

**LASSEN SICH KONTINUIERLICHE KARDIOVASKULÄRE RISIKOFAKTOREN
(HYPERTONIE UND HYPERCHOLESTERINÄMIE)
ANHAND VON GRENZWERTEN DEFINIEREN ?**

**Mathematik der Blutdruck-Häufigkeits-Kurven und
mögliche Lehren aus der
Blutdruck-Entwicklung in der Kindheit und der
Blutdruck-Verteilung in Naturvölkern**

von Johannes Schmidt

In meinem Diskussionsbeitrag will ich an ein Forschungsprojekt dieses Institutes anknüpfen, nämlich an die Herz-As-Studie. Es soll sich dabei um ein Projekt handeln, welches als präventiver Risikofaktorenbeeinflussung-Versuch ein markantes Gewicht auf soziale Risiko-Konstellationen legt.

Eine dabei immer wieder auftauchende wichtige Grösse könnte man mit dem Begriff "Biographie" belegen; dazu gehören etwa "life-events", "hassles", oder einfach Lebensumstände, die zu chronischem, nicht bewältigbarem "Stress" führen können. Eine physiologische Sicht des Stressses würde diesen etwa auffassen als Störung der physiologischen Homöostase, welche als akute Erscheinung funktionelle Störungen und stresshaftes Verhalten, als chronisch ungelöste Erscheinung aber auch organische Veränderungen und pathologisch definierbare Morbidität zur Folge hätte [Noack, Forschungsgesuch].

Ich kann hier nicht weiter auf die psychosozial definierte Grösse des Stressses eingehen, möchte aber festhalten, dass ein wie auch immer geartetes Stress-Phänomen für die Infarkt-Genese wahrscheinlich bedeutsam ist, und dass dabei die Biographie, und nicht ein einmaliger Ist-Zustand eines Menschen bedeutsam ist.

Ich werde im Folgenden versuchen, anhand epidemiologischer Daten und deren Interpretations-Möglichkeiten eine mögliche "physiologische Biographie" in der Infarkt-Karriere aufzuzeigen. Dies wird vorwiegend am Beispiel des sogenannten Risikofaktors Blutdruck geschehen, wobei ähnliche Ueberlegungen aber auch für die "Cholesterin-Biographie" eines Menschen gelten könnten.

Die folgende Kritik am Risikofaktoren-Modell erwuchs vorwiegend aus der mir auch als praktischem Arzt bekannten Tatsache der äusserst geringen individuellen Prädiktionskraft dieses Modells, und der daraus zwingend folgenden unerwünschten

Auswirkungen der Risikofaktoren-Prävention (als individuelle "Hochrisiko"-Strategie).

In einem ersten Teil wird deshalb dieses Problem in seiner ganzen Deutlichkeit erst einmal vor Augen geführt.

UNGELÖSTE PROBLEME IN DER ANWENDUNG KONVENTIONELLER GRENZWERTE

Konzeptionell muss man sich vor Augen halten, dass die Risikofaktoren in grossen Populationen "entdeckt" bzw. erforscht worden sind. Das Risikofaktorenmodell lässt dementsprechend präzise Gruppen-Aussagen zu. Die heute sehr populäre Verwendung des Modells zur Charakterisierung von Risiko-Personen ist jedoch nicht unbedenklich.

One of the conceptual problems or misunderstandings in this respect relate to the concepts of population relative risks and individual attributable risk. Relative risks, from observational and intervention studies, have a potential significance for the etiology and pathogenesis of a disease since they are a convenient measure of the strength of an association between the disease event and a putative cause. But they tell next to nothing about the individual benefit from an intervention. In order to describe benefit and harm of an intervention, attributable risks and benefits are much more valuable. Following table shows what this distinction means in practical terms:

Table: relative und absolute benefit of anti-cholesterolaemic treatment. () = 95% confidence intervals

all infarcts	<u>without</u> treatment	<u>with</u>	<u>relative</u> *	<u>absolute</u> **
Colestyramine	13.3	11.0	17 %	2.3 / 1000 y.
	per 1000 years		(-1% - 33%)	(-0.1 - 4.8)
Clofibrate	7.4	5.9	20 %	1.5 / 1000 y.
	per 1000 years		(3% - 35%)	(0.2 - 2.8)

* = reduction in % ** = difference

The relevant (clinical epidemiological) question is really not only if a risk factor causes a disease, but **how much** it contributes to a disease and how much good and harm is produced by interventions to "treat" risk factors.

Hence, the situation for the treatment of mild to moderate hypertension looks as follows:

**Table: Treatment of Mild to Moderate Hypertension (diast. 90-110 mmHg)
- Benefit or Harm ?**

Benefits and adverse effects	Percentage of treated persons affected by beneficial as compared to adverse effects during 5 years of treatment	
I. BENEFITS*		
	in	of persons treated
Prevention of cardiovascular event	0.8 - 2.4 % **,+	[1,2]
stroke	0.6	[1]
II. ADVERSE EFFECTS RELATED TO DRUGS		
	in	of persons treated
Side-effects severe enough to discontinue treatment	15 - 33 %	[1,3]
Impotence, loss of libido	8 - 17 %	[3-5]++
assessed by spouse	35 %	[5]
Deterioration of quality of life		
assessed by patient	9 - 12 %	[4,5]
by spouse/relatives	75 %	[5]
(by treating doctor	0 %	[5])
III. ADVERSE EFFECTS RELATED TO HYPERTENSION-LABELLING		
	in+++	of persons labelled
Depressive symptoms	12 %	[6]
Sense of poor/fair health	18 %	[6]
Increase of abstenteeism:	from 7 to 12 days	per person/year [7]

+ trial [2] includes "minor" events such as retinopathy, and the difference in women was not statistically significant		
++ trial [4] includes only 24 weeks of observation		
+++ difference as compared to control group		
* No effect on total mortality and myocardial infarction		
** Given range indicates variation among the different studies		

ref: 1) MRC trial [MRC 1985, MRC 1981], 2) Australian trial [Management Committee 1980], 3) HDFP [Curb 1985], 4) [Croog 1986], 5) [Jachuck 1982], 6) [Bloom 1981], 7) [Haynes 1978]		

Beim Betrachten der gesamthaften epidemiologischen Auswirkungen (soweit erfassbar) einer Strategie zur Hypertonie-Erfassung und -Behandlung erkennt man, dass die unerwünschten Effekte bedeutsam sind und nicht sicher von der erwünschten Verhütung einiger weniger Hirnschläge aufgewogen werden. Ich möchte vermuten, dass diese ernüchternde Bilanz kaum zur Kenntnis genommen wird, weil einerseits die Kliniker dem Risikofaktorenmodell nur die qualitative Aussage über den Arteriosklerose-Mechanismus entnehmen wollen, ohne sich um die quantitative Seite zu kümmern, und dass andererseits viele Epidemiologen reduktionistisch nur die bevölkerungsweiten Morbiditätszahlen einer einzigen Krankheit berücksichtigen, ohne sich um die ebenso entscheidende "Mikrowelt" der einzelnen in Patienten-Rollen gedrängten Individuen zu kümmern.

A look at the underlying risk factor model shows that not very much more can be expected from individual treatment of both, hypertension or hypercholesterinaemia. Let's take the example of a 35 year old man with a rather high cholesterol of 8 mmol/l (=310 mg%). With the optimistic assumption of an intervention completely free of adverse effects and capable to reduce this level to 6.7 mmol/l (=260 mg%), which is 16%, the probability of experiencing a myocardial infarction in the next 20 years is reduced from 14 to 8% (according to Framingham tables) [Whyte 1975]. Thus, in no more than 6% of high risk patients treated for 20 years (or 1.5% of high risk patients treated for 5 years), an infarct can possibly be avoided.

This dilemma is rooted in the low sensitivity and specificity of the conventional risk factors in predicting CHD at various cut-off points. Risk factors, though very good predictors on a population base, have a poor individual discriminative power. This means that we have to treat masses of "false-positives" (with a false individual risk prediction) and yet miss a large proportion of "false-negatives".

The example of various blood pressure and cholesterol cut-off levels is given in the following tables:

Table: Specificity and predictive value of systolic BP level as a predictor of 12 CHD incidence (total incidence = 113 per 1000 per 12 years). The Framingham Study, men aged 40-54 at entry.

Cut-off level	Sensitivity	Specificity	Positive predictive value
110 mmHg	98 %	4 %	11 %
120 mmHg	93 %	16 %	12 %
130 mmHg	75 %	37 %	13 %
140 mmHg	54 %	59 %	14 %
150 mmHg	33 %	78 %	16 %
160 mmHg	23 %	87 %	18 %
170 mmHg	16 %	93 %	22 %
180 mmHg	10 %	96 %	25 %
190 mmHg	6 %	98 %	27 %

Sensitivity is the proportion of cases occurring in those classified "hypertensive" as defined by the cut-off level. Specificity is the proportion of non-cases in the corresponding "normotensives". The positive predictive value is the disease-incidence in the "hypertensives".

source: [Epstein 1983]

Table: Cholesterol as a predictor of CHD. 10 years follow-up in the Pooling Project, incidence = 7.7% in 10 years

Cut-off level mmol/l (mg%)	PPV	Sensitivity	Specificity	NPV
7.7 (=300)	13.6	14.8	92.1	92.8
7.1 (=275)	12.5	28.2	83.5	93.3
6.5 (=250)	11.7	48.5	69.2	94.1
5.8 (=225)	11.4	68.0	55.8	95.4
5.2 (=200)	8.6	83.5	25.3	94.8
4.5 (=175)	8.1	94.6	9.5	95.5

overall incidence: 7.7 (all figures in %)

source: [Stamler 1978]

The above figures show that even at high cut-off levels the positive predictive value (ppv) of the risk factor cholesterol for the prediction of a later coronary event is quite low (14% for 7.7 mmol/l). On the other hand, the negative predictive value even at low levels is not very much different from the "negative incidence" (i.e. $100 - 7.7 = 92.3\%$). The screening negatives at a low cut-off level of 4.5 mmol/l can be assured that they will not suffer an infarct in the next 10 years with a probability of 95.5%. However, without screening, the overall probability is almost as high, being 92.3% ($100 - 7.7$).

