Virchows Archiv (1994) 424:307–314

ORIGINAL ARTICLE

Richard E. Tracy · Jaime L. Rios-Dalenz

Rarity of hypertensive stigmata in aging renocortical arteries of Bolivians

Received: 7 October 1993 / Accepted: 23 December 1993

Abstract Numerous reports have accumulated from around the world throughout the twentieth century of small, remote, self-sufficient populations that do not show a rise of blood pressure with age. Knowing that renocortical arteriosclerosis, a defining feature of hypertensive nephrosclerosis, is a close commensurate of blood pressure, it can be predicted that the elderly members of such populations should fail to show arteriosclerosis of hypertensive degree in the renal cortex. Emigrants from such populations sometimes come to medical attention in places like La Paz, Bolivia. Reported here are findings in autopsy samples of kidney tissue examined in La Paz. These samples have revealed remarkably little renovasculopathy at all ages up to 80 years, a phenomenon that has not previously been observed. Because of these findings, it can now be seen as biologically possible for a whole population of elderly persons to avoid renovasculopathy of hypertensive degree, and by implication, perhaps never experience hypertensive cardiovascular disease.

Key words Nephrosclerosis · Arteriolosclerosis Aging · Hypertension

Introduction

It is now widely accepted that atherosclerosis often begins in childhood and tends to progress throughout life (Newman et al. 1991). Although this is less well known for hypertensive disease, the same principle also applies. The prevailing levels of blood pressure in the United States rise between ages 15 and 25 years, and continue to rise thereafter (US Vital and Health Statistics 1986). The sclerosis of small renal arteries that characterizes nephrosclerosis in subjects with essential hypertension can also be seen to begin in children, to increase between ages 15 and 25 years, and to evolve throughout life toward serious complications, usually in old age (Tracy et al. 1990). These two aspects of hypertensive disease, elevated blood pressure and increasingly severe renal arteriosclerosis, have been found to be commensurate with each other among age groups (Tracy et al. 1990) and between populations that are variably affected by the disorder (Tracy et al. 1991, 1992b).

Numerous reports have accumulated throughout the twentieth century of populations that do not show a rise in blood pressure with age (Mancilha Carvalho et al. 1989; Tracy and Toca 1974). These populations all share the common characteristics of small communities of people living close to the earth with little or no connection to the global industrial culture. They also share the characteristics of having no autopsy or surgical specimens available for anatomical study. Given the absence of hypertension in elderly members of these populations, it can be predicted that the renal cortex should fail to reveal a hypertensive degree of arteriosclerosis. A test of this prediction has not yet proven feasible, because the anatomical specimens are inaccessible.

The unusual geographic circumstances of La Paz, Bolivia offered us an opportunity to explore a possible approach to this question. Because of the rugged mountain terrain, the modern city of La Paz is located within a countryside that is heavily populated with campesinos who live in a self-sufficient manner little changed from centuries past. A published survey of blood pressure among the Aymara Indians of Lake Titicaca, less than 100 miles from La Paz, has demonstrated a constancy of average blood pressure over all age groups even to age 90 years (Taboada-Lopez et al. 1987). Immigrants and visitors from the countryside sometimes obtain medical care in the city and occasionally are examined at autopsy. Although the hospital patients do not represent exactly the same population that has provided blood pres-

R. E. Tracy (✉)
Department of Pathology, Louisiana State Medical Center, 1901 Perdido Street, New Orleans, LA 70112, USA

J. Rios-Dalenz
Universidad Mayor de San Andres, Faculdad de Medicina, Enfermeria Nutrition y Tecnologia Medica, Avenida Saavedra No 2246, Casilla No 10367, La Paz, Bolivia

sure survey data, it nevertheless seemed worth exploring the condition of the renocortical arteries in these subjects.

Materials and methods

La Paz cases

The La Paz General Hospital, which is associated with the medial school, serves mostly the indigent peoples of La Paz. Searching the files of autopsies done in this hospital yielded hematoxylin and eosin (H&E) stained paraffin sections of kidney from 27 subjects. These included men and women of ages 15–78 years; 6 subjects were classed as "indiginas" (Aymara Indian), 21 as "mestizo" (mixed), and none as "blanco" (white of Spanish ancestry). The Obrero Hospital serves those employed persons who are covered by social security insurance mechanisms. Available autopsy files yielded slides of kidney tissue from 62 subjects. These included both males and females aged 11–80 years; 20 were classed as "indiginas", 22 as "mestizo", and 20 as "blanco". Causes of death encountered in the series of cases from the two hospitals combined (numbers of cases in parentheses) were infections (30), malignant neoplasms (12), complications of pregnancy (10), chronic pulmonary disease (5), end-stage glomerulonephritis (7), diabetic nephropathy (4), cirrhosis (4), chronic pyelonephritis (1), miscellaneous and uncertain (16). The only case of degenerative cardiovascular disease was a case of dissecting aortic aneurysm, retained in the miscellaneous group. The 12 subjects with primary renal diseases were excluded from the analyses, because these have disease-specific alterations of arterial morphology that are not expected to be representative of the general population. Differences in renovasculopathy between hospitals, sexes and ethnic categories were examined by analysis of variance and found not to show significant differences – all 77 subjects were therefore retained in a single pool.

