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Hypertension and Arteriolar Sclerosis of the Kidney, Pancreas, Adrenal Gland, and Liver

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Summary. Replicate slides of autopsy specimens (kidney, pancreas, adrenal glands, and liver) from 66 hospital patients who had lengthy outpatient records of their blood pressure levels were randomized and graded blindly for the severity of hypertensive fibroproliferative-mediodegeneration lesions of arterioles (arplasia). For all four tissues, the severity of lesions correlated significantly with the level of the blood pressure. Between blood pressure and lesions the correlation coefficient was significantly smaller ($P<0.01$) for liver and adrenal than for kidney. The correlation coefficient was also smaller for pancreas than for kidney, but the statistical significance of the difference ($0.3>P>0.2$) was not conclusive. The results tend to confirm the conclusions of the classic 1937 report of Moritz and Oldt, adding strength to their generalization that "Arteriolar sclerosis is the most common cause of chronic hypertension."

Key words: Arplasia – Arteriolar sclerosis – Hypertension

Introduction

In 1937 Moritz and Oldt published a report concerning the relationship between arteriolar sclerosis and hypertension. A major conclusion of that report was "The objective examination of arterioles in all parts of the body of 100 control cases and 100 cases of chronic hypertension disclosed only one situation in which the presence of arteriolar sclerosis was almost invariably associated with hypertension and where the absence of arteriolar sclerosis almost invariably betokened an absence of high blood pressure. This was in the kidneys ... No comparable correlation could be found in any other organ or tissue." They

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interpreted the results to mean "Arteriolar sclerosis occurs as a primary pathological change ... When the renal arterioles become sclerotic, hypertension is almost invariably present."

The association between microvascular lesions in the kidney and elevated blood pressure is well established. The association of microvascular lesions in various other tissue (e.g., pancreas, liver, adrenal) with high blood pressure is not in dispute. The assertion about the kidney, however, that "No comparable correlation could be found in any other organ or tissue" has never been confirmed or refuted by independent controlled testing. The experiment described in this report was undertaken to repeat this one aspect of the work of Moritz and Oldt using morphometric and statistical tools developed since that time. The findings in this small series are of interest in that our results tend to confirm the 40-year old report, with only one notable reservation. If those conclusions are correct, then they seem to affirm the view that "The effect of renal arteriolar sclerosis in human hypertension appears to be the functional analogue of the renal arterial clamp in experimental hypertension ... Arteriolar sclerosis is the most common cause of chronic hypertension."

This line of reasoning, developed by Goldblatt and his followers, is of necessity indirect because it deals with nonexperimental observation of human autopsies. Given a strong correlation between high blood pressure and arteriolar lesions in the kidney, that correlation could be viewed hypothetically as reflecting lesions caused by hypertension. The strength of the correlation, from this point of view, indicates the degree to which the sought-for cause-and-effect linkage can be measured in practice. Therefore, the finding of a weak correlation between high blood pressure and arteriolar lesions in the liver must, by virtue of consistent adherence to the same logic, mean that lesions of the liver are *not* caused in the main by hypertension. The reasoning is even more easily extended to spleen, intestine, testes, and other tissues where the correlation of lesions with blood pressure is at or near zero. After having invoked outside causes independent of blood pressure to explain lesions in the liver and other tissues, then we are left with a perplexity: Is it easy to view high blood pressure as a dominant cause of lesions only in the kidney and not anywhere else? Are we to presume that the outside causes acting in the liver are not active in the kidney? Moritz and Oldt offered the simple suggestion that perhaps only the outside causes were of important consequence, being distributed among these or those tissues largely at random, and that "When renal arterioles became sclerotic, hypertension is almost invariably present." These observations and reasonings appear to have drifted into obscurity, and would seem to merit reconsideration.

Material and Methods

Collection of Cases. Subjects brought to autopsy were screened for inclusion in this study. If the records of outpatient visits contained blood pressure readings in each of the 6 years preceding death, and at least 10 readings altogether, the subject was accepted. Mean age of the 66 subjects was 68.9 years ($\pm$11.0 SD), and the ages ranged from 33 to 92 years. Cause of death was atherosclerosis-related in 47. Six subjects were white men; 4 were white women; 20, black men; and 36, black women.

