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Histometrical Investigations of Arteries in Reference to Arterial Hypertension

By

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INTRODUCTION

The pathogenesis of hypertensive organ injuries and arterial lesions has been discussed from manifold viewpoints. Though a general agreement is not reached at present, the attempt to correlate high blood pressure itself to the development of hypertensive arterial lesions seems to be one of the most promising approaches to the problem. High blood pressure means an increased load on the circulatory system. Anatomical analysis of increased load on the system is at present only possible with the heart. Cardiac hypertrophy is an expression of accommodation of the organ to increased demand, and on the basis of anatomical changes it is possible to some extent to determine, in what way and to what extent the load is increased. However, cardiac hypertrophy is nothing more than an evidence of increased demand on the organ itself or of elevated blood pressure in large arteries and does not allow an adequate analysis of the character of hypertensive circulatory disturbances in the organs susceptible to hypertensive injuries.

Histological investigations of hypertensive circulatory disturbance have hitherto been practically confined to those of hypertensive arteriolar lesions, which represent already failed accommodation of the arterial system to elevated blood pressure. The direct expression of arterial accommodation to high blood pressure is expected to consist in reinforcement of arterial wall. In arteries of muscular type this will be achieved by medial hypertrophy. In extreme cases the change can easily be recognized by usual histological examinations, but a quantitative evaluation of hypertrophy is almost impossible, because there are no histometrical results available concerning the normal strength of arterial muscular coat. The major difficulty in the investigation of this direction is that arteries in autopsy cases or in histological slides cannot be regarded to correspond to the actual state of arteries in living organism. They are more or less con-

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stricted to the grade which is hardly imaginable when they are in equilibrium with blood pressure. In such a condition, direct measurements of arterial radius or of medial thickness will give only ambiguous and unreliable results. The attempt to avoid the error by means of perfusion of fixatives under certain pressure does not seem to give an essentially improved result, because muscular tension is lost in autopsy materials. In the present investigation a histometrical method*) is proposed, with which cross sections of arteries are reduced to the state, in which internal elastic membrane is perfectly stretched. It is not known, whether the condition represents the actual state of arteries in living organism, but the obtained results are sufficiently constant to warrant effective quantitative treatments of the anatomical strength of arterial media and determination of medial hypertrophy. The grade and distribution of medial hypertrophy in the arterial system will be an effective indicator in hemodynamical analysis of hypertension, just as different localization of cardiac hypertrophy indicates different types of increased load on the organ. On the basis of obtained results, attempts will be made to investigate the development of arteriolar lesions in relation to abnormal circulatory conditions in arterial hypertension.

HISTOMETRICAL TREATMENT OF THE TRUNK OF RENAL ARTERY

Prior to the introduction of the histometrical method proposed by the author, the results of usual histometrical treatment of arteries are presented, because the comparison of the two methods will contribute to clarify the present situation of the problem. In the majority of hitherto reported studies, quantitative evaluations were carried out on the trunk of arteries. A part of arteries was excised from a certain anatomically defined site and treated quantitatively according to the purpose of investigations. In the present study, the trunk of renal artery was employed for histometrical treatment. Renal artery acquired muscular character in several millimeters from the aorta. Exact cross sections of renal arteries about 1 cm apart from the aorta were taken from formalin fixed materials and examined in paraffin sections. At this site, elastic fibers of aortic media had already converged to elastic network of the adventitia and arterial media was practically devoid of thick elastic fibers. Histological slides were magnified, projected on tracing paper and delineated. The area of the media was planimetrically determined. The internal circumference of the media was determined by a curvimeter. In the latter measurement, delicate waving of internal elastic membrane in arterial cross section was neglected and the membrane was treated as if it were represented by an unwaved smooth line. The

*) The essentials of the method were already reported by N. Suwa, T. Takahashi, S. Arai, M. Furuyama and Y. Sasaki in Igakunoayumi, 1961, **37**, 188. Because the report was published in Japanese, the description of the method is reproduced in the present paper.

measurement was to give the radius of arteries as it was in autopsy specimen. The obtained quantities were reduced to the original dimension in histological slides by the calculation of magnifications. The cross sections of arteries in histological slides were rarely circular, but the radius, the distance from the center of arterial lumen to the middle point of the media, was calculated on the assumption, that the artery had an exact circular cross section and the muscular coat was uniform in thickness.

The radius of renal artery of the non-hypertensive determined by the above method revealed a rapid increase in the first two decades after birth and attained a value about 6–7 times larger than that of the newborn. In subsequent ages it still continued slowly to increase with increasing ages. The measurement gave an approximate estimation of the correlation of arterial radius with age, but it revealed at the same time a considerable deviation of individual values. The

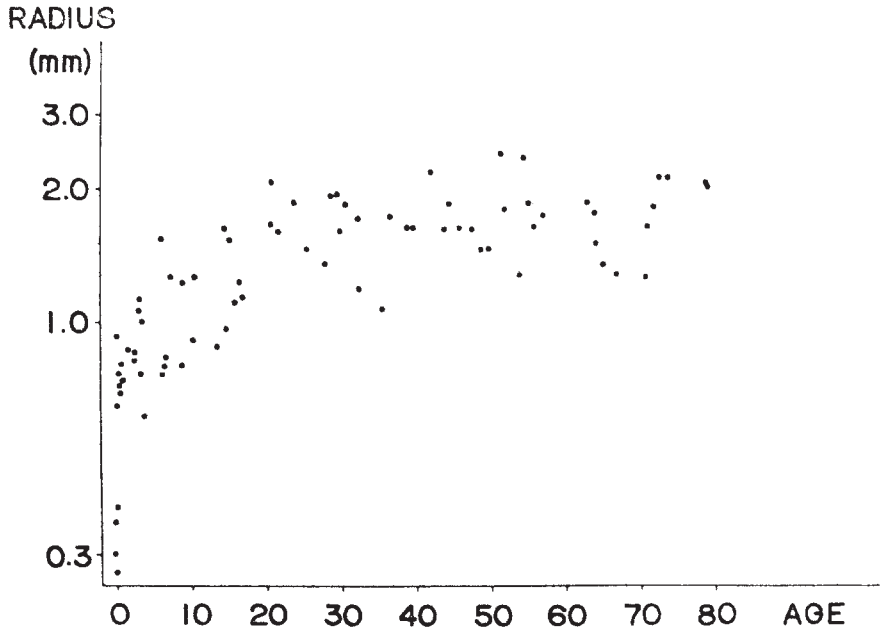

Fig. 1. Radius of the trunk of renal artery of the non-hypertensive in relation to age. Determination by usual histometrical method without stretching internal elastic membrane. Note highly scattered individual values.

major cause of deviation was attributed to varying degrees of arterial constriction in autopsy materials, which were indicated by different grades of waving of internal elastic membrane in arterial cross sections. It could hardly be expected, that this aspect of arteries in histological slides represented the state of arteries in living organism. The apparent constriction of arteries must be due to the major part to post-mortem changes.

Because the apparent constriction of arteries was regarded to be the major cause, which made the values of arterial radius in autopsy materials so divergent,

an attempt was made to eliminate this source of error by reducing arteries to the condition, in which internal elastic membrane was perfectly stretched. If arterial constriction in longitudinal direction is neglected, the surface area of the media in arterial cross section represents a constant quantity, independent of varying grades of arterial constriction. On this assumption, the radius R, the distance from the center of the arterial lumen to the middle point of the media, and medial thickness D of ideal arteries with exactly circular cross section, in which internal elastic membrane is perfectly stretched and medial thickness is uniform in every part of the arterial wall, can be calculated from the following equations.

$$\begin{cases} L = 2\pi(R - D/2) & (1) \\ S = 2\pi RD & (2) \end{cases}$$

L is the length of waved internal elastic membrane in arterial cross section and was measured by attaching thin cotton thread on the line of exactly depicted internal elastic membrane with high magnification. S is the planimetrically determined surface area of the media in arterial cross section. From the above equations R and D are given by:

$$R = \frac{S}{\sqrt{L^2 + 4\pi S} - L} \qquad (3)$$

$$D = \frac{\sqrt{L^2 + 4\pi S} - L}{2\pi} \qquad (4)$$

Fig. 2 shows the values of R of the non-hypertensive in reference to age. The

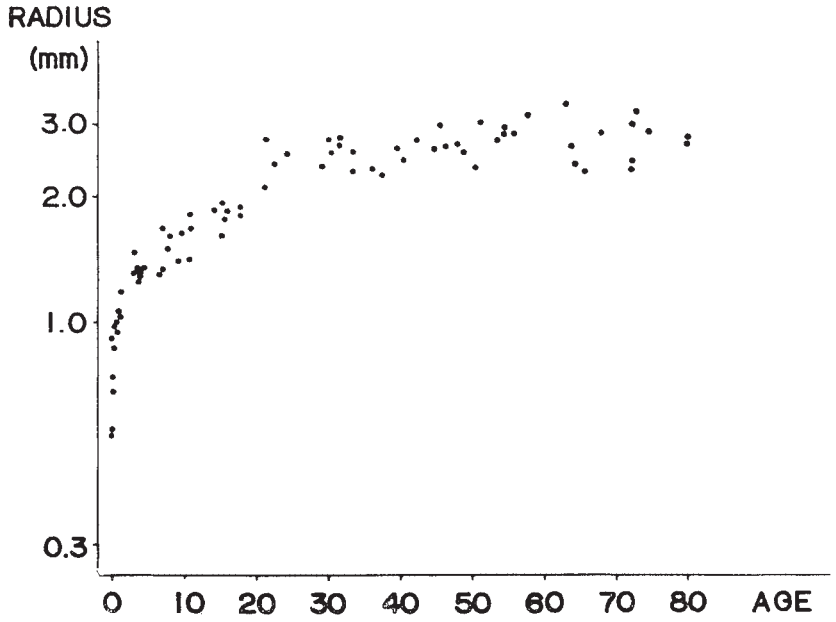

Fig. 2. Radius of the same arterial specimens as in Fig. 1, determined by the histometrical method of the author. Deviations of individual values are distinctly reduced, indicating post-mortem arterial constriction as the major cause of scattered values of arterial radius in autopsy materials.