New Orleans white subjects

Data from two previously reported series of cases (Tracy et al. 1990, 1991) were utilized here to compare with La Paz. Those two series were both obtained from sequential forensic autopsies. From those sources, analyses were done using the 130 white males and 13 white females who died of *basal* causes, i.e. having no condition at autopsy or in clinical records that is known to relate to atherosclerosis or hypertension; these ranged in age from 6 to 69 years. Comparisons of the basal white subjects in New Orleans with other populations have been reported elsewhere (Tracy et al. 1991, 1992b). In these subjects, paraffin sections of kidney tissue were stained with periodic acid-Schiff (PAS), in contrast with the H & E used in La Paz; the preparation of tissues was otherwise essentially the same in both populations.

Morphometry

All arterial profiles encountered while scanning the section under 10× objective lens, up to a maximum of 40 arteries, were examined systematically by previously reported techniques (Tracy et al. 1988a). The outer diameter (OD) of the least axis of the elliptic profile was measured under the 10× objective lens, excluding the adventitia, measuring from one outer media to the other. The thickness of intima (T) was measured under the 40× lens, also along the least axis, using the better presented of the two opposite walls (i.e. lacking tangential sectioning, branch ostium, or artifact). If the two opposite walls were equally well presented, then an average of the two was used. The intima as a percentage of outer diameter (100*T/OD in Fig. 1), averaged over all readings within the size range of 150-300 μm OD, is called R_c; a similar measure

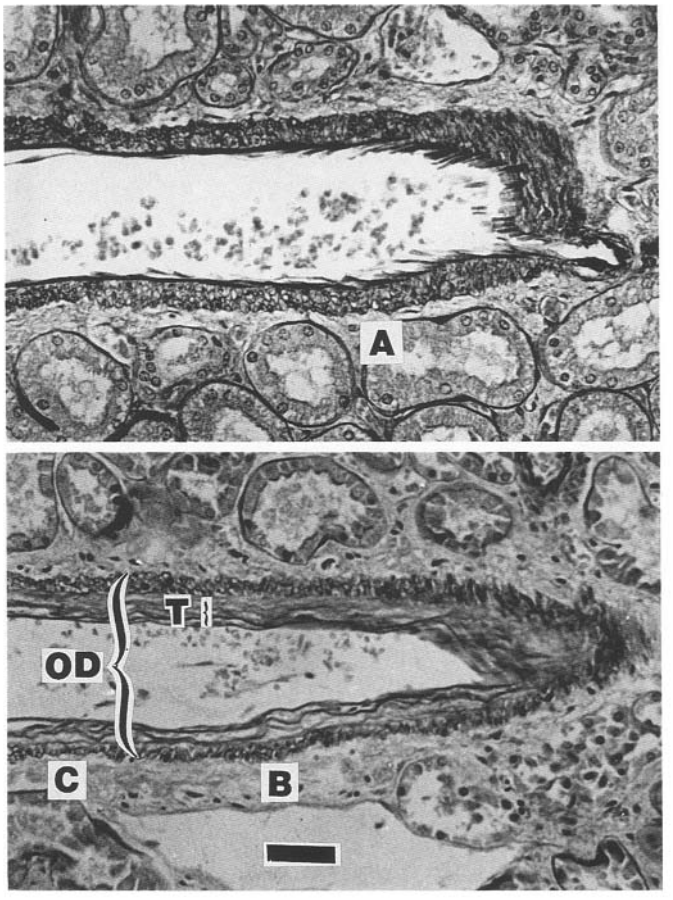

Fig. 1 Examples of the youthful (*above*) and the elderly/hypertensive (*below*) arterial structures are presented. The youthful (normal) media at site *A* contrasts with the reduced media that accompanies intimal fibroplasia at sites *B* and *C*. Intimal thickness (*T*) as a percentage of outer diameter (*OD*) is the pathological variable of interest. Periodic acid-Schiff, *bar* = 50 μm

averaged for vessels of 80–150 μm OD is called R_r. The procedures are the same for PAS and H & E stained specimens. Hyalinized aterioles have been enumerated in the New Orleans subjects (Tracy et al. 1991, 1992b); this was not done in La Paz, because the H & E stain offers little confidence in identifying these structures with quantitative certainty. As a qualitative impression, the hyalinized arterioles were found to be of great rarity in the La Paz specimens, but this is not asserted here as a reliable conclusion.

Standardization between New Orleans and La Paz

A set of six standard kidneys were selected to span the full range of involvement by arterial intimal fibroplasia. Serial sections mounted on two separate slides were stained with PAS and with H & E. The PAS stained slides were evaluated with the PAS stained series of specimens used to represent New Orleans. The H & E stained slides were evaluated along with the H & E stained specimens used to represent La Paz. A regression line derived from the duplicate measurements of the standard slides showed the intercept term not to differ significantly from zero. The regression line forced through the origin yielded $Y = 1.05\,X$ ($R^2 = 0.94$), where X is the measurement of R_c in the H & E stained slides in La Paz and Y is the measurement of R_c in the PAS stained slides in New Orleans; the comparable equation for R_r was $Y = 0.87\,X$ ($R^2 = 0.96$). The regression coefficients do not differ significantly

from unity, and therefore no correction was applied to the La Paz data. If the correction is used, then the data points in Fig. 3 would be raised by 5%, which is judged to be negligible. This standardization procedure cannot correct for possible methodological problems, especially the theoretical concern that postmortem collapse may affect arteries differently in different collection centers. Previous examination of this matter (Tracy et al. 1989) was reassuring, because the degree of collapse was often constant across case groupings and did not vary with intimal thickness. It remains possible, however, that La Paz may differ from New Orleans in the impact of method artifact.