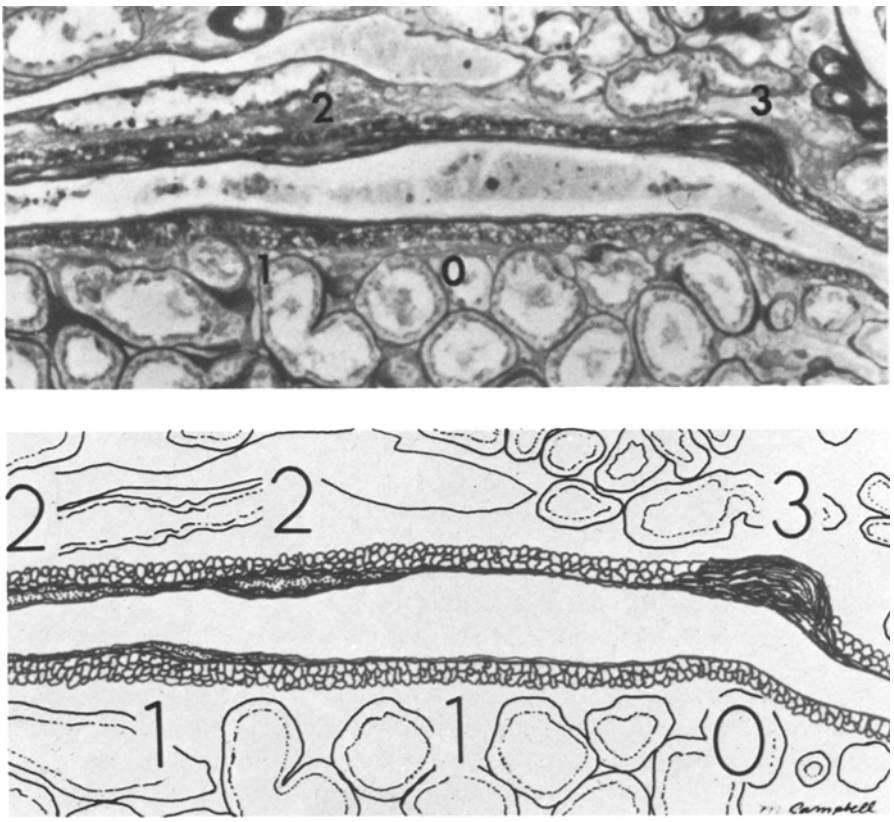

Fig. 1. Examples of grades 0 (normal), 1, 2, and 3 of severity for arplasia. Note that extreme variation from place to place characterizes the lesions and that intimal fibroplasia generally accompanies medial wastage and disappearance. (alcian blue – PAS, X260)

Analysis of Blood Pressure Records. Mean pressure (one-third pulse pressure plus diastolic) was calculated for every reading. A series of averages was computed and subjected to *t*-test. The average of the first two was compared with the average of all remaining values; the average of the first three was compared with all remaining values; and so on. In this sequence of *t*-tests, the *t* having the smallest *p* value was taken as the place to call "transition point." The inherent properties of a series of blood pressure readings that justify this way to identify the transition point were extensively discussed elsewhere (Tracy et. al. 1974a). The average of the mean pressure before (BP_b) and after (BP_a) transition and the duration of BP_a were tested for relationships with lesion measures and age.

Processing of Tissues. Six pieces of tissue were processed from the best preserved regions of kidney, pancreas, adrenal glands, and liver. In some subjects, pancreas or adrenal tissue was autolyzed beyond utility, and those subjects therefore had missing values in the tables of data. Liver was not obtained from four subjects. Each piece of tissue ($6 \times 4 = 24$ per case) was assigned a random number and blocked in paraffin. Sections of 4 μm were mounted one to a slide and stained in a modified Mowry's alcian blue-periodic acid Schiff (PAS) routine (Mowry 1960), in which picric acid is replaced by metanil yellow (Tracy et al. 1974a).

Grading Tissue Sections. After collection of the series of 66 subjects, slides were arranged in order on the originally assigned random numbers. Each of the four sets of tissues was evaluated in that

sequence. Hyaline lesions of afferent arterioles and arterioles of that general size (<50 μm in nonperfused tissue) have been previously shown (Tracy et al. 1974b; Tracy 1970a) to be related to blood pressure less well than fibroproliferative-mediodestructive lesions of somewhat large arterioles (50–500 μm). That finding agrees with the findings of Stoddard and Puchtler (1969) and with those of Fishberg (1925). In this study, only fibroproliferative-mediodestructive lesions were evaluated, and therefore the smallest arterioles were excluded from the grading scheme. The severity of "arplasia" (arterial intimal fibroplasia) was determined by comparing each artery in a section to a panel of photographs arranged 0–4+. Figure 1 illustrates some example lesions. The mean grade was computed for each slide, and the square root of this value averaged over slides was taken as the Index of Arplasia for each tissue following the previously established convention (Tracy et al. 1974a). The method developed for kidney (Tracy 1970b) needed no important modification for other tissues. Evaluation of the adrenal was confined to pericapsular arteries; those within the gland or capsule were excluded.

Statistical Analysis. The significance of the difference between correlated correlation coefficients was computed by the method of Hotelling as reviewed by Dunn and Clark (1971). The use of known magnitudes of measurement error to compute correlation coefficients adjusted for the attenuating effect of such error is described in Appendix I.

Results

Structure of Lesions. Lesions in arterioles of the general size of renal interlobulars most commonly were of the fibroproliferative-mediodegenerative type (an alteration that has been designated "arplasia"). These arterioles seldom had conspicuous hyaline deposits. As illustrated in Figure 1, the thickness of intimal fibrosis tended to increase in company with degeneration and disappearance of the media. Hyalinization without fibrosis or proliferation characterized the lesions of the smallest arterioles of the general size of afferent arterioles (Fig. 2). In the intermediate-diameter range of about 50–150 μm, arterioles commonly manifested a mixture of arplasia and hyaline components.

Figure 2 illustrates some characteristic findings in a representative hypertensive subject: the kinds of lesions seen and the overall average severity of them appeared to the subjective judgment to be about the same in kidney, pancreas, adrenal gland, and liver. Some significant differences, however, emerged from quantitative analysis of objective data.

Correlations. The kidney and liver were both suitable for grading in 62 of the 66 subjects. For these, correlation coefficients of 0.588 and 0.255 for the association between blood pressure and arplasia were significantly different from each other ($P<0.01$) and both were significantly different from zero. Both kidney and adrenal gland were suitable for grading in 58 subjects. Correlations with blood pressure by the respective arplasia indices were 0.588 and 0.350, and also significantly differed from each other and from zero ($P<0.01$; Table 1). Hence, the level of blood pressure (BP_a, after transition) correlated better with the severity of lesions in the kidney than in the liver or adrenal gland.

Adequate samples of both kidney and pancreas were available in 49 subjects. Correlation of blood pressure with arplasia for those subjects were 0.545 and 0.499 respectively. The difference between these coefficients was not statistically significant.