For "hypertension", if we take the currently defined cut-off-level of 140 mmHg into consideration, 86% of the "hypertensives" would not experience a coronary event in 12 years, and 46% of all infarcts would still occur in men with lower than 140 mmHg blood pressure levels.

ALDERMAN concludes: "At the mild level, blood pressure is about as specific as temperature in predicting patient outcome or signaling the proper therapy." [Alderman 1981]

Die Verwendung der einfachen Parameter Spezifität und Sensitivität, sowie insbesondere des positive predictive value, kann uns die relative Unbrauchbarkeit des Risikofaktorenmodells für die individuelle Prävention aufzeigen. Weil in der Regel in solchen Begriffen nicht gedacht wird - und ich möchte noch einmal die den meisten Medizinern unbekannt Grösse des positive predictive value herausstreichen - ist der Begriff der Risikofaktoren in der heutigen Praxis zu einem konfusen

Halbwissen degeneriert.

Eine Kunst der (klinischen) Epidemiologie ist es, statistische Zusammenhänge so zu deuten, dass alle möglichen *biases* (oder Fehlschlüsse) in Betracht gezogen werden, und die verschiedensten Erklärungsvarianten eines solchen Zusammenhangs zu überprüfen. Eine Aufgabe der (klinischen) Epidemiologie ist auch die Erforschung von möglichst genauen Risiko-Prädiktoren, welche Interventionen erlauben, welche möglichst allen "Behandelten" nützen und möglichst alle "Behandlungswürdigen" erfassen (= hohe Spezifität und hohe Sensitivität). Nur wenn dies gelingt, kann eine individuell ausgerichtete Risikofaktoren-Medizin überhaupt deutlich mehr Nutzen als Schaden erzeugen.

Ich werde im Folgenden ein Modell entwickeln und untersuchen, welches mögliche Fehlschlüsse im jetzigen Risikofaktoren-Konzept aufzeigt, gleichzeitig aber auch ein Schlüssel sein könnte, die Aussagekraft von Blutdruck und Cholesterin zu erhöhen.

VERTEILUNG UND ENTWICKLUNG VON BLUTDRUCK-HÖHE BEI KINDERN UND ERWACHSENEN

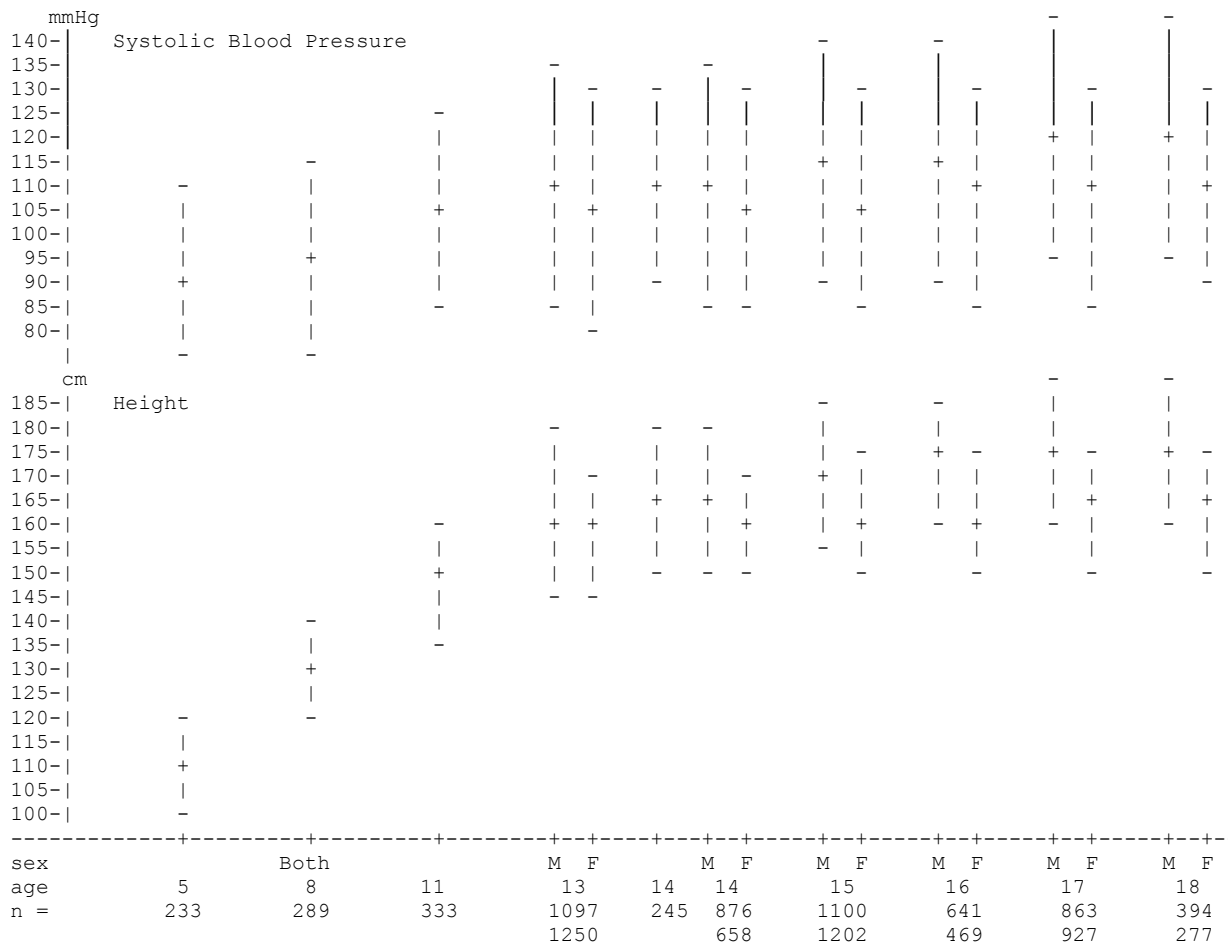
Are the current concepts of "normotension", "borderline", "mild", "moderate", and "severe hypertension" really meaningful?

Two lines of research may help us to better understand the nature and biology of hypertension. One is the epidemiology of the distribution of BP levels in childhood and adolescence, the other is the distribution of physiological characteristics (i.e. "markers") among different BP strata.

Before adulthood, as evidence by a range of studies [Labarthe 1983], the increase of blood pressure starts from a low level at birth with some increase in early infancy, but little further change in early childhood, and further substantial increases in both, systolic and diastolic BP, from early school years through adolescence. The transition into early adulthood shows little change in diastolic, but some increase of systolic BP. The increase of BP with age is particularly marked for systolic pressure. The increase with systolic pressure occurs in both boys and girls, but in boys the raise continues to a later age than in girls. At the age of 20, eventually, there is a considerable difference between boys and girls, boys having a higher systolic BP [Hofman 1984].

This sex difference, however, is exactly paralleled by the development of height, boys growing longer and attaining a higher size. In white Americans, girls reach their maximum mean height of about 162 cm at the age of 15, boys grow until the age of 17, reaching an average height of 175 cm [Baròn 1986]. This is illustrated in the following figure:

Figure: Variation (Mean and "95%-Range" +) of Systolic BP and Height in White Americans during Childhood and Adolescence. Source: [Frerichs 1979], [Baròn 1986]



+ Comprises mean \pm 1.96*SD. This calculation yields the 2.5th and 97.5th percentiles (assuming a Gaussian normal distribution of BP).

TRACKING UND HORSE-RACING

Another interesting finding from these population studies is the appearance of a tracking phenomenon of BP, specially for systolic BP. Children with relatively high BP, say, at age 15 are likely to have a relatively high blood pressure at age 20. Tracking is measured by the correlation of ranks of variables in successive measurements over years. Tracking, even stronger than for BP, has also been found for cholesterol levels. This is shown the following table:

Table: Tracking of anthropometric measures and BP, as measured by the coefficient r of the rank correlation over time in a cohort of children of initial age 6 - 15 [Clarke 1986]

Parameter	2 yers	4	6	8	10
Systolic BP	.44	.35	.28	.26	.24
Diastolic BP	.30	.24	.16	.10	.13
Height	.88	.70	.67	.71	.64
Weight	.87	.75	.72	.70	.65
Quetelet	.86	.79	.73	.69	.67

Tracking of BP is already apparent in infants, albeit weakly [DeSwiet 1976], as well as in little children of age 2. The strength of tracking is weaker in early childhood and significantly increases with aging [Zinner 1978], although this may perhaps be explained by larger measurement errors in little children. Tracking of BP is also apparent in adults, showing correlations as high as 0.5 over a period of 18 years [Kannel 1980].

BP tracking may be stronger than can be measured because of the large intra-individual variability which distorts a correlation. In fact, studies using BP values based on repeated BP readings show consistently higher correlation coefficients than studies based on single measurements [Webber 1986].

Die Entwicklung und die Verteilung des Blutdrucks in der Kindheit fügt sich also praktisch nahtlos in ein Paradigma eines normalen physiologischen Phänomens wie wir es von den pädiatrischen Wachstumskurven kennen. Wie in obiger Figur zum Ausdruck kommt, ist das Bild der "Blutdruckentwicklungs-Kurve" dem Bild der bekannten Wachstumskurve zum Verwechseln ähnlich (vgl. auch weiter unten).