Blood pressure calculated from age and fibroplasia

An equation that allows computation of blood pressure levels expected from age and renocortical arteriosclerosis has been published (Tracy et al. 1988b). The accuracy of that equation has been repeatedly verified for the age range 25–90 years (Tracy et al. 1988a, 1990, 1991, 1992b). [For this purpose, the measure R_c is superior to R_r because the latter is subject to serious method biases from one series of studies to another (Tracy et al. 1988a, 1990, 1991, 1992b)]. Data from the Bogalusa Heart Project have subsequently become available on subjects in the age range 8–27 years (Tracy et al. 1990). This newly available series was combined here with the former series to allow derivation of the revised equation given below. This equation was fitted to data on 126 males, omitting the 17 females, because (a) in the ages below 54 years females have lower pressures than males matched by age and fibroplasia (Tracy et al. 1991, 1992b) and (b) this data set contains too few females of lower ages (17) to allow drawing of a separate equation for them. This newly revised equation now applies to males from ages 8–90 years and to females over age 54 years:

$$M = 53.10 + 1.974\,A - 0.02906\,A^2 + 0.0002317\,A^3 + 1.2306\,R_c + 0.2536\,R_c^2 - 0.009800\,R_c^3 - 0.08302\,AR_c + 0.004300\,AR_c^2 - 0.0006294\,A^2R_c \quad (R^2 = 0.533) \qquad (1)$$

where M is mean blood pressure (systolic+2*diastolic)/3 in mmHg, A is age in years, and R_c is arterial intimal thickness in close level arteries expressed as a percentage of OD (%OD). This equation represents the complete cubic response surface, retaining all coefficients irrespective of statistical significance. A family of curves representing this equation are shown graphically in the figures. In those figures, the lower right region *a* has no grid lines, because the values of R_c and age in that region yield paradoxically high values for blood pressure from Eq. 1; this occurs because the data set that yielded Eq. 1 had insufficient observations in region *a*. It was found here by analysis of variance that arterial intimal fibroplasia (R_c, age adjusted) did not differ significantly between males and females in New Orleans whites nor in La Paz. Therefore, survey data in the United States showing average mean blood pressures in white men and women (US Vital and Health Statistics 1986) can be used to calculate the male minus female differentials to be expected at ages 18–24, 25–34, 35–44, 45–54, and 55–64 years respectively; these are 6.8, 7.0, 4.4, 3.2, and −0.5 mmHg respectively. These listed quantities should be subtracted from the values of M computed for females from Eq. 1. The data set that yielded Eq. 1 had ample numbers of females over age 54 years (56); in this group no significant difference was seen between men and women matched for age and R_c, and therefore no differential needs to be applied at those ages (Tracy et al. 1988b).

Bolivian survey of blood pressure

A survey of blood pressure levels prevailing among Aymara Indians in the region of Lake Titicaca has been reported (Taboada-Lopez et al. 1987). Data from that source were used here to calculate mean arterial pressure M=(systolic+2*diastolic)/3 for comparison with the levels expected from renovasculopathy (R_c) observed in the La Paz specimens, as calculated by Eq. 1. The adjustments for females described in the previous section were applied to the tabulated values used here.

Results

The two measures of nephrosclerosis, R_c and R_r, refer to the fibroplastic intimal thickness of renocortical arteries at the close and remote levels, those with outer diameters of 150–300 μm and 80–149 μm respectively. Results reported here are generally similar for these two measures. Findings for R_c are given here, and the patterns for R_r will then be considered in the Appendix.

Calculating blood pressure from age and nephrosclerosis

Figure 2 presents a graphic diagram of Eq. 1. Each pair of positions on the horizontal and vertical axes (representing respectively age and nephrosclerosis measured by R_c) corresponds to a position near one of the curved lines (representing M). The plotted points represent the 143 New Orleans basal white subjects. The position that each point occupies on the grid of curved lines indicates the level of M that would be calculated through Eq. 1. If