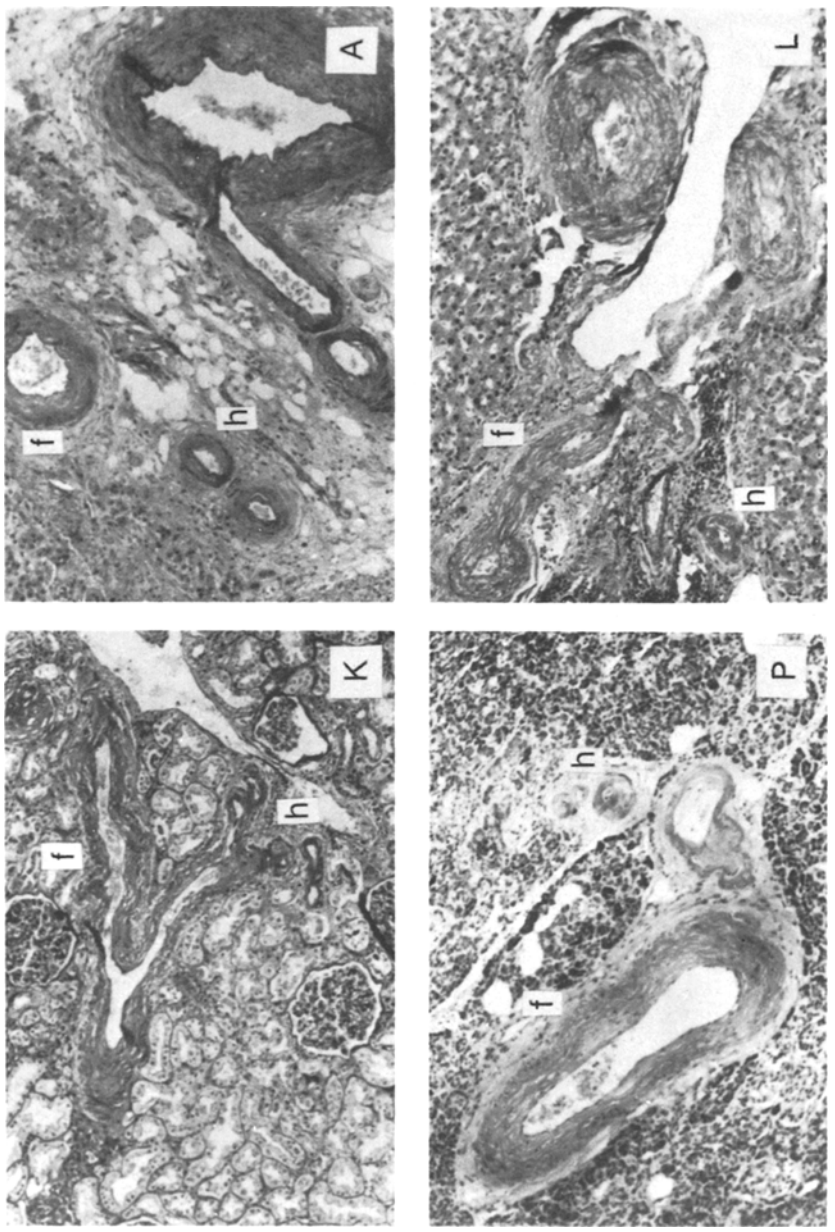

Fig. 2. Representative lesions from the kidney (*K*), pancreas (*P*), adrenal (*A*) and liver (*L*) of a typical hypertensive subject. Fibroproliferative-mediodegeneration (arplasia = *f*) and hyalinization (*h*) are illustrated. Note that the different types of lesions affect arterioles of different sizes. (alcian blue – PAS. X180)

All four tissues were available in 43 subjects (Table 2). The complete correlation matrix reveals no obvious aggregation of variables into separate clusters.

Adjustment of these correlations for the attenuating effects of measurement error (Appendix I) did not alter any of these conclusions.

Table 1. Number of cases, correlation matrix, and Hotelling's *t*-tests of significance for subsamples of subjects having complete data for the selected comparisons[a]

Number of subjects	Variable subscript	Variable	Correlation matrix			*t*-test	
			Blood pressure	Other tissue	Kidney	Raw	Adjusted
49	1	Blood pressure	1	0.499	0.545		
	2	Pancreas	0.499	1	0.693	0.646	0.867
	3	Kidney	0.545	0.693	1		
58	1	Blood pressure	1	0.350	0.588		
	2	Adrenal gland	0.350	1	0.593	2.414	5.124
	3	Kidney	0.588	0.593	1		
62	1	Blood pressure	1	0.255	0.588		
	2	Liver	0.255	1	0.612	5.689	13.44
	3	Kidney	0.588	0.612	1		

[a] Raw $t=(r_{12}-r_{13})\sqrt{(n-3)(1+r_{23})/2D}$; where D is the determinant of the correlation matrix. Adjusted *t*-test was done using new matrices of adjusted coefficient, adj $r=r/\sqrt{(1-S_1/S_2)(1-S_1'/S_2')}$. S_1 and S_1' are the variances due to measurement error for paired variables; S_2 and S_2' are the variances among subjects for the respective variables; these are taken from Table A1.
Blood pressure is BP_a, mean pressure after transition toward the end of life

Table 2. Correlation coefficients among blood pressure (BP) and arplasia indexes of four selected tissues in 43 cases having complete data; all cause-of-death, age, race, sex groups combined

	BP before	Kidney	Pancreas	Adrenal	Liver	Age
BP after	0.350	0.624	0.556	0.394	0.250	−0.162
BP before	–	0.320	0.433	0.541	0.160	0.215
Kidney		–	0.678	0.576	0.641	0.083
Pancreas			–	0.654	0.523	0.036
Adrenal				–	0.641	0.487
Liver					–	0.418

Multiple Regression. Multiple regression techniques to explore age-adjusted relationships between blood pressure and lesions are described in Appendix II. Of special interest is that lesions of the liver and adrenal gland were significantly related to age as well as to level of blood pressure. For these two tissues, age and blood pressure level had partial correlations with lesions that were almost exactly additive, indicating that their contributions to a total correlation were essentially independent of each other. For kidney and pancreas, no correlation of lesions with age was found, and in the multiple regression setting age had no important partial correlation. A difference between liver and adrenal gland having one pattern of correlation with age and blood pressure, and pancreas and kidney having another pattern, is clearly indicated. For all four tissues, the duration of BP_a had no detectable relationships with lesions.