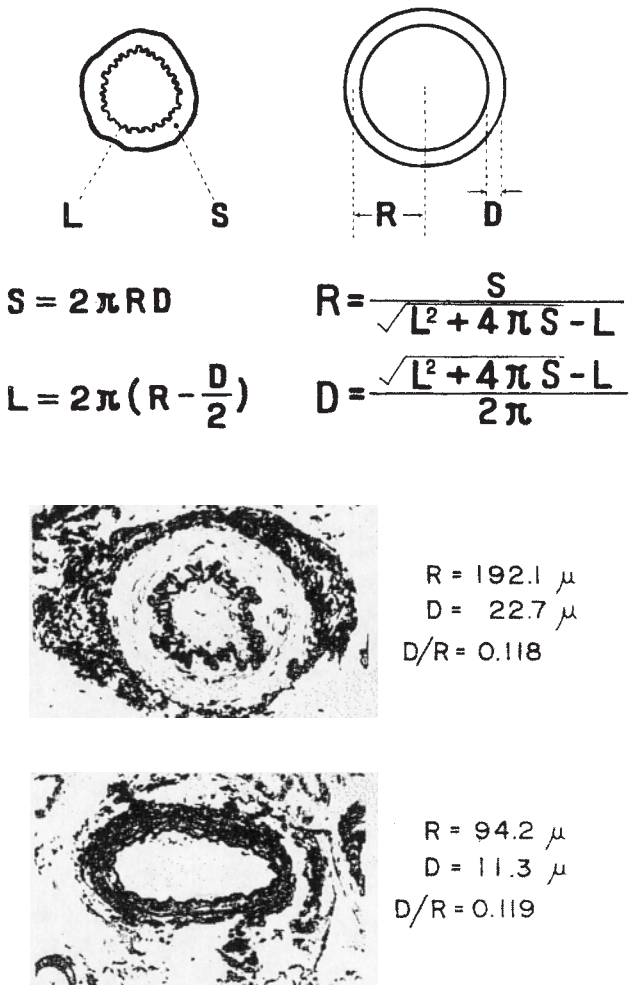

Fig. 3. The principle of the histometrical method of the author is illustrated together with two arterial cross sections of different post-mortem constriction. The different grade of post-mortem constriction is indicated by different waving of internal elastic membrane. Though the two arteries have quite different medial thickness in microscopical impression, the histometrical procedure of the author reveals almost identical media index or D/R ratio of the two arteries. Note the difficulty in the evaluation of medial strength by usual histological examination.

same tendency as in Fig. 1, in which the radius was determined without stretching internal elastic membrane, is clearly reproduced. The most remarkable difference of the two figures is distinctly reduced deviation of individual values in Fig. 2. It is not known, in what condition the arteries are in living organisms in reference to internal elastic membrane, nor is it possible to prescribe a definite radius to living artery, which can change its lumen as a result of active constriction. However, as the adopted procedure gave sufficiently constant and uniform values for arterial radius, the condition could be regarded to be the basic state of arteries and R was defined as anatomical arterial radius. In the following investigations R is employed as the estimate of arterial radius.

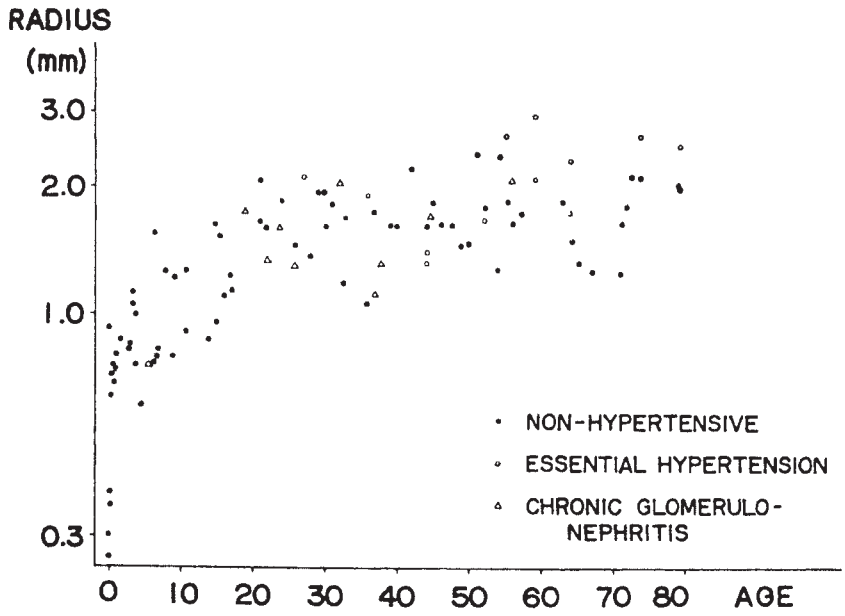

Fig. 4. Radius of the trunk of renal artery of the hypertensive in comparison to that of the non-hypertensive. The histometrical method is the same as in Fig. 1.

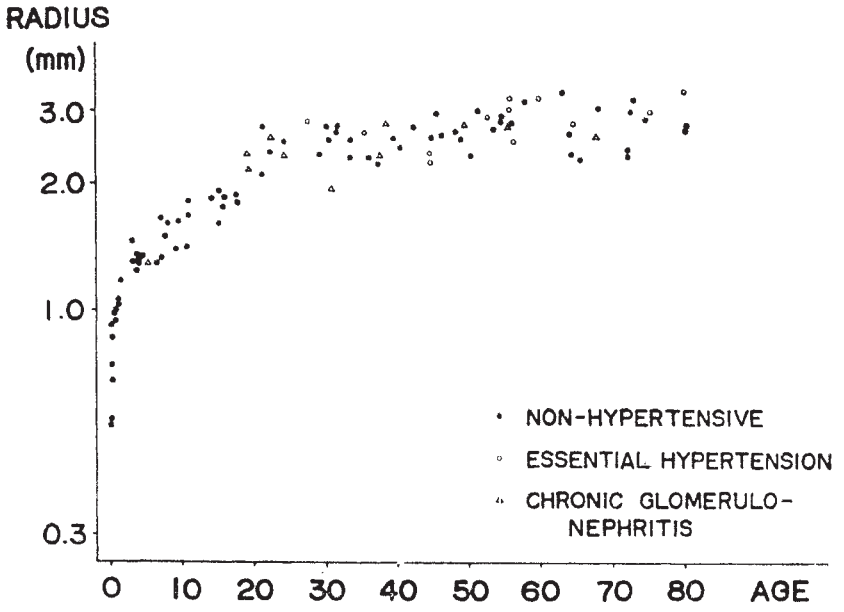

Fig. 5. Arterial specimens of Fig. 4 are treated by the method of the author. High blood pressure does not cause dilatation of arterial trunk. Apparent dilatation of arterial trunk of the aged hypertensive in Fig. 4 is not reproduced in Fig. 5, and is regarded to be due to diminished post-mortem arterial constriction.

Apart from the distinct correlation of R with age, another important fact demonstrated in Fig. 5 is that R is not influenced by high blood pressure. The arterial radius had the same value, whether the artery belonged to the hypertensive

or to the non-hypertensive. The apparent dilatation of renal artery in the aged hypertensive in Fig. 4, in which the radius was determined without stretching internal elastic membrane, was attributed to diminished post-mortem arterial constriction. The effect of hypertension was disclosed in increased S in cases of essential hypertension, but not in cases of chronic glomerulonephritis (Fig. 6).

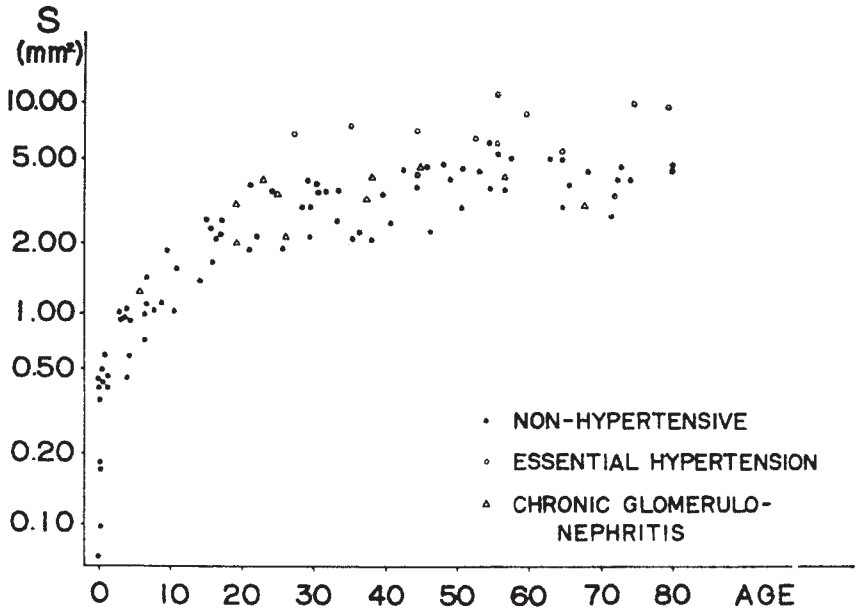

Fig. 6. Surface area of the media in cross section of the trunk of renal artery. The same specimens as in Figs. 4 and 5 are used for the determination. The values of S are elevated in the group of essential hypertension, but not in the group of chronic glomerulonephritis.

