genetic contribution to stroke volume and peripheral resistance was shown by Bielen, Fagard, and Amery (1991). The age dependency of the genetic contribution to these parameters is of special interest because the contribution of the vasculature to high blood pressure is greater in older than in younger people (Lund-Johansen, 1977). By looking only at the age dependency of the genetic contribution to blood pressure, one may miss information about the genetics of mechanisms hypothesized to be involved in the etiology of high blood pressure. Our own data on these underlying mechanisms will become available in the near future.

A general problem in hypertension research, which applies to the study of age dependency of blood pressure, is the difficulty of determining whether abnormalities in blood-pressure-regulating mechanisms (in this case measured in different age groups) are causal factors for, or mere consequences of, elevated pressures. Moreover, conditions that have played a causal role at an early age may have disappeared when measured at a later age. For example an elevated cardiac output is a characteristic of some individuals with early borderline hypertension. With increasing age, the role of peripheral resistance as a determinant of blood pressure becomes more pronounced. Thus, in older people, one might be assessing the genetics of a consequence of elevated pressure instead of the genetics of a causal factor. To properly interpret the age dependency of the genetic contribution to blood pressure and its determinants, therefore, one must place the data in the framework of our knowledge of the etiology of hypertension development.

The study of the genetics of mechanisms involved in blood pressure regulation in young children might bring us closer to causal mechanisms. There is a considerable tracking of blood pressure levels from early to later childhood (Szklo, 1979), and blood pressure at young age is an important predictor of adult levels (Lauer & Clarke, 1989). Though moderately elevated blood pressure is a precursor of essential hypertension, only 20–30% of individuals will eventually reach the hypertensive range. A longitudinal twin study approach will allow examination of the difference in patterning of genetic and environmental factors between those who return to the normotensive range and those who develop hypertension.

The genetic autoregressive simplex model could be used in this respect to construct individual genetic and environmental profiles across time by means of a statistical technique known as Kalman filtering (Boomsma, Molenaar, & Dolan, 1991). Such individual profiles allow us to attribute individual phenotypic change to changes in the underlying genetic or environmental processes. Simulations have shown that these individual estimate can be reliably obtained. Estimation of genetic and environmental profiles across time would permit identification of sources of underlying deviant development in blood pressure for individual subjects.

Williams et al. (1990) have reviewed possible candidates for genetic and environmental causes of the development of hypertension. They expressed the hope that in the near future, biochemical tests and application of gene markers may provide methods for quantitatively assessing a person's risk for hypertension. A possible genetic marker for high blood pressure was identified in the parents of twins from our study: Individuals carrying the α_1-antitrypsin deficiency alleles S and Z had lower blood pressure during rest and stress. This finding replicate that from an Australian twin sample (Boomsma, Orlebeke, Martin, Frants, & Clark, 1991). Determining the balance between environmental and such predisposing genetic factors as early as possible is of utmost importance for preventive purposes, because high blood pressure, once established, is not easily reversed.

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