Dennoch wollen die meisten Risikofaktoren-Forscher aus dem tracking-Phänomen einen bereits in der Kindheit sich abzeichnenden **pathologischen** Hypertonie-Prozess ablesen (z.B. [Hofman 1984]). Allerdings haben diese Autoren auch nie die Hypothese in Betracht gezogen, dass sie mit diesem Phänomen etwas rein physiologisches beschreiben könnten. Wenn Kinder in oberen Blutdruck-Perzentilen auch als Adoleszenten wieder vergleichsweise hohe Blutdruckwerte aufweisen, so muss daraus nicht notwendigerweise abgeleitet werden, dass eine Hypertonie schon im Kindesalter beginnt, sondern es ist ebenso möglich, dass dies Ausdruck der biologischen Normverteilung ist.

In fact, children of the lowest, middle, and highest BP quintile show identical cardiovascular parameters of a wide range, apart from BP level. From a study selecting children who persistently remain in the same systolic BP quintile over years (thus show a regular "percentile-true" development of BP) this can be shown. Left ventricular wall mass is somewhat greater in the upper quintile, though the SD shows considerable overlapping between the upper and lower quintiles (wall mass in upper quintile: 113.3 g, middle quintile: 103.6 g, lower quintile: 106.1, pooled SD: 39.9 g; means are adjusted for sex, height, weight, and skinfold thickness) [Schieken 1981, Schieken 1983]. Children of all BP strata who have remained in their initial (and perhaps "natural") percentile do not show different cardiovascular response during exercise. In these children, however, resting cardiac output (stroke volume x heart rate), but not BP, is a predictor of cardiovascular response under exercise, specifically of vascular resistance. Resting cardiac output, on an average, is not different between the quintiles. At all levels of BP, and unrelated to the BP level, there are children with low cardiac output which shows a high correlation with high systemic vascular resistance. This study shows that the BP level in children who develop BP persistently along a given track may show haemodynamic differences, but these differences are not related to BP level but to other cardiovascular parameters such as resting cardiac output. Other studies in children of the same age range have yielded similar findings of no association between BP level and the haemodynamic parameter cardiac output [Hofman 1982].

It is interesting to note, that in childhood, physiological abnormalities, that could be "markers" of a true hypertensive

development, are not found more frequently among the children with the highest BP levels. This is different in middle aged persons, as will be outlined below.

A positive association between the initial level of BP and subsequent BP increments has been denoted as "horse-racing". Horse-racing is apparent in adults but not in children. It has therefore been concluded, that a homeostatic mechanisms might operate which takes children with high BP back to the mainstream of the distribution, and that with increasing age this mechanism became deficient [Hofman 1984].

Another interpretation of this data, however, is possible: From the two components of BP, one representing normal growth and development, the other reflecting an abnormal hypertensive development, the latter will naturally explain horse-racing in adulthood. Horse-racing in adulthood may occur, because with increasing age upper BP strata are increasingly a selection of subjects with BP increases beyond their normal growth, thus "true" hypertensives. In adulthood, variation in BP increases cannot be explained by normal body growth and may therefore be an expression of real hypertensive development. However, during childhood this selection process, if it occurs at all, cannot produce the same horse-racing effect, because BP increase variation is largely determined by normal growth differences, and this would dilute any variation due to "true" hypertensive developments even if the latter may exist in childhood.

The last figure showed the increase of the mean BP with increasing age during childhood, but also that the variability of BP levels in a given age group is considerable and, in fact, exceeds the longitudinal variation dependent on age (the BP range of 95% of subjects is 4 times the standard deviation, roughly 40 mmHg for systolic BP, whereas the variation due to age differences is about 30 mmHg).

DIE KORRELATION ZWISCHEN BLUTDRUCK UND KÖRPERGRÖSSE

Furthermore, these studies show that the level of blood pressure correlates with such "constitutional factors", as I may call them, as height and weight, and in several studies the correlation between BP and body size has been found substantially stronger than for age. Repeatedly it could be shown that after adjustment for anthropometric measures, no association between age and (systolic) BP level in children could be found [Voors 1977, Schieken 1983]. The relationship between age and BP level, therefore, may be entirely confounded by the development of height and weight. In fact, in one analysis looking at the level **and** trend of systolic BP and height, a significant relationship could be found for both, level and trend over 10 years. A child growing slower than his/her peers also shows, on the average, a slower increase of systolic BP, whereas a child growing faster than the peers shows a faster increase of systolic BP (Spearman correlation coefficient between BP level and height = 0.30; between trend of BP and trend of height growth = .14, $p < .001$) [Lauer 1984].

In a selected population of children, whose systolic BP persisted in the same (and perhaps "natural") quintile over 2 years, it was shown that the distribution of systolic BP levels could be entirely explained by anthropometric measures and sex, irrespective of age. There was no correlation of systolic BP with age if adjustment for sex, height, weight and body mass index (BMI) was made. The same was observed for the heart stroke volume. Other variables such as diastolic BP and vascular

resistance, however, were positively correlated with age beyond what could be explained by the mentioned body measures. Children in the highest BP quintile were significantly taller, heavier, and more obese. The ponderal index (as a measure of obesity) showed no difference between the middle and low quintile [Schieken 1981, Schieken 1983]. This may mean that height is primarily determining BP levels and only in the highest quintile some of the BP variance is explained by obesity.

The correlation between height and systolic BP, which is stronger in adolescence than in early childhood, is specially pronounced during the acceleration of growth and BP during puberty [Hofman 1984]. A large body of observations in fact shows a linear relationship between height and BP [Voors 1977, Lauer 1984].

BARON et al have published results of BP and height measurements in over 10,000 adolescents [Baron 1986]. The data are separately given by age (13,14,..19), sex, and race (black, white, Mexican-American), thus forming 42 sub-populations of the adolescent population, enrolled in the Dallas Independent School District (Texas/USA). Mean height and BP levels have been published from the Bogalusa Heart Study [Frerichs 1979] yielding 4 sub-populations of age 5-14 (5, 8, 11, 14). Small sub-populations with a standard error of mean BP >1 mmHg or mean height >1 cm are excluded from the following analysis in order to eliminate random "noise". This leaves 38 subpopulation of large size with minimal standard errors of mean height and BP (see above).

Table: Correlation Coefficients (r) and Regression Slopes (b) between Height (X Variable) and Systolic BP (Y Variable) between Various Population Subgroups. Children from 4 to 18; Analysis of Data from [Frerichs 1976] and [Baron 1986]. (Small Population Samples with Standard Error of Means > 1 mmHg or > 1cm are excluded.)

		correlation	regression	stat significance
		r	b	p
ALL	n=38	.94	.44	p<.001
MALE	n=17	.92	.62	p<.001
FEMALE	n=17	.56	.25	p<.05
WHITE	n=16	.95	.42	p<.001
BLACK	n=16	.98	.40	p<.001
MEXIC	n=14	.98	.43	p<.001
AGE <14	n=16	.98	.36	p<.001
AGE ≥15	n=22	.93	.63	p<.001

It can be seen that mean population systolic BP levels show a high correlation with mean population height ($r=.94$), throughout age 5 to 18, in both sexes, and in all races. This can be found in various subgroups (r consistently $>.9$), only girls (where the variation is mainly given by age differences) showing a weaker correlation. High correlations can be shown for all age sub-groupings (below age X, above age X). During childhood and adolescence, population differences in BP seem therefore to be almost entirely explainable by height differences. A strong correlation is identical with a linear relationship (a simple BP/height-ratio may therefore be considered a measure of hypertension).

Further interesting findings in this respect comes from the study of differences in BP levels between indigenous Indian populations in South America living at different altitudes. It had long been speculated that the low air oxygen at high altitude might be responsible for a lower observed BP in people living high up in Central and South American "altiplanos" (and various physiological mechanisms were proposed).

However, these differences can also be explained by differences in body size, coastal people and "sierra" people (intermediate) being heavier and taller than "altiplano" people.

Altitude does not emerge as an independent predictor of BP in a multiple regression with body size taken into account, with the exception of systolic BP in females. Moreover, sex differences can be explained by body mass differences. In children, good correlations of systolic BP can be found with height and with weight (for example r for both = about .6 in coastal and altiplano boys). In adults, however, a correlation, albeit weaker, exists rather between BP and ponderosity (Quetelet).

The relationship between body mass and BP can also explain altitude differences observed in Ethiopia and other parts of the world [Makela 1978].

This may suggest that BP variation associated with body size variation is a very universal phenomenon, including adults as well.

Variables which determine the level of BP are multiple and of varying power. They include anatomical and functional size of the vascular bed, cardiac output, sympathetic nervous activity and its modulation through baroreceptor regulation mechanisms, vasoconstriction activated by a number of different hormones, and dietary factors [Chasis 1986].

Total resistance is the sum of vascular resistance plus pressure decrease due to hydrostatic pressure, thus total resistance = vascular resistance + "hydrostatic resistance". This "hydrostatic resistance" would refer to the distance between heart and brain. In taller people, a higher BP is therefore needed to achieve the same brain blood flow, a constant brain vascular resistance given.

Vascular resistance comprises the components "viscosity resistance" and "tubular resistance". Tubular resistance (or tubular pressure decrease) is composed of the "length resistance" and the "diameter resistance". Tubular resistance is directly proportional to the length of a tube, given a constant diameter (Poiseuille). A higher pressure is therefore needed to maintain a constant flow as the length of a blood vessel increases, given a constant diameter. In taller people, a greater tubular resistance would be expected according to the greater total length of their blood vessels. This difference would be somewhat proportional to height. The suggestion that some increase of BP is a haemodynamic necessity for achieving a certain (brain) tissue flow as height increases becomes obvious.

The most powerful determinant of vascular resistance, however, is the vascular diameter, thus vasoconstriction, since the diameter enters the Poisson formula as a factor: $\{1 \div (\text{diameter to the power of } 4)\}$. Vasoconstriction is the overriding determinant of the great **intra**-individual BP level variance.