The reason of the apparently paradoxical result was revealed by quantitative evaluation of interstitial tissue of the media. Arterial media consisted not only of smooth muscle fibers, but also of varying amount of interstitial tissue. The proportion of muscular and interstitial tissues was planimetrically determined on magnified depictions of arterial media. The result is demonstrated in Fig. 7. The quantity of interstitial tissue occupied about 50% of the total quantity of the media in the trunk of renal artery of the non-hypertensive over 30 years of age. The proportion was approximately the same in the group of essential hypertension. Because the total surface area of medial cross section was increased in this group, an increase of absolute muscular quantity of the media was demonstrated. In the group of chronic glomerulonephritis, absolute quantity of muscular element was distinctly increased, but the proportion of interstitial tissue was much lower than that of the non-hypertensive. In the result, medial thickness remained in the normal range in spite of muscular hypertrophy. It was thus indicated, that arterial media responded to elevated blood pressure by muscular hypertrophy,

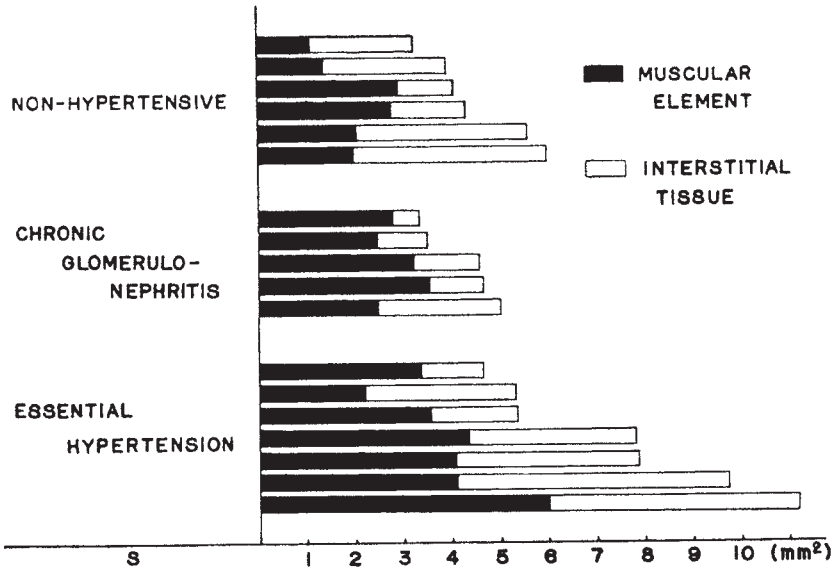

Fig. 7. The quantity of muscular element and interstitial tissue in the trunk of renal artery over 30 years of age. The mean quantity of muscular element in arterial cross section is:

non-hypertensive	$\bar{x}=2.09\pm0.73$ mm²
chronic glomerulonephritis	$\bar{x}=2.93\pm0.57$ mm²
essential hypertension	$\bar{x}=3.97\pm1.04$ mm².

Though the total medial quantity is increased only in the group of essential hypertension, the quantity of muscular element is increased not only in the group of essential hypertension, but also in the group of chronic glomerulonephritis. The difference between the non-hypertensive and each of the two hypertensive groups in the mean quantity of muscular element is significant at 5% level. The difference between chronic glomerulonephritis and essential hypertension is not significant at this level.

regardless of the cause of hypertension, but the effect of muscular hypertrophy could be obscured in the trunk, on account of extremely varying amount of its interstitial tissue. The result suggested the inadequacy of arterial trunk to represent the medial strength of the arterial system.

The quantity of interstitial tissue was reduced with progressive arterial ramification. The proportion of interstitial tissue in branches of 0.5–1.0 mm in radius of the corresponding renal arteries in Fig. 8 was already reduced to about 30%. It was further noticed, neither in the trunk nor in branches of renal artery, the proportion of interstitial tissue was higher in the hypertensive than in the non-hypertensive. The result greatly facilitates the treatment of S or D as the estimate of medial strength. If S or D is found increased in the hypertensive, it indicates at the same time an increase in muscular element, and not an increase of interstitial tissue with unincreased or decreased muscular volume.

APPLICATION OF THE HISTOMETRICAL METHOD ON THE WHOLE LENGTH OF ARTERIAL RAMIFICATION

Apart from the difficulties attaching to the arterial trunk, it is desirable to

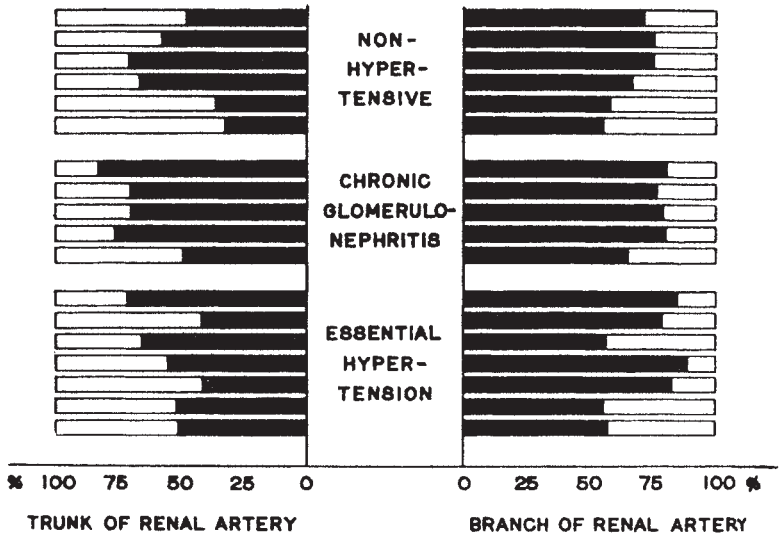

Fig. 8. The relative quantity of muscular element and interstitial tissue of the trunk of renal artery is compared to that of a branch of the same renal artery of 0.5 to 1.0 mm in radius. Muscular element is represented by black bars. The proportion of muscular element is increased in the branches and the deviation of individual values is diminished. The diagram indicates, that the trunk of arteries is an unsuitable part of the artery for histometrical evaluation of medial strength. More constant results are expected from smaller arterial branches.

estimate the medial strength in the whole range of arterial ramification, because perfect regulatory function of arteries can hardly be fulfilled by a small part of their whole length. The author's histometrical method was applied to renal and superior mesenteric arteries. The former was regarded as a representative of organ arteries, associated with high incidence of hypertensive arteriolar lesions, and the latter as one of the arteries, in which the lesions were only rarely encountered. It was expected, that a comparative study of the two arteries would give some clues to elucidate the pathogenesis of hypertensive arteriolar lesions.

About 20 exact cross sections of each arterial system were selected from histological slides, ranging from arterial trunk to the smallest arteries with distinctly discernible internal elastic membrane. Arterial branches with distinct fibrosis or other degenerative changes of the media were excluded from the investigation. The lower limit of determined arterioles was about 10μ in radius. Larger branches could be vertically excised and embedded in paraffin, and there was no difficulty in obtaining exact cross sections. Cross sections of smaller branches were determined by microscopical examination of histological slides. It was noticed that arteries of autopsy materials were only rarely circular in cross section. They were more or less compressed by the surrounding tissue, because they were not expanded by blood pressure. The sections of arteries in which internal elastic membrane was sharply linear and muscle fibers of the media were longitudinally demonstrated, were regarded to be sufficiently exact

cross sections. The extent of possible errors arising from inaccurately selected cross sections could be mathematically determined. If the angle of deviation was smaller than 30°, the errors of R and D were estimated to be smaller than 7.6% and 7.3%, respectively. The errors of D/R is accordingly negligible, and regression equations from the measurements are not seriously influenced by errors of this range.

The selected arterial cross sections were magnified to dimensions sufficient for the determination of S and L, projected on tracing paper and delineated. The whole procedure was the same as described in the measurement of arterial trunk.

A regular relation was found between R and D. The values of R and D calculated from equations (3) and (4), when plotted on a logarithmic scale, gave a distinct linear regression with relatively small deviations. Accordingly, the relation could be expressed by a general formula, $\hat{Y}=bX+A$, in which $X=\log R$, $Y=\log D$ and b and A were constants. The regression coefficient b was given by $b=Sxy/Sx^2$, in which $Sx^2=\Sigma(X_i-\bar{x})^2$ and $Sxy=\Sigma(X_i-\bar{x})(Y_i-\bar{y})$, $\bar{x}$ and $\bar{y}$ being the mean of X and Y, respectively. Accordingly, the relation of R and D was expressed by $D=aR^b$, in which $\log a=A$. This is one of the most familiar biological functions and is known as Huxley's formula of allometric growth.

A representative case is shown in Fig. 9. Each of the two arteries is composed of two parts divided at $R=100\mu$. In the region $R>100\mu$, regression

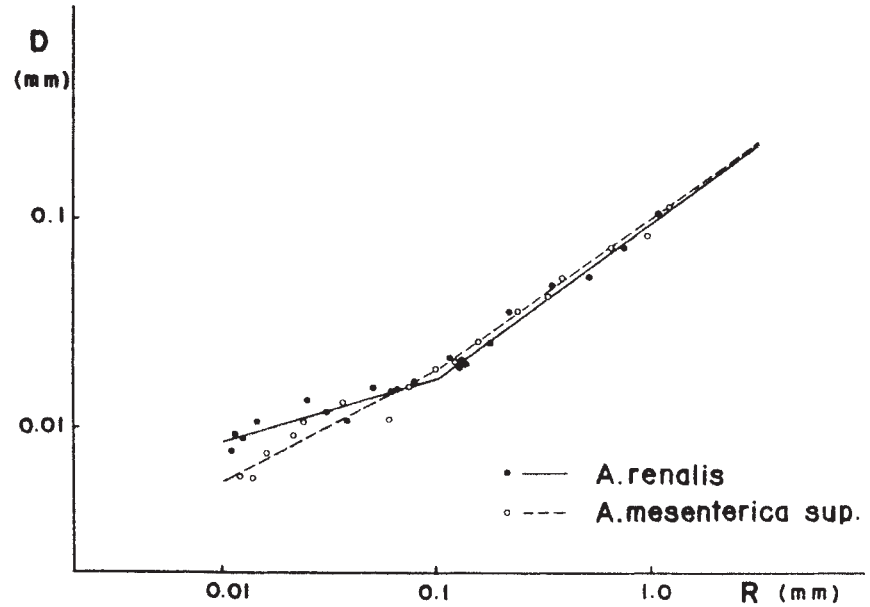

Fig. 9. Arterial pattern of a 1-year-4-month-old female. Death by acute dyspepsia. Equations expressed in mm for renal artery are $D=0.099R^{0.75}$ ($R>100\mu$) and $D=0.035R^{0.30}$ ($R<100\mu$), and those for superior mesenteric artery are $D=0.100R^{0.74}$ ($R>100\mu$) and $D=0.059R^{0.50}$ ($R<100\mu$). Note the deflection of regression lines at $R=100\mu$, especially of renal artery.