Discussion

Stoddard and Puchtler (1969) noted that "hyperplastic arteriosclerosis affects the interlobar and arcuate arteries and may extend to the interlobular arteries. It is an intimal proliferation of concentric lamellae of connective tissue which may in time be accompanied by atrophy of the media. Hyaline sclerosis of renal arterioles is ... most severe in preglomerular arterioles. It often extends to interlobular arteries but rarely into a glomerulus except in diabetics." These observations bear emphasis because they often are not considered when interpreting functional studies of hypertension. As Fishberg (1925) explained it, "As far back as 1868, Johnson described hypertrophy of the media as a characteristic in granular kidney and most current textbooks contain the same statement but, as a matter of fact one finds in arteriosclerosis a gradual and progressive atrophy of the medial muscle with replacement fibrosis." A comprehensive discussion of the reduction of the ratio of lumen diameter to wall thickness by structural remodeling of the arteriolar wall rather than hypertrophy has been given by Short (1966, 1967) and others (Tracy et al. 1966). That is a separate topic. Our findings agree with the view that *lesions* dominate the picture in the tissues of hypertensives. Functional data about the overall behavior of a whole organ's vascular bed should, because of the *lesions*, not be interpreted in terms of a large solitary nephron. The single nephron model that applies adequately to the *normal* kidney is not appropriate when *lesions* appear.

The qualitative structure of arteriolar lesions is not entirely identical in kidney, pancreas, adrenal gland, and liver; each tissue has its own characteristic subtle differences from the others. Nevertheless, at present for practical purposes we can accept Fishberg's (1925) conclusion that the structural characteristics of "... the arteriolar lesions so constantly accompanying essential hypertension are essentially identical in the various organs." For semiquantitative scaling, the thickness of the fibroplastic type of lesion, appropriately measured against the general size of the affected vessel, can be used in essentially the same way in all four tissues.

The use of product-moment correlation coefficients in this study places a perspective on the findings that is somewhat different from most previous reports. Moritz and Oldt (1937), for instance, selected 100 subjects from the high end and 100 from the low end of the blood pressure spectrum, excluding an unspecified number of subjects with intermediate levels. They also classed each *specimen* (e.g., kidney or pancreas from a subject) by its degree of vascular disease into grades zero, mild, or severe. Their analysis is essentially a 2×3 (blood pressure by lesion categories) contingency table, one such table for each tissue. In this context, the authors concluded". ... at the time of death almost every chronic hypertensive (97 %) has renal arteriolar sclerosis in some degree, that few non-hypertensives (12 %) have any renal arteriolar sclerosis, and that in only 2 % of the non-hypertensives is there more than mild arteriolar nephrosclerosis ... No comparable correlation could be found in the case of any other organ or tissue."

We used correlation coefficients because we needed efficient use of quantitative information with the small numbers of subjects available to us. In the

comparisons between kidney and liver and between kidney and adrenal gland, our results agree with those of Moritz and Oldt (1937) that kidney lesions correlated with blood pressure levels significantly better than did those of other tissues. Only one disagreement emerged. We failed to confirm their conclusion that the pancreas differs significantly from the kidney in the magnitude of the correlation between lesions and blood pressure ($r = 0.499$ and 0.545 respectively). Using these two coefficients in the multivariate context of intercorrelations, we can show that these differences could be declared significant if they had been determined from about 250 subjects rather than 66. If we had been able to continue collecting suitable autopsy specimens, the larger number of subjects (250) is the projected estimate of what would be needed to provide sufficient information to detect (statistically) a significant difference.

This study differed from that of the 1937 report in several ways. We confined our attention to fibroproliferative-mediodegenerative lesions of interlobular arteries and excluded hyaline lesions of arterioles. Our grading of tissues was on a continuous, quantitative scale using specially prepared replication of slides instead of a semiquantitative score to be assigned subjectively to each tissue. Average blood pressure was used on a continuous scale instead of being classed into hypertensive and normotensive. Most important, the previous study discarded an unspecified number of subjects having blood pressure between the rather stringently defined exceptionally low (normotensive) and high (hypertensive) extremes. Presumably a large number of such intermediate subjects were excluded. Discarding the middle range would be expected to magnify any underlying natural correlation, and the amount of the magnification cannot be computed. Given these numerous points of difference between the two studies, it seems remarkable that the meaningful results are so closely similar. Our failure to confirm the significance of the statistical difference between kidney and pancreas might easily be the consequence of having too few subjects.

We have estimated the correlations between blood pressure and arteriolar lesions of the kidney to be 0.545, 0.588, and 0.624 in different assortments of subjects (0.758 after adjustment for measureable sources of error, cf. Appendix I). In earlier reports of other assortments of subjects (Tracy et al. 1970c; Tracy et al. 1974a) the estimates were 0.696 and 0.620. These are the minimum magnitudes of association that are measurable in practice. For liver the comparable correlations were 0.255 and 0.250 (Table 1 and 2) and these were less than those for the kidney to a statistically significant degree. Measurable sources of method error could not explain the substantially lower value for the liver (Appendix I). Subjects with renal lesions and high blood pressure sometimes lacked appropriately severe lesions in the liver; mild renal lesions accompanying low blood pressure was sometimes found in subjects with severe liver lesions. Our ability to reproduce these observations of Moritz and Oldt, together with our ability to show that the findings cannot be explained by artifacts of method error, indicates that a biological explanation is required to account for them.