Teologically speaking, if the ultimate aim of the pressure/resistance-ratio is adequate tissue flow (i.e. $\text{Flow} = P \div R$) then increased resistance due to naturally greater body size must be compensated by greater BP levels. Vasodilation/-constriction is designed for **intra**-individual adaptations and not to compensate for **inter**-individual differences of peripheral resistance due to different body size, since this would compromise the range of the **intra**-individual adaptation.

However, BP level correlate not only with height, but with weight, as has been mentioned, and with various ponderosity indices as well [Clarke 1986]. Weight, height, and BMI all show a good to very good **intra**-individual correlation (tracking) over two and even a moderate to good correlation over 10 years. Changes in ponderosity are associated with changes in BP (as measured by changes in percentile) in either direction, and the BP changes are not dependent on initial BP levels [Clarke 1986]. In this respect weight is a stronger determinant of BP than height, the initial weight percentile and trends of moving to another percentile over time being more closely related to level and trend of BP than can be found for height [Lauer 1984]. It is also interesting to note that the strong correlation between ponderosity and BP level is even better in young ages than in older age groups and adults [Voors 1977]. This may be explained by a dilution effect in older ages since non-anthropometric components of BP variation, supposedly, become increasingly important (see also "horse-racing"). VOORS et al themselves

observe that "only well after adult stature has been attained are there new increases in BP levels independent of height and presumably related to a different set of causes." [Voors 1977].

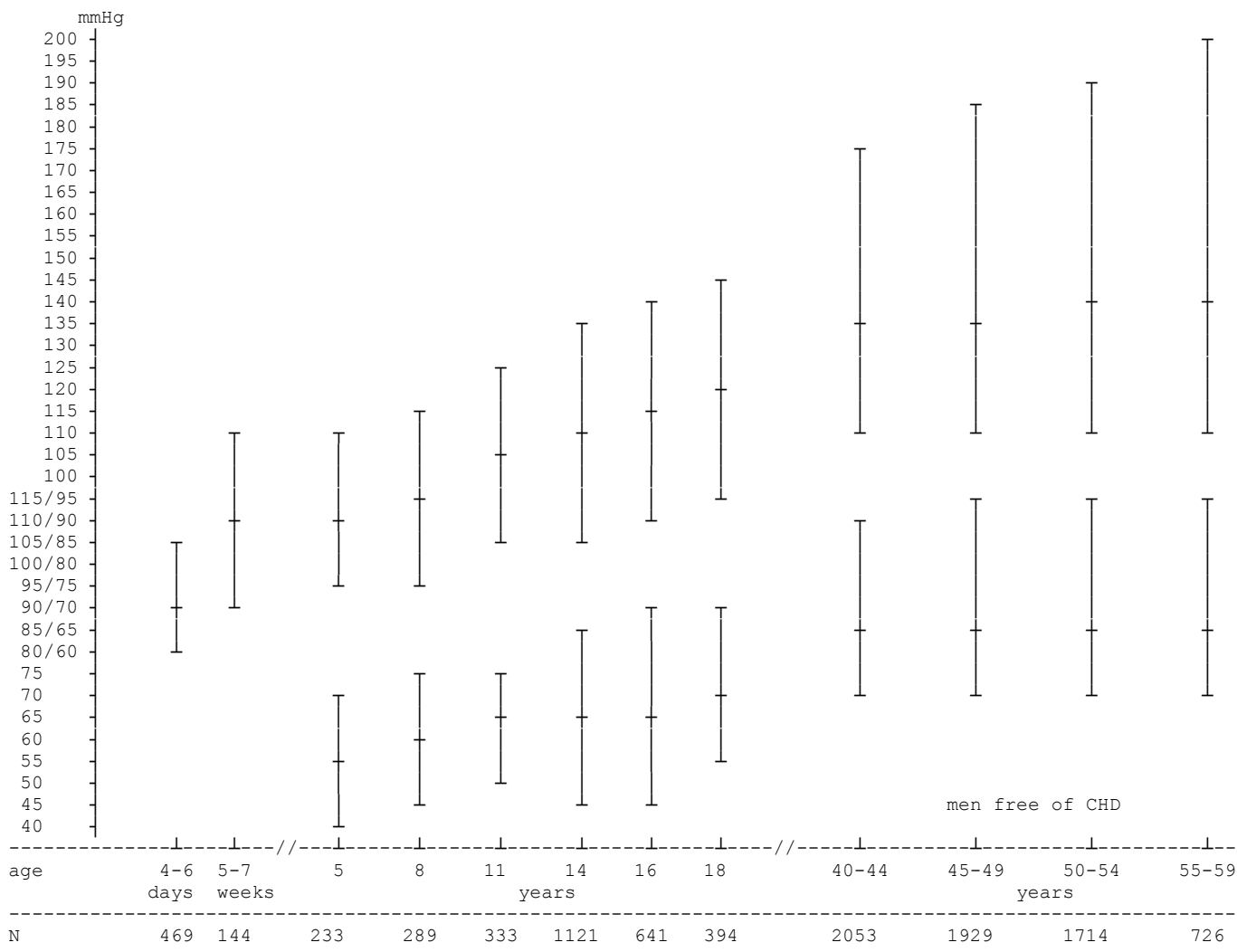
BIOLOGISCHE NORMVERTEILUNG: "BLUTDRUCK-WACHSTUMSKURVEN"

As a consequence, BP variation in children may be first of all a normal and non-pathological expression on biologic normal distribution, which is related to the size of the body. It has been suggested, therefore, that tall (and heavy) children have higher BP levels than smaller children at similar age, and that this dependence of BP on body size should be taken into consideration when assessing the clinical significance of a high BP [Voors 1977].

There are no reasons, however, why the same should not apply for adults. In fact, once growth is completed, mean BP in various age groups indeed stays relatively stable in subjects free of cardiovascular disease, but shows the same magnitude of variability between individuals.

This can be tentatively shown in the following figure:

Figure: Variation of BP at Different Age; Mean and "95%-Range". Children and Adolescents of Both Sexes (≥ 14 years) and Adults of Male Sex; Whites. Source: [DeSwiet 1976], [Frerichs 1979], [Baron 1986], [Pooling Project 1978]



It becomes evident that the conceptual understanding of the biology of "normal" blood pressure could somehow be similar to our understanding of normal growth in terms of height and weight.

Specially the concept of normal weight lends itself as a paradigm how the biology of normal blood pressure could be understood. A high weight can either mean normal weight in a tall person or overweight in a smaller person, and it would be inappropriate to define overweight on the basis of the weight alone. Moreover, in assessing the nutritional status in children it seems to be more appropriate to measure deviations of a child's individual normal weight track (like with the growth chart type "Morley") than to measure the weight percentile of a child at one point in time (like with the growth chart type "Gomez"). What really matters, is how steep the growth curve of a child is and not its absolute weight. Eventually, if the weight of any person exceeds a high value, say, one hundred kilograms, abnormal weight is almost certain, although in a few very tall and muscular it still could be normal.

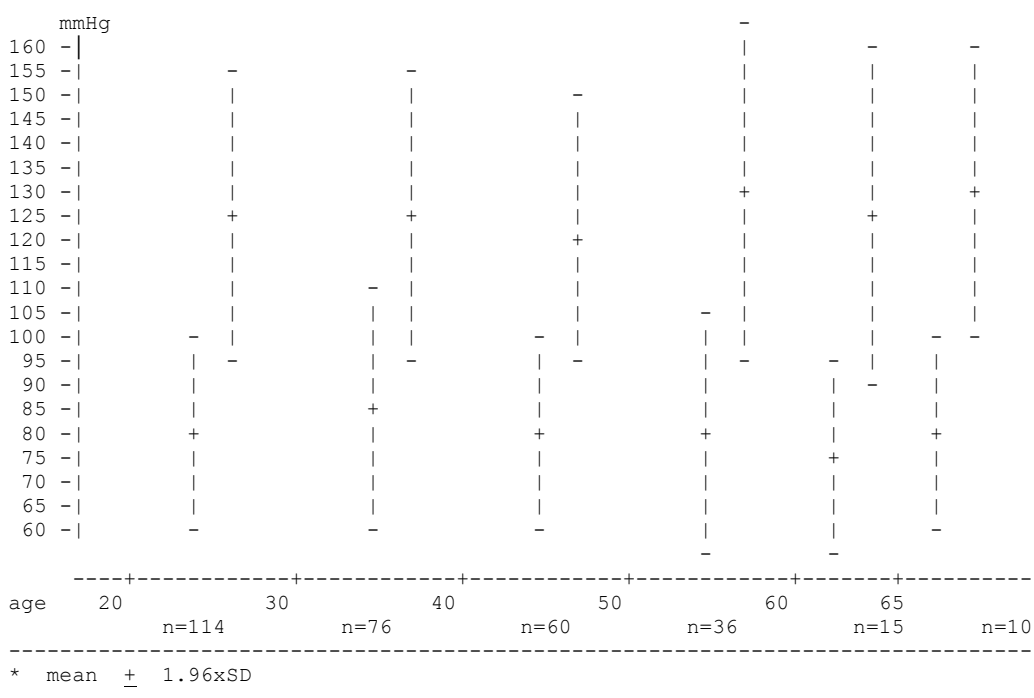
BLUTDRUCK-VERTEILUNGSKURVEN IN "NICHT-ZIVILISIERTEN" POPULATIONEN UND DIE FORM VON BLUTDRUCK-VEREITEILUNGSKURVEN

In order to understand and examine the variability of

biologically normal blood pressure, eventually, is most revealing to study BP distributions in non-industrialised populations where CHD is very uncommon or virtually absent. In many of these populations in the Pacific [Prior 1974], in Africa [Shaper 1967, Epstein 1967], or in South-America [Makela 1978], BP does not appreciably increase with age during adulthood, once growth is completed.