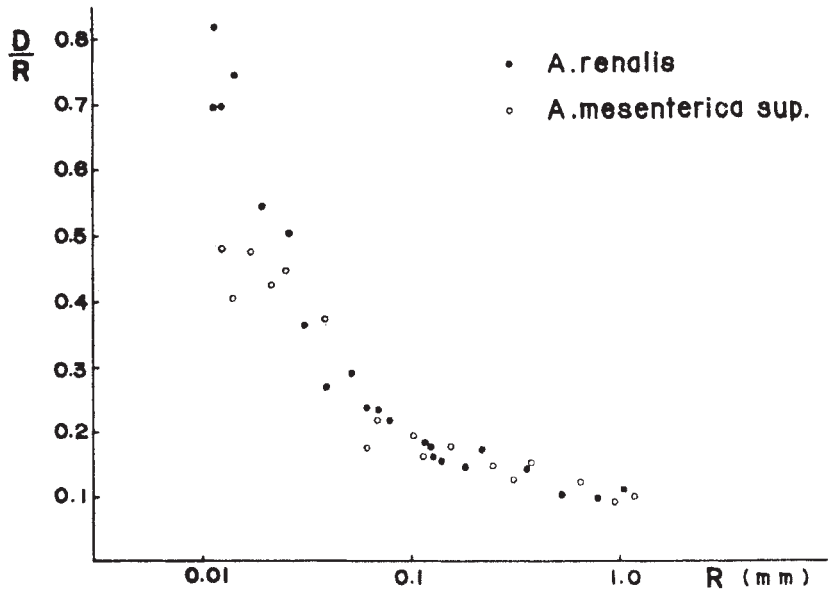

Fig. 10. Media index or D/R ratio of the arteries in Fig. 9 is demonstrated in relation to arterial radius. Note a rapid elevation of the index with decreasing arterial radius in the region $R<100\mu$. Arterioles are accordingly equipped with excessively strong muscular coat, though blood pressure is assumed considerably lowered in the region. This will indicate, that arterioles are the most active part in the whole range of arterial branches in the normal regulation of blood stream.

coefficient b is only a little smaller than 1, while in the region $R<100\mu$ the value of b is distinctly lower. This indicates a rapid elevation of the ratio D/R in the region of small arteries. The junction of the two parts of each artery at $R=100\mu$ is not influenced by the growth and anatomical structure of the organ. In the kidney of the newborn the arterial branch at $R=100\mu$ corresponds to A. interlobaris or to A. arciformis, while in the adult the region is represented by the proximal part of A. interlobularis. The difference between the regression equations of the two parts of each artery must be attributed to still unclarified different physical conditions of blood circulation and not to the principle of anatomical structure of the organ.

The deflection of linear regression at $R=100\mu$ was not caused by varying amount of interstitial tissue of the media according to arterial ramification. In Fig. 11, values of R and D of renal artery of a 24–year–old non–hypertensive male are demonstrated with the determination of muscular element in each of the selected arterial cross sections. The deflection of linear regression at $R=100\mu$ was not eliminated, even if the artery was entirely reduced to muscular element.

In the part $R<100\mu$, renal artery has always a smaller regression coefficient than superior mesenteric artery, indicating remarkable development of muscular coat in arteriolar region. In the region $R>100\mu$, the ratio D/R is always higher in superior mesenteric artery. This means that superior mesenteric artery has stronger muscular coat in this region in comparison to renal artery of the same

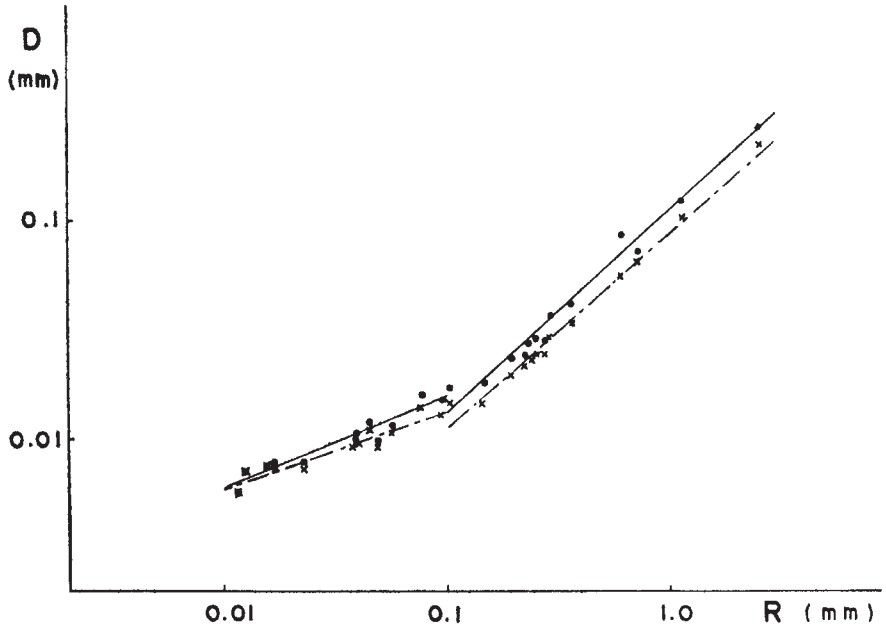

Fig. 11. Renal artery of a 24-year-old non-hypertensive male. The values by the author's histometrical method are given by black dots. In each cross section of arterial branches, relative quantity of muscular element is planimetrically determined, and the medial thickness is adjusted to represent the thickness of muscular element. The obtained values are given by × in the diagram. Regression equations for total medial thickness are $D=0.11R^{0.92}$ ($R>100\mu$) and $D=0.041R^{0.42}$ ($R<100\mu$). Those for muscular element are $D=0.088R^{0.90}$ ($R>100\mu$) and $D=0.030R^{0.35}$ ($R<100\mu$). Regression equations are expressed in mm. Note persisting deflection of the regression line at $R=100\mu$, even if the media is reduced to muscular element. The quantity of interstitial tissue is reduced with reduction of arterial radius.

radius. The histometrical difference suggests different regulatory function of the two arteries, which will be discussed later.

STATISTICAL TREATMENTS OF HISTOMETRICAL RESULTS

Because the results of the present histometrical investigation revealed a linear regression, it is adequate to note necessary statistical treatments of regression to facilitate further investigations. Individual measurements of an artery are distributed around the regression equation $\hat{Y}=bX+A$. The character of the distribution can be estimated by the distribution of $Y_i-\hat{Y}_i$ around the mean O. Y_i is a value obtained by actual measurements. The hypothesis of normal distribution of $Y_i-\hat{Y}_i$ was not rejected with the relatively small number of measurements about 20. It was further not demonstrated, that the value $Y_i-\hat{Y}_i$ was correlated to X. Accordingly, on the assumption that $Y_i-\hat{Y}_i$ is normally distributed and there is no difference in the values of $Y_i-\hat{Y}_i$ according to the dimension of arterial branches, subsequent statistical treatments can be employed for the comparison of two given arterial systems.

When two regression equations are obtained from two sample groups or from two arterial systems, comparison of the two regression equations is necessary to determine, whether the two sample groups belong to two different populations. In other words, it must be tested, whether the two arterial systems are of different characters. The test is performed on the regression coefficient and on the elevation of the regression equation at a given X separately. The regression equations of two sample groups are given by $\hat{Y}_1=b_1X+A_1$ and $\hat{Y}_2=b_2X+A_2$, respectively. Of each sample group, n is the number of samples, $Sd^2y\cdot x$ is $\Sigma(Y_i-\hat{Y}_i)^2$, Sx^2 is the sum of squares of the deviations from $\bar{x}$, the sample mean for X, and x^2 is $(X-\bar{x})^2$. The sample standard deviation of the regression coefficient is given by $\sqrt{Sd^2y.x\,/\,Sx^2\,(n-2)}$, and the significance of the difference in regression coefficients is tested by the following formula.

$$t=|b_1-b_2|\,/\,\sqrt{S_1d^2y\cdot x\,/\,S_1x^2\,(n_1-2)+S_2d^2y\cdot x\,/\,S_2x^2\,(n_2-2)} \qquad (5)$$

The sample standard deviation of $\hat{Y}$ is given by $\sqrt{\dfrac{Sd^2y\cdot x}{n-2}\left(\dfrac{1}{n}+\dfrac{x^2}{Sx^2}\right)}$ and the significance of the difference in the elevation of regression equations or of estimated Y at a given X is tested by the following formula.

$$t=|\hat{Y}_1-\hat{Y}_2|\Big/\sqrt{\frac{S_1d^2y\cdot x}{n_1-2}\left(\frac{1}{n_1}+\frac{x_1^2}{S_1x^2}\right)+\frac{S_2d^2y\cdot x}{n_2-2}\left(\frac{1}{n_2}+\frac{x_2^2}{S_2x^2}\right)} \qquad (6)$$

If $S_1d^2y\cdot x/(n_1-2)$ and $S_2d^2y\cdot x/(n_2-2)$ are not significantly different in the F-test, the terms may be estimated by $(S_1d^2y\cdot x+S_2d^2y\cdot x)/(n_1+n_2-4)$, and if the difference between x_1^2 and x_2^2 is small, as it is usually the case, they may be substituted by x_T^2, the square of the deviation of X from the total mean. The formulae (5) and (6) are then transformed as follows.

$$t=|b_1-b_2|\Big/\sqrt{\frac{(S_1x^2+S_2x^2)\,(S_1d^2y\cdot x+S_2d^2y\cdot x)}{S_1x^2\cdot S_2x^2\cdot(n_1+n_2-4)}} \qquad (7)$$

$$t=\frac{|\hat{Y}_1-\hat{Y}_2|}{\sqrt{\dfrac{(n_1+n_2)\,(S_1d^2y\cdot x+S_2d^2y\cdot x)}{n_1n_2\,(n_1+n_2-4)}+\dfrac{(S_1x^2+S_2x^2)\,(S_1d^2y\cdot x+S_2d^2y\cdot x)}{S_1x^2\cdot S_2x^2\cdot(n_1+n_2-4)}\,x_T^2}} \qquad (8)$$

The last formula indicates, that the difference of estimated Y is tested in reference to the error, composed of two parts, the error of elevation at the adjusted means and the error due to the deviation of regression coefficients. If the obtained value of t is larger than that in the table of t-distribution at a desired level and with the degree of freedom n_1+n_2-4, the difference of the regression coefficients or the difference of estimated Y at the given X of the two sample groups is significant at the level. In other words, the two arteries may be regarded to be different in the slope of their regression equations or to be different in their medial thickness at the radius corresponding to X.