In those subjects with lengthy documentation of normal blood pressure (confirmed by the absence of significant renal lesions), severe arteriolar lesions sometimes found in the liver must be explained by outside causes not related to blood pressure. The necessity to invoke such outside causes, at least in a limited

context, appears well established. The place where this is most clearly apparent is the spleen. Arteriolar sclerosis is seen in the spleen in many young normotensive subjects, often to a severe degree. Moritz and Oldt have shown this also in the intestine, skeletal muscle, and testis so clearly that we felt no need to reexamine those tissues. On the hypothesis that hypertension dominates the causation of lesions in the kidney, we are forced to consider the various ways that two sets of causes might interact differently in various parts of the body. Each of the two sets of causes, the hypertension and the outside influences, could hypothetically contribute from 0% to 100% to the causation of arteriolar sclerosis in this or that tissue. Locally selective susceptibilities and resistances to the effects of each of the two sets of causes would have to be considered differently in each tissue.

The study reported by Moritz and Oldt, which we have in one aspect largely confirmed, raises some issues that would not otherwise require consideration. Outside causes of lesions besides hypertension, and locally selective protection against one or the other sets of causation in this or that tissue, are concepts that emerge from the study of autopsied human subjects, as done here. These findings and the issues that they raise seem to require reemphasis, because they now appear to be well enough documented to require integration into an overall theory of hypertension.

These newly reintroduced issues can be examined along with data of another sort (Tracy et al. 1974a, b). When blood pressure measurements were followed up for several years, 25 of 49 hypertensive subjects were observed to become normotensive for periods ranging from 2 months to 18 years. The spontaneous disappearance of hypertension could not be related to heart failure or to medication, but did characteristically accompany cancer. In seven of seven former hypertensives who died of cancer, hypertension vanished in the presence of cancer. In the 25 subjects whose hypertension disappeared, renal arteriolar sclerosis averaged significantly less than in the subjects who remained hypertensive to the time of death. Among those subjects whose records initially indicated normotensive blood pressures, 15 were subsequently documented to become hypertensive and they remained so for periods ranging from 2 months to 28 years. The average renal arplasia in those 15 subjects was severe. The duration of the newly acquired high level or low level of BP_a was unrelated to the severity of arplasia. After a spontaneous onset of sustained high blood pressure, the severity of renal lesions did not increase with time; after spontaneous disappearance of hypertension, lesion severity was immediately lessened and did not decline further with time. In both situations there was no lag between the changing level of blood pressure and the extent of lesions; the duration of the newly acquired high or low levels was inconsequential. No effect by duration of BP_a on extent of lesions in any of the four tissues examined in this study could be detected (cf. footnote, Table A2), in agreement with the former findings.

These results support the view that renal arteriolar lesions come and go-sometimes progressing, sometimes regressing-spontaneously, for unknown reasons largely without regard to blood pressure, but that the level of blood pressure is determined in large part by the extent of arteriolar lesions in the kidney. Coleman et al. (1975) commented, "We are also left wondering what, in

this scheme, might prevent the occurrence of a vicious cycle of high blood pressure causing renal constriction and renal constriction causing, as Goldblatt has shown, an even higher pressure. Such a vicious cycle would undoubtedly go to completion very rapidly. In contrast, essential hypertensives often show a relatively stable pressure over several decades." In the vicious circle of high blood pressure leading to lesions followed by high blood pressure, etc., the stage of lesions of unknown origin followed by high blood pressure appears to be the dominant force. This interpretation is in keeping with the findings of this and all other reported quantitative studies of autopsied human subjects. Widening of the discussion into clinical or experimental areas is beyond the scope of this report.

Conclusions

Our results confirm the report of Moritz and Oldt (1937) that blood pressure tends to be reflected by the severity of lesions of arterioles in other tissues besides the kidney. This finding appears well established. Our results further reproduce the observations that blood pressure is reflected more strongly by lesions in the kidney than by lesions in the liver or the adrenal gland. Our failure to confirm a similar conclusion with regard to the pancreas is perplexing and might derive from difference of method, or possibly from an excessively small number of subjects in our study. The conclusion of biological importance, that lesions of arterioles in the kidney are preeminent over those in all other tissues in their synchrony with blood pressure, has been largely confirmed but remains in doubt with respect to the pancreas.

Appendix I: Correlation Coefficient with Effect of Measurement Errors Removed

The statistical association between quantities observed in biological systems is almost always obscured by many extraneous sources of variability entering into the quantities. In spite of the extraneous influences, summary data for a large group of subjects often exhibit a certain amount of statistical regularity so that general trends can be observed in search of biological relationships. Obviously, if a researcher can control the major sources of external influences, then biological relationships of interest should be more readily discerned. One major source of external variability in many situations is measurement error, i.e., the failure of two observations, made independently and under the same conditions, to be identical. Refining techniques and training observers can reduce measurement errors considerably; however, biological data will virtually always contain a certain amount of uncontrolled measurement error.

Measurement errors have an attenuating effect on the correlation coefficient in the sense that the magnitude of the correlation coefficient diminishes as that of measurement errors increases (Walker et al. 1953). Although often overlooked, it is possible to estimate variability due to measurement errors and adjust the usual correlation coefficient so that the revised value estimates the underlying association in the absence of measurement errors. In this context, if biological variability and measurement errors were the only sources of variabili-

ty present, the revised value would provide an estimate of the underlying association which is larger in magnitude than the unadjusted estimate.