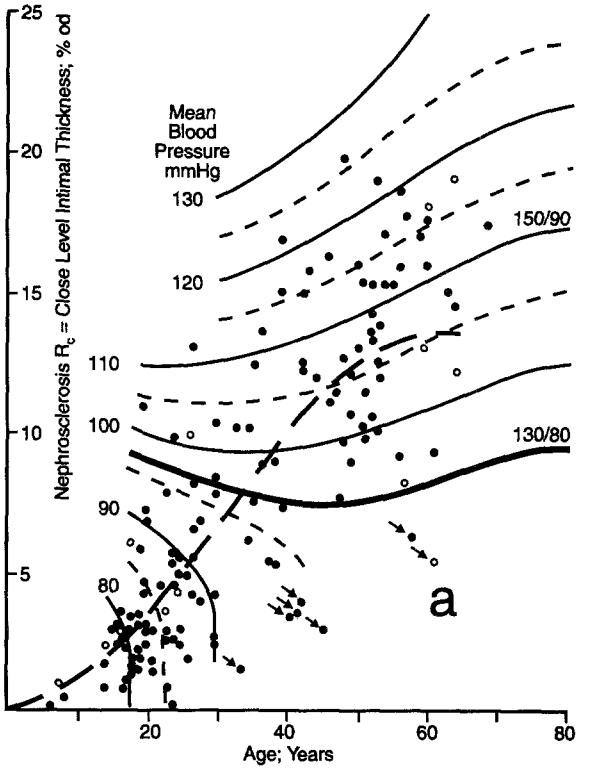

Fig. 2 The family of curves is a graphic depiction of Eq. 1, which is used to calculate expected mean blood pressure from age and nephrosclerosis (R_c). Each spot represents a New Orleans basal white subject. The broken curve of sigmoid shape represents Eq. 2, the cubic regression line fit to these data points. The symbol *a* is introduced to aid discussion. (● =male; ○ =female)

the arbitrarily chosen curve marked 110 mmHg is used to define hypertension (a level that would, for example, correspond to 150/90 mmHg systolic/diastolic), then the 23 subjects plotted above this line will be designated hypertensive (29% of the 80 subjects over age 26 years). The seven plotted points that fall slightly outside of the lower edge of the pattern of blood pressure lines (arrows in Fig. 2) have indeterminate blood pressure, because Eq. 1 cannot be applied beyond the range of data that generated the equation. It is reasonable that so few cases fall in region *a*, because the pattern was developed from an earlier series of cases also assembled in New Orleans.

Progression of nephrosclerosis in New Orleans basal white subjects

The broken line in Fig. 2 that marks a sigmoid curve of arterial fibroplasia (R_c) increasing with age represents Eq. 2, which is the regression line fit to these data points (Appendix). This curve illustrates that the average basal New Orleans white subject, growing and maturing along the curve from age 15 to 25 years, crosses successive blood pressure lines from left to right on the diagram. This pattern of crossings shows that the rising of blood pressure through these ages is only partly linked to worsening nephrosclerosis, but also manifests some degree of rising pressure that is independent of anatomical changes in the kidney. After age 30 years, however, the crossing of successive blood pressure lines is due almost entirely to a progression from below upward in the diagram. This pattern of crossings shows that the rising of blood pressure with further aging after age 30 years is closely linked to the progression of nephrosclerosis, as reflected in the measure of arteriosclerosis, R_c. After age 50 years, the average rate of progression of nephrosclerosis slackens, and the sigmoid curve no longer crosses blood pressure lines. This result yields the prediction that basal cases (i.e. those free of atherosclerosis related clinical conditions) should show no further increase of blood pressure after age 50 years.

Progression of nephrosclerosis in La Paz

Each of the data points plotted in Fig. 3 represents a subject evaluated in La Paz. These points are nearly all situated near or below the lower margin of the pattern of grid lines that were drawn for New Orleans, a finding that is especially clear because of the presence of numerous points in region *a*. The broken line that represents Eq. 4, describing the average progression of arterial fibroplasia with age along a sigmoid curve, has a shape similar to that of New Orleans, but with a much lower position in the graph. At age 30 years, the curve crosses the line for mean blood pressure 90 mmHg, and at age 40 years, it crosses the line for 95 mmHg. Thereafter, no more lines are crossed, yielding the prediction that blood pressure should not rise with further aging in the population averages.

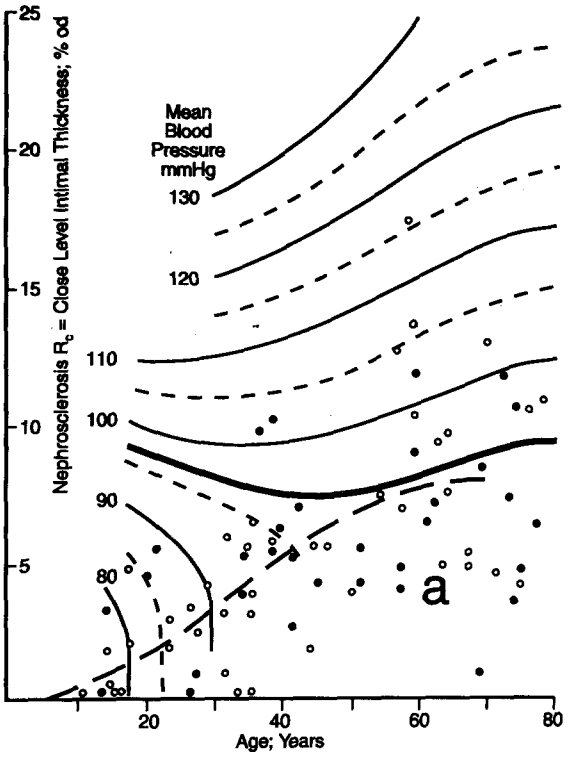

Fig. 3 As in Fig. 2; data from La Paz, broken curve represents Eq. 4. (● = male; ○ = female)