HISTOMETRICAL CHARACTERIZATION OF THE ARTERIES OF THE NON-HYPERTENSIVE

For the estimation of medial hypertrophy of the arteries of the hypertensive, a preliminary investigation is required about the normal range of arterial media in the corresponding age groups. Renal and superior mesenteric arteries of 45 autopsy cases, from 4 months to 75 years of age, were selected for the study. In all examined cases registered blood pressure was in the normal range and there was no clinical history of confirmed hypertension. The autopsy revealed no cardiac hypertrophy, nor any organ changes attributable to hypertension. The two arterial systems were treated by the above-mentioned histometrical

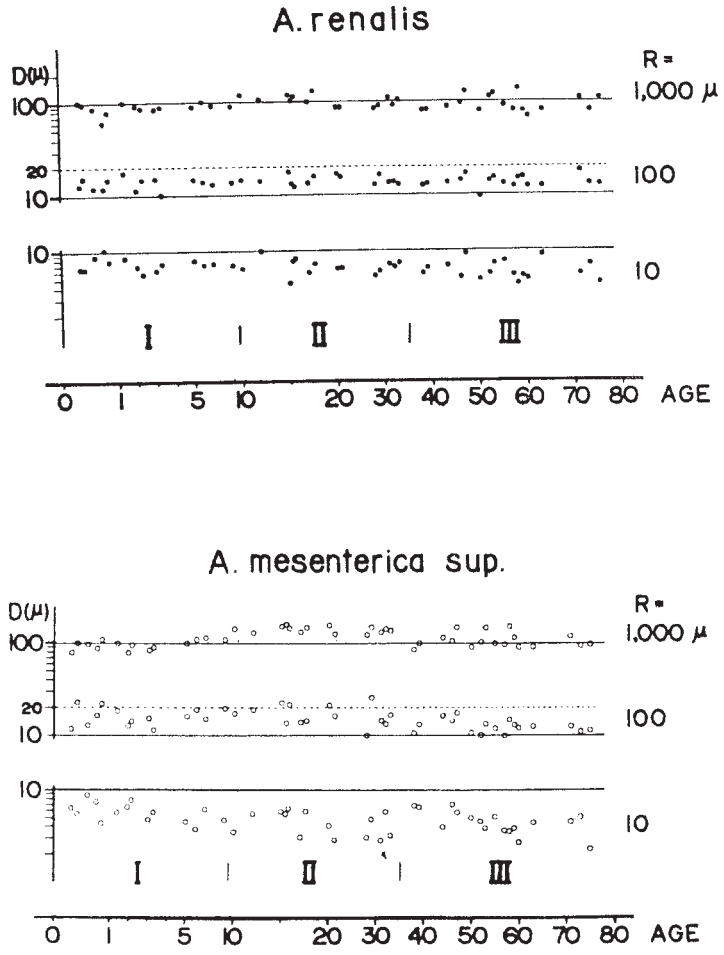

Fig. 12. Estimated D of the non-hypertensive at $R=1000\mu$, $R=100\mu$ and $R=10\mu$ is presented in relation to age. The values of estimated D at a given radius are strikingly constant throughout the life. Estimated D at $R=10\mu$ gradually falls with advancing age. Estimated D at $R=1000\mu$ of superior mesenteric artery attains the highest level in the second and third decades and declines with advancing age. The majority of the cases of the aged non-hypertensive is represented by cases of malignant tumor, and it remains unclarified, whether the decline of estimated D in this age group can be attributed to normal aging process, or to secondary atrophy due to general cachexia.

procedures and the regression equation was determined in each part of each artery, divided at $R=100\mu$. From the equations the estimated value of D could easily be calculated at any given R. The estimated D at three points, $R=1000\mu$, $R=100\mu$ and $R=10\mu$, gave a complete set of values, with which the character of the media was expressed in the whole arterial length. The point $R=100\mu$ was the junction of two parts of each artery with different regression equations. Accordingly, estimated D at $R=100\mu$ was not identical according to the equation employed. The mean of two values of $\hat{Y}$ or log D, obtained from each of the equations, was used as the estimate of medial strength at this point. Fig. 12 demonstrates the values of estimated D at the three points in relation to age. The value of estimated D at a given R is strikingly constant throughout the life. The recognizable variations of estimated D with age were that it fell gradually with advancing ages both in renal and superior mesenteric arteries at $R=10\mu$, and that it attained the highest level at $R=1000\mu$ in the second and third decades.

The examined cases were separated into three age groups of 0–9, 10–35 and 36–80 years, so that the values of estimated D were approximately uniform within each age group. In each of the three age groups Sx^2 and Sxy were pooled of each part of each artery and designated as ΣSx^2 and ΣSxy, respectively. All individual measurements in each age group were pooled of each part of each artery and the total means $\bar{x}_t$ and $\bar{y}_t$ were calculated by $\Sigma SX/\Sigma n$ and $\Sigma SY/\Sigma n$, SX and SY being the sum of X and Y in individual cases. The common regression equations were then determined by $(Y-\bar{y}_t)=\frac{\Sigma Sxy}{\Sigma Sx^2}(X-\bar{x}_t)$. The common regression equations of each age group are demonstrated in Fig. 13 and Table I. In all age groups, superior mesenteric artery had a higher value of estimated D than renal artery at $R=1000\mu$. On the contrary, estimated D of superior mesenteric artery at $R=10\mu$ was lower than that of renal artery. The difference was statistically significant in all age groups.**)

DETERMINATION OF MEDIAL HYPERTROPHY IN THE HYPERTENSIVE

In the previous section of the report, the range of estimated D of the non-hypertensive was discussed of the two arterial systems. On the basis of the result it is now possible theoretically to decide, if a given artery belongs to the non-hypertensive or not, by the determination of the upper rejection limit of estimated D of the non-hypertensive. Logarithm of the upper rejection limit of

**) The reason, why the "common", instead of the "total", regression equations were employed in the comparison of renal and superior mesenteric arteries, was that a highly significant correlation was confirmed between estimated D of the two arteries. The case, which had relatively high estimated D of renal artery had simultaneously relatively elevated estimated D of mesenteric artery, and vice versa. Because estimated D of the arteries could not be regarded to be two independent variables, common regression equations were preferred, in which between class deviations were eliminated.

TABLE I.

Age Group	Artery		n	$D=aR^b$ (mm)	$\hat{Y}=bX+A$ (log μ)	d. f. n-N-1	Sx^2	$Sd^2y.x/(n-N-1)$
I	A. renalis	$R>100\mu$	132	$D=0.085R^{0.78}$	$\hat{Y}=0.7867X-0.4294$	117	13.6418	0.002847
		$R<100\mu$	187	$D=0.022R^{0.25}$	$\hat{Y}=0.2506X+0.6075$	172	14.5054	0.002718
	A. mesenterica superior	$R>100\mu$	145	$D=0.098R^{0.82}$	$\hat{Y}=0.8223X-0.4751$	130	17.0828	0.003606
		$R<100\mu$	137	$D=0.051R^{0.47}$	$\hat{Y}=0.4779X+0.2784$	122	9.2377	0.004388
II	A. renalis	$R>100\mu$	144	$D=0.100R^{0.84}$	$\hat{Y}=0.8410X-0.5222$	129	21.3891	0.004161
		$R<100\mu$	132	$D=0.036R^{0.37}$	$\hat{Y}=0.3720X+0.4453$	117	8.7268	0.004384
	A. mesenterica superior	$R>100\mu$	150	$D=0.140R^{0.93}$	$\hat{Y}=0.9325X-0.6483$	135	25.9968	0.004693
		$R<100\mu$	108	$D=0.073R^{0.61}$	$\hat{Y}=0.6159X+0.0160$	93	6.5664	0.005486
III	A. renalis	$R>100\mu$	183	$D=0.092R^{0.83}$	$\hat{Y}=0.8323X-0.5315$	165	28.3098	0.004108
		$R<100\mu$	127	$D=0.033R^{0.37}$	$\hat{Y}=0.3760X+0.3914$	109	7.0415	0.003914
	A. mesenterica superior	$R>100\mu$	194	$D=0.106R^{0.90}$	$\hat{Y}=0.9006X-0.6751$	176	32.2776	0.006253
		$R<100\mu$	118	$D=0.031R^{0.42}$	$\hat{Y}=0.4233X+0.2348$	100	5.9016	0.004853

The number of measurements pooled for each common regression equation is given by n. N is the number of cases in each age group, which is given in Table II.