In the present study, the component of variability due to measurement error was estimated and found to be of a reasonable order of magnitude relative to the total variability. The remainder of Appendix I is concerned with the derivation of a useful formula for the adjusted correlation coefficient together with illustrating its application in terms of the data presented.

Suppose that for each subject i, variables u and v are measured with m_i independent replicates of u and n_i independent replicates of v all made under the same conditions. Let $\bar{u}_i$ and $\bar{v}_i$ be the respective means of these observations for the i-th subject. The usual formula for the correlation coefficient can be applied using the $\bar{u}_i$ and $\bar{v}_i$ to obtain an estimate of the statistical association between u and v and this has the form

$$r_{\bar{u}\bar{v}} = s_{\bar{u}\bar{v}} / \sqrt{s_{\bar{u}} s_{\bar{v}}} \tag{A1}$$

where $s_{\bar{u}\bar{v}}$ is the sample covariance between the $\bar{u}_i$ and the $\bar{v}_i$, $s_{\bar{u}}$ is the sample variance of the $\bar{u}_i$, and $s_{\bar{v}}$ is the sample variance of the $\bar{v}_i$. The resulting value of $r_{\bar{u}\bar{v}}$ is an estimate of the association between u and v. This notation will be used throughout to denote the covariance, the variance, and the correlation coefficient of the variable(s) in the subscript. In general, the variables u and v may be influenced by measurement errors. Let x and y denote the hypothetical true values of u and v, free of error; i.e., let $u-x=e$ and $v-y=f$ be the respective measurement errors made in observing these two variables. An estimate of the correlation between x and y is desired from the observed quantities $\bar{u}_i$ and $\bar{v}_i$. Assuming error terms e and f are independent of each other and of x and y, it is easy to show that the covariance between u and v is the same as the covariance between x and y; i.e., $s_{\bar{u}\bar{v}} = s_{xy}$. Based on the average variances for $\bar{u}_i$ and $\bar{v}_i$, respectively, the variances for $\bar{u}$ and $\bar{v}$ over the entire sample of N subjects are

$$s_{\bar{u}} = s_x + c_m s_e$$

and

$$s_{\bar{v}} = s_y + c_n s_f$$

where

$$c_m = \frac{1}{N} \Sigma \left(\frac{1}{m_i} \right)$$

and

$$c_n = \frac{1}{N} \Sigma \left(\frac{1}{n_i} \right).$$

Hence,

$$r_{xy} = \frac{s_{xy}}{\sqrt{s_x s_y}} = \frac{s_{xy} / \sqrt{s_{\bar{u}} s_{\bar{v}}}}{\sqrt{\left(\frac{s_{\bar{u}} - c_m s_e}{s_{\bar{u}}} \right) \left(\frac{s_{\bar{v}} - c_n s_f}{s_{\bar{v}}} \right)}}. \tag{A2}$$

Letting $d_e = c_m s_e / s_{\bar{u}}$ and $d_f = c_n s_f / s_{\bar{v}}$ the above equation simplifies to

$$r_{xy} = r_{\bar{u}\bar{v}} / \sqrt{(1-d_e)(1-d_f)} \tag{A3}$$

which is the adjusted correlation coefficient.

As an example we find in Table 2 that the correlation between kidney and pancreas is 0.678. This is $r_{\bar{u}\bar{v}}$, the correlation between means of actually measured variables including error. The variances among replicate slides from Table A1 are $s_e = 0.071$ and $s_f = 0.046$ for kidney and pancreas respectively; hence $c_m s_e = 0.0118$ and $c_n s_f = 0.0077$ where $c_m = c_n = 1/6$. The variances among cases of the means of six slides are given in Table A1 to be 0.448 and 0.297; these are our estimates of $s_{\bar{u}}$ and $s_{\bar{v}}$. Substituting into Eq. (A3) yields (where adj denotes adjusted)

$$\text{adj}\, r = 0.678 \Big/ \sqrt{\left(1 - \frac{0.0118}{0.448}\right)\left(1 - \frac{0.0077}{0.297}\right)} = 0.696.$$

This is the estimated "true" correlation between arplasia indices of kidney and pancreas if these estimated magnitudes of error were absent.

The situation with regard to blood pressure is somewhat different. Blood pressure as recorded in hospital charts fluctuates from time to time with a measurable variance. This was 20.6 averaged over subjects in this study. Another source of error, however, should also be considered. When pressure is measured simultaneously in the two arms, directly by arterial puncture and indirectly by ballon cuff, the two readings usually differ. On the average, the mean of these differences tends toward zero. The variance of the differences, however, is substantial. It has been estimated as 70.6 mm Hg for the mean pressure [(S $+2$D)] $\div 3$ (Tracy 1970c). Given that we are dealing with two uncorrelated sources of error and that the variance of the sum equals the sum of the variances, the variances from these two sources of error can be added in the final assessment and used as s_f in Eq. (A3); i.e., $s_f = 20.6 + 70.6 = 91.2$. Also from Table A1, $s_{\bar{v}} = 299$.

Therefore, the correlations between blood pressure level and lesion severity in the kidney and between blood pressure level and lesion severity in the pancreas, adjusted for error as estimated by prior measurement, are:

$$\text{adj}\, r = 0.624 \Big/ \sqrt{\left(1 - \frac{0.0118}{0.448}\right)\left(1 - \frac{91.2}{299}\right)} = 0.758,$$

$$\text{adj}\, r - 0.556 \Big/ \sqrt{\left(1 - \frac{0.0077}{0.297}\right)\left(1 - \frac{91.2}{299}\right)} = 0.676.$$

Using these three adjusted correlations in the Hotelling test yields $t = 1.152$ for the difference between 0.758 for the kidney and 0.676 for the pancreas. Similarly adjusted tests were done for the comparisons in Table 1, and the t values are entered there.