Prediction of blood pressure in La Paz

Table 1 presents data obtained from a published survey of campesinos living near La Paz. Those data were used to calculate *M* observed in men and women of various age groups. The data on nephrosclerosis and age shown in Fig. 3 were used to calculate the expected *M* levels using Eq. 1, and these expected values are also given in Table 1. For females, the adjustments explained in the methods were applied as required. The results show that the average *M* observed in the pool of age groups 16–40 years was 85.2 mmHg, and the comparable level expected from renovasculopathies was 84.0 mmHg; this result could be taken to indicate some degree of agreement for these age and sex groups overall, even though large inconsistencies are seen in some specific comparisons. For the pool of age groups 41–80 years, however, the observed and expected *M* averaged overall 86.9 and 96.0 mmHg respectively; the observed levels are substantially and consistently lower than the expectations in the older age ranges. Another striking discrepancy seen in Table 1 is that women of ages 16–50 years are expected to show lower blood pressures than men, but no such sex difference was observed in the survey data. Table 1 clearly demonstrates that blood pressure levels observed in the survey data on villagers conspicuously differ in a number of ways from the levels expected from autopsy findings in the nearby city.

Table 1 Mean blood pressure levels among Aymara Indians of Bolivia, and levels expected from renovasculopathies measured in La Paz by age and sex (*M* male, *F* female)

Age (years)	Number of cases		Blood pressure (BP; mmHg)							
			Published survey[a]				Calculated Mean BP[b]			
			Systolic		Diastolic		Observed[c]		Expected[d]	
	M	F	M	F	M	F	M	F	M	F
11–15	19	34	97	109	64	72	75	84	75	75
16–20	27	25	116	115	72	76	87	89	81	74
21–30	48	56	110	106	70	70	83	82	87	80
31–40	62	53	107	111	72	73	84	86	93	89
41–50	43	42	109	110	73	73	85	85	96	93
51–60	25	32	116	115	79	75	91	88	96	96
61–70	15	21	113	117	72	74	86	88	96	96
71–80	15	18	105	123	71	73	82	90	96	96

[a] Survey data are obtained from Toboada-Lopez et al. 1987
[b] Mean BP is (systolic + 2*diastolic)/3
[c] Calculated from the survey data
[d] Calculated from R_c using Eq. 1 together with the adjustment for females given in the methods

Table 2 Regression coefficients and their standard errors (SE) relating sex, age (*A*), and a cubic function of age to arterial intimal fibroplasia at the close (R_c) and remote (R_r) levels in seven populations (*NOB* New Orleans black, *NOW* New Orleans white, *NS* not significantly different from zero, *NT* no test performed due to lack of females)

Population	Number of cases	Age range	Regression coefficients $X10^{-3}$						
			C[a]	(SE)	A	A^2	A^3	Sex[b]	R^2
Close level arteries, R_c									
NOB	121	11–62	11.49	(0.40)	NS	NS	NS	NS	0.516
Tokyo	61	2–54	10.45	(0.61)	NS	NS	NS	1.9 (0.9)	0.516
NOW	143	7–65	9.91	(0.30)	NS	NS	NS	NS	0.639
Guatemala	75	15–51	8.97	(0.50)	NS	NS	NS	NT	0.432
Mexico	113	13–64	6.81	(0.37)	NS	NS	NS	NT	0.410
La Paz	75	11–80	5.66	(0.31)	NS	NS	NS	NS	0.450
Remote level arteries, R_r									
NOB	121	11–62	5.39	(0.31)	NS	NS	NS	NS	0.381
Tokyo	61	2–54	3.74	(0.28)	NS	NS	NS	NS	0.359
NOW	143	7–65	5.02	(0.22)	NS	NS	NS	NS	0.547
Guatemala	75	15–51	4.18	(0.29)	NS	NS	NS	NT	0.297
Mexico	113	13–64	0.81	(0.78)[c]	NS	NS	0.0033 (0.0001)	NT	0.353
La Paz	76	11–80	2.25	(0.24)	NS	NS	NS	NS	0.242

[a] C is calculated by $A^2(1-0.01A)$ when R_c is the dependent variable and is $A^2(1-0.076A)$ when R_r is the dependent variable. C is forced into the equation in all instances; all equations are forced through the origin
[b] Sex = 0 for males and 1000 for females (coefficients are to be multiplied by 10^{-3} because the decimal points have been shifted for typographic convenience)
[c] IF the A^3 term is omitted, then the coefficient for C is 2.98 with $R^2 = 0.326$

Discussion

Microscopic renocortical arteries have long been known to undergo progressive fibroplastic intimal thickening with age. This process was found here, in New Orleans and La Paz, to begin in childhood and to progress throughout life in accordance with sigmoid growth curves. The shapes of the growth curves appear similar in Figs. 2 and 3, except for slower progression throughout in La Paz. Mathematically, the growth curves could be described as identical except for a single parameter that governs the variable rates of progression of fibroplasia from one population to another (Appendix). These results imply several important biological conclusions: (1) differences between populations begin to appear early in life, and are already substantial by

age 25 years; (2) the population differences seen in young adults continue to widen in a consistent way throughout life; (3) the period of life that shows the fastest growth of arterial intimal fibroplasia is in the ages 25–55 years; the growth rate slows after age 55 years. These three provisional conclusions are all offered with some reservations, because they derive from the cross-sectional data of this paper, and not from a properly designed longitudinal study.