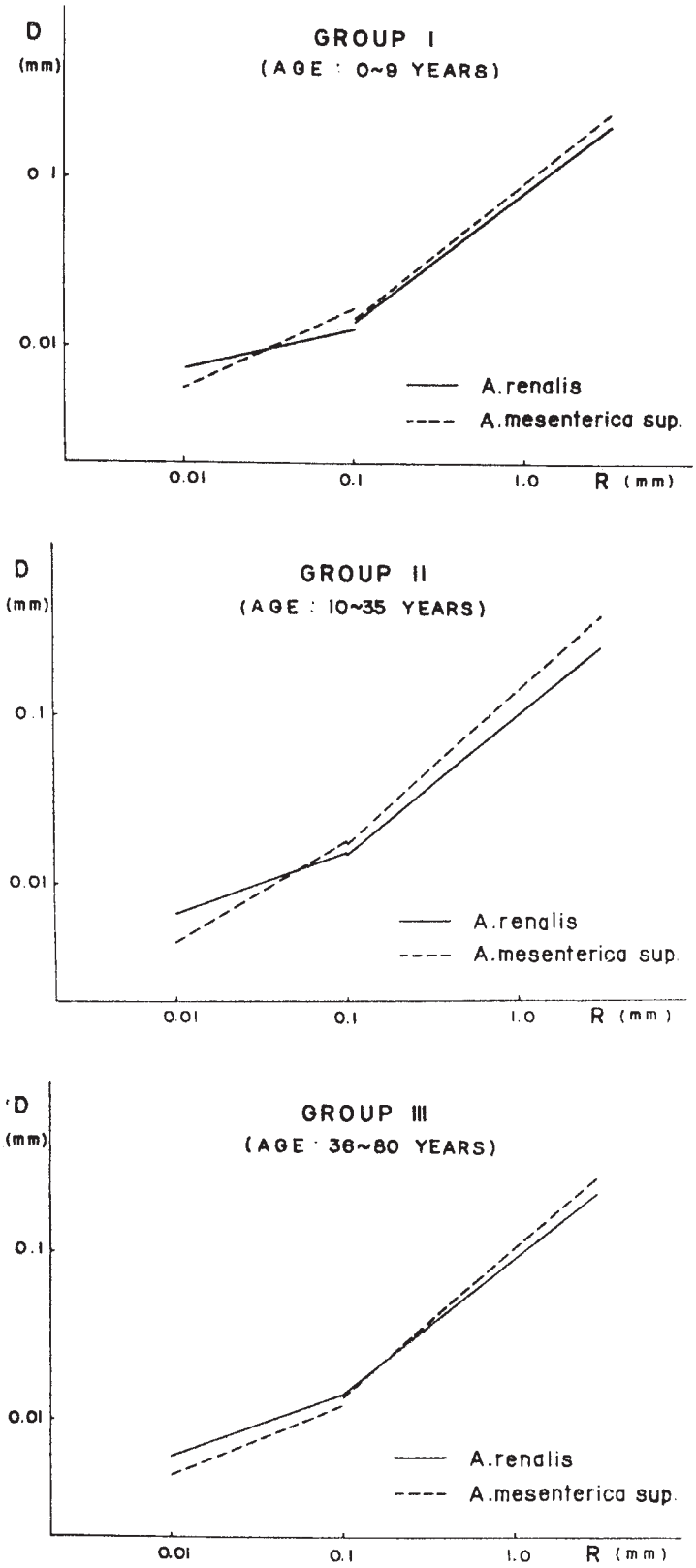

Fig. 13. The cases in Fig. 12 are divided into 3 age groups and common regression equations of each age group are diagrammatically shown. Though the general characteristics of the arterial pattern, stronger muscular coat at $R=1000\mu$ of superior mesenteric artery and at $R=10\mu$ of renal artery, are clearly recognized in all age groups, the difference of the two arteries is most remarkable in the second age group. In this age group, muscular coat of superior mesenteric artery is 40% stronger than that of renal artery at $R=1000\mu$, and muscular coat of renal artery is 50% stronger than that of superior mesenteric artery at $R=10\mu$.

estimated D at a given R is determined by $\bar{Y}+ts\sqrt{(N+1)/N}$, in which $\bar{Y}$ is the mean of estimated Y or $\hat{Y}$ from individual regression equations, N is the number of regression equations, s is the sample standard deviation of $\hat{Y}$, and t is given by the table of t-distribution at 5% level with the degree of freedom N–1. The obtained values of the upper rejection limit, together with those of $\bar{Y}$, at $R=1000\mu$, $R=100\mu$ and $R=10\mu$ are given in Table II. If estimated D from the regression equation of renal or superior mesenteric artery of any autopsy case is found over the upper rejection limit of the corresponding artery at any of the above radii, it is concluded that the artery does not belong to the non-hypertensive and has hypertrophied media.

Table II.

	Age Group	N	Upper Rejection Limit of Estimated D (μ) ($\alpha=0.05$)		
			$R=10\mu$	$R=100\mu$	$R=1000\mu$
A. renalis	I	14	10.26 (7.26)	18.38 (13.41)	118.0 (88.09)
	II	14	10.11 (6.64)	18.45 (14.27)	137.4 (102.0)
	III	17	9.83 (5.98)	18.63 (13.58)	145.2 (93.40)
A. mesenterica superior	I	14	9.98 (5.75)	26.25 (15.92)	126.5 (96.27)
	II	14	8.52 (4.27)	29.42 (16.57)	171.6 (140.0)
	III	17	8.69 (4.41)	17.67 (12.42)	135.2 (105.4)

The mean of estimated D at each radius is given by the figure in parenthesis just below the rejection limit. N is the number of cases in each age group.

In Fig. 14, a case of essential hypertension is demonstrated in comparison to the regression equation of the non-hypertensive of the corresponding age group. The measured values of D are evidently higher in the hypertensive case in the whole range of arterial branches and regression equations of both renal and superior mesenteric arteries are elevated. Medial hypertrophy is clearly indicated. But the grade of hypertrophy is not uniform in every part of the arteries. It is most conspicuous in the region $R>100\mu$, while in the range $R<100\mu$ it is much less prominent. Because medial hypertrophy is expected to be different according to the region of arterial branches, it is necessary to examine, what part of which artery is most liable to hypertrophy in responce to elevated blood pressure.

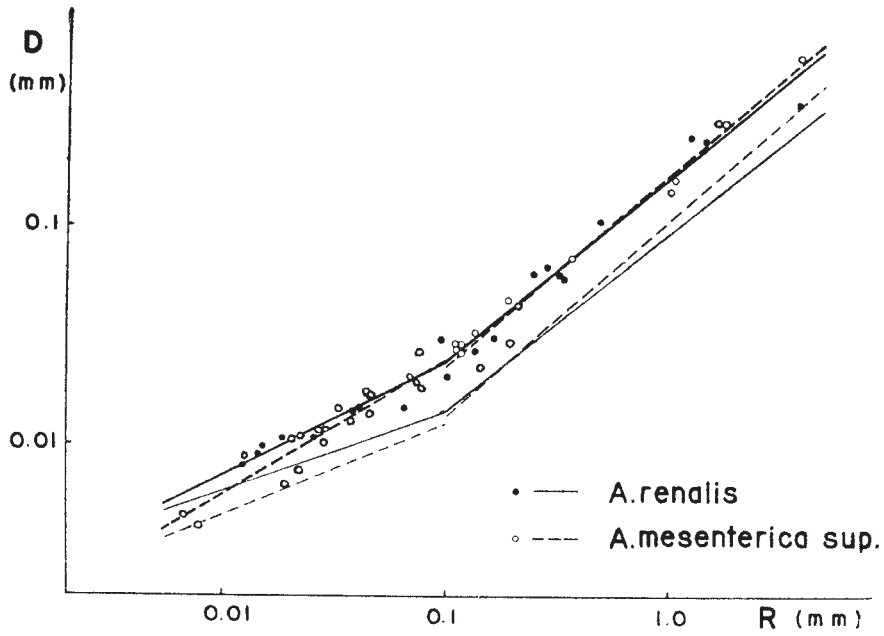

Fig. 14. A 55-year-old male with pronounced hypertension. Registered blood pressure was 230/118 mmHg. Sudden death by cerebral hemorrhage. Equations expressed in mm are:

for renal artery, $D=0.16R^{0.85}$ ($R>100\mu$) and $D=0.075R^{0.50}$ ($R<100\mu$),

for sup. mesenteric artery, $D=0.16R^{0.89}$ ($R>100\mu$) and $D=0.088R^{0.57}$ ($R<100\mu$).

In the lower part of the figure, common regression equations of the non-hypertensive of the corresponding age group are demonstrated for comparison. Note distinct hypertorphy of larger branches and much less pronounced hypertorphy of small arteries. Elevation of estimated D in comparison to the common regression equations of the non-hypertensive is shown in the following table.

	$R=10\mu$	$R=100\mu$	$R=1000\mu$
Renal artery	24%	71%	75%
Sup. mesenteric artery	40%	86%	60%

In Table III, renal and superior mesenteric arteries of cases with arterial hypertension of different origins and grades are presented. In all examined cases the value of estimated D at $R=100\mu$ of renal artery is over the upper rejection limit and medial hypertrophy of renal artery is confirmed. This indicates a high reliability of renal artery at $R=100\mu$ as an anatomical equivalent of arterial hypertension. It is not only because the deviations of estimated D are relatively small at this point of renal artery, but also because this part is really most active in responce to hypertension. In Fig. 16, a case of moderate hypertension is demonstrated. Definite hypertrophy of renal artery is confirmed only at $R=100\mu$. At $R=10\mu$ and $R=1000\mu$, estimated D of renal artery does not exceed the upper rejection limit. Because of the almost selective elevation of D/R at $R=100\mu$, renal artery loses its normal arterial pattern, characterized by