Table A1. Number of subjects, mean arplasia index, sources of variation for tissue index (2-way ANOVA; slides x subjects = 6 X N) for selected tissues; subsamples having complete data for paired comparisons between tissues

	Number of subjects	Mean index	Variance among slides[a]	Variance among subjects[b]
Kidney	66	1.57	0.071	0.448
Pancreas	49	1.17	0.046	0.297
Adrenal	58	0.94	0.105	0.223
Liver	62	0.75	0.077	0.198
BP_a	66	114.1	(91.2)	298.9

[a] In the computation of adjusted correlations ($r_{xy}=r_{\bar{u}\bar{v}}/\sqrt{(1-cs_e/s_{\bar{u}})(1-cs_f/s_{\bar{v}})}$ table entries here are used as s_e and s_f for appropriate pairings; $c=1/6$ (i.e., 6 replicate slides in all cases) for tissues and $c=0.152$ for BP (i.e., $(\Sigma 1/n)/N$, where n is number of reading in subject i and N is number of subjects). For BP, variance of 91.2 is a sum of two components as explained in the text

[b] These are used as $s_{\bar{u}}$ or $s_{\bar{v}}$ as appropriate for selected pairings

Notice that the ratio of the variances for error to variances for subjects is greater for blood pressure (30.5%) than for tissue lesions (6.4%). For purposes of this kind of study, the barriers to accurate assessment of blood pressure are more substantial than are the imprecisions of measurement of tissue lesions. Of particular interest is that the evaluations of the impact of measurement error carried out in this appendix, while increasing the correlation coefficients, do not alter the conclusions in the body of this paper.

Appendix II: Multiple Regression Analysis

Variables offered for analysis by multiple regression were Kid, Pan, Adr, and Liv (arplasia indices for kidney, pancreas, adrenal, and liver respectively), BP_a, BP_b (average mean pressure after and before transition), Age (age at autopsy), and Prod (product of P_a minus P_b times the duration of the pressure difference from transition to death).

The bivariate correlation of Kid with BP_a, $r=0.556$, was improved only to $r=0.609$ by inclusion of Age, Prod, and BP_b. Age entering at the second step was barely significant at $P<0.05$, but Prod at the third step and BP_b at the fourth were not (Table A2). These results and the structure of the final equation agree with the results of a series of 155 cases previously reported (Tracy et al. 1974a, b). However, 49 of the present 66 cases were also among the 155 cases in the former series and therefore the findings in the two studies are not wholly independent. We can say only that no disagreements have emerged.

Results for the pancreas were in some ways similar to those for the kidney. The bivariate correlation between Pan and BP_a ($r=0.500$) was improved by the full equation ($r=0.581$) only slightly. Instead of Age it was BP_b that added a small but significant partial correlation in the second step (Table A2). For both pancreas and kidney, the bivariate correlations of lesions with Age, $r=0.043$ and 0.048, have no statistical significance and reflect the clear prominence of BP_a in the presence of no noticeable Age effect.

Table A2. Forward stepwise regression of arplasia indices in four tissues on selected variables[a]

Dependent variable		Independent variable order of entry				Constant	Multiple R
		1st	2nd	3rd	4th		
Kidney	Variable	*BP_a*	*Age*	Prod	BP_b	0.173	0.609
66 cases	Coefficient	9.80	4.15	0.04	0.11		
	% Variance	34.6	2.6	0.0	0.0		
	F-test	12.87	2.29	0.01	0.00		
Pancreas	Variable	*BP_a*	*BP_b*	Age	Prod	−0.365	0.581
49 cases	Coefficient	8.30	2.37	2.77	−0.33		
	% Variance	25.0	6.7	1.0	1.2		
	F-test	8.30	0.54	0.77	0.74		
Adrenal	Variable	*Age*	*BP_a*	*BP_b*	Prod	−0.875	0.683
58 cases	Coefficient	11.63	5.14	3.82	−0.04		
	% Variance	23.2	19.6	4.8	0.1		
	F-test	21.87	5.91	2.46	0.04		
Liver	Variable	*Age*	*BP_a*	BP_b	Prod	−0.292	0.443
62 cases	Coefficient	8.64	3.91	0.69	0.21		
	% Variance	9.1	10.1	0.1	0.4		
	F-test	8.95	1.85	0.05	0.30		

[a] Variables offered for entry were blood pressure before and after transition (BP_b and BP_a respectively), age at autopsy (Age), and the product (Prod) = ($BP_a - BP_b$) *DUR where DUR is the duration of BP_a between age of transition and death. Coefficients have been multiplied $\times 10^3$. Italics indicated $P < 0.05$ on entry, % Variance is the reduction at each step of forward entry, F-test is for significance of the first backward step of elimination form the full equation

These results contrast rather sharply with the findings for Adr and Liv. In those tissues the bivariate correlations of lesions with BP_a (0.350 and 0.255) were sharply increased by simultaneously considering Age (0.683 and 0.443 respectively, Table A2). Indeed, the bivariate correlations of lesions with Age exceeded those for BP_a (0.482 and 0.302 respectively). The partial correlations of BP_a and of Age with lesions were both slightly improved over bivariate correlations, and such improvement was true for both tissues.