Conclusion 1 indicates that adolescence and young adult years have a special importance in the evolution of hypertensive disease. The kind of arterial intimal fibroplasia that characterizes benign nephrosclerosis (and indeed is a major defining feature of this pathological entity) begins in most individuals at a time of life when hypertension is very nearly nonexistent. Whatever the unknown etiological agents might be that vary between populations, be they environmental or genetic, they must be viewed as acting early in life, and as showing that action directly in the form of anatomical changes in the artery wall.

Conclusion 2 bears upon a question that has been posed in earlier publications (Tracy et al. 1991, 1992b, 1993). It was asked whether the population variations might be fully established by age 25 years with no further widening of the differences in later ages. The addition here of data from La Paz helps to define this issue more clearly. The differences between populations can now be seen as substantially greater at age 60 than at age 30 years. This result is so conspicuous in a comparison of Figs. 2 and 3 that a statistical test is not needed. (The test to compare New Orleans with La Paz shows $t = 9.9$ compared with $t = 3.3$ required for $P < 0.001$). The result suggests that whatever might be the unknown etiological agents that vary between populations, they could be viewed as acting throughout life in a manner similar to their actions during youth. This deduction is, however, in some doubt because of the possibility of cohort effects. The older subjects lived through different historical times than did the young subjects, and they may not have followed the same course of disease progression. This possibility can be tested only by following cohorts over time; until this is done, the exact meaning of conclusion 2 is uncertain.

Conclusion 3 indicates what might seem to be a counterintuitive concept. Whereas hypertension and nephrosclerosis are most commonly looked upon as diseases of old age, we nevertheless find here that their rates of progression are slowest late in life. The leveling off of the curve late in life, as reported before in data from New Orleans and Honolulu (Tracy 1992a), has been held in some doubt. The doubt arises in part because of possible cohort effects, but also because mortality from hypertensive complications depletes the population of its most seriously affected members. The autopsied subjects plotted in Fig. 2 were carefully screened to exclude any that were known to have hypertension, diabetes, heart disease, or other atherosclerosis-associated condition. Moreover, those who died at younger ages from hypertensive complications have been lost from the population, and this would be expected to deplete the upper range of R_c among the elderly in Fig. 2. The impact of these exclusions upon the precise shape of the growth curve is difficult to assess. For La Paz, however, the only exclusion that was applied to the subjects plotted in Fig. 3 was the deletion of those with chronic renal diseases (which alter arterial morphology in disease-specific ways); the causes of death in La Paz otherwise included only one subject with an atherosclerosis-related condition (dissecting aortic aneurysm), and that one subject was retained in the series. These results therefore lend confidence to the view that the flattening of the curve into old age is biologically real, supporting the same view that has been defended elsewhere on other grounds (Tracy et al. 1990). This result is inconsistent with the suggestion of a vicious cycle (Bell and Clawson 1928) wherein renocortical arteriosclerosis causes high blood pressure which accelerates arteriosclerosis and so on. Such a cycle should accelerate in the end stages, and no such acceleration has been found here.

In Fig. 2, the symbol *a* is introduced to mark a position beyond age 55 years with nephrosclerosis of a degree shown by the average New Orleans basal white subject of age 20 years. This portion of the chart is empty; its upper margin is approached by only seven of the plotted points (*arrows*). Region *a* also holds no grid lines to designate blood pressure levels, because the population that was used to construct the grid lines (New Orleans) contained no subjects in this range of the graph. Moreover, no subjects had previously been observed at position *a* in any other population [although Mexico (Tracy 1992) and Guatemala (Tracy et al. 1992a) were poorly represented in this age range]. In Fig. 3, position *a* is richly populated with plotted points. Indeed, nearly three fifths of the 31 La Paz subjects over age 55 years fall below the bold curve marked 130/80 mmHg which borders the lower limits of the grid depicting the range observed in New Orleans. The average La Paz subject of age 55 years or more has severity of nephrosclerosis similar to that of age 30 years in New Orleans basal white subjects. This result would lead us to predict that significant arterial disease should be seen in elderly La Paz residents about as often as in New Orleans residents at age 30 years. Arteries in La Paz rarely grow old in the way that is nearly always seen in New Orleans. It is therefore biologically possible for humans to avoid the emergence of hypertensive stigmata in the kidneys, not just as occasional individuals but as a general property of a whole population.

The blood pressure levels observed in survey data of Bolivian campesinos were found to be substantially lower than expected from the severity of renovasculopathy measured in La Paz specimens (Table 1). Possible explanations for this discrepancy include: method bias between Bolivia and the United States in the measurement of blood pressure or of vasculopathy; differences between the La Paz and the campesino populations such that the city residents might show higher blood

pressures if these should become known; inappropriate application of Eq. 1 to this range of nephrosclerosis, because the La Paz data fall outside the range of the data that generated the equation. It is tempting to speculate that an effect of dietary sodium, as demonstrated by the INTERSALT study (Mancilha Carvalho et al. 1989), might explain these discrepancies; perhaps the campesinos consume less salt than is usual in the New Orleans population that was used to construct the expected blood pressure levels in Table 1. A restriction of dietary sodium would be expected to lower prevailing levels of blood pressure.