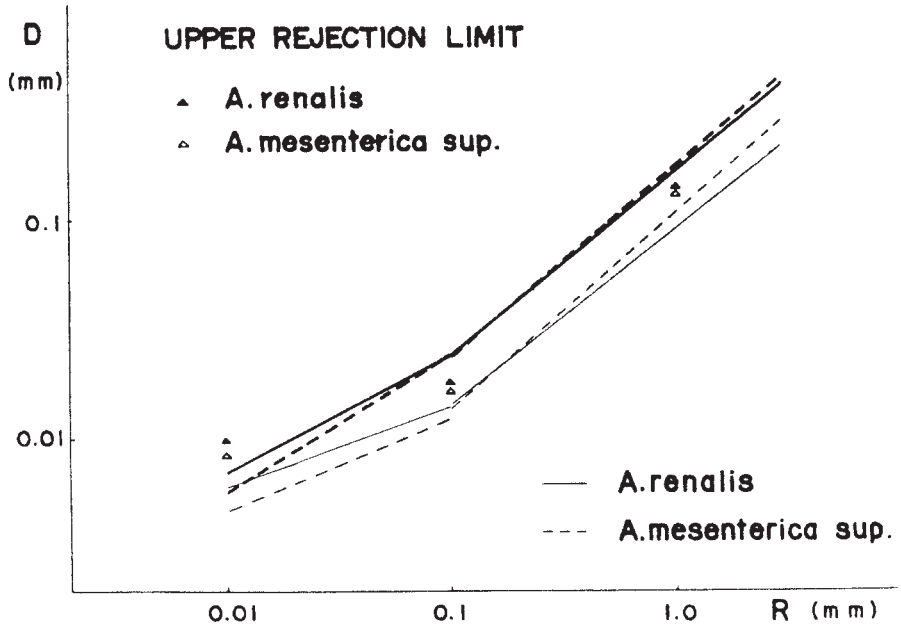

Fig. 15. Medial hypertrophy in the case of Fig. 14 is evaluated in reference to the upper rejection limit of estimated D of the non-hypertensive. The values of estimated D at $R=100\mu$ and $R=1000\mu$ are found above the upper rejection limit in renal and superior mesenteric arteries. Neither renal, nor superior mesenteric, artery exceeds the rejection limit at $R=10\mu$. Note only insignificant or absent medial hypertrophy in the arteriolar region, in spite of conspicuous hypertrophy of larger arterial branches.

Table III.

	Age & Sex	Estimated $D(\mu)$						Blood Pressure mmHg
		$R=10\mu$		$R=100\mu$		$R=1000\mu$		
		A. renalis	A. mesenterica sup.	A. renalis	A. mesenterica sup.	A. renalis	A. mesenterica sup.	
Chronic glomelulonephritis	6 ♀	9.04	6.78	25.92*	19.71	143.3*	151.4*	218/160—182/140
	17 ♂	7.53	4.48	20.96*	18.44	117.7	138.8	160/92—156/98
	19 ♂	6.41	6.01	20.21*	18.51	125.2	136.0	160—180
	19 ♀	11.21*	7.89	22.05*	19.66	110.4	145.3	138/90
	22 ♂	10.21*	8.68	21.05*	17.63	132.5	138.0	224/110—146/70
	23 ♂	10.87*	7.51	29.53*	30.19*	129.0	198.3*	252/144—112/88
	30 ♀	7.64	7.09	19.01*	18.00	142.1*	144.2	170/90—160/80
Essential hypertension	23 ♂	8.43	5.37	18.50*	15.45	113.3	133.1	160/90
	25 ♂	9.97*	6.49	29.68*	27.25	173.6*	195.1*	244/170—170/140
	30 ♂	8.68	3.91	25.74*	26.33	173.2*	177.0*	252/160—190/130
	31 ♂	9.05	5.35	24.44*	25.57	211.9*	261.0*	260—230
	35 ♂	7.17	5.59	28.77*	23.78	192.6*	203.0*	260/170
	55 ♂	7.41	6.34	23.28*	23.38*	163.1*	169.1*	230/118
	58 ♂	4.90	3.63	20.35*	17.16	115.8	137.0*	180/102—150/80
	80 ♀	5.22	4.16	20.09*	16.69	143.0	133.1	200/120

Values above the upper rejection limit at 5% level are indicated by an asterisk.

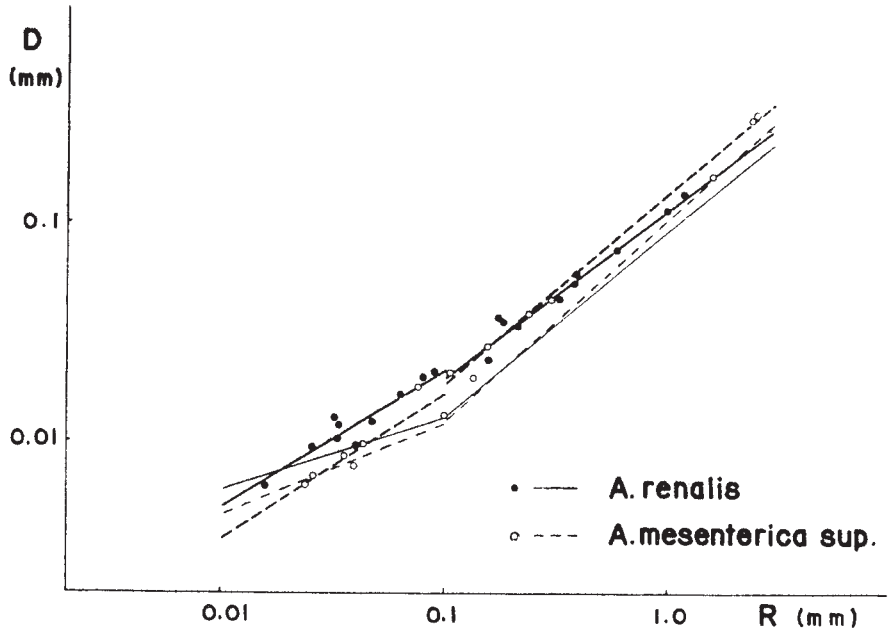

Fig. 16. Arterial pattern in moderate hypertension. A 58-year-old male with registered blood pressure 180/102 to 150/80 mmHg. Death by esophageal cancer. In the lower part of the figure, common regression equations of the non-hypertensive of the corresponding age group are presented. Equations expressed in mm are:
for renal artery, $D=0.11R^{0.76}$ ($R>100\mu$) and $D=0.096R^{0.64}$ ($R<100\mu$),
for sup. mesenteric artery, $D=0.13R^{0.84}$ ($R>100\mu$) and $D=0.075R^{0.65}$ ($R<100\mu$).
Elevation of estimated D in comparison to the common regression equations of the non-hypertensive is shown in the following table.

	$R=10\mu$	$R=100\mu$	$R=1000\mu$
Renal artery	−18%	50%	24%
Sup. mesenteric artery	−18%	38%	30%

strong muscular coat in arteriolar region. The regulatory activity of arterioles is regarded to be partly transferred to the region around $R=100\mu$. Larger branches of both renal and superior mesenteric arteries were also relatively sensitive to elevated blood pressure and exhibited definite medial hypertrophy at $R=1000\mu$ in the majority of cases with essential hypertension.

Contrary to the generally accepted view, arteriolar regions were most insensitive to hypertension in the whole range of arterial branches. At $R=10\mu$ only a few cases exhibited distinct medial hypertrophy of renal artery. The majority of such cases belonged to those of chronic glomerulonephritis in younger ages. It was not clarified in the present investigation, whether arteriolar hypertrophy in cases of chronic glomerulonephritis could simply be attributed to the reaction of well-preserved arterioles of younger persons, or to abnormally enhanced arteriolar activity in this disease. In the group of essential hypertension, only a case of juvenile malignant hypertension with excessively high blood

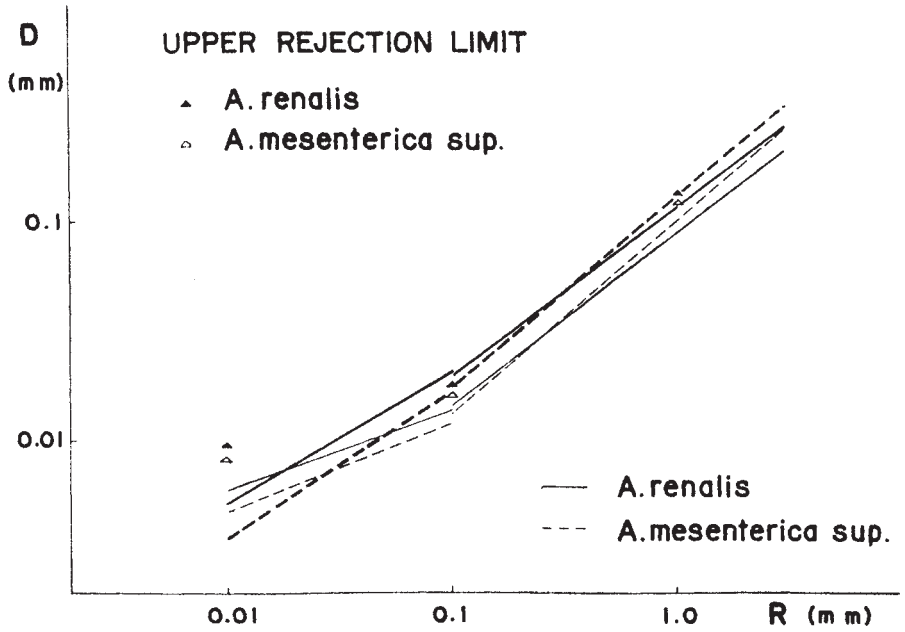

Fig. 17. The case in Fig. 16 is evaluated in reference to the upper rejection limit of the non-hypertensive. In renal artery, significant hypertrophy is confirmed only at $R=100\mu$. In superior mesenteric artery, estimated D at $R=1000\mu$ is found over the rejection limit. Arteriolar regions are not hypertrophied. Though registered blood pressure indicates rather moderate or transient hypertension in this case, hypertensive transformation of arterial pattern is already established.

pressure demonstrated medial hypertrophy at $R=10\mu$ of renal artery. In all other cases of this group, estimated D at $R=10\mu$ remained in the normal range. In none of the examined cases medial hypertrophy was confirmed at $R=10\mu$ of superior mesenteric artery.

The present investigation revealed a distinct difference in the grade of medial hypertrophy in responce to hypertension according to different regions of arterial branches. Arterial branches larger than 100μ in radius exhibited definite medial hypertrophy, but the region $R<100\mu$ was rather insensitive, and medial hypertrophy practically ceased to be noticed at $R=10\mu$. In the result, a transformation of arterial pattern was brought about in hypertension with diminished difference in regression coefficients between the two parts of arteries divided at $R=100\mu$. The whole range of arterial ramification tended to be represented by a single regression equation. This suggested, that medial hypertrophy, which was originally the expression of arterial accommodation to increased load, could induce abnormal circulatory regulation in some arterial systems, on account of its unequal distribution.