The results tend to recall the reasoning of Moritz and Oldt that arteriolar sclerosis "... was essentially an aging phenomenon which developed precociously in some individuals... When the renal arterioles became sclerotic, hypertension is almost invariably present." This interpretation of the results fits well for data on kidney, adrenal, and liver. Blood pressure had small correlation with lesions in liver and adrenal, and therefore the relationship with age stands out. With the kidney, lesions were so strongly reflected in the blood pressure that age had no chance to show its effect. (The complete reasoning here is somewhat subtle. This series of cases was heavily weighted in particular with young hypertensive subjects, because those subjects were most apt to have the requisite clinical record of pressure readings and therefore to be included in this series. Hence, BP_a did not correlate with Age. Because Kid and BP_a are so strongly associated, Kid also therefore lost its correlation with Age. Liv and Adr, however, did not

Table A3. Forward stepwise regression of blood pressure after transition on selected variables in 43 cases in which complete data were available[a]

	Independent variable order of entry						Constant	Multiple R
	1st	2nd	3rd	4th	5th	6th		
3rd step								
Variable name	*Kid*	Age	BP_a				65.03	0.694
Coefficient	38.4	−0.410	0.252					
% Variance[b]	38.9	4.6	3.3					
F-test[c]	22.13	4.71	3.15					
6th step								
Variable name	*Kid*	Age	BP_b	Pan	Liv	Adr	71.06	0.715
Coefficient	36.2	−0.374	0.114	9.4	−13.6	12.2		
% Variance	38.9	4.6	3.3	1.3	1.1	0.9		
F-test	8.71	2.26	0.45	0.57	1.19	0.67		

[a] Arplasia indexes for kidney (Kid), pancreas (Pan), liver (Liv), and adrenal (Adr). BP_b is blood pressure before transition. $BP_a = 42.9\,Kid - 0.34\,Age + 83.61$. Mult $R = 0.659$ was the equation after the second step

[b] The reduction achieved on entry

[c] The amount achievable on removal on the first backward step from the complete equation

have the close association with BP_a, and therefore could reveal more clearly their link to Age.)

The findings with regard to the pancreas do not at first glance appear to support this simple interpretation. Another way of looking at the data is therefore helpful. In 43 cases, data were available for all tissues. Those data allowed testing of BP_a as simultaneously dependent on Kid, Pan, Adr, Liv, Age, and BP_b (Table A3). The raw correlation between BP_a and Kid of 0.624 was increased slightly but not significantly ($P = 0.05$) by Age (note the negative coefficient) and BP_b. At no step up to the complete equation did Pan, Adr, or Liv add appreciably to the multiple R. The easiest interpretation of this outcome is that Kid and Pan are so closely alike ($r = 0.678$ between the two variables) that Pan is nearly as good as Kid for predicting BP_a – not because Pan has an effect on blood pressure but because it tells us what Kid will prove to be. If this reasoning is true, then only a larger series of cases can resolve the matter. The significance of the difference of the two correlations BP_a vs Kid and BP_a vs Pan, whether yes or no, is required for a convincing conclusion.

We cannot help wonder what might be the nature of the apparently random factors that alter local tissue reactivity of the arterioles to developing lesions differently from one tissue to another. Some subjects have much disease in the liver and little in the adrenal gland whereas in other subjects this pattern is reversed. Although these variations appear to be random, nevertheless how are they mediated? To the extent that blood pressure governs formation of lesions, it may be that this influence is most important in the pancreas and kidney. Such an interpretation would explain some peculiar features of these data. This

conclusion, however, is reaching beyond the grasp of this single small series of cases. What emerges clearly is that these data are incompatible with the view of blood pressure as the sole or major cause of lesions in the liver or adrenal gland (and, as shown by Moritz and Oldt, spleen, intestine, and testes). A self-consistent theory can be constructed without invoking, at this time, a lesion-causing effect of blood pressure. What remains undecided is whether a minor degree of blood pressure effect should be added onto the clearly dominant actions of outside causes.

References

Coleman TG, Guyton AC, Young EB, DeClue JW, Norman RA, Manning RD (1975) The role of the kidney in essential hypertension. Clin Exp Pharm Physiol 12:571–581

Dunn OJ, Clark V (1971) Comparison of tests of the equality of dependent correlation coefficients. J Am Statistical Assoc 66:904–908

Fishberg AM (1925) Anatomic findings in essential hypertension. Arch Intern Med 35:650–668

Moritz AR, Oldt MR (1937) Arteriolar sclerosis in hypertensive and non-hypertensive individuals. Am J Pathol 13:679–728

Mowry RW (1960) Alcian blue and alcian blue-periodic acid Schiff stains for carbohydrate. AFIP Manual of Histologic and Special Staining Technics, 2nd edn. Armed Forces Institute of Pathology Washington p 142–144

Short D (1966) The vascular fault in chronic hypertension. Lancet 2:1302–1304

Short D (1967) The nature of the increased vascular resistance in chronic hypertension. Am Heart J 73:840–841

Stoddard LD, Puchtler H (1969) Human renal vascular lesions and hypertension. Pathol Ann 4:253–268

Tracy RE (1970a) Correlation of lengthy hospital records of blood pressure with nephrosclerosis. Am J Epidemiol 91:32–37

Tracy RE (1970b) Quantitative measures of the severity of hypertensive nephrosclerosis. Am J Epidemiol 91:25–31

Tracy RE (1970c) Weighted means of systolic and diastolic blood pressure in the comparison of direct with indirect measurements. Am J Epidemiol 91:21–24

Tracy RE, Overll EO (1966) Arterioles of perfusion-fixed hypertensive and aged kidneys. Arch Pathol 82:526–534

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

Tracy RE, Tabares Toca V (1974b) Nephrosclerosis and blood pressure II. Reversibility of proliferative arteriosclerosis. Lab Invest 30:30–34

Walker HM, Lev J (1953) Statistical inference. Henry Holt and Company New York p 299–301

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