The following figure shows the BP distribution in a Indian population with a low CHD incidence and in which hypertension is "rare" (no exact figures are given) [Sievers 1966]. These people live a traditional life-style, characterized by living in widely scattered camps, consisting of an extended family, usually matrilocal in nature [DeStefano 1979]:

Figure: BP Distribution (Mean and "95%-Range" *) of Men in CHD-free Tribal Population: Navajo Indian Reservation. [DeStefano 1979]



It can be seen that BP does not increase with age. It is obvious at the same time, that BP in this CHD-free population is distributed over a wide range, reaching well into ranges currently defined hypertensive. Data about BP distribution in Kenyan nomads [Rose 1985] confirm that "healthy" systolic BP levels may range from about 60 to 160 mmHg (95% interval: 89-145 mmHg) of the population.

It is evident that a wide range of BP values, reaching into currently defined hypertensive levels, is a "natural" feature which can be observed in CHD-free populations.

The shape of BP distributions is little reported in the published data. Nonetheless, from a few papers the following statistical peculiarity is apparent:

"Healthy" populations (in terms of absence CHD) show a symmetrical unimodal normal distribution of BP with mean, median (= 50th percentile), and middle being basically identical (e.g. Kenyan Nomads [Rose 1985] (see figure below), boys of age 7 to 11 years in Zurich/Switzerland [Leumann 1981], or infants in London [DeSwiet 1976]) whereas "sick" populations show an asymmetrical unimodal BP distribution with a positive skewness, i.e. the middle is above the mean and the upper end of the distribution shows a longer tail (e.g. civil servants in London [Rose 1985], or U.S. adult population (National Health Survey) [McFate Smith 1977], Pooling Project [Pooling Project 1978]).

It is possible, therefore, that the degree of skewness of a population BP distribution shows a relationship to the degree of mean BP rise with age (i.e. the slope of this rise). A very comprehensive review on geographical differences in BP distribution by EPSTEIN and ECKOFF, however, does not address this question [Epstein 1967].

The following figure shows the distribution of systolic BP in Kenyan nomads:

Figure: Systolic BP Distribution in Kenyan Nomads *, Fitting a (Symmetrical) Mathematical Normal Distribution With Mean=117 mmHg and SD=14 mmHg

Observed BP in Kenyan nomads

- 69	.3	
70 - 79	.5	#
80 - 89	2.3	##
90 - 99	8.5	#####
100 - 109	20	#####
110 - 119	27.5	#####
120 - 129	23	#####
130 - 139	12.5	#####
140 - 149	4.3	####
150 -	1.1	#
	100 %	MEAN = 117, MEDIAN = 117, MIDDLE = 117 2.5th PERCENTILE = 89 97.5th PERCENTILE = 145 SKEWNESS = 0

Corresponding Gaussian distribution defined by mean=116.8 and SD=14.2

- 80	.4	
80 - 90	2.5	##
90 - 100	8.9	#####
100 - 110	19.8	#####
110 - 120	27.3	#####
120 - 130	23.5	#####
130 - 140	12.5	#####
140 - 150	4.1	####
150 - 160	.9	#
160 -	.1	
	100 %	MEAN, MEDIAN, MIDDLE = 117 2.5th PERCENTILE = 89 97.5th PERCENTILE = 145

 * in mmHg

Approximate, adapted from figure displayed in [Rose 1985]
 The mean is indirectly calculated as the sum of all products of the middle of a column multiplied by its proportion of subjects.

It can be seen that the shape of the frequency distribution is completely normal in mathematical terms. Moreover, the range

is defined by a standard deviation of about 14 mmHg, thus 95% of all BP levels are within a range of some 50-60 mmHg (= 97.5th - 2.5th percentile or 4 x SD).

In a CHD-prone population, such as American males, the BP distribution has a different shape. This is illustrated by the data from the Pooling Project [Pooling Project 1978].

Figure: Skewing of Population BP Distribution at Different Adult Age, U.S. Males. Systolic BP. (Source: [Pooling Project 1978])

Men Age 40-44 (n = 2167)			Men Age 45-49 (n = 2130)		
- 99	.2		.4		
100 - 109	3.3	###	3.6	###	
110 - 119	14.5	#####	12.2	#####	
120 - 129	24.6	#####	22.5	#####	
130 - 139	24.7	#####	22.2	#####	
140 - 149	16.9	#####	17.1	#####	
150 - 159	7.0	#####	9.2	#####	
160 - 169	4.7	#####	6.3	#####	
170 - 179	2.3	##	3.1	###	
180 - 189	1.1	#	1.4	#	
190 - 299	.2		1.0	#	
200 -	.6		1.0	#	
100 %			100 %		
	MEAN = 135, MEDIAN = 133, MIDDLE = 142			MEAN = 138, MEDIAN = 135, MIDDLE = 146	
	++ P 2.5 = 109, P 79.5 = 176			P 2.5 = 108, P 97.5 = 185	
	+ SKEWNESS = 5.3 %, 95% RANGE = 67			SKEWNESS = 6.2 %, 95% RANGE = 77	
Men Age 50-54 (n = 1939)			Men Age 55-59 (n = 830)		
- 99	.4		.4		
100 - 109	2.9	###	1.8	##	
110 - 119	10.5	#####	10.1	#####	
120 - 129	19.3	#####	16.9	#####	
130 - 139	21.9	#####	20.7	#####	
140 - 149	17.0	#####	18.9	#####	
150 - 159	11.2	#####	11.7	#####	
160 - 169	7.3	#####	8.3	#####	
170 - 179	4.2	###	5.3	###	
180 - 189	2.4	##	2.1	##	
190 - 299	1.3	#	1.4	#	
200 -	1.7	#	2.4	#	
100 %			100 %		
	MEAN = 141, MEDIAN = 138, MIDDLE = 150			MEAN = 143, MEDIAN = 140, MIDDLE = 155	
	P 2.5 = 109, P 97.5 = 192			P 2.5 = 111, P 97.5 = 199	
	SKEWNESS = 6.7 %, 95% RANGE = 83			SKEWNESS = 8.2 %, 95% RANGE = 88	

+ Skewness is given as $(100\% \times [\text{middle} - \text{mean}] \div \text{mean})$ and is (i.e. middle-mean difference) significantly different from 0 in all age groups (paired t-test: $p < .001$). The increase of skewness with age (i.e. increasing middle-mean difference), is highly significant, too (ANOVA: $p < .001$).

++ 2.5th and 97.5th percentiles. Percentiles are calculated by determining their column and then their relative point within a column (linear approximation for median, logarithmic fit for other percentiles).

The skewness of the BP distribution in this population is well apparent. Moreover, the skewness is increasing with age as indicated by the increasing deviation of the distribution mid-point from the mean. Analysis of variance (ANOVA), comparing each middle - mean differences by using the standard deviation of the BP distribution in each age group, leaves no doubt about the significance of this phenomenon which is suggested by other studies as well (National Health Survey, distribution graphs displayed in [McFate Smith 1977]).

This increasing skewness also corresponds with an increase in the BP range as given by the "95% range" (97.5th percentile -

2.5th percentile). Whereas the systolic BP range for 95% of the Kenyan nomads is only about 55 mmHg it is 1.2 times larger in 40 year old and 1.6 times larger in 60 year old American males. At the same time, the lower end of the distributions, as indicated by the 2.5th percentiles, changes very little with an increase of only about 3 mmHg in 15 years. This indicates that only a section of the population, and not everybody, is contributing to the average BP rise with age in western societies.

Diastolic BP shows similar features, albeit with a less pronounced increase of distribution skewness with increasing age.

Theoretically, a Gaussian normal distribution represents a continuous probability distribution, thus a probability distribution of a continuous random variable (such as BP). Variation causing effects, be it a single effect or a set of effects, must operate at random in the entire population (and not only in a sub-population). Such effects, for example, can be measurement errors or random "natural" biological effects which determine individual BP deviations from a population mean (perhaps "natural" variations of the anatomy of the vascular bed and of body size which determines variations in peripheral resistance and thus BP variation).

The appearance of a normal (or in some instances log-normal) distribution of most, if not all, physiological and anatomical parameters in healthy people is indeed a universal phenomenon. Examples are the distribution of height, head circumference, hemoglobin etc. . This observation does not allow a great deal of biological inference and it can not be concluded that a statistical normal BP distribution necessarily indicates a biologically normal distribution. For example, an adverse environmental effect may quite generally affect a whole population and if everybody is exposed to this effect the resulting distribution would still be Gaussian, but with a different mean. Nevertheless, it appears that a Gaussian normal (or log-normal) distribution is a necessary, but not sufficient, condition for biological normalcy of a population distribution. A skewed distribution is resulting if components, causing variation, are only distributed in a sub-set of the population. Such components, presumably, are not biologically normal since they are not universal. Skewing of a distribution may therefore indicate that (pathological) effects on BP levels in only a part of the population are in operation.

Applying the above considerations, the shape of the BP distribution in Kenyan nomads indicates that there is no suggestion of a pathological factor determining BP variation in a subset. Together with the virtual absence of (premature) cardiovascular disease this may well mean that the above BP distribution over the whole range is in fact "natural" without bearing any pathological components.

BLUTDRUCK-GRENZWERT:

KEINE UNTERSCHIEDUNG VON "NORMAL" UND "PATHOLOGISCH" MÖGLICH

Ideally, a test or cut-off point should be able to distinguish healthy from sick individuals und thus the healthy from the sick sub-population. Many tests achieve this to a great extent, because the test values in sick individuals are well apart from the values in healthy individuals. For example, liver cell enzymes are far exceeding normal plasma values in case of liver cell damage. The liver enzyme distribution in a mixed population of healthy persons and cirrhotic patients shows a very distinct bimodal shape and there is hardly any overlapping between the two sub-populations.