Another important feature of Table 1 is the absence of a sex difference in blood pressure at ages 20–50 years among the Aymara Indians. At these ages in the United States, women show substantially lower blood pressure than men (US Vital and Health Statistics 1986). Whether this dramatic difference between populations might be accompanied by a similar contrast in organic disease is an interesting speculation. For instance, would the coronary arteries in La Paz fail to show a sex difference of the kind that is so dramatic in New Orleans (Tejada et al. 1968)? The matter could be of fundamental theoretical importance.

The data provided by the specimens examined in La Paz have filled an important gap in our understanding of the progression of hypertension-related arteriosclerosis with age in the renal cortex. In previously studied populations, blood pressure was seen to rise with age in company with rapid development of renocortical arteriosclerosis in mathematically expected proportion to each other; this outcome seemed to show the process to be an inescapable component of aging. In La Paz, the progression of arterial fibroplasia in the renal cortex was sufficiently slow that the degree required to imply elevated blood pressure was not achieved at any age. It can now be seen as biologically possible, as an ordinary characteristic of the population, for elderly persons to avoid renovasculopathy of hypertensive degree, and, by implication, to escape hypertensive cardiovascular disease. This opens for the first time a new avenue for investigating anatomically defined manifestations of disease in relation to the lifestyles and genetics of different populations, and persons within those populations, for clues to the mysterious causes of this important disease.

References

Bell ET, Clawson BJ (1928) Primary (essential) hypertension. A study of four hundred and twenty cases. Arch Pathol 5:939–1002

Mancilha Carvalho JJ, Baruzzi RG, Howard PF, Poulter N, Alpers MP, Franco LJ, Marcopito LF, Spooner VJ, Dyer AR, Elliott P, Stamler J, Stramler R (1989) Blood pressure in four remote populations in the INTERSALT study. Hypertension 14:238–246

Newman WP, Wattigney W, Berenson GS (1991) Autopsy studies in United States children and adolescents. Relationship of risk factors to atherosclerotic lesions. Ann N Y Acad Sci 623:16–25

Taboada-Lopes GT, Plazo JO, Flores MC de, Claure ML de, San Martin R (1987) Presion arterial en una poblacion Aymara residente de altura. Salud Boliv 5:45–50

Tejada C, Strong JP, Montenegro MR, Restrepo C, Solberg LA (1968) Distribution of coronary and aortic atherosclerosis by geographic location, race, and sex. Lab Invest 18:509–526

Tracy RE (1992) Nephrosclerosis from childhood to old age: a viewpoint. Geriatr Nephrol Urol 1:201–211

Tracy RE, Toca VT (1974) Nephrosclerosis and blood pressure. I. Rising and falling patterns in lengthy records. Lab Invest 30:20–29

Tracy RE, Velez-Duran M, Heigle T, Oalmann MC (1988a) Two variants of nephrosclerosis separately related to age and blood pressure. Am J Pathol 131:270–282

Tracy RE, MacLean CJ, Reed DM, Hayashi T, Gandia M, Strong JP (1988b) Blood pressure, nephrosclerosis, and age: autopsy findings from the Honolulu Heart Project. Mod Pathol 1:420–427

Tracy RE, Heigle TJ, Velez-Duran M (1989) Evidence for the failure of the Laplace law as a sole explanation for wall thickening of arteries in hypertensive and aging normotensive kidneys. Arch Pathol Lab Med 113:342–349

Tracy RE, Berenson G, Wattigney W, Barrett TJ (1990) The evolution of benign arterionephrosclerosis from age 6 to 70 years. Am J Pathol 136:429–439

Tracy RE, Bhandaru SY, Oalmann MC, Guzman MA, Newman WP III (1991) Blood pressure and nephrosclerosis in black and white men and women aged 25 to 54. Mod Pathol 4:602–609

Tracy RE, Berenson GS, Cueto-Garcia L, Wattigney WA, Barrett TJ (1992a) Nephroscerlosis and aortic atherosclerosis from age 6 to 70 years in the United States and Mexico. Virchows Arch [A] 420:479–488

Tracy RE, Malcom GT, Oalmann MC, Qureshi U, Ishii T, Velez-Duran M (1992b) Renal microvascular features of hypertension in Japan, Guatemala, and USA. Arch Pathol Lab Med 116:50–55

Tracy RE, Guzman MA, Oalmann MC, Newman WP III (1993) Nephrosclerosis in three cohorts of black and white men born 1925 to 1944, 1934 to 1953, and 1943 to 1962. Am J Hypertens 6:185–192

US Vital and Health Statistics (1986) Blood pressure levels in persons 18–74 years of age in 1976–80, and trends in blood pressure from 1960 to 1980 in the United States. National Health Survey Series 11, No. 234, pp 48–53. DHHS Publication (PHS) 86-1684