DISCUSSION

The histometrical procedures of the author revealed a regular relation existing

between anatomical arterial radius and medial thickness, and made possible to define medial hypertrophy in autopsy cases as an anatomical estimate of elevated blood pressure with considerable accuracy. Because the thickness of the media or the medial area in arterial cross sections is a function of arterial radius, it is impossible to confirm medial hypertrophy without an adequate treatment of arterial radius in autopsy materials, which has hitherto been only quite insufficiently taken into consideration in histometrical treatments of arteries.

In an application of the obtained relation to analysis of hemodynamical aspects of hypertension, a brief theoretical consideration is necessary, regarding physical factors which influence the property of arterial wall. The general relation of tension of vascular wall (T), intravascular blood pressure (P) and vascular radius (R) is given by the formula, $T=PR$. In arteries of muscular type, T may be regarded to be sustained practically by active muscular contraction of the media. Increased tension of vascular wall can only be compensated by enhanced muscular activity. When increased load on the arterial wall due to elevated blood pressure lasts over a certain length of time, enhanced muscular activity is anatomically recognized as increased muscular volume or hypertrophy of the media. In this state, T will be expressed by $T=D/F$, in which D is the anatomical medial thickness and F is a biological function. Substituting T by D/F, the above formula is transformed to $D/R=FP$. F is determined first of all by R and to some extent by arterial system, age and so forth, but is not regarded to be essentially influenced by P. The assumption is justified, because the increase of D/R in the region $R>100\mu$, where blood pressure is approximately the same as in large arteries, was practically proportional to clinically registered elevation of arterial blood pressure. Accordingly, D/R is expressed by the product of blood pressure and a function independent of blood pressure. The ratio D/R is defined as media index and employed as an anatomical estimate of elevated blood pressure in the corresponding part of the corresponding artery. The elevation of the index is regarded to indicate elevated blood pressure, so far as arteries of the same radius, of the same organ and of the same age group are compared.

In the non-hypertensive, the different pattern of renal and superior mesenteric arteries indicates a rather fundamental difference in regulatory activity of the two arteries. Larger branches of renal artery have distinctly weaker muscular coat than those of superior mesenteric artery, but the relation is reversed in the region of small arteries, and renal artery clearly predominates in its medial strength. The difference indicates, that the major regulatory function of superior mesenteric artery is located in its relatively large branches. In renal artery, regulatory activity of larger branches must be much less important in comparison to superior mesenteric artery and blood stream is regarded to attain the region of small arteries smaller than 100μ in radius without remarkably lowered

blood pressure. In the region of small arteries, renal artery is equipped with strong muscular coat, which rapidly increases in quantity with reduction of arterial radius. This indicates the significance of small branches of renal artery in the normal regulation of renal circulation.

In the hypertensive, not only arterial media is hypertrophied, but the characteristics of the arterial pattern according to organs are obscured. The cause of this tendency is the transformation of arterial pattern in hypertension. It is brought about by pronounced medial hypertrophy in the region $R>100\mu$, while arterioles fail to hypertrophy to the same extent. The result is an elevation of the regression coefficient in the region $R<100\mu$, and the entire arterial branches can approximately be represented by a single regression equation. It is further suggested, that a rapid fall of blood pressure will take place in the vicinity of $R=100\mu$. In the kidney of the adult, the region corresponds to proximal interlobular arteries.

The histometrical result sufficiently corresponds to histological findings of the kidney in essential hypertension. Arterial branches from interlobar to arcuate arteries have well-preserved and hypertrophied muscular coat, without increase in medial interstitial tissue. Fibrous thickening of the intima is minimum, and the region represents the best preserved part of the entire vascular system of the kidney. The muscular coat in proximal interlobular arteries is also hypertrophied. Occasional histological impression, as if the media were rather atrophied in this region of renal artery, can to the major part be attributed to fibroelastic thickening of the intima, which may encumber post-mortem arterial constriction. The muscular volume is usually found increased, even after considerable advancement of intimal thickening. Hypertensive arterial lesions, which involve not only the intima but also the muscular coat, begin to develop and to predominate from intermediate to distal interlobularis.

The trunk of renal artery over 30 years of age had distinctly increased interstitial tissue. This degenerative process, progressive with age, continuously involves arterial branches of the next order, but only exceptionally attains interlobar artery, and the region from interlobar to arcuate arteries is liable to be exposed to increased hemodynamical load. It is easily comprehended, that the influence of medial degeneration in the proximal part of arteries is more pronounced in renal, than in superior mesenteric artery, because the latter has a much longer stretch from the trunk to arterioles. The total length of renal artery may be regarded to be shortened in advanced ages, so far as its regulatory function is concerned. Hypertension exaggerates the effect of this physiological aging process and demands enhanced activity of intermediate arterial branches of limited length.

The result of the present investigation indicates, that hypertensive arteriolar lesions, which are found in the region $R<100\mu$ of renal artery, can hardly be a

direct result of elevated blood pressure in this part. If the small branches of renal artery are exposed to high blood pressure in an average, it is very difficult to understand, why medial hypertrophy in arterioles fails to develop to the extent observed in larger branches. That renal arterioles can hypertrophy under some conditions is demonstrated in cases of chronic glomerulonephritis, and in such cases hypertensive arteriolar lesions, if present, are not so prominent as in cases with essential hypertension. At present, it is appropriate to assume, that occasional excessive constriction of hypertrophied arterial branches in the vicinity of 100μ in radius causes temporary ischemic endothelial damage of peripheral arterioles and increases plasmal insudation into arteriolar wall. Hypertenisve arteriolar lesions are then one of the expressions of circulatory disharmony, induced by the abnormal arterial pattern in the hypertensive. In this respect it is interesting, that hypertensive arteriolar lesions are much more frequently observed in renal, than in superior mesenteric, artery. Normal circulatory regulation of renal artery, which mainly depends on the activity of arterioles will be incompatible with the transformation of arterial pattern, characterized by hypertrophied larger branches. Superior mesenteric artery is regarded to retain its normal regulatory function even in hypertension, because the activity of larger arterial branches is rather accentuated and not affected by hypertensive transformation of arterial pattern. The importance of the original physiological arterial pattern as one of the predisposing factors of hypertensive circulatory disturbance in some arterial systems is suggested by the author's histometrical investigation. Further systematical studies of a larger number of arterial systems are required, of which only renal and superior mesenteric arteries were discussed in the present paper.

SUMMARY

1) A histometrical method was described, with which arterial cross sections of autopsy cases were reduced to the state, in which internal elastic membrane was perfectly stretched. The distance from the center of the arterial lumen to the middle point of the media in this condition was defined as anatomical arterial radius, R, and the thickness of the media in this condition as anatomical medial thickness, D. The values of R and D were determined by $R=\frac{S}{\sqrt{L^2+4\pi S}-L}$ and $D=\frac{\sqrt{L^2+4\pi S}-L}{2\pi}$, respectively, in which L was the length of internal elastic membrane and S was the surface area of the muscular coat in arterial cross section.

2) A regular relation was confirmed between R and D, which was represented by a general equation $D=aR^b$, a and b being constants. On a logarithmic scale, the relation gave a linear regression and was represented by a linear regression equation $\hat{Y}=bX+A$, in which $X=\log R$, $Y=\log D$ and $A=\log a$. Statistical

treatments of the histometrical results were discussed.

3) The histometrical method was applied to renal and superior mesenteric arteries. Non-hypertensive cases were divided into 3 age groups, and in each age group common regression equations were determined of each artery to demonstrate the characteristics of arterial pattern. Each artery was composed of two parts divided at $R=100\mu$. In the part $R>100\mu$, b was smaller than, but very close to, 1. Superior mesenteric artery had stronger muscular coat than renal artery at $R=1000\mu$. In the other part, $R<100\mu$, b was remarkably lower than 1, especially in renal artery, indicating rapid elevation of the ratio D/R with reduction of arterial radius. At the point $R=10\mu$, renal artery had a higher value of D/R. The difference of arterial pattern was discussed in relation to different regulatory function of the two arteries.

4) The ratio D/R was defined as media index and employed as the estimate of medial strength. The value of the index was determined to the major part by blood pressure, arterial radius and arterial system, and to a lesser extent by age. Media index of the non-hypertensive was strikingly constant at a given radius of a given arterial system, in spite of remarkable arterial growth with age, with the exception at $R=10\mu$, where the index gradually fell with age. By an elevation of media index medial hypertrophy was defined and hypertension was concluded.

5) Upper rejection limit of estimated D from the regression equations of the non-hypertensive was statistically determined at $R=1000\mu$, $R=100\mu$ and $R=10\mu$ of each artery. Arteries with larger estimated D than the upper rejection limit at any R were not regarded to belong to the non-hypertensive. The rejection limit at $R=100\mu$ of renal artery was the most effective and reliable anatomical standard in screening hypertensive cases.

6) In the hypertensive, medial hypertrophy was confirmed in both renal and superior mesenteric arteries. Medial hypertrophy was very unequal according to the dimension of arterial branches. It was prominent in the region $R>100\mu$, but less pronounced in the region $R<100\mu$, and practically ceased to be noticed at $R=10\mu$ in the majority of cases with essential hypertension. Blood pressure was regarded to be abruptly lowered in the vicinity of $R=100\mu$ and arterioles were in all probability not exposed to abnormally high blood pressure in an average. The unequal medial hypertrophy induced a transformation of general arterial pattern in hypertension.

7) Possible disharmony in regulatory function of renal artery in hypertension was discussed on the basis of the above result. Regulatory activity of arterioles in the normal kidney was regarded to be transferred to larger branches in hypertension. The development of hypertensive arteriolar lesions was attributed to temporary ischemia, enhanced endothelial permeability and increased plasmal insudation in arteriolar region, induced by occasional excessive constriction of larger arterial branches with hypertrophied media.

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