However, this is quite different for the distribution of BP and cholesterol. As shown earlier, using the initial cholesterol or BP levels to separate the sub-population with subsequent CHD is quite impossible (low positive predictive value, low sensitivity and specificity). At a cut-off level of 140 mmHg, for example, we arrive at a sensitivity of little more than 50 percent and yet a specificity of only some 60 percent. With a higher cut-off level we can increase the specificity but at the

cost of an even lower sensitivity, e.g. 93 percent specificity and 16 percent sensitivity if a cut-off level of 170 mmHg is used. But even with this very low sensitivity in the prediction of CHD the positive predictive value is just 22 percent. This means that, even if we choose the 16 percent of the population most at risk (as with a cut-off point of 170 mmHg), less than a fourth will actually develop CHD in the next 12 years.

This clearly illustrates again the formidable dilemma in using risk factor levels as a diagnostic guide other than in terms of a community diagnosis (i.e. the "sick population" approach [Rose 1985]). Simply termed, the dilemma is rooted in the huge overlapping with regards to the BP levels of the "healthy" and "sick sub-population".

This is the basis for the observation that the shape of the overall BP distribution is distinctly unimodal (however skewed) without any revelation of two distinct sub-populations. "Hypertensive" BP levels can therefore only be arbitrarily defined as pointed out by PICKERING, all attempts by PLATT to eke out a bimodality in the BP distribution failed [Epstein 1983]. PICKERING's suggestion that hypertension (as a disease and a risk for disease) is merely the upper end of a biological continuum has become the currently accepted view, but may not be the end of the story.

**MATHEMATIK DES STATISTISCHEN ZUSAMMENHANGS
ZWISCHEN BLUTDRUCK UND INFARKT-HÄUFIGKEIT**

Blutdruck- und entsprechende Risikoverteilungen können mathematisch auch auf eine neue Weise formuliert werden:

Figure: Study of Effect of BP Increase in Various Proportions of Population on Skewness* of Frequency Distribution

Baseline (approximate "norm" in CHD-free population) (Gaussian normal distribution defined by mean = 120 and SD = 14)

70-80	.2	
80-90	1.4	#
90-100	6.1	#####
100-110	16.1	#####
110-120	26.2	#####
120-130	26.2	#####
130-140	16.1	#####
140-150	6.1	#####
150-160	1.4	#
160-170	.2	
100 %	MEAN = 120	SD = 14
	2.5th PERCENTILE = 92.6,	97.5th PERCENTILE = 147.4, 95% RANGE = 54.9

* Skewness given as: 100% x (middle-mean) ÷ mean

Figure continued next page ...

Figure: Effect of BP Increase on Skewness of Frequency Distribution - continued

		1) new distribution (graphically uniform)	2) sub-population without increase	3) sub-population with increase	4) new distribution (graphically distinct)
after 30 units increase in 10 % of population					
70-80	.2				.0016
80-90	1.3	#	#		.00706 #
90-100	5.5	#####	#####		.0309 #####
100-110	14.5	#####	#####		.135 #####
110-120	23.8	#####	#####		.585 #####
120-130	24.2	#####	#####		2.5 #####
130-140	16.1	#####	#####		10 #####
140-150	8.1	#####	#####		32.5 #####
150-160	3.9	####	#		67.6 #
160-170	1.8	##			89.9
170-180	.6	#			97.6
180-190	.1				100
100 % new MEAN = 123, MEDIAN = 122, MIDDLE = 126.6					% increasers
SKEWNESS = 2.9 %					
2.5th PERCENTILE = 93.1, 97.5th PERCENTILE = 160, 95% RANGE = 67.0					
after 30 units increase in 20 % of population					
70-80	.2				.00359
80-90	1.1	#	#		.0159 #
90-100	4.8	#####	#####		.0696 #####
100-110	12.9	#####	#####		.304 #####
110-120	21.3	#####	#####		1.31 #####
120-130	22.2	#####	#####		5.45 #####
130-140	16.1	#####	#####		20 #####
140-150	10.1	#####	#####		52 #####
150-160	6.4	#####	#		82.5 #
160-170	3.4	###			95.2
170-180	1.2	#			99.2
180-190	.3				100
100 % new MEAN = 126, MEDIAN = 124.4, MIDDLE = 129.8					% increasers
SKEWNESS = 3 %					
2.5th PERCENTILE = 93.9, 97.5th PERCENTILE = 165.7, 95% RANGE = 71.8					
after 30 units increase in 30 % of population					
70-80	.1				.00617
80-90	1	#	#		.0272 #
90-100	4.2	####	####		.119 #####
100-110	11.3	#####	#####		.52 #####
110-120	18.8	#####	#####		2.22 #####
120-130	20.2	#####	#####		8.99 #####
130-140	16.1	#####	#####		30 #####
140-150	12.1	#####	####		65.1 ###
150-160	8.9	#####	#		89 #
160-170	5	#####			97.2
170-180	1.8	##			99.2
180-190	.4				99.9
190-200	.1				100
100 % new MEAN = 129, MEDIAN = 127.2, MIDDLE = 132.1					% increasers
SKEWNESS = 2.4 %					
2.5th PERCENTILE = 94.9, 97.5th PERCENTILE = 169.4, 95% RANGE = 74.5					
after 30 units increase in 40 % of population					
70-80	.1				.00955
80-90	.8	#	#		.0422 #
90-100	3.6	####	####		.185 #####
100-110	9.7	#####	#####		.805 #####
110-120	16.3	#####	#####		3.42 #####
120-130	18.2	#####	#####		13.3 #####
130-140	16.1	#####	#####		40 #####
140-150	14.1	#####	####		74.5 #####
150-160	11.3	#####	#		92.9 #
160-170	6.6	#####	#		98.1 #
170-180	2.4	##			99.6
180-190	.6	#			100
190-200	.1				100
100 % new MEAN = 132, MEDIAN = 130.7, MIDDLE = 133.5					% increasers
SKEWNESS = 1.1 %					
2.5th PERCENTILE = 96.1, 97.5th PERCENTILE = 170.9, 95% RANGE = 74.8					

Skewness given as: 100% x (middle-mean) ÷ mean
 Figure continued next page ...

Figure: Effect of BP Increase on Skewness of Frequency Distribution - continued

	1) new distribution (graphically uniform)	2) sub-population without increase	3) sub-population with increase	4) new distribution (graphically distinct)
after 30 units increase in 50 % of population				
70-80	.1			.0144
80-90	.7 #	#		.0633 #
90-100	3 ###	###		.278 ###
100-110	8.2 #####	#####		1.2 #####
110-120	13.8 #####	#####		5.05 #####
120-130	16.1 #####	#####		18.8 #####
130-140	16.1 #####	#####		50 #####
140-150	16.1 #####	###		81.5 #####
150-160	13.8 #####	#		95.1 #
160-170	8.2 #####			98.7
170-180	3 ###			99.8
180-190	.7 #			100
190-200	.1			100
100 % new MEAN = 135, MEDIAN = 135, MIDDLE = 135				
SKEWNESS = 0 %				
2.5th PERCENTILE = 97.5,				
97.5th PERCENTILE = 172.5,				
95% RANGE = 75.0				
for comparison:				
Gaussian distribution =>				
with identical				
95% limits				
			70-80 .2	
			80-90 .7 #	
			90-100 2.4 ##	
			100-110 6.2 #####	
			110-120 12.1 #####	
			120-130 18 #####	
			130-140 20.6 #####	
			140-150 18 #####	
			150-160 12.1 #####	
			160-170 6.2 #####	
			170-180 2.4 ##	
			180-190 .7 #	
			190-200 .2	
				MEAN = 135, SD = 19.12
				2.5th PERCENTILE = 97.5,
				97.5th PERCENTILE = 172.5
after 30 units increase in 75 % of population				
80-90	.3			.19
90-100	1.5 ##	##		.826 ##
100-110	4.2 ###	###		3.52 ###
110-120	7.6 #####	#####		13.7 #####
120-130	11.1 #####	#####		40.9 #####
130-140	16.1 #####	###		75 #####
140-150	21.2 #####	#		92.9 #
150-160	20 #####			98.4
160-170	12.1 #####			99.8
170-180	4.5 #####			99.9
180-190	1 #			100
190-200	.1			100
100 % new MEAN = 142.5, MEDIAN = 144.3, MIDDLE = 138.9				
SKEWNESS = -2.5 %				
2.5th PERCENTILE = 102.2, 97.5th PERCENTILE = 175.7, 95% RANGE = 73.4				
% increasers				
after 30 units increase in 100 % of population				
100-110	.2			100
110-120	1.4 #			100
120-130	6.1 #####			100
130-140	16.1 #####			100
140-150	26.2 #####			100
150-160	26.2 #####			100
160-170	16.1 #####			100
170-180	6.1 #####			100
180-190	1.4 #			100
190-200	.2			100
100 % MEAN = 150, MEDIAN = 150, MIDDLE = 150				
SKEWNESS = 0 %				
2.5th PERCENTILE = 122.4, 97.5th PERCENTILE = 177.6, 95% RANGE = 55.2 *				
(* The difference of 54.9 - 55.2 as compared to the baseline distribution is due to minimal errors in the calculation procedure)				

Skewness given as: 100% x (middle-mean) ÷ mean				

This figure shows how, theoretically, a skewed unimodal frequency distribution may be the composite of two "hidden" separate distributions. With the assumption of a "natural" normal

distribution one can define a "sick sub-population" as those with BP rises beyond that "natural" level. It is further assumed that these increasers are to be evenly distributed over the entire "natural" range of BP levels.