Appendix

Modeling of growth curves

Backward stepwise fitting of cubic regression equations was done to relate R_c and R_r to age in New Orleans and La Paz, using the SAS package of programs (SAS Institute, Cary, N.C.). In all instances, the intercept terms and the first-order terms on age were not significantly different from zero. Regression equations forced through the origin and omitting the nonsignificant term, A, were therefore applied subsequently throughout, using A to denote age in years, and R_c and R_r to denote arterial intimal thickness in OD at the close and remote levels respectively. The New Orleans data were described by $R_c = 0.01052\,A^2 - 0.0001107\,A^3$ and $R_r = 0.00484\,A^2 - 0.0000347\,A^3$ (143 cases including basal males and females). The La Paz data were described by $R_c = 0.00544\,A^2 - 0.0000539\,A^3$ and $R_r = 0.00241\,A^2 - 0.0000196\,A^3$ (77 cases including males and females without chronic renal diseases). Simple rearrangements of these equations reveal close approximations to the expressions $R_c = \alpha A^2 (1 - 0.01\,A)$ and $R_r = \beta A^2 (1 - 0.0076\,A)$, where α and β are empirical parameters. When recalculated in these forms, the four equations were, without significant deterioration of the residual error term ($P < 0.01$), determined to be for New Orleans:

$$R_c = 0.00991\ A^2\ (1 - 0.01\ A) \quad (R^2 = 0.639) \tag{2}$$

$$R_r = 0.00502\ A^2\ (1 - 0.0076\ A) \quad (R^2 = 0.547) \tag{3}$$

and for La Paz:

$$R_c = 0.00566\ A^2\ (1 - 0.01\ A) \quad (R^2 = 0.450) \tag{4}$$

$$R_r = 0.00225\ A^2\ (1 - 0.0076\ A) \quad (R^2 = 0.242) \tag{5}$$

(Residuals from three of these equations were found to follow normal frequency distributions. The fourth instance, that for R_r in New Orleans was nearly normal, and showed a normal distribution after removal of seven high outliers and two low outliers.)

Progression of nephrosclerosis measured by R_r

The evolution of R_r on age differs from that of R_c in two notable ways. Firstly the term $A^2\ (1 - 0.0076\ A)$ was found for R_r in Eq. 3 and 5, in contrast to the term $A^2\ (1 - 0.01\ A)$ for R_c in Eqs. 2 and 4. The smaller coefficient, 0.0076, indicates that the inflection point of the sigmoid growth curve, after which the growth rate of arterial fibroplasia declines, is at a later age in the smaller, remote branches of the arterial tree, reflected in R_r. (Setting the second derivatives equal to zero in Eqs. 2 and 3 determines the inflection points to be at ages 43.9 years for R_r, and 33.7 years for R_c.) Secondly the coefficients for the term $A^2\ (1 - 0.01\ A)$ relating to R_c are 0.00991 for New Orleans and 0.00566 for La Paz, a factor 75% greater in New Orleans, whereas the coefficients of $A^2\ (1 - 0.0076\ A)$ relating to R_r are 0.00502 for New Orleans and 0.00225 for La Paz, a factor 123% greater in New Orleans. The greater severities of renocortical arterial fibroplasia seen in New Orleans are more conspicuously shown in the smaller remote level than in the larger close level arteries.

Other populations

The archive of specimens at Lousiana State Medical Center in New Orleans contains kidney specimens from Japan, Guatemala, and Mexico as well as black and white subjects in New Orleans. Comparisons of renovasculopathies observed in these populations with each other and with New Orleans whites have been reported (Tracy et al. 1991, 1992a, b), and will not be repeated here. These specimens are of use, however, for a newly emerged purpose. We have seen that R_c and R_r relate to age in accordance with simple models that show only one coefficient differing between La Paz and New Orleans whites (Eqs. 2–5). The question arises, therefore, whether the same models can also be used to describe other populations. The question was tested with forward stepwise multiple regression. At the first step, the variable $C = A^2\ (1 - 0.01\ A)$ was entered when relating R_c to age and $C = A^2\ (1 - 0.0076\ A)$ when relating R_r to age. In all instances, the intercept terms were not significantly different from zero, and the regressions were forced through the origin. Subsequent entry of A, A^2, or A^3 into an equation, by significant increase in the R^2, was judged to represent statistically significant rejection of the model. Rejection in this sense was encountered in only one of the 12 trials, for the variable R_r in Mexico (Table 2). A significant coefficient for the term A^3 indicates that the flattening of the sigmoid growth curve into old age is lessened or reversed in this one situation. (The model omitting the A^3 term had $R^2 = 0.326$ compared with 0.353 when the A^3 term is included; although statistically significant, the discrepancy is not of large effect. The rejection of the model in this one instance is therefore not of impressive magnitude.) This outcome indicates that sigmoid growth curves similar to those in Figs. 2 and 3 can successfully describe the progression of R_c and R_r with age in these additional four populations (with one weak exception in the Mexican data). A difference between sexes was also tested by defining the variable $S = 0$ for males and $S = 1000$ for females, and offering this variable for entry into the stepwise procedure. The only significant sex effect was found in Japan, wherein the females showed R_c of 1.9% OD greater than males (Table 2). (Residuals from the equations were tested for normality of distribution. The outcomes that failed to follow normal distributions were for R_c in Mexico, and for R_r in New Orleans black, Mexico, and Japan; these departures from normality were small and in all instances resulted from upward skew generated by a few outliers.)