It appears that, depending on the proportion of the population contributing to major BP increases beyond a hypothetical baseline distribution, skewness of the resulting new hypothetical distribution is affected in different ways. It can be seen that only changes in a sub-population smaller than 50 percent lead to a positive skewness whereas increases in exactly 50 percent do flatten the curve without a skewing effect. Increases in more than 50 percent, on the other hand, lead to a negative skewness.

At the same time it is apparent that the proportion of increasers within the strata of the new resulting distribution is steadily increasing (in an exponential fashion) with increasing BP levels. However, over the entire overlapping zone, we find within each stratum individuals belonging either to the increasers (hypothetical "sick sub-population") or to the sub-population maintaining its initial "natural" levels (the hypothetical "healthy sub-population").

EINE NEUE HYPERTONIE-DEFINITION

Now, theoretically, the gate has been opened to a revision of the current risk factor model and the historical PLATT-PICKERING controversy can be re-opened. This will, however, rather be a revision of PICKERING's view than a step back to PLATT's single gene theory.

PLATT proposed that the BP distribution is in fact bimodal, where the skewing towards the upper range of BP levels may be accounted for by a separable population with an inherited condition of high BP. He maintained that this condition could be determined by one single gene (quoted from: [McFate Smith 1977] and [Epstein 1967]).

PICKERING pointed out that hypertension as a disease is only the upper end of a biologic continuum whose causes are multifactorial. He observed that no dividing line can be drawn between a normotensive and a hypertensive subset, and appreciated the fact that every increment of a population BP level is associated with an increase of CHD (and stroke) incidence, no "normal" BP level protecting from later cardiovascular disease. He stated very categorically that 'normotension and hypertension are not merely meaningless concepts, they are wrong.' Further, 'the quantitative relationship between arterial pressure and its consequences is the chief evidence for the hypothesis that essential hypertension represents a kind of disease hitherto unrecognized by medicine, a disease in which the deviation from the norm is one of degree, not of kind, a quantitative rather than a qualitative disease' [Pickering 1972].

PLATT was wrong. On the basis of BP levels alone no distinct dividing line can be drawn between "sick" and "healthy". PICKERING's great historical contribution was to lead the prevalent thinking away from monocausal etiological theories towards multifactorial theories. On the basis of BP level alone, no individual prediction whether future disease really will occur or not can in fact be made, as clearly shown by the specificity and sensitivity of BP level as a disease predictor. Therefore, even with BP level being a clear risk factor for later disease, it is only the interaction of BP level with other factors which determines the actual outcome, hence the strong suggestion of multiple factors determining BP level and disease consequences. The fact that the factor in question is neither necessary nor sufficient for the development of later disease makes it a "contributory" factor within a set of other (known, or rather unknown) factors [Susser 1975].

PICKERING's concept ignores the universal biological phenomenon of "normal distributions" as on [as been introduced above. Further, associations between risk factors and disease found on a population level cannot be so readily translated to the individual level. The association between BP level and CHD is, naturally, based on comparisons of population groups and not

of individuals since group comparison is the essence of any biological research. This association is so strongly confirmed with a wealth of data. However, a very solidly proven association, the possibility of a confounding bias always exists. This is to say that the association between BP level and CHD may be spurious and not a direct one. For example, an unknown factor may cause both, BP increase and, in an unrelated pathway, CHD. BP increase is then an epiphenomenon of a disease process causing disease by other mechanisms than high BP.

The confounding bias to be considered here, however, is within the variable BP, a confounding effect which is, to my knowledge, unconsidered in literature. I introduce it as the "biographical fallacy". It means that the individual history of a variable may confound the association between the level of a variable and disease. It may therefore be fallacious to conclude that the (amount of) level of a variable is associated to disease, where in fact it may be the amount of level change in an individual's history. The above mathematical studies of hypothetical population distribution dynamics have revealed this theoretical possibility. This was ignored by PICKERING.

The simple fact that BP levels are normally distributed over a wide range in CHD-free population (Kenyan nomads) is powerfully contradicting the theory that hypertension is merely a quantitative disease, the higher the BP the more "sickness". Although it is true in "sick populations", this is not the case in "healthy populations" and the theory fails to achieve universality. This was ignored in the current concept.

In the light of the alternative mathematical modelling of the association between BP levels and CHD, this contradiction can be solved and a new definition of hypertension emerges.

Hypertension may be defined as: A BP increase beyond a given initial normal value during an individual's biography, while the individual "baseline" value is subject to wide "natural" variation.

The proposed new modelling of BP variation is summarized in the following table:

Table: Components of BP Variation, A New Model as Compared to the Current Concept

	Proposed new model	Current Model
Normal individual level (baseline)	natural variation over a wide range (ca. systolic 75-165 mmHg)	one normal level (arbitrarily defined)
Hypertensive component	BP level above individual baseline	BP above set arbitrary level (usually above 140/90 mmHg)

A systolic BP of 130 mmHg, for example, could mean a hypertensive component of 30 in an individual with a baseline value of 100, but 0 in an individual with a baseline value of 130. "Hypertensive" values of systolic 160-170 mmHg may represent a pure normal component in a few people, but a composite of a lower normal baseline and a hypertensive component in most people with such high values.

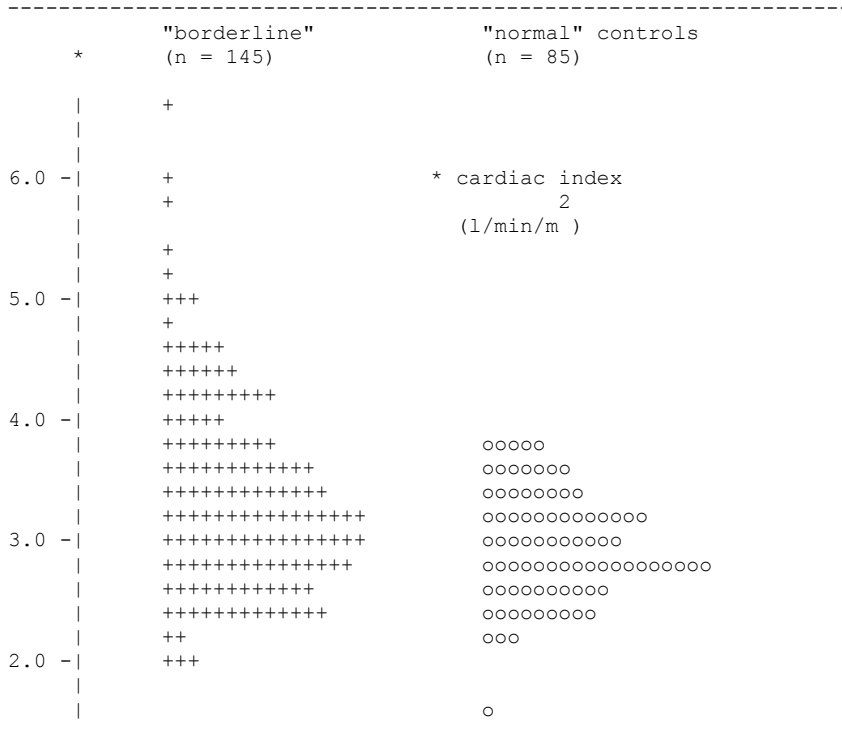
**VERTEILUNG VON (PATHO-)PHYSIOLOGISCHEN "MARKERN"
IN VERSCHIEDENEN BLUTDRUCK-STRATA**

The second line of research which can enlighten the nature of normal blood pressure and hypertension, eventually, are findings about the heterogeneity of persons with identical BP levels. Possibly, similar differentiations in relation to cholesterol levels are possible. Variables to classify "normotensives" and "hypertensives" into different subgroups are found in various disciplines of research.

According to the model, we expect with every BP level increment a rising proportion of "significant increasers" (however this eventually will be defined). It is therefore to be expected, that in researching "hypertension", subjects with pathophysiological features of hypertensives as well as normal parameters in this group will be found. Further, in the group of "normotensives", some increasers, albeit in an increasingly low proportion, have to be expected as well. If we hypothesize that increase may be associated with pathophysiological changes we would expect a "hypertensive pathophysiology" in some normotensive subjects as well.

The distribution of hemodynamic patterns in different BP strata is one example. Cardiac output, on the average, is abnormally increased in "borderline hypertensives", as compared to "normotensives" [Julius 1977]. However, most of the borderline subjects are within the supposed normal range and only a minority accounts for the increase. The distribution is distinctly skewed. The distribution in the "normotensive" subjects is more symmetrical, but some little skewing is apparent, as shown in the following figure:

Figure: Distribution of Cardiac Index (Measure of Cardiac Output) in "Borderline Hypertensives" and "Normotensives" [Julius 1977]



Further, from two large treatment studies we know that only a minority of untreated mild hypertensives experiences a continuous increase of blood pressure levels, and that well half of "mild hypertensives" will show a spontaneous decline of BP reaching again normotensive levels over a period of a few years. And only those people with a sustained or progressive hypertension had some benefit from treatment. However, subjects exceeding mild hypertension limits do not differ in baseline characteristics such as sex, age, and cholesterol, but a family history of hypertension was more frequent in this group (p = 0.04, one-sided) [Management Committee 1982].

Fluctuations in plasma renin activities in both clinical and experimental hypertension has for a long time led to the conclusion that this hormone has no physiological role in essential hypertension. Today, however, it is widely believed that the variation in renin activity indicates different physiological subsets of hypertension [Laragh 1986]. With the new model

in mind, one could hypothesise, that differences in renin activity may actually distinguish "true hypertension" from "false positive hypertension".

From limited data, "low-renin" hypertensives appear to have a distinctly better prognosis than "high-renin" hypertensives [Brunner 1972]. (In the study in question, however, the inception cohort on which these observations are based was poorly defined.)

Within hypertensives, there appears to be a subgroup with high plasma catecholamine levels and hemodynamic changes related to increased sympathetic activity, and these differences within hypertensives appear more pronounced than differences between hyper- and normotensives. Although this data are cross-sectional and time sequence of cause and effect is therefore obscure, it is interesting to note that a sub-classification into "high-noradrenaline" and "low-noradrenaline" subjects can in fact be made among hypertensives as well as in normotensives [Kopin 1981].

Preliminary data from a small study show the following distribution pattern of "high-noradrenaline" subjects in different BP strata:

Table: Distribution of "high-noradrenaline" status (defined as values above mean+1*SD) [DeChamplain 1981]

Group/Stratum	N	"high-noradrenaline"
Normotensives (1)	35	14.3 %
Labile Hypertensives (2)	40	37.5 %
Sustained Hypertensives (3)	27	29.6 %
2) vs.1): p=.03 [2)+3)] vs.1): p=.01 3) vs.1): NS		

The Framingham Heart and Eye Studies [Sperduto 1986] show a significant association between retinopathy (age-adjusted) and hypertension (> 160/95 mmHg). This association is dose-dependent, the proportion of retinopathy being higher in moderate/severe hypertensives than in mild hypertensives.

The morphologic changes of the retina that are associated with hypertension show a wide variety of features, and different classifications exist. In many cases the signs of arteriosclerosis are present in the absence of hypertension. Also, retinal findings are often absent in mild hypertension, and arterial narrowing is not present unless the diastolic pressure is over 110 mmHg [Matas 1977, Van Buchem 1964].

These are only a few data to underly on one hand the heterogeneity of "normotensives", "borderline" and "mild hypertensives", and on the other hand similarities between these groups. In some instances, the prognosis might be determined in a much stronger way by these markers than by the BP level as such. A subset of mild to moderate hypertensives can be more similar to a subset of normotensives if we look at presumably pathological patterns which themselves may be related to a progressive hypertensive development.

In this context, it is interesting to note that in the Framingham study, the prediction of cardiovascular disease as measured by the regression coefficient is identical, whether the lowest, highest, or mean of three office measurements is used [Kannel 1980].

DISKUSSION

Die heute als gültig betrachtete Theorie, dass die Blutdruck-Höhe als solche einen Risikofaktor darstelle, und dass jeder höhere Wert im Vergleich zweier Individuen auch ein erhöhtes Krankheits-Risiko bedeute, hat nicht alle Erklärungsmöglichkeiten des statistischen Zusammenhangs zwischen Erkrankungs-Häufigkeit und Blutdruck-Höhe ausgeschöpft. Die eher spekulative als bewiesene Auffassung, dass die physikalische Eigenschaft des Blutdruckes, sogenannte Scherkräfte, eine direkte Ursache von Arterienwand-Schädigungen sei, hat wohl immer wieder zu stark die Denkmöglichkeiten der Risikofaktoren-Modellierung eingeengt.

Aufgrund des bisher gesichteten vielfältigen Materials kann nämlich festgestellt werden, dass grössere Blutdruck-Streuungen

schon in der Kindheit zum normalen biologischen Wachstum gehören, und dass dementsprechend auch in der Erwachsenen-Population von einer breiten "normalen Basis-Streuung" ausgegangen werden kann. Diese natürliche breite Streuung scheint durch Körpermasse mitbestimmt zu sein. In "nicht-zivilisierten" Gesellschaften besteht ein Zusammenhang zwischen Blutdruckhöhe und Infarkthäufigkeit nicht, obwohl auch in diesen Gesellschaften eine breite Blutdruck-Streubreite und "hypertensive" Blutdruckwerte vorkommen.

On a theoretical level, the here proposed model constitutes a more powerful theory than the current risk factor concept. It is able to explain all major features of the risk factor disease association, such as the (exponential) "dose-response" association, it does not fail to incorporate the concept of a normal baseline distribution, and is not refuted by the fact that "healthy" populations, though having varying BP levels over a wide range, do not show a dose-dependent relationship between risk factor level and disease, by virtue of the absence of the disease.

"Puzzling" phenomena can now be explained: Based on this model one would expect the phenomenon of "horse-racing" in adults, but not in children (see there). At around age 20 BP distribution is Gaussian in shape revealing little "increaser movements". Most "high" BP levels are probably still biologically normal in nature, an expression of "natural" variation. Youngsters in the upper part of the distribution, in this model, are just understood to follow their individual "natural" track and there is no reason why they should have steeper increases (i.e. "horse-racing"). With increasing age, however, as "increaser movements" start to happen, there will be an selection of increasers in the upper part of the distribution, hence the appearance of "horse-racing". However, individuals who naturally belong to upper percentiles would not be expected to "take part in the horse-race". PICKERING observed the existence of such individuals, but he classified it a rather puzzling exception [Pickering 1972].

However, a "nuisance" of this model is its difficult operationability. It is difficult enough to diagnose and research the moderately reliable variable BP level, measuring BP increase reliably will pose enormous difficulties and cannot be done at one point in time. Further, the hypothetical variable is not just the rate of increase but the increase beyond an individual's natural baseline value which we may call the "individual excess level" (imagine screening for hypertension, defined as the "individual excess level"). This difficulty is much more pronounced for currently defined "mild" to "moderate" hypertension. Above a certain high level, also the new model defines everybody as hypertensive.

A number of studies have actually researched the relationship between risk factor changes and subsequent disease, using data from the Framingham study and the Seven Countries Study [Farchi 1981, Woodbury 1981, Hofman 1983a]. All studies

found a significant independent relationship between the amount of BP change and subsequent disease if initial BP level was considered. However, there was no such independent association with the attained level taken into account. Based on the current theory that the actual level is harmful, the attained level, indeed, has to be considered [Hofman 1983b]. HOFMAN therefore concludes that it does not matter what change has taken place, but only what level has been attained.

However, as I have shown, the risk of the attained level can be confounded by the hypothetical increaser state, i.e. the "individual excess level". From the kind of statistical association one cannot conclude if the risk of BP change is confounded by BP level or if the risk of BP level is confounded by BP increase. Nevertheless, with the new model, some relationship of increase with subsequent disease, independent of the attained level, should be expected, since it assumes the "individual excess level" and thus the rate of change to be a better predictor than the attained level.

Approaches to defining the rate of change, however, are some kind of "fishing expeditions" and in fact the operational definitions of rate of risk factor change are all varying in the studies done so far. HOFMAN et al concede that their model might dilute a true relation between rise of BP and risk [Hofman 1983a]. HOFMAN et al use the median change in an initial observation period as the dividing line between "small increase" and "large increase". However, in view of this dilution a more distinct separation should perhaps be defined, e.g. by comparing the lower tercile with the upper tercile.

Moreover, these studies have all been done in men of age 45 to 75 and therefore fail to take into account increases earlier in the biography of these people. In fact, most of the increase in the mean systolic BP in the "Thousand Aviator Cohort" seemed to occur within some five years around the age of 30 with little mean changes before and after [Oberman 1967]. This suggests a failure of the above studies to pick up the important BP rises. In a large cohort of some 4000 initially young men of age 25 - 34 the variable rate of change was defined by the simple (age-adjusted) BP difference between two measurements 5 years apart [Rabkin 1979]. In most other studies the rate of change was defined as the slope of a linear regression on multiple individual measurements over time, sometimes adjusted for regression to the mean. The simple difference might best mirror the hypothetical "individual excess level" which conceptually is rather a difference ("excess level") and not so much the speed of the increase. In the 26-year follow-up of this study, a greater positive change in systolic BP was found in those developing CHD than in those remaining free of the disease.

Ob mit einem möglichen Risikofaktor Hypertonie, definiert als "individueller Exzess-Level", eine bessere Prädiktionskraft erzielt werden kann als mit der konventionellen Hypertonie-Definition bleibt vorläufig unbeantwortet. In einem Forschungsprojekt zum Herzinfarkt gilt es jedoch zu berücksichtigen, dass die Hypertonie im konventionellen Sinn in

zweifacher Hinsicht nur Epiphänomen-Charakter hat ohne ursächlicher Risikofaktor für den Herzinfarkt zu sein. Erstens hat keine der zahlreichen Interventionsstudien eine Herzinfarkt-Verringerung durch eine "Hypertonie"-Behandlung ergeben, sodass die Hypertonie wahrscheinlich nur ein erhöhtes Risiko anzeigt, ohne ursächlich an der Herzinfarkt-Pathogenese beteiligt zu sein. Zweitens ist es theoretisch wahrscheinlich, dass der Zusammenhang zwischen Blutdruck-Höhe und Infarkt-Häufigkeit durch den "echteren" Zusammenhang zwischen Blutdruck-Anstieg über den individuellen Ausgangswert hinaus und der Infarkt-Häufigkeit bestimmt wird.

An important (and exciting) feature of the new model is its re-emphasis of a persons/patients history. Therefore, life events, be it the development of obesity, the family history or the exposure to chronic "distress" situations, and their effect on BP changes can become an important focus.

An dieser Stelle wird der Bogen wieder geschlossen zur eingangs erfolgten Anknüpfung an die Herz-As-Studie. Es stellt sich insbesondere die Frage, wieweit eine "physiologische Biographie" im dargelegten Sinne wohl korreliert mit einer psychosozialen Biographie einer Infarkt-Karriere.

Daraus ergeben sich einige interessante Fragen, die ich gerne diskutieren möchte.

1) Besteht die Möglichkeit, im deskriptiven Teil der Herz-As-Studie (Kohortenstudie) die hypothetische neue Hypertonie-Definition zu testen ?

2) Wieweit sollten die der Herz-As-Studie zugrundeliegenden (hierarchischen) Modelle die hypothetische neue Hypertonie-Definition integrieren ? Insbesondere, könnte das "causal intervention model", welches die Hypercholesterinämie und die Hypertonie als intervenierende Variablen auffasst, nicht sinnvoll mit dem neuen Modell verfeinert werden ?

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